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SYSTEMATIC REVIEWS AND META-ANALYSES

The effects of foods on LDL cholesterol levels: A systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials

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Abstract *Aims:* To systematically evaluate the evidence regarding the effects of foods on LDL cholesterol levels and to compare the findings with current guidelines.
Data synthesis: From inception through June 2019, we searched PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for guidelines, systematic reviews, and RCTs (for coffee intake only) of at least 13 days duration. Additionally, we searched Trip database for guidelines from 2009 through Oct 2019. Language was restricted to English. The strength of evidence was evaluated using The Grading of Recommendations Assessment, Development, and Evaluation (GRADE). A total of 37 guidelines, 108 systematic reviews, and 20 RCTs were included. With high evidence, foods high in unsaturated and low in saturated and *trans* fatty acids (e.g. rapeseed/canola oil), with added plant sterols/stanols, and high in soluble fiber (e.g. oats, barley, and psyllium) caused at least moderate (i.e. 0.20–0.40 mmol/L) reductions in LDL cholesterol. Unfiltered coffee caused a moderate to large increase. Soy protein, tomatoes, flaxseeds, and almonds caused small reductions. With moderate evidence, avocados and turmeric caused moderate to large reductions. Pulses, hazelnuts, walnuts, high-fiber/wholegrain foods, and green tea caused small to moderate reductions, whereas sugar caused a small increase. Other identified foods were either neutral or had low or very low evidence regarding their effects.
Conclusions: Several foods distinctly modify LDL cholesterol levels. The results may aid future guidelines and dietary advice for hypercholesterolemia.

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Introduction

Lifestyle management remains the foundation for the prevention of cardiovascular disease (CVD). Dietary guidelines targeting healthy individuals [1], dyslipidemia [2], or CVD prevention [3] typically advocate healthy dietary patterns such as the Mediterranean diet. However, there has been a call for more food-based dietary advice [4]. The effects of individual foods on CVD outcomes are challenging to study in randomized controlled trials (RCTs), whereas effects on risk factors can be determined from strictly controlled interventions of shorter duration. Moreover, the dietary choices that influence the level of low-density lipoprotein (LDL) cholesterol are distinctly different from those concerning hypertriglyceridemia, which can be improved by omega-3 supplements and reduced intakes of alcohol or carbohydrates [2]. This distinction may require clarification, as only LDL cholesterol is considered as a critical [5], causal, and cumulative risk factor [2]; and represents the primary target for CVD risk reduction [2]. The potential for improvement in LDL cholesterol through diet is also substantial, as demonstrated by studies combining several foods, e.g. the Portfolio diet, which emphasizes nuts, plant protein, plant sterols, and soluble fiber [6]. In recent years, several additional foods have emerged as potentially effective. Thus, a detailed update would be valuable, both to caregivers and to individuals seeking to improve their cholesterol levels. This study aimed to systematically evaluate the evidence from RCTs reporting effects of foods on LDL cholesterol levels and to compare the findings with current guidelines.

Methods

The study contains both an umbrella review of guidelines and systematic reviews, and a systematic review and meta-analysis of RCTs.

Data sources and searches

Based on preliminary searches, seven foods were selected, for which evidence for effects was indicated but not considered unequivocal; garlic, coffee, tea, cocoa/chocolate, probiotics, nuts, and soy protein. Searches were then performed in two predetermined steps. First, PubMed and Cochrane Database of Systematic Reviews were searched for guidelines (considered separately) and systematic reviews concerning the effects of foods on LDL cholesterol levels. Second, for the selected foods above, we set out to perform our own systematic reviews (and meta-analyses) of RCTs, if they had not been included in any published systematic review with low risk of bias. This second search for RCTs was performed in PubMed and Cochrane Central Register of Controlled Trials. The search strategies were developed with assistance from librarians at Falu hospital and are described in Supplemental Table 1. The first search (for guidelines and systematic reviews) was performed on 13 March 2018 and the second search (for RCTs) on 2 May 2018. Both were updated on 4 June 2019. A complementary search for guidelines was performed in Trip database on 31 Oct 2019, as several guidelines had been recently updated. Abstracts were screened by both authors; in cases of disagreement, the paper was generally included for further review. The bibliographies of included RCTs were screened for other potentially relevant studies.

Study selection

For both searches, the target population was adults who were not treated with lipid-lowering medications. The interventions of interest were foods or nutrients related to specific foods; but not supplements, weight loss diets, or dietary patterns. The outcome was LDL cholesterol in mmol/L (conversion factor from mg/dL 0.02586). Comparison foods and no treatment were acceptable as controls. Language was restricted to English. Guideline documents should be publically available, related to dyslipidemia or CVD prevention, and be no older than 10 years. In the second search (for RCTs), at least a 13-day isocaloric intervention was required. No other restrictions were applied.

Data extraction and risk of bias assessment

Available data were extracted from articles read in full text. Authors were contacted if required. Risk of bias in systematic reviews was assessed (by both authors) using a modified version of the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) tool. For low risk of bias grading, a reproducible search strategy was mandatory. Additionally, at most one of the following criteria was allowed omitted: having at least two independent reviewers; searching at least two databases; providing a complete list of excluded studies read in full text, with reasons; providing a table describing relevant details of included studies; and providing a risk of bias assessment of included studies. Narrative reviews and systematic reviews not classified as having low risk of bias were excluded from the qualitative summary. Excluded studies near the threshold were however mentioned in text (but not in main tables and figures) if their results could affect the overall conclusions. The RCTs found during the second search were assessed (by both authors) using the Cochrane Risk of Bias Tool 2.0. We did not rely on previously performed evaluations of the evidence. Instead, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) strength of evidence was determined for each systematic review, by predetermined criteria for risk of bias, inconsistency, indirectness, imprecision, publication bias, large effects, dose–response relationship, and opposing bias. In marginal cases, discussions were extended until a consensus was reached, applying overall judgments. For each food, the effect and strength of evidence were then evaluated, taking into account all included systematic reviews, bearing in mind that some RCTs may be included in several different systematic reviews.

Data synthesis and analysis

Meta-analyses were conducted using Review Manager 5.3. In studies with several study arms, the weighted averages of means and standard deviations were calculated. The mean change from baseline was used whenever standard deviations were given or possible to calculate. Otherwise, the end-of-study means and standard deviations were used, at the latest available time point. Crossover studies were combined with parallel RCTs in the meta-analyses, with adjusted weights; in cases where the variances of mean differences were unavailable, a correlation R = 0.82 was imputed (the calculated mean from studies with available data), and sensitivity analyses were performed with a more conservative weighting of R = 0.5. If heterogeneity was considered low or moderate (I^2<50%), fixed effects models were preferred. As sensitivity analyses, only the end-point data (with imputed data on standard deviations if missing) were used, parallel and crossover studies were analysed separately, and only one arm per study (the most relevant) was included. Estimated food doses were calculated as weighted means from included studies with reported data, using the weights from the corresponding meta-analyses.

The study was conducted according to the Swedish Agency for Health Technology Assessment and Assessment of Social Services Method Handbook [7] and the Cochrane Handbook for Systematic Reviews of Interventions [8]. The review protocol is available at www.crd.york.ac.uk/PROSPERO, identifier: CRD42018089661. No ethics approval was required.

Results

The study selections in the two searches are presented as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts (Fig. 1A and B). Two hundred potential systematic reviews were read in full text, and 108 were included in the qualitative summary (Supplemental Table 2).

Thirty-seven guideline documents were identified (Supplemental Table 3). Their recommendations were partly consistent but also included some variations. Several recommended a Mediterranean (advice included in 11 guidelines), Dietary Approaches to Stop Hypertension (DASH, 6 guidelines), or a similar dietary pattern; high in fruits and vegetables, nuts, non-tropical oils, legumes, whole-grain/high-fiber foods, and fish. Single guidelines recommended other dietary patterns, e.g. vegetarian/vegan, plant-based wholefood, Portfolio, low-fat, or Therapeutic Lifestyle Changes diet. Seven guidelines recommended foods high in or enriched with plant sterols and/or stanols. Seven guidelines recommended soy products. Restrictions in sugar and soft drinks (16 guidelines), *trans* fatty acids (17 guidelines) or saturated fatty acids (24 guidelines) were common. Some included restrictions in red or processed meats (14 guidelines), salt (9 guidelines), alcohol (8 guidelines), refined carbohydrates (6 guidelines) or dietary cholesterol (11 guidelines). Only one guideline advised against unfiltered coffee intake. Brief summaries of each guideline's dietary recommendations and evidence gradings (included in 15 guidelines) are listed in Supplemental Table 3. In addition, two WHO reports were found, which described the effects of saturated and *trans* fatty acids on LDL cholesterol. These were not published in peer-reviewed journals and did not fulfil the AMSTAR criteria for systematic reviews, but were still considered relevant for evaluation (see Fatty foods, below).

All of the pre-specified foods except coffee were included in published systematic reviews with low risk of bias. Thus, coffee was the only food included in the second search for RCTs, from which 20 RCTs (1518 participants) fulfilled our inclusion criteria and were included in the qualitative summary (Table 1). Nineteen RCTs (1335 participants) were included in the meta-analyses (Fig. 2). The overall estimates of the effect and strength of and evidence for each food are summarized in Table 2. The effects of foods with moderate or high evidence are further visualized in Fig. 3. The excluded systematic reviews and RCTs are listed, with reasons, in Supplemental Tables 4 and 5.

Alcohol

One study conducted in 1999 was excluded, while one systematic review conducted in 2011 was included. There was a tendency towards a small reduction in LDL cholesterol but the evidence was considered very low.

Chocolate and cocoa

Two studies conducted in 2006–2016 were excluded, while five systematic reviews conducted in 2010–2016 were included. Overall, the evidence was considered very low for a small reduction in LDL cholesterol by chocolate and cocoa.

Dairy

Two studies conducted in 2015–2018 were excluded. One systematic review on dairy products conducted in 2013 was rated as having unclear/low risk of bias, but was included. Increased dairy intake had no clear effect on LDL cholesterol, but the evidence was considered very low. For high-fat dairy products (which are high in SFA), see also Fatty foods. For yogurt, see Probiotics.

Eggs and other cholesterol-rich foods

One systematic review on cholesterol conducted in 2015 and two on eggs conducted in 2017–2018 were included. As discussed in the most recent systematic review, there may be large individual differences in response to dietary cholesterol, which may partly explain the inconsistency of the results. However, with regard to the overall claim that dietary cholesterol and eggs can increase LDL cholesterol, the evidence was considered low for a small effect.

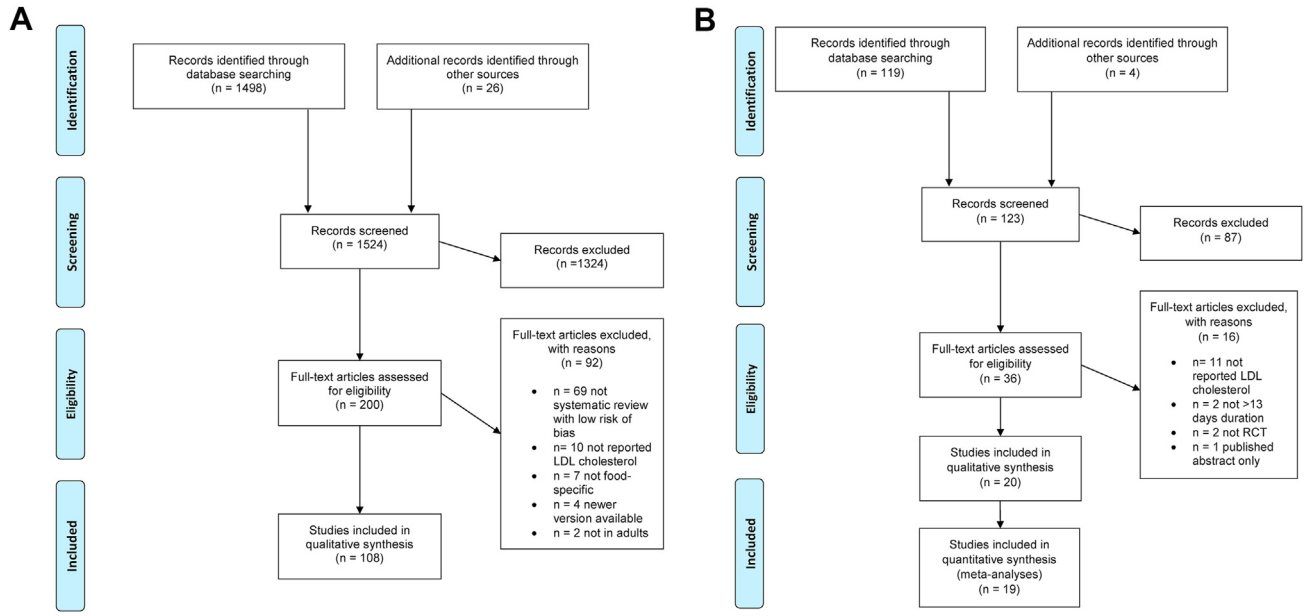


Figure 1 A. Flow chart for the first search (for systematic reviews). B. Flow chart for the second search (for randomized controlled trials on coffee).

Fatty foods

The two WHO documents [5,9] from 2016 presented meta-regressions from well-controlled dietary RCTs for each percentage energy replacement of SFA and *trans* fatty acid intakes by other types of fats or carbohydrate. The reductions were largest when SFA or *trans* fatty acids were replaced by MUFA and PUFA, with high GRADE evidence according to their authors.

Twenty-four studies conducted in 1992–2018 were excluded, while 15 systematic reviews conducted in 2009–2018 were included. Among individual foods, the results were most clear for rapeseed/canola oil; in a systematic review conducted in 2019, the evidence was considered high for a moderate (0.20–0.40 mmol/L) to large reduction in LDL cholesterol, when approximately 17 percent of energy intake (%E) (weighted mean in 5 of 9 RCTs which reported units as %E) of rapeseed/canola oil (representing about half of total fat intake in most Western populations) replaced foods high in SFA. There was also low evidence for a potential beneficial effect of polyphenols on LDL cholesterol, as demonstrated in studies on olive oil.

For α-linolenic acid (ALA), in two systematic reviews conducted in 2016–2018, the evidence was considered low and moderate for no clear effect on LDL cholesterol. Note that ALA and flaxseed oil are presented together in Table 2 (for flaxseeds, see Nuts and seeds, below). For marine omega-3 sources, the evidence was considered moderate for a very small increase.

Fiber and whole grains

Twelve studies conducted in 1997–2018 were excluded, while 13 systematic reviews conducted in 2010–2018 were included. The evidence was most clear for soluble (or viscous) fibers, e.g. psyllium (weighted mean dose 11 g per day compared with foods without or low in fiber or containing insoluble fiber, in 29 of 29 comparisons with units reported as g per day) or β-glucans from barley (weighted mean dose 5.6 g per day of β-glucan compared with diets low in β-glucan, in 14 of 14 RCTs which reported units as g per day) or oats (weighted mean dose 4.8 g per day of β-glucan compared with food products without soluble fiber or high in insoluble fiber, in 33 of 33 comparisons with units reported as g per day), with high evidence for moderate reductions in LDL cholesterol. The effects of other types of fiber (approximate weighted mean dose 12 g per day compared with lower-fiber diets, in 27 of 34 RCTs which reported units as g per day) and wholegrain (approximate weighted mean dose 90 g per day compared with lower-wholegrain diets, mostly in weight stable conditions, in 25 of 28 comparisons with units reported as g per day) on LDL cholesterol were slightly less clear (moderate evidence, small reductions). For pulses (weighted mean dose 114 g wet weight per day compared with usual diets, in 2 of 4 RCTs which reported units in this format), there was moderate evidence for a small to moderate reduction in LDL cholesterol (see also under Protein-rich foods).

In a series of reviews [10] conducted in 2019, results on blood lipids were also presented for starch digestability and glycemic index of carbohydrate. These results and other systematic reviews on dietary patterns low in glycemic index or glycemic load were considered outside the scope of this review.

Fruits, berries, and vegetables

Five studies conducted in 2015–2018 were excluded, while eight systematic reviews conducted in 2011–2018 were

Table 1 Characteristics of the 20 included RCTs that evaluated the effect of coffee on LDL cholesterol.

Author, year	Design	Interventions/ comparison	Daily dose (mean ± SD and/or range)	Duration	Participants analysed, *n* overall (per group, % male)	Population	Age in years (mean ± SD and/or range)	Baseline LDL-C (mean ± SD mmol/L)	Risk of bias	Country	Funding
Agudelo-Ochoa [26], 2016	Parallel	Three groups: high vs medium chlorogenic acid coffee vs no coffee[a]	400 mL (780 mg chlorogenic acids in high and 420 mg in medium group)	8 w	74 (24 + 25 + 25, 51%)	Healthy	20–60	2.78 ± 0.59	Some concerns (randomization)	Colombia	N/A
Ahola [30], 1991	Crossover	Boiled coffee vs boiled and filtered coffee[c]	6–10 dL	4 w	20 (15%)	Healthy	45 ± 8	3.8 ± 0.9	Some concerns (randomization)	Finland	Food Research Foundation
Aro [31], 1985	Crossover	Three interventions: instant coffee vs instant tea vs rosehip 'tea'[a,b]	8 cups	3 w	12 (50%)	Healthy	33–45	3.02 ± 0.19	Some concerns (randomization)	Finland	N/A, Academy of Finland
Aro [32], 1987	Crossover	Three interventions: boiled coffee vs filtered coffee vs tea[b,c]	8 cups	4 w	42 (50%)	Hyper-cholesterolemic	49 (31–60)	6.04 ± 0.16	Some concerns (randomization)	Finland	Finnish Food Research Foundation
Aro [33], 1990	Crossover	Boiled coffee vs filtered coffee[c]	5.7 (2–14) cups	4 w	41 (32%)	Healthy	45 (23–61)	~3.5	Some concerns (randomization)	Finland	Food Research Foundation
Bak [34], 1989	Parallel	Three groups: boiled coffee vs filtered coffee vs no coffee[a,c]	4–6 cups	12 w	101 (33 + 34 + 34, 48%)	Healthy	26 ± 4	3.2 ± 1.1	Some concerns (randomization)	Netherlands	Committee on Physiological Effects of Coffee, Netherlands Prevention Fund and Netherlands Heart Foundation
Corrêa [35], 2013	Crossover	Medium-light vs medium roast coffee[e]	3 or 4 cups	4 w	20 (30%)	Healthy	50 ± 9	3.1 ± 0.5	Some concerns (randomization)	Brazil	FAPESP, National Council for Scientific and Technological Development
D'Amicis [36], 1996	Parallel	Three groups: espresso vs mocha vs tea[b]	3.1 ± 1.2 vs 2.8 ± 1.1 cups (espresso, 25–35 mL/cup and mocha, 40–50 mL/cup)	6 w	84 (28 + 28 +28, 100%)	Healthy soldiers	27 ± 1	3.0 ± 0.6	Some concerns (randomization)	Italy	Institute for Scientific Information on Coffee
Dusseldorp [37], 1990	Crossover	Regular coffee vs decaffeinated coffee[d]	4–6 cups	6 w	45 (49%)	Healthy	38 ± 7 (25–45)	N/A	Low	Netherlands	Netherlands Heart Foundation
Dusseldorp [38], 1991	Parallel	Three groups: boiled coffee vs boiled and filtered coffee vs no coffee[a,c]	6 cups (0.9 L)	79 d	64 (22 + 21 +21, 52%)	Healthy	39 ± 8	3.4 ± 0.8	Some concerns (randomization)	Netherlands	Netherlands Heart Foundation

(*continued on next page*)

Table 1 (*continued*)

Author, year	Design	Interventions/ comparison	Daily dose (mean ± SD and/or range)	Duration	Participants analysed, *n* overall (per group, % male)	Population	Age in years (mean ± SD and/or range)	Baseline LDL-C (mean ± SD mmol/L)	Risk of bias	Country	Funding
Fried [39], 1992	Parallel	Four groups: regular coffee in high vs low dose vs decaffeinated coffee vs no coffee[a,d]	720 mL in high dose and de-caffeinated groups, 360 mL in low dose group	8 w	100 (25 + 25 + 25 + 25, 100%)	Healthy	44 ± 10	3.3 ± 0.8	Some concerns (randomization)	USA	National Coffee Association and Outpatient Clinical Research Center from the National Institutes of Health, Bethesda
Kempf [40], 2015	Parallel	Dark roast vs medium roast coffee[e]	4–5 cups	3 mo	114 (56 + 58, 34%)	Overweight	49 ± 12	3.5 ± 0.9	Some concerns (randomization)	Germany	Tchibo GmbH
Rosmarin [41], 1990	Crossover	Coffee vs no coffee[a]	3.6 (2.1–6.7) cups	2 mo	21 (100%)	Healthy, white	35 ± 6 (22–45)	3.2 ± 0.8	Low	USA	University Physicians Foundation of the University of Tennessee
Sanguigni [42], 1995	Crossover	Regular moka vs decaffeinated moka[d]	3 cups	5 w	49 (51%)	Healthy	23 (21–28)	2.7 ± 0.6	Some concerns (randomization)	Italy	N/A
Shaposhnikov [43], 2018	Parallel	Three groups: high vs low dose coffee vs water[a]	5 (high dose, water) or 3 (low dose) cups	8 w	160 (53 + 53 + 54, N/A)	Healthy (56% overweight)	51 ± 12	N/A	Some concerns (randomization)	Netherlands	Kraft Foods and University of Olso
Superko [44], 1991	Parallel	Three groups: regular coffee vs decaffeinated coffee vs no coffee[a,d]	4.5 ± 1.1 (3–6) cups	8 w	181 (62 + 61 + 58, 100%)	Healthy	46 ± 10	3.7 ± 0.9	Some concerns (randomization)	USA	National Institutes of Health
Urgert [45], 1996	Parallel	Cafetiere vs filtered coffee[c]	5–6 cups (0.9 L)	24 w	46 (22 + 24, 50%)	Healthy	29 ± 10	3.0	Some concerns (randomization)	Netherlands	Netherlands Heart Foundation through the Netherlands Organisation of Scientific Research
Wahrburg [25], 1994	Parallel	Three groups: regular arabica coffee vs arabica decaffeinated coffee vs arabica/ robusta decaffeinated coffee[d]	750–1000 mL	6 w	116 (39 + 39 + 38, 51%)	Healthy students	25 ± 3	3.4 ± 0.6	Some concerns (randomization)	Germany	Institute for Scientific Information on Coffee
Wedick [46], 2011	Parallel	Three groups: instant regular coffee vs instant decaffeinated coffee vs water[a,d]	5 cups (885 mL)	8 w	45 (16 + 14 + 15, 36%)	Healthy, overweight	41 ± 13	2.5 ± 0.8	Low	USA	Boston Obesity Nutrition Research Center and National Center for Research Resources

Yamaguchi [27], 2007	Parallel	Five groups: Regular coffee vs zero-dose vs low-dose vs middle-dose vs high-dose hydroxyhydroquinone coffee	1 cup (183 mL)	4 w	183 (37 + 37 + 37 + 35 + 37, 50%)	Mildly hypertensive	49 ± 10	3.3 ± 0.8	Some concerns (randomization)	Japan	Kao Corporation

Abbreviations: mo – months, LDL – low-density lipoprotein, N/A – not available, RCT – randomized controlled trial, w – weeks.
Included in corresponding meta-analyses (Fig. 2A–E):
[a] Filtered compared with no coffee.
[b] Coffee compared with tea.
[c] Filtered compared with unfiltered coffee.
[d] Regular compared with decaffeinated coffee.
[e] Darker compared with lighter roast.

included. For tomatoes (approximate weighted mean dose of tomatoes or tomato products 300 g per day compared with cucumber or a usual diet without tomatoes, in 2 of 6 RCTs which reported units as g per day), the evidence was considered high for a small to moderate reduction in LDL cholesterol. As non-randomized trials and many different foods were included in the review on lycopene [11] conducted in 2011, which contributed to the reduction in the level of evidence, we relied mostly on the evidence of the systematic review on tomatoes [12] conducted in 2017.

Despite their moderate to large effect on LDL cholesterol, the evidence for avocados (substituted for other fat sources in 10 of 12 RCTs and added to the habitual diet in 2 of 10 RCTs, approximate weighted mean dose 219 g per day in 5 of 14 comparisons with units reported as g per day, or 22.5 %E in 3 of 14 comparison with units reported in this format, or 1 avocado per day in 2 of 14 comparisons with units reported in this format) was only considered moderate, due to risk of bias and inconsistency. Berries and other fruits and vegetables caused small to moderate reductions, but the evidence was considered very low.

Garlic

Two studies conducted in 2016–2019 were excluded, while three systematic reviews conducted in 2013–2017 were included. In the two studies not restricted to individuals with diabetes, the evidence was low (specifically for garlic powder) or very low for a small to moderate effect on LDL cholesterol.

Grapes and wine

One systematic review of grape polyphenols conducted in 2017 was included. Only two of its 29 RCTs demonstrated an effect. Although no meta-analysis was performed, the evidence was considered very low for no clear effect on LDL cholesterol.

Herbs

Three studies conducted in 2007–2015 were excluded, but no systematic reviews were included.

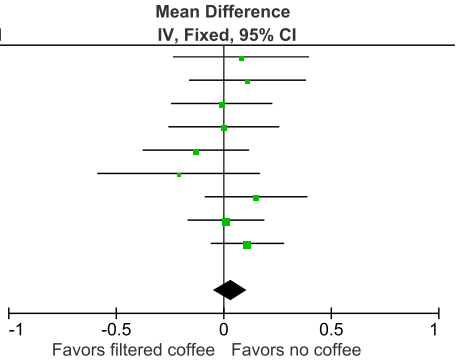
Nuts and seeds

Seven studies conducted in 2010–2018 were excluded, while nine systematic reviews conducted in 2005–2018 were included. High evidence was demonstrated for almonds (weighted mean dose 60 g per day compared with no almonds or a variety of provided control foods, from 18 of 18 RCTs which reported units as g per day). Moderate evidence was demonstrated also for hazelnuts (reported mean dose 39 g per day compared with control diets without hazelnuts, in 3 RCTs which were included in a Bayesian meta-analysis) and walnuts (approximate weighted mean dose 46 g, in 22 of 24 RCTs which reported units as g per day, or 16 %E, in 14 of 24 RCT which reported units as %E; compared with a variety of control diets low in walnuts).

A

Study or Subgroup	Filtered coffee Mean	SD	Total	No coffee Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Agudelo-Ochoa 2016	2.85	0.63	49	2.77	0.67	25	6.1%	0.08 [-0.24, 0.40]
Aro 1985	3.24	0.34	12	3.13	0.34	12	8.3%	0.11 [-0.16, 0.38]
Rosmarin 1990	3.29	0.39	21	3.3	0.39	21	11.0%	-0.01 [-0.25, 0.23]
Shaposhnikov 2018	3.3	0.75	107	3.3	0.8	53	9.2%	0.00 [-0.26, 0.26]
Wedick 2011	2.59	0.4	30	2.72	0.4	15	10.0%	-0.13 [-0.38, 0.12]
Bak 1989	-0.03	0.69	34	0.18	0.89	34	4.3%	-0.21 [-0.59, 0.17]
Dusseldorp 1991	0.09	0.39	21	-0.06	0.4	21	10.8%	0.15 [-0.09, 0.39]
Fried 1992	0.05	0.41	75	0.04	0.39	25	19.2%	0.01 [-0.17, 0.19]
Superko 1991	0	0.6	123	-0.11	0.52	58	21.1%	0.11 [-0.06, 0.28]
Total (95% CI)			**472**			**264**	**100.0%**	**0.03 [-0.05, 0.11]**

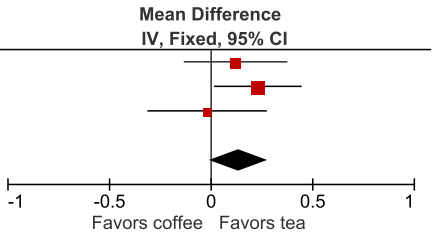
Heterogeneity: Chi² = 5.59, df = 8 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)



B

Study or Subgroup	Mean Difference	SE	Coffee Total	Tea Total	Weight	Mean Difference IV, Fixed, 95% CI
Aro 1985	0.12	0.13	12	12	31.8%	0.12 [-0.13, 0.37]
Aro 1987	0.23	0.11	42	42	44.4%	0.23 [0.01, 0.45]
D'Amicis 1996	-0.02	0.15	56	28	23.9%	-0.02 [-0.31, 0.27]
Total (95% CI)			**110**	**82**	**100.0%**	**0.14 [-0.01, 0.28]**

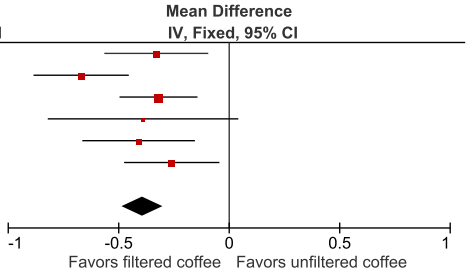
Heterogeneity: Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)



C

Study or Subgroup	Mean Difference	SE	Filtered Total	Unfiltered Total	Weight	Mean Difference IV, Fixed, 95% CI
Ahola 1991	-0.33	0.12	20	20	15.9%	-0.33 [-0.57, -0.09]
Aro 1987	-0.67	0.11	42	42	18.9%	-0.67 [-0.89, -0.45]
Aro 1990	-0.32	0.09	41	41	28.2%	-0.32 [-0.50, -0.14]
Bak 1989	-0.39	0.22	34	33	4.7%	-0.39 [-0.82, 0.04]
Dusseldorp 1991	-0.41	0.13	21	22	13.5%	-0.41 [-0.66, -0.16]
Urgert 1996	-0.26	0.11	24	22	18.9%	-0.26 [-0.48, -0.04]
Total (95% CI)			**182**	**180**	**100.0%**	**-0.39 [-0.49, -0.30]**

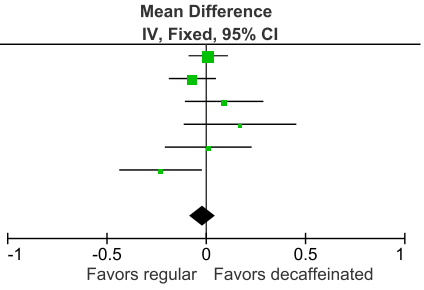
Heterogeneity: Chi² = 8.75, df = 5 (P = 0.12); I² = 43%
Test for overall effect: Z = 8.20 (P < 0.00001)



D

Study or Subgroup	Regular coffee Mean	SD	Total	Decaffeinated coffee Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dusseldorp 1990	3.41	0.24	45	3.4	0.24	45	40.0%	0.01 [-0.09, 0.11]
Sanguigni 1995	2.67	0.3	49	2.74	0.3	49	27.8%	-0.07 [-0.19, 0.05]
Wahrburg 1994	3.38	0.51	39	3.29	0.52	77	10.0%	0.09 [-0.11, 0.29]
Wedick 2011	2.67	0.39	16	2.5	0.4	14	4.9%	0.17 [-0.11, 0.45]
Fried 1992	0.05	0.35	50	0.04	0.5	25	8.2%	0.01 [-0.21, 0.23]
Superko 1991	-0.11	0.52	62	0.12	0.65	61	9.1%	-0.23 [-0.44, -0.02]
Total (95% CI)			**261**			**271**	**100.0%**	**-0.02 [-0.08, 0.04]**

Heterogeneity: Chi² = 7.92, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 0.57 (P = 0.57)



E

Study or Subgroup	Darker Mean	SD	Total	Lighter Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Corrêa 2013	3.5	0.29	20	3.4	0.29	20	77.2%	0.10 [-0.08, 0.28]
Kempf 2014	3.43	0.84	56	3.44	0.96	58	22.8%	-0.01 [-0.34, 0.32]
Total (95% CI)			**76**			**78**	**100.0%**	**0.07 [-0.08, 0.23]**

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)

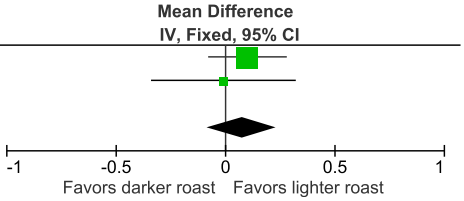


Figure 2 Forest plots of the effect of coffee intake on LDL cholesterol. A. Filtered coffee compared with no coffee intake. B. Coffee compared with tea intake. C. Filtered compared with unfiltered coffee intake. D. Regular compared with decaffeinated coffee intake. E. Darker compared with lighter roast coffee intake. Units are in mmol/L. Ahola 1991, Aro 1985, Aro 1987, Aro 1990, Corrêa 2013, Dusseldorp 1990, Rosmarin 1990, and Sanguigni 1995 are crossover studies. Data are expressed as end-of-study means±standard deviations, means±standard deviations in absolute change from baseline, or mean differences±standard errors.

Table 2 GRADE table for the effects of foods on LDL cholesterol.

Food	Effect on LDL cholesterol[a]	GRADE evidence
Foods high in n-6 PUFA and/or MUFA and low in SFA; e.g. canola oil	Moderate to large reduction[b]	High ⊕⊕⊕⊕
Foods high in soluble fiber; e.g. psyllium, oats, and barley	Moderate reduction	High ⊕⊕⊕⊕
Foods with added plant sterols or stanols	Moderate reduction	High ⊕⊕⊕⊕
Flaxseeds (whole)	Small to moderate reduction	High ⊕⊕⊕⊕
Soy protein	Small to moderate reduction	High ⊕⊕⊕⊕
Tomatoes	Small to moderate reduction	High ⊕⊕⊕⊕
Almonds	Small reduction	High ⊕⊕⊕⊕
Fish	No clear effect	High ⊕⊕⊕⊕
Decaffeinated coffee (in place of regular coffee)	No effect	High ⊕⊕⊕⊕
Filtered coffee	No effect	High ⊕⊕⊕⊕
Foods high in SFA or *trans* fatty acids (i.e. solid and tropical fats)	Moderate to large increase[b]	High ⊕⊕⊕⊕
Unfiltered coffee (in place of filtered coffee)	Moderate to large increase	High ⊕⊕⊕⊕
Avocados	Moderate to large reduction	Moderate ⊕⊕⊕O
Turmeric	Moderate to large reduction	Moderate ⊕⊕⊕O
Hazelnuts	Small to moderate reduction	Moderate ⊕⊕⊕O
Pulses	Small to moderate reduction	Moderate ⊕⊕⊕O
Green tea	At least small reduction	Moderate ⊕⊕⊕O
Fiber, whole grains	Small reduction	Moderate ⊕⊕⊕O
Walnuts	Small reduction	Moderate ⊕⊕⊕O
Darker roast coffee	No clear effect	Moderate ⊕⊕⊕O
Fructose (in place of sucrose/glucose)	No clear effect	Moderate ⊕⊕⊕O
Marine oils (high in long-chain n-3 PUFA)	Very small increase	Moderate ⊕⊕⊕O
Free sugars	Small increase	Moderate ⊕⊕⊕O
Coffee (in place of tea)	Small to moderate increase	Moderate ⊕⊕⊕O
Garlic powder	Small to moderate reduction	Low ⊕⊕OO
Probiotics and prebiotics	Small to moderate reduction	Low ⊕⊕OO
Cumin	Small to moderate reduction	Low ⊕⊕OO
Ginger	Small reduction	Low ⊕⊕OO
Eggs	Small increase[c]	Low ⊕⊕OO
Foods high in resistant starch	Small reduction	Low ⊕⊕OO
High-polyphenol olive oil (in place of low-polyphenol)	Small reduction	Low ⊕⊕OO
Foods high in α-linolenic acid, e.g. flaxseed oil	No clear effect	Low ⊕⊕OO
Foods high in medium-chain (in place on of long-chain) SFA	No clear effect	Low ⊕⊕OO
Grapefruits	No effect	Low ⊕⊕OO
Berries	Small to moderate reduction	Very low ⊕OOO
Garlic	Small to moderate reduction	Very low ⊕OOO
Black tea	At least small reduction	Very low ⊕OOO
Dark chocolate/cocoa products	At least small reduction	Very low ⊕OOO
Alcoholic drinks	Small reduction	Very low ⊕OOO
Dairy products (all, high-fat, low-fat)	No clear effect	Very low ⊕OOO
Grape polyphenols	No clear effect	Very low ⊕OOO
Synbiotics	No clear effect	Very low ⊕OOO
Whey protein	No clear effect	Very low ⊕OOO
Fruit juice	No effect	Very low ⊕OOO
Red meat	No effect	Very low ⊕OOO
Sweeteners	No effect	Very low ⊕OOO

Abbreviations: GRADE − The Grading of Recommendations Assessment, Development, and Evaluation, LDL − low-density lipoprotein, MUFA − monounsaturated fatty acids, PUFA − polyunsaturated fatty acids, SFA − saturated fatty acids.

[a] Small <0.20, moderate 0.20−0.40, large reduction >0.40 mmol/L.

[b] For comparison between foods high in MUFA and/or PUFA vs. SFA and/or *trans* fatty acids.

[c] Possibly larger effect in some individuals and little effect in other individuals

Their effects on LDL cholesterol were small or possibly moderate (for hazelnuts). Notably, in the systematic review [13] conducted in 2009, the 10 RCTs evaluating the effects of consuming whole flaxseeds included two RCTs on ground flaxseeds and one RCT on defatted flaxseeds. Still, (whole) flaxseeds obtained high evidence for a small reduction in LDL cholesterol (weighted mean dose 38 g per day compared with a variety of control foods or a diet without flax seeds, in 11 of 11 comparisons with units reported as g per day). For flaxseed oil, see also Fatty foods, above.

One systematic review on tree nuts [14] conducted in 2015 was considered just outside the set AMSTAR

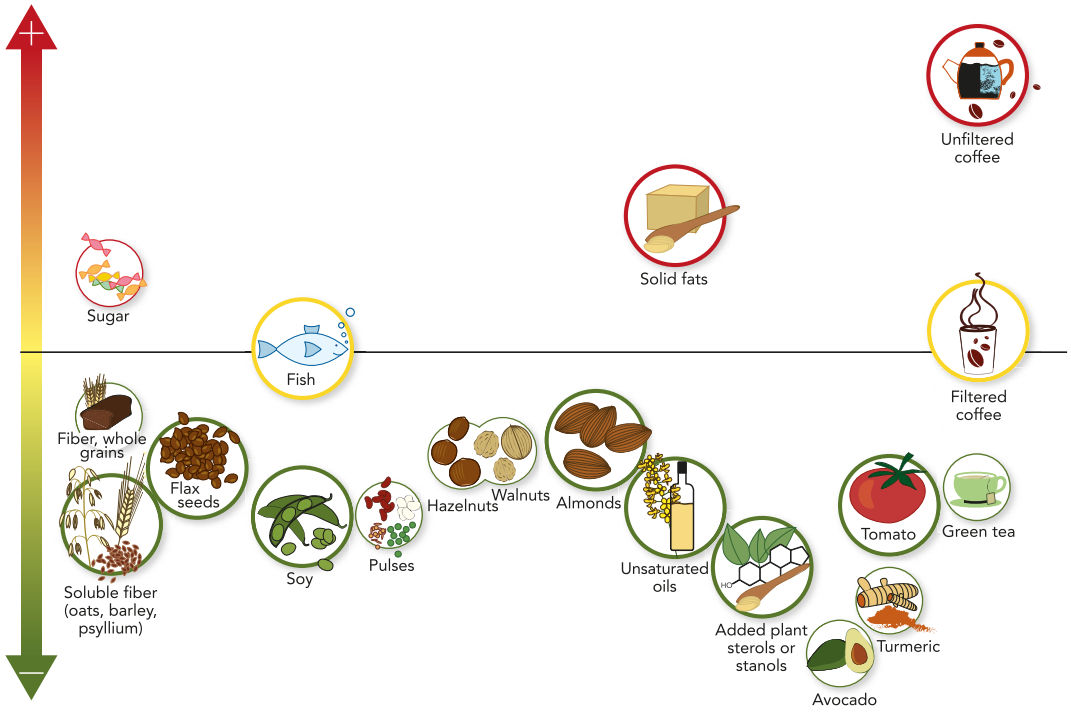


Figure 3 Foods that modify LDL cholesterol by effect and strength of evidence. Larger circles indicate high GRADE evidence. Smaller circles indicate moderate GRADE evidence.

threshold. It was nonetheless the largest systematic review, with 42 RCTs and 2102 participants included, and thus merits mentioning. The LDL cholesterol reduction was small but highly significant (mean and 95% CI −0.12 (−0.14 to −0.11) mmol/L) and the evidence for tree nuts overall was considered high. However, evidence gradings and effects are presented separately for individual nuts and seeds in Table 2.

Plant sterols and stanols

Seven studies conducted in 2007–2014 were excluded, while five systematic reviews from conducted in 2005–2016 were included. There was high evidence for a moderate reduction in LDL cholesterol by foods enriched with plant sterols and stanols (approximate weighted mean dose 2.2 g per day compared with diets without foods enriched with plant sterols and stanols, in 58 of 59 RCTs which reported units as g per day).

Probiotics and prebiotics

Five studies conducted in 2016–2018 were excluded, while 19 systematic reviews conducted in 2011–2019 were included. Most of the papers considered probiotics of various bacterial strains. Some studies were restricted to specific populations, e.g. individuals with diabetes. One systematic review [15] conducted in 2011 provided moderate evidence for a small reduction in LDL cholesterol by probiotics. However, three similar and larger systematic reviews [16–18] conducted in 2015 only provided low or very low evidence for reductions in LDL cholesterol by probiotics. Thus, we considered the overall evidence for probiotics and prebiotics as low for a small to moderate effect on LDL cholesterol. For synbiotics, there was no clear effect on LDL cholesterol and very low evidence.

Protein-rich foods

Eleven papers conducted in 2010–2019 were excluded, while seven systematic reviews conducted in 2008–2019 were included. Soy protein (weighted mean dose 26 g per day compared with non-soy protein, in 42 of 42 comparisons with units reported as g per day) obtained high evidence for a small to moderate reduction in LDL cholesterol, albeit based on a dated systematic review conducted in 2008. For plant protein (soy, pulses, and nuts combined), the overall evidence was considered moderate for a small reduction in LDL cholesterol. Fish intake (approximate weighted mean 86 g per day compared with a diet without or low in fish, in 11 of 14 RCTs which reported units as g per day) had high evidence for no clear effect on LDL cholesterol, but foods from animal sources other than eggs had no clear evidence for effects on LDL cholesterol (see Eggs and cholesterol above).

One systematic review on red meat [19] conducted in 2019 was excluded as it fell just outside the set risk of bias threshold. If included, its results would have indicated (with high evidence) no overall effect of red meat on LDL cholesterol (−0.03 (−0.08 to 0.02) mmol/L), which was consistent with the included systematic review conducted in 2017. However, compared with plant protein sources, red meat caused a small to moderate increase in LDL cholesterol (0.20 (0.07–0.33) mmol/L). Compared with fish

intake, red meat instead caused a small to moderate reduction in LDL cholesterol (−0.17 (−0.26 to −0.09) mmol/L). There were no clear effects on LDL cholesterol for other comparisons.

Rice

One study conducted in 2015 was excluded, but no systematic reviews were included.

Salt

One study conducted in 2017 was excluded, but no systematic reviews were included.

Spices

One study conducted in 2014 was excluded, while three systematic reviews study conducted in 2017−2018 were included. For turmeric, the results on LDL cholesterol were only expressed as standardised mean difference (−0.34 (−0.53 to −0.15), I^2 = 42%) in the systematic review [20] conducted in 2017, because one RCT did not clearly report units. After contacting its authors, we were able to reproduce the results of the meta-analysis as weighted mean difference. The effect of turmeric (approximate weighted mean dose compared with placebo or no turmeric intake was 2.3 g per day, in 2 of 6 RCTs which reported units in this format, or 600 mg of curcuminoids, in 4 of 6 RCTs which reported units in this format) on LDL cholesterol was moderate to large, without substantial heterogeneity (−0.35 (−0.48 to −0.22) mmol/L, I^2 = 25%, Supplemental Fig. 1). The evidence was considered moderate, downgraded for indirectness. For cumin [21] and ginger [22], the evidence was considered low for a small (to moderate) effect on LDL cholesterol.

Sugar

Three studies conducted in 2013−2018 were excluded, while three systematic reviews from 2014 to 2017 were included. The largest systematic review, on free sugars [23] conducted in 2014, demonstrated a small increase in LDL cholesterol with moderate evidence, when approximately 17 %E of sugar (weighted mean in 12 of 22 RCTs which reported units as %E) or 80 g per day (weighted mean in 12 of 22 RCTs which reported units as g per day) was compared with lower sugar intakes isocalorically or *ad libitum*. For fructose compared with sucrose/glucose, there was no clear effect on LDL cholesterol but high imprecision and moderate evidence.

Sweeteners

One systematic review conducted in 2011 was included. No meta-analysis was performed but none of the five included RCTs demonstrated significant effects on LDL cholesterol. The number of participants was low and the evidence was very low for a lack of effect on LDL cholesterol.

Tea

Two studies conducted in 2008−2012 were excluded, while 11 systematic reviews on the effects on LDL cholesterol of green tea, black tea, or both conducted in 2011−2018 were included. The systematic review on both green and black tea [24] conducted in 2013 stood out, with large reductions in LDL cholesterol compared with the later and more comprehensive systematic reviews, but was restricted to RCTs of at least three months duration. Taken together, we judged the evidence somewhat conservatively as moderate for green tea (weighted mean dose 263 mg of catechins which corresponds to about 2−5 cups per day, in 17 of 17 RCTs which reported units as g per day in the systematic review from 2016) and very low for black tea, for an at least small reduction in LDL cholesterol.

Other foods

In addition to the abovementioned individual foods and food groups, one systematic review and network meta-analysis from 2018 was included. In 66 RCTs of at least four weeks duration with a total of 3595 participants, the authors indirectly compared 10 different food groups: refined grains, whole grains, fruits and vegetables, nuts, legumes, eggs, dairy, red meat, fish, and sugar-sweetened beverages. According to its authors, the GRADE evidence was very low or low for all effects of foods on LDL cholesterol.

Coffee

A series of meta-analyses on five different comparisons was conducted. Nine RCTs compared filtered coffee vs. no coffee (Fig. 2A), three compared coffee vs. tea (Fig. 2B), six compared filtered vs. unfiltered coffee (Fig. 2C), six compared regular vs. decaffeinated coffee (Fig. 2D), and two compared different coffee roasts (Fig. 2E). Most studies had some concerns of risk of bias related to incomplete reporting of randomization/allocation concealment, but none were considered of high risk. We found no indications of publication bias or small study effects, although reliable investigations by tests or funnel plots were prevented by the limited number of studies in each analysis. The sensitivity analyses only marginally affected the results (data not shown).

The most notable effect on LDL cholesterol was observed when filtered coffee was replaced with unfiltered coffee, e.g. Scandinavian style boiled coffee at a mean daily dose of 6.1 cups (high evidence, further upgraded for large effects). By contrast, 4.6 daily cups of filtered coffee did not increase the LDL cholesterol level compared with water or no coffee intake (high evidence).

Compared with tea, 6.8 daily cups of coffee (mocha, espresso, instant, or filtered coffee) tended to increase LDL

cholesterol in our meta-analysis of three RCTs. The evidence was considered moderate (downgraded for imprecision). However, as noted above (see Tea), tea intake may decrease LDL cholesterol.

No clear effects on LDL cholesterol were observed when comparing regular coffee with decaffeinated coffee (high evidence) or when comparing coffee based on the roasting process (moderate evidence). One study [25] conducted in 1994 also compared (decaffeinated) coffee from different beans (arabica compared with arabica/robusta blend), also with no effect on LDL cholesterol. Two RCTs compared special coffees (different levels of chlorogenic acids and hydroxyhydroquinone) for which no meta-analysis was performed, but there was no significant effect on LDL cholesterol in either study [26,27].

Discussion

In this umbrella review of guidelines and systematic reviews, as well as systematic review and meta-analysis of RCTs on coffee, previously established evidence was consolidated for the beneficial effects of foods high in unsaturated and low in saturated or *trans* fatty acids, e.g. non-tropical oils in place of solid animal and industrially processed fats; for soluble/viscous fiber, especially from oats, barley, and psyllium; for functional foods with added plant sterols and stanols; and for foods rich in plant proteins, especially soybeans. It was also established with high evidence that tomatoes, whole flaxseeds, and almonds can reduce LDL cholesterol, whereas boiled/unfiltered coffee can increase it. There was moderate evidence for beneficial effects by avocados, hazelnuts, and walnuts (high in unsaturated fatty acids), and pulses (high in soluble fiber and plant protein); by turmeric and green tea; and for a small detrimental effect by free sugars.

Current guidelines for dyslipidemia and CVD prevention were fairly consistent and similar to recommendations for healthy populations, but did not always evaluate the strength of evidence for their included advice. Notably, some foods were not explicitly included in any of these guidelines despite moderate or strong evidence in their favor, e.g. flaxseeds, tomatoes, turmeric, avocados, and green tea. Unfiltered coffee was mentioned only in one guideline, despite its clear detrimental effect on blood lipids. Conversely, much emphasis was put on other foods (e.g. sugar) with less clear evidence regarding effects on LDL cholesterol. However, some of the included guidelines included other aspects than hypercholesterolemia, e.g. effects on triglycerides or hypertension, which may partly explain this discrepancy. Also, potential adverse effects on body weight by energy-dense foods should be taken into account, as most studies have been performed in isocaloric or even hypocaloric conditions, and weight gain may increase LDL cholesterol levels.

We demonstrated clear effects for the comparison between unfiltered and filtered coffee, in line with results from subgroup analyses in a previous (excluded) meta-analysis and with recently published results from pooled Norwegian cohorts, in which total cholesterol, CVD mortality, and mortality was higher in persons consuming unfiltered compared with filtered coffee [28]. Unfiltered coffee contains high levels of the diterpenes kahweol and cafestol, providing a mechanistic link. For several other foods, the cholesterol-lowering mechanisms are at least partly unknown. Various suggested mechanisms have been discussed in previous systematic reviews but are not always clearly established. For instance, the effects of turmeric may not be related to the polyphenol curcumin, as there was no clear effect in the excluded review on curcumin supplementation [29]. Better biological understanding (including potential adverse effects or drug interactions) could increase the incentive to include novel foods (e.g. tomatoes, turmeric, and green tea) in future dietary recommendations and help identify other relevant foods. The presence or absence of a known plausible mechanism could also warrant additional modifications of the strength of evidence, as this feature is not fully captured by the GRADE criteria. For complex foods such as probiotics and prebiotics, improved biological understanding may be required before further attempts to systematically evaluate the effects. Narrative reviews by field experts may even be preferred until then.

The present study has limitations. The searches were only performed in two databases. Only English literature was included, and no grey literature. Despite the large scope of the study, only two reviewers were included, which increases vulnerability to bias and errors. Also, the majority of the results relies on the work of others and potential conflicts of interest in the included systematic reviews were not considered. Although they were still evaluated for important information, many systematic reviews were excluded based on the strict criteria of our modified version of the AMSTAR tool, which in other cases may have disregarded importance biases, due to its abbreviated form. In addition, systematic reviews may not have been published for all relevant foods. Thus, all effective foods may not have been captured by our searches. Also, considerable uncertainties exist for the effect estimates for most included foods. Beneficial effects may be exaggerated, particularly when the quality of evidence is less than high. Moreover, it is implausible that all included foods would jointly produce additive effects, although such have been demonstrated for certain food combinations [6]. Furthermore, the illustration (Fig. 3/ Graphical abstract) does not fully take into account potential replacement foods. For some individuals, reduced intakes of foods high in SFA or sugar may be more achievable and thus effective than attempts to increase consumption of foods high in unsaturated fatty acids or soluble fiber, and vice versa. Both strategies may provide beneficial effects on LDL cholesterol depending upon individual background intakes and preferences. Moreover, we cannot with this approach precisely establish which

food doses are required for clinically meaningful effects. The weighted mean doses should for some foods be considered as rough approximations, as all RCTs did not always report doses in the same units. However, the highlighted foods may principally modify LDL cholesterol levels, at least at intake levels that have been acceptable in short-term interventions.

Future studies should further investigate foods whose effects showed moderate (e.g. turmeric and green tea) or low evidence (e.g. eggs, garlic, cumin, ginger, and probiotics). Moreover, the effects of red meat may require further clarification. By contrast, the evidence seems unequivocal for plant sterols, soluble fiber, unfiltered coffee, and possibly soy, as these foods were upgraded even beyond the threshold for high evidence. The short- and longer-term effects of several of the highlighted foods in combination may also warrant further research in RCTs, as well as combining the evidence on LDL cholesterol for individual foods with long-term observational studies on CVD morbidity and mortality. Although LDL cholesterol is causally related to atherosclerotic CVD, foods are complex by nature and may have divergent effects on both known and unknown risk factors. In such instances, priority should always be given to patient-oriented health outcomes.

In conclusion, several foods can distinctly modify LDL cholesterol levels. This updated summary of the accumulated evidence may help inform clinicians and future guidelines for dyslipidemia and CVD prevention.

Declaration of competing interest

There are no conflicts to report.

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Deviations from protocol

Total cholesterol was stated as a secondary outcome of interest. However, in order to keep the report concise, we chose to focus only on the primary outcome of interest, LDL cholesterol. Also, results as percentage change was omitted as this was seldom given. A complementary search for guidelines was performed in the Trip database.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.12.032.

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