National Institute for Health and Care Excellence

Final

Cardiovascular disease: risk assessment and reduction, including lipid modification

[B] Evidence review for dietary cholesterol strategies

NICE guideline NG238 (CG181)

Evidence review underpinning recommendation 1.3.2 in the NICE guideline

May 2023

Final

Developed by National Institute for Health and Care Excellence

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1. Dietary cholesterol

1.1. Review question

What is the clinical and cost effectiveness of dietary cholesterol strategies compared with usual diet for adults without established CVD and with established CVD?

1.1.1. Introduction

The 2014 update of CG181 includes recommendations for lifestyle interventions for reducing risk of CVD. This update focusses only on dietary cholesterol strategies. It was previously recommended that reductions in dietary cholesterol intake were made to reduce cardiovascular risk, based on the understanding at that time that changes in dietary cholesterol modify blood lipids and other risk factors and that these changes were associated with reductions in morbidity and mortality from cardiovascular events. However, it has been suggested that the evidence and understanding on how this relates to cardiovascular risk has changed since the last update of the guideline. The updated review will therefore look at the recent evidence for this area to inform up-to-date recommendations on the topic.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease
Intervention	• Reduced dietary cholesterol (e.g. reduced egg consumption or specified limits on daily/weekly intake of cholesterol from dietary sources) • Lower dietary cholesterol intake (cohort studies)
Comparison	• No dietary cholesterol intervention or usual diet • Higher dietary cholesterol intake (cohort studies)
Outcomes	• All-cause mortality (time-to-event) • Cardiovascular mortality (time-to-event) • Non-fatal myocardial infarction (time-to-event) • Non-fatal stroke (time-to-event) • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) • Quality of life (continuous), any validated scores
Study design	• RCTs • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data • Cohort studies that adequately control for confounders if insufficient RCT data are available

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

No relevant clinical studies comparing dietary cholesterol with no dietary cholesterol were identified.

See also the study selection flow chart in Appendix C.

1.1.4.2. Excluded studies

No evidence from RCTs or interventional cohort studies was identified that matched the review protocol. A number of prospective prognostic studies were found which examined the association of egg consumption with CVD outcomes, and there were systematic reviews of these studies. Prognostic studies examine selected predictive variables or risk factors and assess their influence on patient outcomes, in this case dietary cholesterol consumption would be the prognostic factor or predictor variable. RCTs are considered the best evidence to inform effectiveness of interventions or treatment strategies as they enable control for between group variables, including known and unknown prognostic factors. Therefore, prognostic studies are not usually considered for review questions about interventions, and these were not included in the CG181 on cardioprotective diets.

Some RCTs were identified that examined egg consumption versus no egg consumption, but the follow-ups were less than 1 year and the outcomes were clinical biochemistry tests or tests for atherosclerosis. Some older RCTs identified in this review looked at dietary cholesterol but the actual interventions included other advice such as increasing polyunsaturated fat, decreasing saturated fat, and stopping smoking and so these interventions did not match the review protocol.

See the excluded studies list in Appendix G.

1.1.5. Summary of studies included in the effectiveness evidence

There was no effectiveness evidence.

1.1.6. Economic evidence

1.1.6.1. Included studies

No health economic studies were included.

1.1.6.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.1.7. Summary of included economic evidence

No health economic studies were included.

1.1.8. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9. Evidence statements

1.1.9.1. Effectiveness/Qualitative

- No relevant published evidence was identified.

1.1.9.2. Economic

- No relevant economic evaluations were identified.

1.1.10. The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee agreed that the following outcomes were the most important to inform recommendations:

- All-cause mortality
- CVD mortality
- Stroke
- Combined major CVD events (incl. CVD death, myocardial infarction, and stroke).

The committee agreed that evidence that changes in dietary cholesterol can impact the risk of major cardiovascular events were essential to forming recommendations. They also agreed that clinical biochemistry tests or tests for atherosclerosis were not appropriate surrogates for the impact of dietary cholesterol strategies on cardiovascular health. However, there was no relevant evidence identified for this review question.

1.1.10.2. The quality of the evidence

The evidence review found no RCTs or interventional cohort studies that matched the review protocol.

The committee agreed to discuss any revisions to the existing recommendation based on informal consensus and their expert opinion and knowledge of other relevant guidance.

1.1.10.3. Benefits and harms

Since there was no new clinical evidence to review, the committee discussed the benefits and harms of the existing recommendation on a cardioprotective diet for the management of dietary cholesterol. The previous recommendation from the 2014 update of CG181 was:

> 1.2.1 Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats. Further information and advice can be found on the NHS Eat well webpage.

The committee noted that this recommendation was adopted based on the Joint British Societies' guidance (JBS2, 2005), rather than being based on any evidence directly reviewed by the committee. They also noted that the subsequent update to the Joint British Societies' guidance, JBS3 (2014), had removed this recommendation, based on a systematic review showing little evidence to support an association between dietary cholesterol and coronary heart disease risk in the general population, with the caveat that it may have a detrimental effect in people who react to dietary cholesterol with a large increase in plasma cholesterol (hyper-responders). The committee were aware of this systematic review, but it did not meet the protocol criteria for the guideline review as it included prognostic association data rather than intervention studies with an RCT or comparative cohort design. The committee agreed

that the definition of 'hyper-responders' was unclear. They agreed it wasn't necessary to make a statement similar to that in JBS3 about hyper-responders in the updated recommendation.

Based on this information and the lack of new comparative clinical evidence from intervention studies, the committee agreed that there was no evidence to support a limit of 300mg per day of dietary cholesterol. They also noted that organisations like the American Heart Association have acknowledged that it is impractical to set limits on dietary cholesterol intake as a method of reducing the risk of CVD events. Additionally, the committee agreed that saturated fat intake has a greater impact on a person's cholesterol profile and corresponding risk of CVD events.

1.1.10.4. Cost effectiveness and resource use

The committee agreed that not advising people to restrict cholesterol intake would have no implications for resource use. The updated recommendation was considered to be in line with current practice.

1.1.10.5. Other factors the committee took into account

The committee agreed that the guidance on limits on macronutrients as a proportion of a person's daily diet in the recommendation (e.g. total fat less than 30%, saturated fat less than 7%) would be difficult to interpret and implement for most people. The committee agreed that it may be more effective to provide broader guidance advising people to increase their intake of fruits and vegetables rather than provide percentage limits on fat consumption. However, this was beyond the remit of this update and this evidence had not been reviewed.

1.1.11. Recommendations supported by this evidence review

This evidence review supports recommendation 1.3.2.

1.1.12. References

1. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A Review protocols

A.1 Review protocol for dietary cholesterol

ID	Field	Content
0.	PROSPERO registration number	CRD42022345768
1.	Review title	Dietary cholesterol strategies for primary prevention and secondary prevention of cardiovascular disease (CVD) in adults.
2.	Review question	What is the clinical and cost effectiveness of dietary cholesterol strategies compared with usual diet for adults without established CVD and with established CVD?
3.	Objective	The aim of this review is to update the evidence on the effectiveness of dietary strategies to reduce cholesterol intake. This is important because the current recommendations may be inconsistent with new evidence indicating that dietary cholesterol, including egg consumption, may not have an adverse impact on CVD risk.
4.	Searches	Key paper: Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. American Journal of Clinical Nutrition. 2015; 102(2):276-294 (REF ID:83.) The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

ID	Field	Content
		• Date limitations – none • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Primary and secondary prevention of cardiovascular disease
6.	Population	Inclusion: Adults (aged 18 years and older) with or without established CVD, including those with type 1 diabetes, type 2 diabetes or chronic kidney disease. Exclusion: • Children aged < 18 years of age • People with familial hypercholesterolaemia. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes • People receiving renal replacement therapy
7.	Intervention	Reduced dietary cholesterol (e.g. reduced egg consumption or specified limits on daily/weekly intake of cholesterol from dietary sources) Lower dietary cholesterol intake (cohort studies)

ID	Field	Content
8.	Comparator	No dietary cholesterol intervention or usual diet Higher dietary cholesterol intake (cohort studies)
9.	Types of study to be included	Inclusion: • RCTs • Systematic reviews of RCTs • Published NMAs and IPDs of RCT data will be considered for inclusion. • Cohort studies that adequately control for confounders if insufficient RCT data are available. The decision about whether sufficient RCT data are available will be made by committee discussion based on the body of evidence across all outcomes. Exclusion: • Cross over RCTs • Non-randomised studies not accounting for the key confounding variables (either by stratification, matching or multivariable analysis) • Follow-up < 1 year • Conference abstracts Key confounders to be adjusted for in non-randomised studies are: • Primary or secondary prevention populations (with or without established CVD) • Age • Studies not accounting for both of these in either the design or analysis method will be excluded. • Other important confounding factors are: • Sex • Smoking • Hypertension • Chronic kidney disease • Diabetes status

ID	Field	Content
		• Weight/BMI • Dietary variables: e.g. fibre, energy, and saturated fat. • Socio economic status • Ethnicity • Physical activity • Total fat • Trans fat • PUFA • Alcohol intake Information on whether these factors have been accounted for will be extracted from all included studies to inform the committee discussion and risk of bias assessment.
10.	Other exclusion criteria	Studies of interventions or dietary strategies to reduce cholesterol (e.g. plant stanols and sterols) Non-English language studies. Conference abstracts will be excluded as there are already many full text published studies available in the CG181 analysis.
11.	Context	This will update CG181 guidance. New evidence and expert feedback indicates that advice given on dietary cholesterol in recommendation 1.2.1, is inconsistent with new evidence indicating that dietary cholesterol, including egg consumption, may not have an adverse impact on CVD risk. There is a potential need to review recommendation 1.2.1, which advises limiting intake of dietary cholesterol to less than 300 mg/day.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • Cardiovascular mortality (time-to-event) • Non-fatal myocardial infarction (time-to-event)

ID	Field	Content
		• Non-fatal stroke (time-to-event) • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) • Quality of life (continuous), any validated scores Time points: • The minimum follow-up is 1 year • The longest available follow-up will be used for each trial, and all these timepoints will be pooled. Cholesterol levels will not be included as a surrogate outcome for CVD risk because it is whether or not a CVD event occurs that is important to patients. However, details of the LDL-cholesterol reduction during treatment (continuous; final score in preference to change score if available) will be extracted, although not analysed as an outcome. This will provide useful information on the observed achieved reductions or increase with reference to the dietary cholesterol levels. This will contextualise the risk reductions for the listed outcomes in terms of the LDL-cholesterol reduction that led to that effect. For MI and stroke, non-fatal events will be the preferred outcome measure. However, if only total (fatal and non-fatal) events are reported in a trial this will be included for these outcomes. This will not be downgraded for indirectness as the effect on fatal and non-fatal ischaemic events is similar.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

ID	Field	Content
		A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the following checklists as described in Developing NICE guidelines: the manual. Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Non randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. As no studies in CG181 assessed dietary cholesterol as the sole intervention, new data will not be meta-analysed with data included in CG181. For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported in addition to risk ratios. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are

ID	Field	Content
		differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence. For continuous outcomes, if the same outcome is reported on different numerical scales these will be pooled where possible. If the studies use the same outcome measured in different units, this will be converted one to another using a simple multiplier. Otherwise, the standardised mean difference will be calculated if different scales are used for the same outcome across studies. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups, including studies at higher risk of bias, using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ If published individual participant data meta-analyses are included, any additional studies identified for inclusion (that are not included within the published analysis) will be analysed separately, and individual participant data will not be sought. Where meta-analysis is not possible, data will be presented and quality assessed individually per study and outcome. Data from observational studies will be considered for meta-analysis. Pooling of outcome data will only be conducted if the populations, interventions, comparisons and confounders accounted for are sufficiently similar between studies.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:

ID	Field	Content			
		• Level of dietary cholesterol intake reduction compared to control (or absolute level of intake in experimental group e.g. >900 mg/d, 650-899 mg/d and <650 mg/d) • Age: <75 versus ≥75 • Sex • Ethnicity/family origin: black, Asian, white, mixed, other • People with versus without a family history of CVD • Socioeconomic group • Presence versus absence of CKD • Presence versus absence of autoimmune disease • Presence versus absence of serious mental illness			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	21.03.2022			
21.	Anticipated completion date	19.04.2023			
22.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☑
		Piloting of the study selection process		☑	☑

ID	Field	Content		
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
23.	Named contact	5a. Named contact NICE Guideline Development Team NGC 5b Named contact e-mail CVDupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From the NICE Guideline Development Team NGC: • Serena Carville, Guideline lead • Eleanor Samarasekera, Senior systematic reviewer • Maheen Qureshi, Systematic reviewer • Kate Lovibond, Health economist • Lina Gulhane, Information specialist		
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded		

ID	Field	Content	
		in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10178	
28.	Other registration details	NA	
29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Cardiovascular disease; lipid modification; cholesterol; diet.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years • Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies included in the 2014 CG181 update and published between 2007 and 2014 CG181 cut-off date (November 2013) will be reconsidered for inclusion as per this protocol. Studies identified in the update search published since November 2013 will be considered for inclusions as per this protocol. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014)[1] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.

- If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.

	• Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'. • Studies published before 2007 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

B.1 Clinical search literature search strategies: Cardiovascular disease prevention: dietary cholesterol strategies for adults

The literature searches detailed below are for the review:

What is the clinical and cost effectiveness of dietary cholesterol strategies compared with usual diet for adults without established CVD and with established CVD?

They complied with the methodology outlined in Developing NICE guidelines: the manual.(NICE2014)

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 June 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 June 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 6 of 12, June 2022 Cochrane Central Register of Controlled Trials to Issue 6 of 12, June 2022	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filter used
Epistemonikos (The Epistemonikos Foundation)	Inception to 13 June 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32

34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	case report/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
54.	52 not 53
55.	limit 54 to English language
56.	exp *Diet/ or exp *Diet Therapy/
57.	exp *Cholesterol/
58.	56 and 57
59.	*Cholesterol, Dietary/
60.	((diet* or consum* or eat* or intake) adj3 (lipid* or fat or fats or cholesterol* or epicholesterol*)).ti,ab.
61.	(serum adj2 (cholesterol* or epicholesterol)).ti,ab.
62.	((fat or fats) adj2 (saturate* or unsaturate* or polyunsaturate*)).ti,ab.
63.	(egg* adj3 (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)).ti,ab.
64.	DIABEGG.ti,ab,kf.
65.	or/58-64
66.	55 and 65
67.	Meta-Analysis/
68.	Meta-Analysis as Topic/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.
76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	randomized controlled trial.pt.
79.	controlled clinical trial.pt.
80.	randomi#ed.ab.
81.	placebo.ab.
82.	randomly.ab.
83.	clinical trials as topic.sh.
84.	trial.ti.
85.	or/78-84
86.	exp *Cohort studies/
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	or/86-88
90.	66 and (77 or 85 or 89)

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/

23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	case report/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
56.	54 not 55
57.	exp *Diet/ or exp *Diet Therapy/
58.	exp *Cholesterol/
59.	57 and 58
60.	*Cholesterol, intake/
61.	((diet* or consum* or eat* or intake or amount*) adj3 (lipid* or fat or fats or cholesterol* or epicholesterol*)).ti,ab.
62.	(serum adj2 (cholesterol* or epicholesterol)).ti,ab.

63.	((fat or fats) adj2 (saturate* or unsaturate* or polyunsaturate*)).ti,ab.
64.	(egg* adj3 (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)).ti,ab.
65.	DIABEGG.ti,ab,kf.
66.	or/59-65
67.	56 and 66
68.	random*.ti,ab.
69.	factorial*.ti,ab.
70.	(crossover* or cross over*).ti,ab.
71.	((doubl* or singl*) adj blind*).ti,ab.
72.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
73.	crossover procedure/
74.	single blind procedure/
75.	randomized controlled trial/
76.	double blind procedure/
77.	or/68-76
78.	systematic review/
79.	Meta-Analysis/
80.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
81.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
82.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
83.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
84.	(search* adj4 literature).ab.
85.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
86.	cochrane.jw.
87.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
88.	or/78-87
89.	*longitudinal study/
90.	*retrospective study/
91.	*prospective study/
92.	*cohort analysis/
93.	(cohort adj (study or studies or analys* or data)).ti,ab.
94.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
95.	or/89-94
96.	67 and (77 or 88 or 95)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] this term only
#2.	MeSH descriptor: [Heart Diseases] this term only
#3.	MeSH descriptor: [Myocardial Ischemia] this term only

#4.	MeSH descriptor: [Angina Pectoris] explode all trees
#5.	MeSH descriptor: [Coronary Disease] this term only
#6.	MeSH descriptor: [Coronary Artery Disease] this term only
#7.	MeSH descriptor: [Coronary Stenosis] explode all trees
#8.	MeSH descriptor: [Myocardial Infarction] this term only
#9.	MeSH descriptor: [Heart Failure] explode all trees
#10.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#11.	MeSH descriptor: [Vascular Diseases] this term only
#12.	MeSH descriptor: [Atrial Fibrillation] this term only
#13.	MeSH descriptor: [Hypertension] this term only
#14.	MeSH descriptor: [Atherosclerosis] this term only
#15.	MeSH descriptor: [Peripheral Vascular Diseases] this term only
#16.	MeSH descriptor: [Peripheral Arterial Disease] this term only
#17.	MeSH descriptor: [Arteriosclerosis] this term only
#18.	MeSH descriptor: [Cerebrovascular Disorders] this term only
#19.	MeSH descriptor: [Stroke] explode all trees
#20.	MeSH descriptor: [Brain Ischemia] explode all trees
#21.	MeSH descriptor: [Heart Arrest] explode all trees
#22.	((cardiovascular or cardio vascular) near/3 (event* or disease* or disorder*)):ti,ab,kw
#23.	((coronary or peripheral vascular or heart or peripheral arter*) near/3 (disease* or event* or disorder*)):ti,ab,kw
#24.	(MI or myocardial infarct*):ti,ab,kw
#25.	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab,kw
#26.	(CVD or CHD or CAD or PAD or CVA):ti,ab,kw
#27.	(hypertension or hypertensive*):ti,ab,kw
#28.	((high or raised or elevated) near/2 (blood pressure or bp)):ti,ab,kw
#29.	(atheroscleros* or arterioscleros*):ti,ab,kw
#30.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke):ti,ab,kw
#31.	(ACS or angina or acute coronary syndrome*):ti,ab,kw
#32.	(AF or atrial fibrillation):ti,ab,kw
#33.	((chronic or congestive) near/2 heart failure):ti,ab,kw
#34.	(or #1-#33)
#35.	conference:pt or (clinicaltrials or trialsearch):so
#36.	#34 not #35
#37.	MeSH descriptor: [Diet] explode all trees
#38.	MeSH descriptor: [Diet Therapy] explode all trees
#39.	#37 or #38
#40.	MeSH descriptor: [Cholesterol] explode all trees
#41.	#39 and #40
#42.	MeSH descriptor: [Cholesterol, Dietary] explode all trees

#43.	((diet* or consum* or eat* or intake) near/3 (lipid* or fat or fats or cholesterol* or epicholesterol*)):ti,ab
#44.	serum near/2 (cholesterol* or epicholesterol):ti,ab
#45.	((fat or fats) near/2 (saturate* or unsaturate* or polyunsaturate*)):ti,ab
#46.	(egg* near/3 (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)):ti,ab
#47.	DIABEGG:ti,ab
#48.	(or #41-#47)
#49.	#36 and #48

Epistemonikos search terms

1.	(title:(egg* AND (diet* OR consum* OR eat* OR intake OR cholesterol* OR amount* OR number* OR high*)) OR abstract:(egg* AND (diet* OR consum* OR eat* OR intake OR cholesterol* OR amount* OR number* OR high*))) OR (title:((title:((fat OR fats) AND (saturate* OR unsaturate* OR polyunsaturate*)) OR abstract:((fat OR fats) AND (saturate* OR unsaturate* OR polyunsaturate*)))) OR abstract:((title:((fat OR fats) AND (saturate* OR unsaturate* OR polyunsaturate*)) OR abstract:((fat OR fats) AND (saturate* OR unsaturate* OR polyunsaturate*))))) OR (title:((title:(serum AND (cholesterol* OR epicholesterol)) OR abstract:(serum AND (cholesterol* OR epicholesterol)))) OR abstract:((title:(serum AND (cholesterol* OR epicholesterol)) OR abstract:(serum AND (cholesterol* OR epicholesterol))))) OR (title:((title:((diet* OR consum* OR eat* OR intake) AND (lipid* OR fat OR fats OR cholesterol* OR epicholesterol*)) OR abstract:((diet* OR consum* OR eat* OR intake) AND (lipid* OR fat OR fats OR cholesterol* OR epicholesterol*)))) OR abstract:((title:((diet* OR consum* OR eat* OR intake) AND (lipid* OR fat OR fats OR cholesterol* OR epicholesterol*)) OR abstract:((diet* OR consum* OR eat* OR intake) AND (lipid* OR fat OR fats OR cholesterol* OR epicholesterol*))))) AND (title:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*"))) OR abstract:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR

	"brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*"))))

B.2 Health Economics literature search strategies:

Health economic evidence was identified by conducting literature searches as below.
The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 13 June 2022	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 13 June 2022	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health	Inception – 13 June 2022	English language

Database	Dates searched	Search filters and limits applied
Technology Assessment (INAHTA)		

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/

35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	case report/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to English language
54.	exp *Diet/
55.	exp *Diet Therapy/
56.	Diet, healthy/
57.	(Mediterranean adj3 (food* or nutrition* or eat* or diet*)).ti,ab,kf.
58.	("DASH" adj diet*).ti,ab,kf.
59.	(diet* adj2 (therap* or change* or intervention* or treatment* or approach* or strateg* or modif* or restrict* or pattern* or health* or adjust or alter*)).ti,ab,kf.
60.	exp *plant oils/
61.	((plant* or vegetable* or rapeseed or corn or cottonseed or linseed or olive or peanut or rice bran or safflower or sesame or soybean or sunflower or nut or groundnut or walnut or avocado) adj2 (oil* or spread* or butter*or fat*)).ti,ab,kf.
62.	*Cholesterol, Dietary/
63.	((diet* or consum* or eat* or intake or amount* or food*) adj3 (lipid* or fat* or cholesterol* or epicholesterol*)).ti,ab.
64.	(serum adj2 (cholesterol* or epicholesterol)).ti,ab.
65.	((fat or fats) adj2 (saturate* or unsaturate* or polyunsaturate*)).ti,ab.
66.	(egg* adj3 (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)).ti,ab.
67.	DIABEGG.ti,ab,kf.
68.	or/54-67
69.	53 and 68
70.	economics/
71.	value of life/
72.	exp "costs and cost analysis"/

73.	exp Economics, Hospital/
74.	exp Economics, medical/
75.	Economics, nursing/
76.	economics, pharmaceutical/
77.	exp "Fees and Charges"/
78.	exp budgets/
79.	budget*.ti,ab.
80.	cost*.ti.
81.	(economic* or pharmaco?economic*).ti.
82.	(price* or pricing*).ti,ab.
83.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
84.	(financ* or fee or fees).ti,ab.
85.	(value adj2 (money or monetary)).ti,ab.
86.	or/70-85
87.	69 and 86
88.	limit 87 to yr="2014 -Current"

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/

23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	case report/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract or conference paper).pt.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	exp *Diet/
56.	exp *Diet Therapy/
57.	(Mediterranean adj3 (food* or nutrition* or eat* or diet*)).ti,ab,kf.
58.	("DASH" adj diet*).ti,ab,kf.
59.	(diet* adj2 (therap* or change* or intervention* or treatment* or approach* or strateg* or modif* or restrict* or pattern* or health* or adjust or alter*)).ti,ab,kf.
60.	exp *plant oils/
61.	((plant* or vegetable* or rapeseed or corn or cottonseed or linseed or olive or peanut or rice bran or safflower or sesame or soybean or sunflower or nut or groundnut or walnut or avocado) adj2 (oil* or spread* or butter*or fat*)).ti,ab,kf.

62.	*Cholesterol, Dietary/
63.	*Cholesterol, Intake/
64.	((diet* or consum* or eat* or intake or amount* or food*) adj3 (lipid* or fat* or cholesterol* or epicholesterol*)).ti,ab.
65.	(serum adj2 (cholesterol* or epicholesterol)).ti,ab.
66.	((fat or fats) adj2 (saturate* or unsaturate* or polyunsaturate*)).ti,ab.
67.	(egg* adj3 (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)).ti,ab.
68.	DIABEGG.ti,ab,kf.
69.	or/55-68
70.	54 and 69
71.	health economics/
72.	exp economic evaluation/
73.	exp health care cost/
74.	exp fee/
75.	budget/
76.	funding/
77.	budget*.ti,ab.
78.	cost*.ti.
79.	(economic* or pharmaco?economic*).ti.
80.	(price* or pricing*).ti,ab.
81.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
82.	(financ* or fee or fees).ti,ab.
83.	(value adj2 (money or monetary)).ti,ab.
84.	or/71-83
85.	70 and 84
86.	limit 85 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Cardiovascular Diseases
#2.	MeSH DESCRIPTOR Heart diseases
#3.	MeSH DESCRIPTOR Myocardial Ischemia
#4.	MeSH DESCRIPTOR Angina Pectoris EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Coronary Disease
#6.	MeSH DESCRIPTOR Coronary Artery Disease
#7.	MeSH DESCRIPTOR Coronary Stenosis EXPLODE ALL TREES
#8.	MeSH DESCRIPTOR Myocardial Infarction
#9.	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Arrhythmias, cardiac
#11.	MeSH DESCRIPTOR Atrial fibrillation
#12.	MeSH DESCRIPTOR Vascular Diseases
#13.	MeSH DESCRIPTOR Hypertension

#14.	MeSH DESCRIPTOR Atherosclerosis
#15.	MeSH DESCRIPTOR Peripheral Arterial Disease
#16.	MeSH DESCRIPTOR Peripheral Vascular Diseases
#17.	MeSH DESCRIPTOR Arteriosclerosis
#18.	MeSH DESCRIPTOR Cerebrovascular Disorders
#19.	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
#20.	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES
#21.	MeSH DESCRIPTOR heart arrest EXPLODE ALL TREES
#22.	(cardiovascular or cardio vascular) AND (event* or disease* or disorder*)
#23.	(coronary or peripheral vascular or heart or peripheral arter*) AND (disease* or event* or disorder*)
#24.	(MI or myocardial infarct*)
#25.	(heart or cardiopulmonary or cardiac) AND (death* or arrest* or attack*)
#26.	(CVD or CHD or CAD or PAD or CVA)
#27.	(hypertension or hypertensive*)
#28.	(high or raised or elevated) AND (blood pressure or bp)
#29.	(atheroscleros* or arterioscleros*)
#30.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke)
#31.	(ACS or angina or acute coronary syndrome*)
#32.	(AF or atrial fibrillation)
#33.	(chronic or congestive) AND (heart failure)
#34.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
#35.	MeSH DESCRIPTOR Diet EXPLODE ALL TREES
#36.	MeSH DESCRIPTOR Diet Therapy EXPLODE ALL TREES
#37.	MeSH DESCRIPTOR Diet, Healthy EXPLODE ALL TREES
#38.	(Mediterranean) AND (food* or nutrition* or eat* or diet*)
#39.	("DASH") AND (diet*)
#40.	(diet*) AND (therap* or change* or intervention* or treatment* or approach* or strateg* or modif* or restrict* or pattern* or health* or adjust or alter*)
#41.	MeSH DESCRIPTOR Plant Oils EXPLODE ALL TREES
#42.	(plant* or vegetable* or rapeseed or corn or cottonseed or linseed or olive or peanut or rice bran or safflower or sesame or soybean or sunflower or nut or groundnut or walnut or avocado) AND (oil* or spread* or butter*or fat*)
#43.	MeSH DESCRIPTOR Cholesterol, Dietary EXPLODE ALL TREES
#44.	(diet* or consum* or eat* or intake or amount* or food*) AND (lipid* or fat* or cholesterol* or epicholesterol*)
#45.	(serum) AND (cholesterol* or epicholesterol)
#46.	(fat or fats) AND (saturate* or unsaturate* or polyunsaturate*)
#47.	(egg*) AND (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*)
#48.	(DIABEGG)

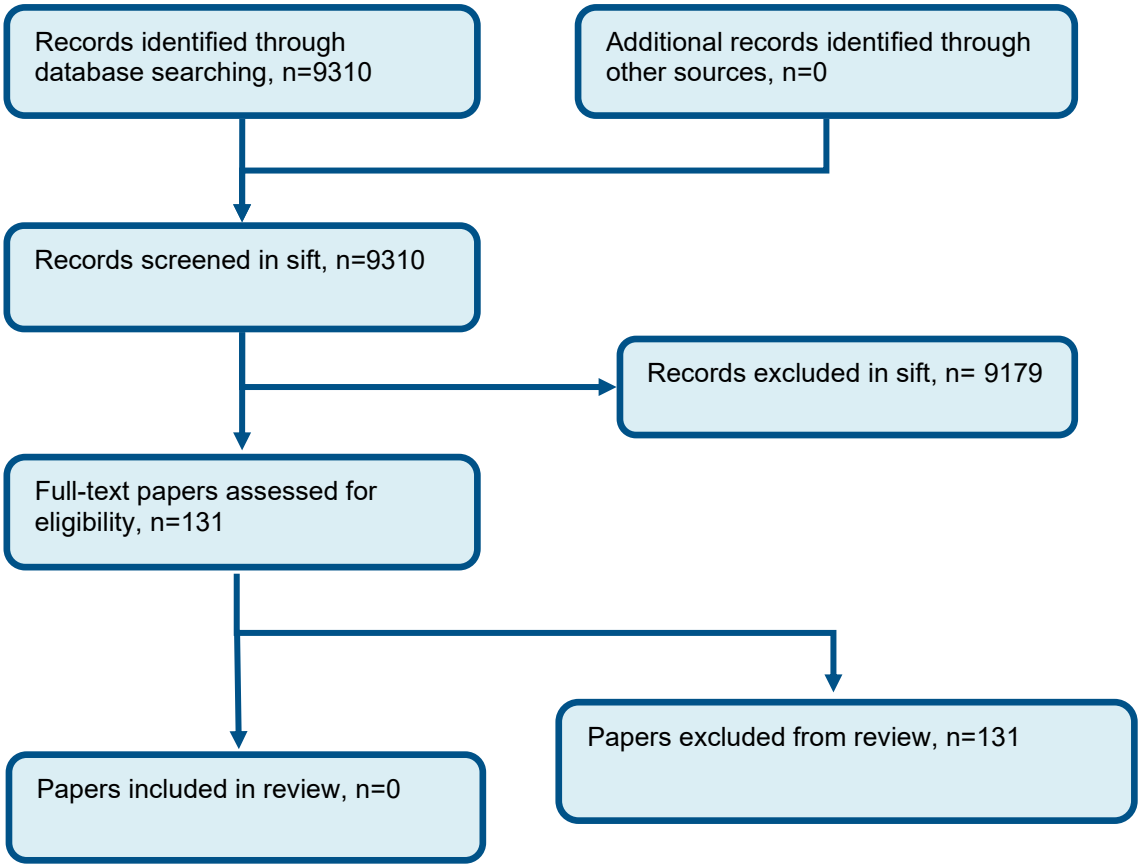
#49.	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
#50.	#34 AND #49
#51.	* IN NHSEED
#52.	#50 AND #51
#53.	* IN HTA
#54.	#50 AND #53

INAHTA search terms

1.	((("Cholesterol, Dietary"[mhe]) OR ((fat or fats) AND (saturated or unsaturated)) OR ((diet* or food*) AND (lipid* or fat* or cholesterol* or epicholesterol*)) OR ((plant* or vegetable* or rapeseed or corn or cottonseed or linseed or olive or peanut or rice bran or safflower or sesame or soybean or sunflower or nut or groundnut or walnut or avocado) AND (oil* or spread* or butter* or fat*)) OR ("Plant Oils"[mhe]) OR ((diet*) AND (therap* or change* or intervention* or treatment* or approach* or strateg* or modif* or restrict* or pattern* or health* or adjust or alter*)) OR ((DASH) AND (DIET*)) OR ((Mediterranean) AND (food* or nutrition* or eat* or diet*)) OR ("Diet, Healthy"[mhe]) OR ("Drug Therapy"[mhe]) OR ("Diet"[mhe])) AND ("Cardiovascular Diseases"[mhe])) OR (((DIABEGG) OR (((fat or fats) and (saturate* or unsaturate* or polyunsaturate*))) OR ((serum and (cholesterol* or epicholesterol))) OR (((diet* or consum* or eat* or intake or amount*) AND (lipid* or fat or fats or cholesterol* or epicholesterol*)) OR ("Cholesterol, Dietary"[mhe]) OR (("Diet"[mhe] or "Diet Therapy"[mhe] and "cholesterol"[mhe])[mh])) OR (DIABEGG) OR ((egg* and (diet* or consum* or eat* or intake or cholesterol* or amount* or number* or high*))) OR (((fat or fats) and (saturate* or unsaturate* or polyunsaturate*))) OR ((serum and (cholesterol* or epicholesterol))) OR (((diet* or consum* or eat* or intake or amount*) AND (lipid* or fat or fats or cholesterol* or epicholesterol*)) OR ("Cholesterol, Dietary"[mhe]) OR (("Diet"[mhe] or "Diet Therapy"[mhe] and "cholesterol"[mhe])[mh]))

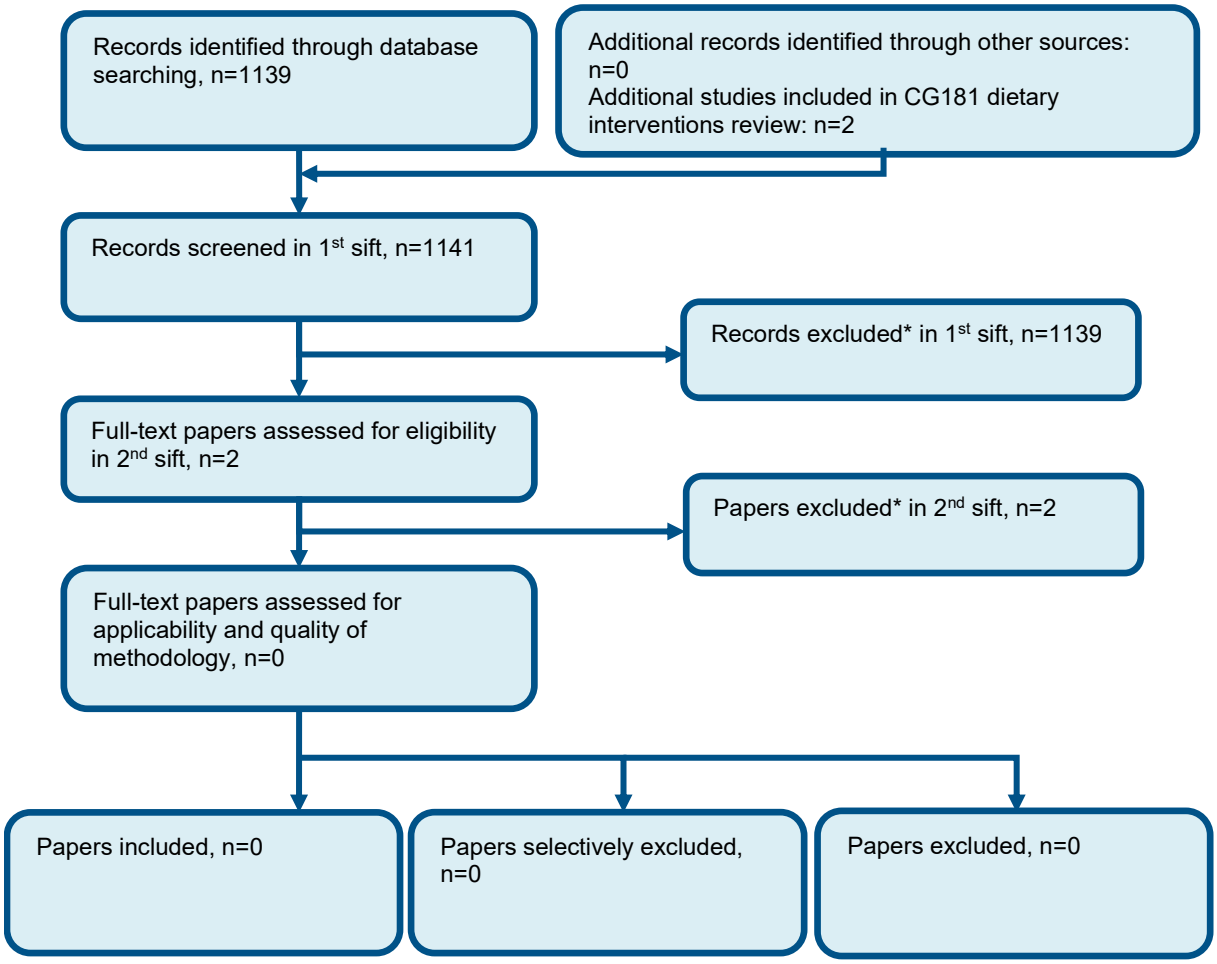
Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of dietary cholesterol



Appendix D Economic evidence study selection

Figure 2: Flow chart of health economic study selection for the guideline – dietary cholesterol



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix E Economic evidence tables

None.

Appendix F Health economic model

This area was not prioritised for new cost-effectiveness analysis.

Appendix G Excluded studies

G.1 Clinical studies

Table 3: Studies excluded from the clinical review

Study	Exclusion reason
Abdollahi, Anna M, Virtanen, Heli E K, Voutilainen, Sari et al. (2019) Egg consumption, cholesterol intake, and risk of incident stroke in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. The American journal of clinical nutrition 110(1): 169-176	- Non-randomised study: prognostic design
Alexander, Dominik D, Miller, Paula E, Vargas, Ashley J et al. (2016) Meta-analysis of Egg Consumption and Risk of Coronary Heart Disease and Stroke. Journal of the American College of Nutrition 35(8): 704-716	- Systematic review of prognostic studies
Amsterdam, E A; Hyson, D; Kappagoda, C T (1994) Nonpharmacologic therapy for coronary artery atherosclerosis: results of primary and secondary prevention trials. American heart journal 128(6pt2): 1344-52	- Review article but not a systematic review
Anonymous (1986) Coronary heart disease death, nonfatal acute myocardial infarction and other clinical outcomes in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. The American journal of cardiology 58(1): 1-13	- Study does not contain an intervention relevant to this review protocol
Anonymous. (2004) The less than dramatic impact on CVD of dietary cholesterol. Canadian family physician Medecin de famille canadien 50: 1488-1489	- Not a peer-reviewed publication
Arora, R.C.; Agarwal, N.; Singh, D.K. (1991) A study of short term lipoprotein changes induced by single high cholesterol diet in healthy and diseases human volunteers. Materia medica Polona. Polish journal of medicine and pharmacy 23(4): 299-301	- Follow-up < 1 year
Atkins, D, Psaty, B M, Koepsell, T D et al. (1993) Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. Annals of internal medicine 119(2): 136-45	- Systematic review of prognostic studies
Ballesteros, M., Valenzuela, F., Robles, A. et al. (2014) One egg a day does not increase the risk for cardiovascular disease in diabetic patients. FASEB Journal 28(1suppl1)	- Follow-up < 1 year
Ballesteros, Martha Nydia, Valenzuela, Fabrizio, Robles, Alma E et al. (2015) One Egg per Day Improves Inflammation when Compared to an Oatmeal-Based Breakfast without Increasing Other Cardiometabolic Risk Factors in Diabetic Patients. Nutrients 7(5): 3449-63	- Study design not relevant to this review protocol - cross over RCT - Follow-up < 1 year
Bamfo, R. and Jamerson, K. (2008) Therapeutic lifestyle changes diet vs atkins diet for efficacy of	- Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
cholesterol lowering. Ethnicity and Disease 18(2suppl1): 171-s173	
Barratt, A, Reznik, R, Irwig, L et al. (1994) Work-site cholesterol screening and dietary intervention: the Staff Healthy Heart Project. Steering Committee. American journal of public health 84(5): 779-782	- Follow-up < 1 year
Bell, M and Dippe, S E (1988) Recognition and treatment of hypercholesterolemia in a family practice center. The Journal of family practice 26(5): 507-13	- Study design not relevant to this review protocol Retrospective audit
Berger, S., Raman, G., Vishwanathan, R. et al. (2014) Dietary cholesterol and heart health: A systematic review and meta-analysis. FASEB Journal 28(1suppl1)	- Systematic review of prognostic studies
Berger, Samantha, Raman, Gowri, Vishwanathan, Rohini et al. (2015) Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. The American journal of clinical nutrition 102(2): 276-94	- Systematic review of prognostic studies
Blankenhorn, D.H. et al. (1989) CLAS: The Cholesterol Lowering Atherosclerosis Study effects of diet in the placebo group. Atherosclerosis VIII: proceedings of the 8th International Symposium on Atherosclerosis. ICS817: 741-750	- Study does not contain an intervention relevant to this review protocol
Blesso, Christopher N, Andersen, Catherine J, Barona, Jacqueline et al. (2013) Effects of carbohydrate restriction and dietary cholesterol provided by eggs on clinical risk factors in metabolic syndrome. Journal of clinical lipidology 7(5): 463-71	- Follow-up < 1 year
Brown, W V (1990) Clinical trials including an update on the Helsinki Heart Study. The American journal of cardiology 66(6): 11a-15a	- Review article but not a systematic review
Bucher, HC; Griffith, LE; Guyatt, GH (1999) Systematic review on the risk and benefit of different cholesterol-lowering interventions. Arteriosclerosis, thrombosis, and vascular biology 19(2): 187-95	- Systematic review does not contain factors of interest Statins, fibrates, resins, hormones
Carson, Jo Ann S, Lichtenstein, Alice H, Anderson, Cheryl A M et al. (2020) Dietary Cholesterol and Cardiovascular Risk: A Science Advisory From the American Heart Association. Circulation 141(3): e39-e53	- Review article but not a systematic review
Cheng, Pengfei, Pan, Junxi, Xia, Jinjun et al. (2018) Dietary cholesterol intake and stroke risk: a meta-analysis. Oncotarget 9(39): 25698-25707	- Systematic review of prognostic studies
Chrysant, Steven G and Chrysant, George S (2021) The Debate Over Egg Consumption and Incident Cardiovascular Disease. Cardiology in review 29(5): 238-244	- Systematic review of prognostic studies
Clifton, P.M., Kestin, M., Abbey, M. et al. (1990) Relationship between sensitivity to dietary fat	- Follow-up < 1 year

Study	Exclusion reason
and dietary cholesterol. Arteriosclerosis 10(3): 394-401	
Constance, C (2009) The good and the bad: what researchers have learned about dietary cholesterol, lipid management and cardiovascular disease risk since the Harvard Egg Study. International journal of clinical practice. Supplement: 9-43	- Review article but not a systematic review
Dehghan, Mahshid, Mente, Andrew, Rangarajan, Sumathy et al. (2020) Association of egg intake with blood lipids, cardiovascular disease, and mortality in 177,000 people in 50 countries. The American journal of clinical nutrition 111(4): 795-803	- Non-randomised study: prognostic design
Djousse, Luc and Gaziano, J Michael (2008) Egg consumption and risk of heart failure in the Physicians' Health Study. Circulation 117(4): 512-6	- Non-randomised study: prognostic design
Djousse, Luc and Gaziano, J Michael (2008) Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. The American journal of clinical nutrition 87(4): 964-9	- Duplicate reference
Djousse, Luc and Gaziano, J Michael (2009) Dietary Cholesterol and Coronary Artery Disease: A Systematic Review. Current Atherosclerosis Reports 11: 418-422	- Systematic review of prognostic studies
Djousse, Luc, Zhou, Guohai, McClelland, Robyn L et al. (2021) Egg consumption, overall diet quality, and risk of type 2 diabetes and coronary heart disease: A pooling project of US prospective cohorts. Clinical nutrition (Edinburgh, Scotland) 40(5): 2475-2482	- Systematic review of prognostic studies
Drouin-Chartier, Jean-Philippe, Chen, Siyu, Li, Yanping et al. (2020) Egg consumption and risk of cardiovascular disease: three large prospective US cohort studies, systematic review, and updated meta-analysis. BMJ (Clinical research ed.) 368: m513	- Systematic review of prognostic studies
Drouin-Chartier, Jean-Philippe, Schwab, Amanda L, Chen, Siyu et al. (2020) Egg consumption and risk of type 2 diabetes: findings from 3 large US cohort studies of men and women and a systematic review and meta-analysis of prospective cohort studies. The American journal of clinical nutrition 112(3): 619-630	- Duplicate reference
Dussaillant, Catalina, Echeverría, Guadalupe, Rozowski, Jaime et al. (2017) Egg intake and diabetes mellitus type 2: A review of the scientific literature. Rev. chil. nutr 44(4): 393-399	- Full text paper not available
Díez-Espino J, Basterra-Gortari FJ, Salas-Salvadó J et al. (2017) Egg consumption and cardiovascular disease according to diabetic	- Non-randomised study: prognostic design

Study	Exclusion reason
status: The PREDIMED study. Clinical nutrition (Edinburgh, Scotland) 36(4): 1015-1021	
Fallah-Moshkani, Roohallah, Saadatnia, Mohammad, Shakeri, Forough et al. (2017) A case-control study on egg consumption and risk of stroke among Iranian population. Journal of health, population, and nutrition 36(1): 28	- Study design not relevant to this review protocol - Non-randomised study: case-control
Fernandez, M.L. and Andersen, C.J. (2014) Effects of dietary cholesterol in diabetes and cardiovascular disease. Clinical Lipidology 9(6): 607-616	- Review article but not a systematic review
Fuller NR, Caterson ID, Sainsbury A et al. (2015) The effect of a high-egg diet on cardiovascular risk factors in people with type 2 diabetes: the Diabetes and Egg (DIABEGG) study-a 3-mo randomized controlled trial. The American journal of clinical nutrition 101(4): 705-713	- Follow-up < 1 year
Fuller, Nicholas R, Sainsbury, Amanda, Caterson, Ian D et al. (2018) Effect of a high-egg diet on cardiometabolic risk factors in people with type 2 diabetes: the Diabetes and Egg (DIABEGG) Study-randomized weight-loss and follow-up phase. The American journal of clinical nutrition 107(6): 921-931	- Follow-up < 1 year
Fuller, Nicholas R, Sainsbury, Amanda, Caterson, Ian D et al. (2015) Egg Consumption and Human Cardio-Metabolic Health in People with and without Diabetes. Nutrients 7(9): 7399-420	- Review article but not a systematic review
Gao, Min, Jebb, Susan A, Aveyard, Paul et al. (2021) Associations between dietary patterns and the incidence of total and fatal cardiovascular disease and all-cause mortality in 116,806 individuals from the UK Biobank: a prospective cohort study. BMC medicine 19(1): 83	- Study does not contain an intervention relevant to this review protocol
Geiker, N R W, Larsen, M Lytken, Dyerberg, J et al. (2018) Egg consumption, cardiovascular diseases and type 2 diabetes. European journal of clinical nutrition 72(1): 44-56	- Systematic review of prognostic studies
Godos, Justyna, Micek, Agnieszka, Brzostek, Tomasz et al. (2021) Egg consumption and cardiovascular risk: a dose-response meta-analysis of prospective cohort studies. European journal of nutrition 60(4): 1833-1862	- Systematic review of prognostic studies
Goldberg S, Gardener H, Tiozzo E et al. (2014) Egg consumption and carotid atherosclerosis in the Northern Manhattan study. Atherosclerosis 235(2): 273-280	- Non-randomised study: prognostic design
Gorder, D D, Dolecek, T A, Coleman, G G et al. (1986) Dietary intake in the Multiple Risk Factor Intervention Trial (MRFIT): nutrient and food group changes over 6 years. Journal of the American Dietetic Association 86(6): 744-51	- Review article but not a systematic review

Study	Exclusion reason
Greene, Christine M, Zern, Tosca L, Wood, Richard J et al. (2005) Maintenance of the LDL cholesterol:HDL cholesterol ratio in an elderly population given a dietary cholesterol challenge. The Journal of nutrition 135(12): 2793-8	- Follow-up < 1 year
Griffin, J.D. and Lichtenstein, A.H. (2013) Dietary Cholesterol and Plasma Lipoprotein Profiles: Randomized Controlled Trials. Current Nutrition Reports 2(4): 274-282	- Systematic review of prognostic studies
Guo, Jing, Hobbs, Ditte A, Cockcroft, John R et al. (2018) Association between egg consumption and cardiovascular disease events, diabetes and all-cause mortality. European journal of nutrition 57(8): 2943-2952	- Non-randomised study: prognostic design
Habak, P A; Schrott, H G; Connor, W E (1974) The cholesterol hypothesis and the coronary primary prevention trial. IMJ. Illinois medical journal 146(1): 28-contd	- Review article but not a systematic review
He, H., Zhang, T., Zhou, J. et al. (2019) Associations of physical activity and egg intake with hypertension among Chinese middle-aged and older population. Scientific reports 9(1): 7722	- Study does not contain an intervention relevant to this review protocol
Herron, Kristin L, Vega-Lopez, Sonia, Conde, Karin et al. (2002) Pre-menopausal women, classified as hypo- or hyperresponders, do not alter their LDL/HDL ratio following a high dietary cholesterol challenge. Journal of the American College of Nutrition 21(3): 250-8	- Study does not contain an intervention relevant to this review protocol
Hjermann, I. (1983) A randomized primary preventive trial in coronary heart disease: The Oslo study. Preventive Medicine 12(1): 181-184	- Study does not contain an intervention relevant to this review protocol
Hjermann, I. (1981) Intervention on smoking and eating habits in healthy men carrying high risk for coronary heart disease. The Oslo study. Acta Medica Scandinavica 210(suppl651): 281-284	- Study does not contain an intervention relevant to this review protocol
Holme, I (1990) An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. Circulation 82(6): 1916-24	- Systematic review of prognostic studies
Holme, Ingar and Tonstad, Serena (2013) Association of coronary heart disease mortality with risk factors according to length of follow-up and serum cholesterol level in men: the Oslo Study cohort. European journal of preventive cardiology 20(1): 168-75	- Non-randomised study: prognostic design
Hu, F B, Stampfer, M J, Rimm, E B et al. (1999) A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA 281(15): 1387-94	- Non-randomised study: prognostic design
Imran, M., Anjum, F.M., Butt, M.S. et al. (2014) Incorporation of nutritionally important fatty acids into eggs and evaluation of "Bio-Omega-3" eggs in humans with moderate hypercholesterolemia. Pakistan Journal of Nutrition 12(10): 907-911	- Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
Jang, Jiyoung, Shin, Min-Jeong, Kim, Oh Yoen et al. (2018) Longitudinal association between egg consumption and the risk of cardiovascular disease: interaction with type 2 diabetes mellitus. Nutrition & diabetes 8(1): 20	- Non-randomised study: prognostic design
Ji, Naiwen, Huang, Zhe, Zhang, Xinyuan et al. (2021) Association between egg consumption and arterial stiffness: a longitudinal study. Nutrition journal 20(1): 67	- Non-randomised study: prognostic design
Jiang, Z. and Sim, J.S. (1993) Consumption of n-3 polyunsaturated fatty acid-enriched eggs and changes in plasma lipids of human subjects. Nutrition 9(6): 513-518	- Study design not relevant to this review protocol
Kannel, W B, Neaton, J D, Wentworth, D et al. (1986) Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. American heart journal 112(4): 825-36	- Non-randomised study: prognostic design
Katz, David L, Evans, Marian A, Nawaz, Haq et al. (2005) Egg consumption and endothelial function: a randomized controlled crossover trial. International journal of cardiology 99(1): 65-70	- Study design not relevant to this review protocol - cross over RCT
Katz, David L, Gnanaraj, Joseph, Treu, Judith A et al. (2015) Effects of egg ingestion on endothelial function in adults with coronary artery disease: a randomized, controlled, crossover trial. American heart journal 169(1): 162-9	- Study design not relevant to this review protocol - cross over RCT
Khalighi Sikaroudi, Masoumeh, Soltani, Sepideh, Kolahdouz-Mohammadi, Roya et al. (2020) The responses of different dosages of egg consumption on blood lipid profile: An updated systematic review and meta-analysis of randomized clinical trials. Journal of food biochemistry 44(8): e13263	- Follow-up < 1 year
Klangjareonchai, T., Putadechakum, S., Sritara, P. et al. (2012) The effect of egg consumption in hyperlipidemic subjects during treatment with lipid-lowering drugs. Journal of Lipids 2012: 672720	- Follow-up < 1 year
Krittanawong, C., Tunhasiriwet, A., Tweet, M.S. et al. (2015) Egg consumption and risk of cardiovascular disease: A systematic review and meta-analysis. Circulation 132(suppl3)	- Systematic review of prognostic studies
Krittanawong, Chayakrit, Narasimhan, Bharat, Wang, Zhen et al. (2021) Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. The American journal of medicine 134(1): 76-83e2	- Systematic review of prognostic studies
Kunutsor, Setor K; Laukkanen, Jari A; Virtanen, Jyrki K (2022) Egg and cholesterol intake, apolipoprotein E4 phenotype and risk of venous	- Systematic review of prognostic studies

Study	Exclusion reason
thromboembolism: findings from a prospective cohort study. The British journal of nutrition: 1-23	
Lajous, Martin, Bijon, Anne, Fagherazzi, Guy et al. (2015) Egg and cholesterol intake and incident type 2 diabetes among French women. The British journal of nutrition 114(10): 1667-73	- Non-randomised study: prognostic design
LaRosa, J C, Applegate, W, Crouse, J R 3rd et al. (1994) Cholesterol lowering in the elderly. Results of the Cholesterol Reduction in Seniors Program (CRISP) pilot study. Archives of internal medicine 154(5): 529-39	- Non-randomised study: prognostic design
Larsson, Susanna C; Akesson, Agneta; Wolk, Alicja (2015) Egg consumption and risk of heart failure, myocardial infarction, and stroke: results from 2 prospective cohorts. The American journal of clinical nutrition 102(5): 1007-13	- Non-randomised study: prognostic design
Larsson, Susanna C; Virtamo, Jarmo; Wolk, Alicja (2012) Dietary fats and dietary cholesterol and risk of stroke in women. Atherosclerosis 221(1): 282-6	- Non-randomised study: prognostic design
Lau, D C W (2009) Dietary cholesterol and other nutritional considerations in people with diabetes. International journal of clinical practice. Supplement: 15-51	- Review article but not a systematic review
Leren, P (1967) The effect of a cholesterol lowering diet in male survivors of myocardial infarction. (A controlled clinical trial). Nordisk medicin 77(21): 658-661	- Population not relevant to this review protocol
Li, Yuehua, Zhou, Chenghui, Zhou, Xianliang et al. (2013) Egg consumption and risk of cardiovascular diseases and diabetes: a meta-analysis. Atherosclerosis 229(2): 524-30	- Systematic review of prognostic studies
Ma, Wancheng, Zhang, Yanyan, Pan, Li et al. (2022) Association of Egg Consumption with Risk of All-Cause and Cardiovascular Disease Mortality: A Systematic Review and Dose-Response Meta-analysis of Observational Studies. The Journal of nutrition	- Systematic review of prognostic studies
MacDonald, Conor-James, Madika, Anne-Laure, Bonnet, Fabrice et al. (2020) Cholesterol and Egg Intakes, and Risk of Hypertension in a Large Prospective Cohort of French Women. Nutrients 12(5)	- Non-randomised study: prognostic design
Mah, Eunice; Chen, C-Y Oliver; Liska, DeAnn J (2020) The effect of egg consumption on cardiometabolic health outcomes: an umbrella review. Public health nutrition 23(5): 935-955	- Systematic review of prognostic studies
Marventano, Stefano, Godos, Justyna, Tieri, Maria et al. (2020) Egg consumption and human health: an umbrella review of observational studies. International journal of food sciences and nutrition 71(3): 325-331	- Systematic review of prognostic studies
Matsuoka, R, Usuda, M, Masuda, Y et al. (2017) Lactic-fermented egg white reduced serum cholesterol concentrations in mildly	- Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
hypercholesterolemic Japanese men: a double-blind, parallel-arm design. Lipids in health and disease 16(1): 101	
Mazidi, Mohsen, Katsiki, Niki, Mikhailidis, Dimitri P et al. (2019) Egg Consumption and Risk of Total and Cause-Specific Mortality: An Individual-Based Cohort Study and Pooling Prospective Studies on Behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Journal of the American College of Nutrition 38(6): 552-563	- Systematic review of prognostic studies
McNamara, D J (2000) The impact of egg limitations on coronary heart disease risk: do the numbers add up?. Journal of the American College of Nutrition 19(5suppl): 540s-548s	- Review article but not a systematic review
Miettinen, M (1975) Prevention of coronary heart disease by cholesterol lowering diet. Postgraduate medical journal 51(8): uppl-51	- Review article but not a systematic review
Miettinen, M, Turpeinen, O, Karvonen, M J et al. (1983) Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. International journal of epidemiology 12(1): 17-25	- Study does not contain an intervention relevant to this review protocol
Missimer, A., DiMarco, D., Vergara-Jimenez, M. et al. (2015) Intake of 2 eggs or oatmeal for breakfast does not increase biomarkers for heart disease while eggs improve liver enzymes and raise HDL cholesterol in young healthy individuals. FASEB Journal 29(1meetingabstracts)	- Follow-up < 1 year
Missimer, A., Dimarco, D.M., Andersen, C.J. et al. (2017) Consuming two eggs per day, as compared to an oatmeal breakfast, increases plasma ghrelin while maintaining the LDL/HDL ratio. Nutrients 9(2): 89	- Follow-up < 1 year
Missimer, Amanda, DiMarco, Diana M, Andersen, Catherine J et al. (2017) Consuming Two Eggs per Day, as Compared to an Oatmeal Breakfast, Decreases Plasma Ghrelin while Maintaining the LDL/HDL Ratio. Nutrients 9(2)	- Follow-up < 1 year
Mohammadifard, Noushin, Taheri, Marzieh, Haghighatdoost, Fahimeh et al. (2022) Egg consumption and risk of cardiovascular events among Iranians: results from Isfahan Cohort Study (ICS). European journal of clinical nutrition	- Non-randomised study: prognostic design
Mousavi, Seyed Mohammad, Zargarzadeh, Nikan, Rigi, Somaye et al. (2022) Egg Consumption and Risk of All-Cause and Cause-Specific Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Advances in nutrition (Bethesda, Md.)	- Systematic review of prognostic studies
Nakamura, Y., Okamura, T., Kita, Y. et al. (2017) Re-evaluation of the relations of egg consumption to serum total cholesterol, cause-	- Non-randomised study: prognostic design

Study	Exclusion reason
specific and all-cause mortality. Circulation 135(supplement1)	
Nakamura, Yasuyuki, Iso, Hiroyasu, Kita, Yoshikuni et al. (2006) Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. The British journal of nutrition 96(5): 921-8	- Non-randomised study: prognostic design
Nakamura, Yasuyuki, Okamura, Tomonori, Tamaki, Shinji et al. (2004) Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). The American journal of clinical nutrition 80(1): 58-63	- Non-randomised study: prognostic design
Nettleton, Jennifer A, Steffen, Lyn M, Loehr, Laura R et al. (2008) Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. Journal of the American Dietetic Association 108(11): 1881-7	- Non-randomised study: prognostic design
Nikolaus, T, Schlierf, G, Vogel, G et al. (1991) Treatment of coronary heart disease with diet and exercise--problems of compliance. Annals of nutrition & metabolism 35(1): 1-7	- Study does not contain an intervention relevant to this review protocol
Njike, Valentine, Faridi, Zubaida, Dutta, Suparna et al. (2010) Daily egg consumption in hyperlipidemic adults--effects on endothelial function and cardiovascular risk. Nutrition journal 9: 28	- Follow-up < 1 year
Park, Seon-Joo, Jung, Ji-Hye, Choi, Sang-Woon et al. (2018) Association between Egg Consumption and Metabolic Disease. Korean journal for food science of animal resources 38(2): 209-223	- Systematic review of prognostic studies
Qin, Chenxi, Lv, Jun, Guo, Yu et al. (2018) Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. Heart (British Cardiac Society) 104(21): 1756-1763	- Non-randomised study: prognostic design
Richard, Caroline, Cristall, Lisa, Fleming, Emily et al. (2017) Impact of Egg Consumption on Cardiovascular Risk Factors in Individuals with Type 2 Diabetes and at Risk for Developing Diabetes: A Systematic Review of Randomized Nutritional Intervention Studies. Canadian journal of diabetes 41(4): 453-463	- Systematic review of prognostic studies
Romano, G., Tilly-Kiesi, M.K., Patti, L. et al. (1998) Effects of dietary cholesterol on plasma lipoproteins and their subclasses in IDDM patients. Diabetologia 41(2): 193-200	- Follow-up < 1 year
Rong, Ying, Chen, Li, Zhu, Tingting et al. (2013) Egg consumption and risk of coronary heart	- Systematic review of prognostic studies

Study	Exclusion reason
disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ (Clinical research ed.) 346: e8539	
Rose, G; Tunstall-Pedoe, H D; Heller, R F (1983) UK heart disease prevention project: incidence and mortality results. Lancet (London, England) 1(8333): 1062-6	- Study does not contain an intervention relevant to this review protocol
Rouhani, Mohammad Hossein, Rashidi-Pourfard, Nafiseh, Salehi-Abargouei, Amin et al. (2018) Effects of Egg Consumption on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Journal of the American College of Nutrition 37(2): 99-110	- Follow-up < 1 year
Ruggiero, Emilia, Di Castelnuovo, Augusto, Costanzo, Simona et al. (2021) Egg consumption and risk of all-cause and cause-specific mortality in an Italian adult population. European journal of nutrition 60(7): 3691-3702	- Non-randomised study: prognostic design
Sacks, F M, Rouleau, J L, Moye, L A et al. (1995) Baseline characteristics in the Cholesterol and Recurrent Events (CARE) trial of secondary prevention in patients with average serum cholesterol levels. The American journal of cardiology 75(8): 621-3	- Study does not contain an intervention relevant to this review protocol
Sawrey-Kubicek, L., Zhu, C., Stevens, A. et al. (2017) Whole egg increases high density lipoprotein-cholesterol (HDL-C) levels in overweight postmenopausal women. FASEB Journal 31(1supplement1)	- Follow-up < 1 year
Sawrey-Kubicek, Lisa, Zhu, Chenghao, Bardagjy, Allison S et al. (2019) Whole egg consumption compared with yolk-free egg increases the cholesterol efflux capacity of high-density lipoproteins in overweight, postmenopausal women. The American journal of clinical nutrition 110(3): 617-627	- Follow-up < 1 year
Scrafford, Carolyn G, Tran, Nga L, Barraj, Leila M et al. (2011) Egg consumption and CHD and stroke mortality: a prospective study of US adults. Public health nutrition 14(2): 261-70	- Non-randomised study: prognostic design - Systematic review of prognostic studies
Shin, J.-Y.; Xun, P.; He, K. (2012) Egg consumption and risk of cardiovascular disease: Meta-analysis. Diabetes 61(suppl1): a379-a380	- Systematic review of prognostic studies
Shin, Jang Yel, Xun, Pengcheng, Nakamura, Yasuyuki et al. (2013) Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. The American journal of clinical nutrition 98(1): 146-59	- Systematic review of prognostic studies
Sleight, P (1992) Cholesterol and coronary heart disease mortality. Australian and New Zealand journal of medicine 22(5suppl): 576-9	- Review article but not a systematic review
Spence, J David; Jenkins, David J A; Davignon, Jean (2012) Egg yolk consumption and carotid plaque. Atherosclerosis 224(2): 469-73	- Non-randomised study: prognostic design

Study	Exclusion reason
Stamler, J and Shekelle, R (1988) Dietary cholesterol and human coronary heart disease. The epidemiologic evidence. Archives of pathology & laboratory medicine 112(10): 1032-40	- Review article but not a systematic review
Stamler, J; Wentworth, D; Neaton, J D (1986) Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 256(20): 2823-8	- Non-randomised study: prognostic design
Stone, N J (1993) Diet, blood cholesterol levels, and coronary heart disease. Coronary artery disease 4(10): 871-81	- Review article but not a systematic review
Stupin, A, Rasic, L, Matic, A et al. (2018) Omega-3 polyunsaturated fatty acids-enriched hen eggs consumption enhances microvascular reactivity in young healthy individuals. Physiologie appliquee, nutrition et metabolisme [Applied physiology, nutrition, and metabolism] 43(10): 988-995	- Study does not contain an intervention relevant to this review protocol
Takagi, Hisato, Hari, Yosuke, Nakashima, Kouki et al. (2020) Egg Consumption and Coronary Artery Disease: A Nice Knockdown Argument. Angiology 71(7): 589-601	- Systematic review of prognostic studies
Tang, Hui, Cao, Yi, Yang, Xiang et al. (2020) Egg Consumption and Stroke Risk: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Frontiers in nutrition 7: 153	- Systematic review of prognostic studies
Tillotson, JL, Bartsch, GE, Gorder, D et al. (1997) Food group and nutrient intakes at baseline in the Multiple Risk Factor Intervention Trial. American journal of clinical nutrition 65(1suppl): 228S-257S	- Study does not contain an intervention relevant to this review protocol
Tran, Nga L, Barraj, Leila M, Heilman, Jacqueline M et al. (2014) Egg consumption and cardiovascular disease among diabetic individuals: a systematic review of the literature. Diabetes, metabolic syndrome and obesity : targets and therapy 7: 121-37	- Systematic review of prognostic studies
Virtanen JK, Mursu J, Virtanen HE et al. (2016) Associations of egg and cholesterol intakes with carotid intima-media thickness and risk of incident coronary artery disease according to apolipoprotein E phenotype in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. The American journal of clinical nutrition 103(3): 895-901	- Non-randomised study: prognostic design
Vorster, H.H., Venter, C.S., Silvis, N. et al. (1988) Influence of a habitual high egg intake on serum lipid levels in a rural coloured population. South African Medical Journal 74(11): 554-559	- Non-randomised study: prognostic design

Study	Exclusion reason
Wang, Ke, Wang, Lu, Liu, Linjiong et al. (2022) Longitudinal association of egg intake frequency with cardiovascular disease in Chinese adults. Nutrition, metabolism, and cardiovascular diseases : NMCD 32(4): 908-917	- Non-randomised study: prognostic design
Weggemans, R M; Zock, P L; Katan, M B (2001) Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. The American journal of clinical nutrition 73(5): 885-91	- Systematic review of prognostic studies
Xia, Peng-Fei, Pan, Xiong-Fei, Chen, Chen et al. (2020) Dietary Intakes of Eggs and Cholesterol in Relation to All-Cause and Heart Disease Mortality: A Prospective Cohort Study. Journal of the American Heart Association 9(10): e015743	- Non-randomised study: prognostic design
Xu, Lin, Lam, Tai Hing, Jiang, Chao Qiang et al. (2019) Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. European journal of nutrition 58(2): 785-796	- Non-randomised study: prognostic design
Yang, Peng-Fei, Wang, Chun-Rui, Hao, Fa-Bao et al. (2022) Egg consumption and risks of all-cause and cause-specific mortality: a dose-response meta-analysis of prospective cohort studies. Nutrition reviews 80(7): 1739-1754	- Systematic review of prognostic studies
Ylilauri, Maija Pt, Voutilainen, Sari, Lonnroos, Eija et al. (2017) Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischaemic Heart Disease Risk Factor Study. The American journal of clinical nutrition 105(2): 476-484	- Non-randomised study: prognostic design
Yu-Poth, S, Zhao, G, Etherton, T et al. (1999) Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. The American journal of clinical nutrition 69(4): 632-46	- Systematic review of prognostic studies
Zamora-Ros, Raul, Cayssials, Valerie, Cleries, Ramon et al. (2019) Moderate egg consumption and all-cause and specific-cause mortality in the Spanish European Prospective into Cancer and Nutrition (EPIC-Spain) study. European journal of nutrition 58(5): 2003-2010	- Non-randomised study: prognostic design
Zazpe, I, Beunza, J, Bes-Rastrollo, M et al. (2011) Egg consumption and risk of cardiovascular disease in the SUN Project. European journal of clinical nutrition 65(6): 676-82	- Non-randomised study: prognostic design
Zhao, B, Gan, L, Graubard, BI et al. (2022) Associations of Dietary Cholesterol, Serum Cholesterol, and Egg Consumption With Overall	- Systematic review of prognostic studies

Study	Exclusion reason
and Cause-Specific Mortality, and Systematic Review and Updated Meta-Analysis. Circulation	
Zhao, Bin, Gan, Lu, Graubard, Barry I et al. (2022) Associations of Dietary Cholesterol, Serum Cholesterol, and Egg Consumption With Overall and Cause-Specific Mortality: Systematic Review and Updated Meta-Analysis. Circulation 145(20): 1506-1520	- Systematic review of prognostic studies
Zhong, Victor W, Van Horn, Linda, Cornelis, Marilyn C et al. (2019) Associations of Dietary Cholesterol or Egg Consumption With Incident Cardiovascular Disease and Mortality. JAMA 321(11): 1081-1095	- Non-randomised study: prognostic design
Zhuang, Pan, Wu, Fei, Mao, Lei et al. (2021) Egg and cholesterol consumption and mortality from cardiovascular and different causes in the United States: A population-based cohort study. PLoS medicine 18(2): e1003508	- Non-randomised study: prognostic design

G.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2007 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 4: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	