# SYSTEMATIC REVIEW
## An Introduction

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# Agenda

Basic concepts in systematic review

systematic review process

Search strategies and data filtering

Critical appraisal
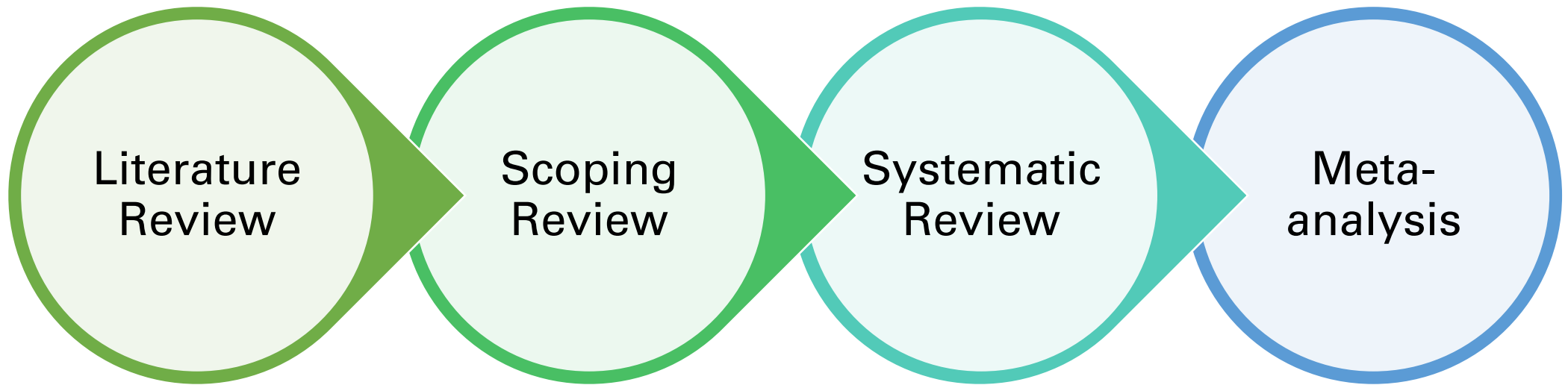
# Disclaimer

- This presentation does not contain legal advices or provide scientific conclusions.

- The content does not serve as a standard practice or guidelines in conducting a systematic review in substantiating health claims or food-health relationship.

- The audiences may need some background in understanding or conducting a clinical research study.

Flexible ⟵────────────────⟶ Rigorous

Broad ⟵────────────────⟶ Specific

Heterogeneous ⟵────────────────⟶ Homogeneous

Literature Review ▸ Scoping Review ▸ Systematic Review ▸ Meta-analysis

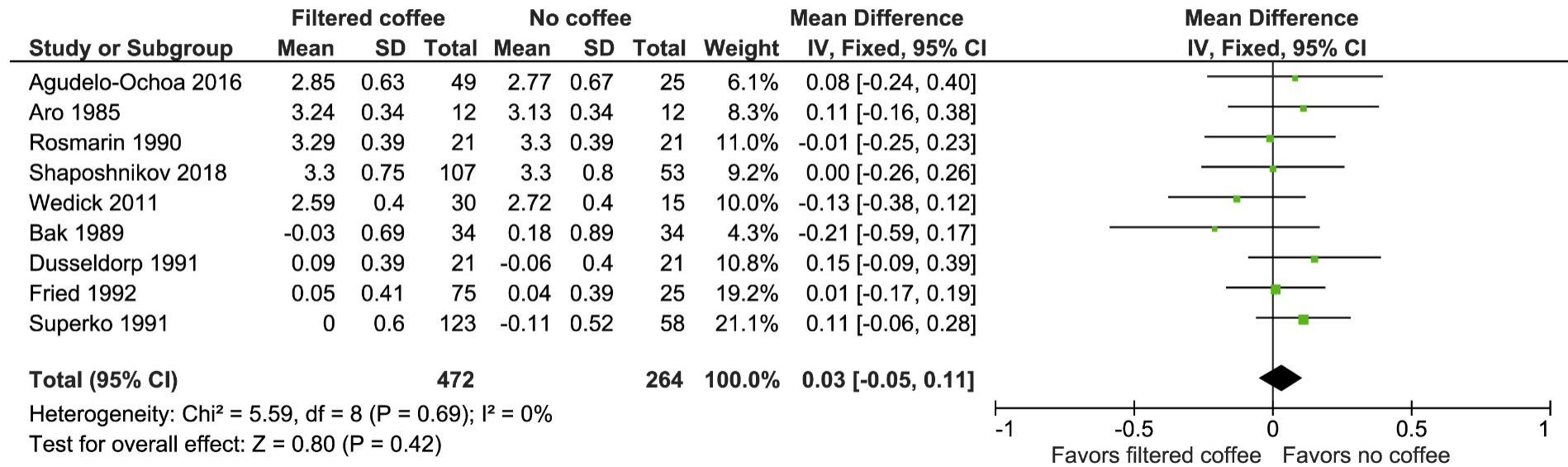| | Traditional Literature Reviews | Scoping reviews | Systematic reviews |
|---|---|---|---|
| A priori review protocol | No | Yes (some) | Yes |
| Registration of the review protocol | No | No[a] | Yes |
| Explicit, transparent, peer reviewed search strategy | No | Yes | Yes |
| Standardized data extraction forms | No | Yes | Yes |
| Mandatory Critical Appraisal (Risk of Bias Assessment) | No | No[b] | Yes |
| Synthesis of findings from individual studies and the generation of 'summary' findings[c] | No | No | Yes |

[a]Current situation; this may change in time. [b]Critical appraisal is not mandatory, however, reviewers may decide to assess and report the risk of bias in scoping reviews. [c]By using statistical meta-analysis (for quantitative effectiveness, or prevalence or incidence, diagnostic accuracy, aetiology or risk, prognostic or psychometric data), or meta-synthesis (experiential or expert opinion data) or both in mixed methods reviews

Munn, Z., Peters, M.D.J., Stern, C. *et al.* Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* **18,** 143 (2018). https://doi.org/10.1186/s12874-018-0611-x
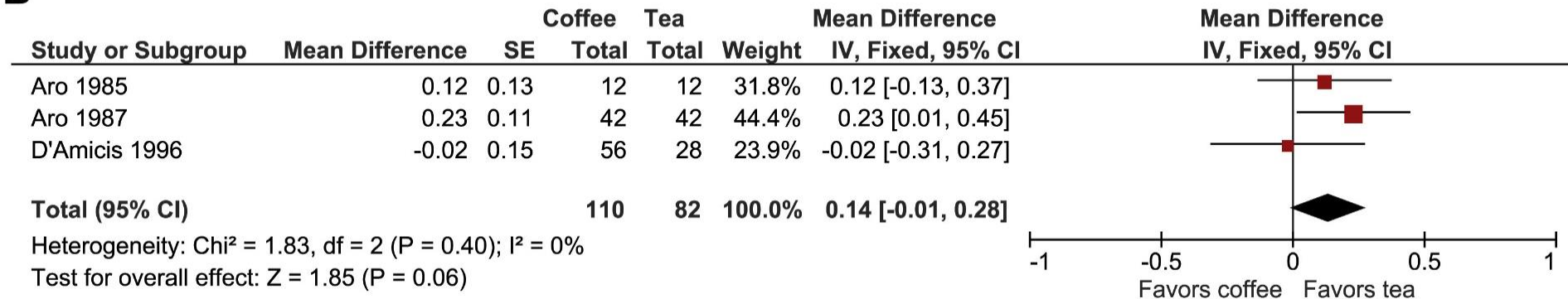
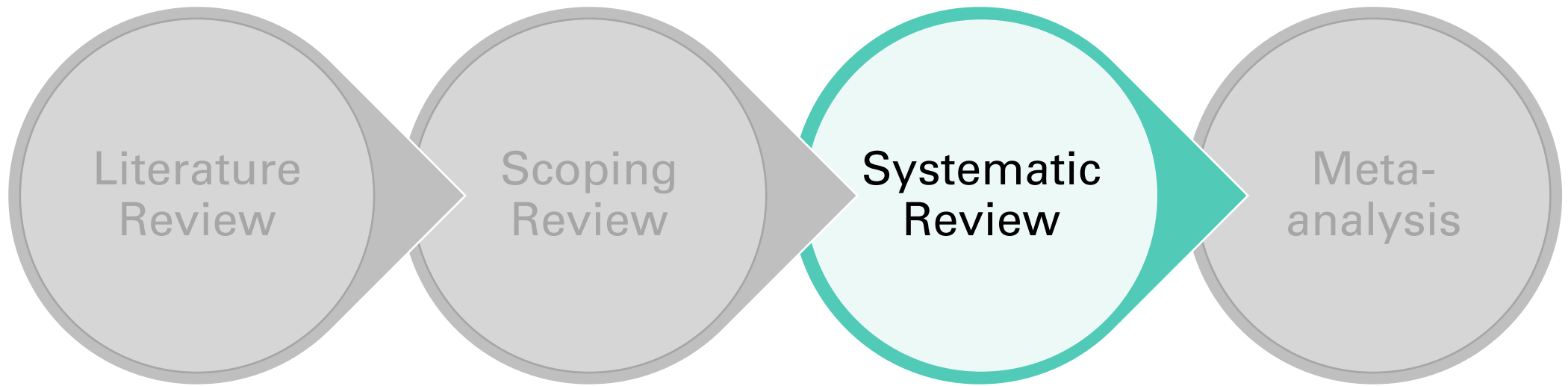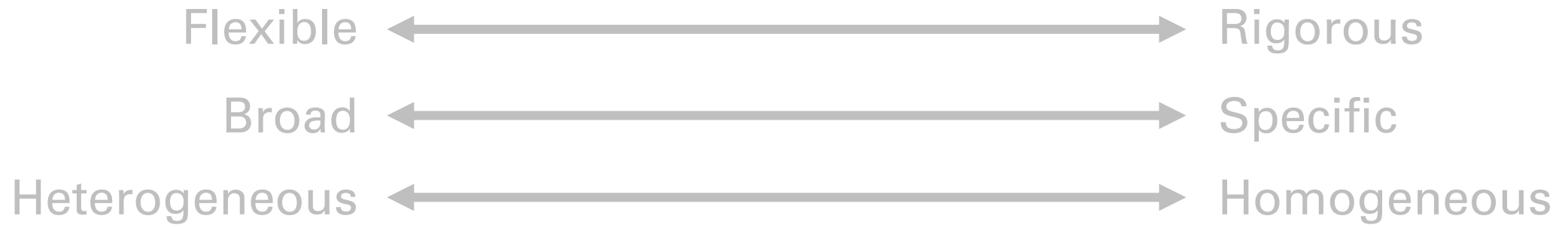| Scoping Review | Systematic Review |
|---|---|
| Research question(s) often broad | Focused research question with narrow parameters |
| Inclusion/exclusion can be developed post hoc | Inclusion/exclusion usually defined at outset |
| Quality not an initial priority | Quality filter often applied |
| May or may not involve data extraction | Detail data extraction |
| Synthesis more qualitative, typically not quantitative | Quantitative synthesis often performed as well as qualitative synthesis, depending on the evidence found |
| Used to identify parameters and gaps in a body of literature | Normally assess the quality of studies and generates a conclusion relating to the focused research question |

Brien, S.E., Lorenzetti, D.L., Lewis, S., Kennedy, J. & Ghali, W.A., 2010, 'Overview of a formal scoping review on health system report cards', *Implementation Science* 5(1), 2. https://doi.org/10.1186/1748-5908-5-2

**A**

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

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

Favors filtered coffee    Favors no coffee

**B**

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

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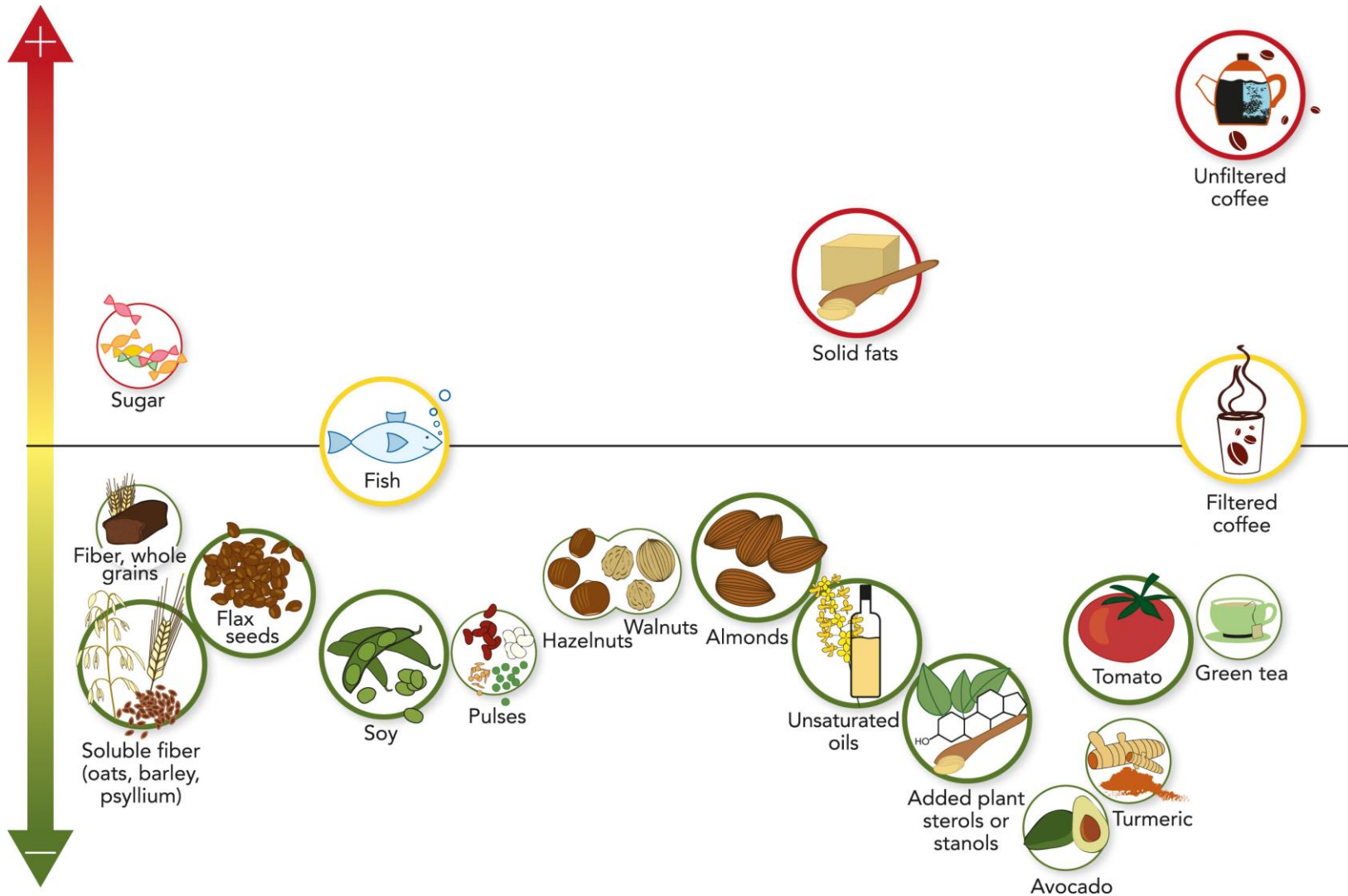Test for overall effect: Z = 1.85 (P = 0.06)

Favors coffee    Favors tea



Schoeneck, M., & Iggman, D. (2021). The effects of foods on LDL cholesterol levels: A systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials. *Nutrition, Metabolism and Cardiovascular Diseases*, 31(5), 1325-1338. https://doi.org/10.1016/j.numecd.2020.12.032

Schoeneck, M., & Iggman, D. (2021). The effects of foods on LDL cholesterol levels: A systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials. *Nutrition, Metabolism and Cardiovascular Diseases*, *31*(5), 1325-1338. https://doi.org/10.1016/j.numecd.2020.12.032

## Guiding Principles/ Standards of Evidence for the Substantiation of Food Health Claim
**(Health Canada, 2011)**

- Systematic approach
- Transparency
- Comprehensiveness
- Human evidence
- High level of certainty
- Demonstration of causality
- Biological relevance of the claimed effect
- Feasibility of consumption of effective dose
- Health claim wording
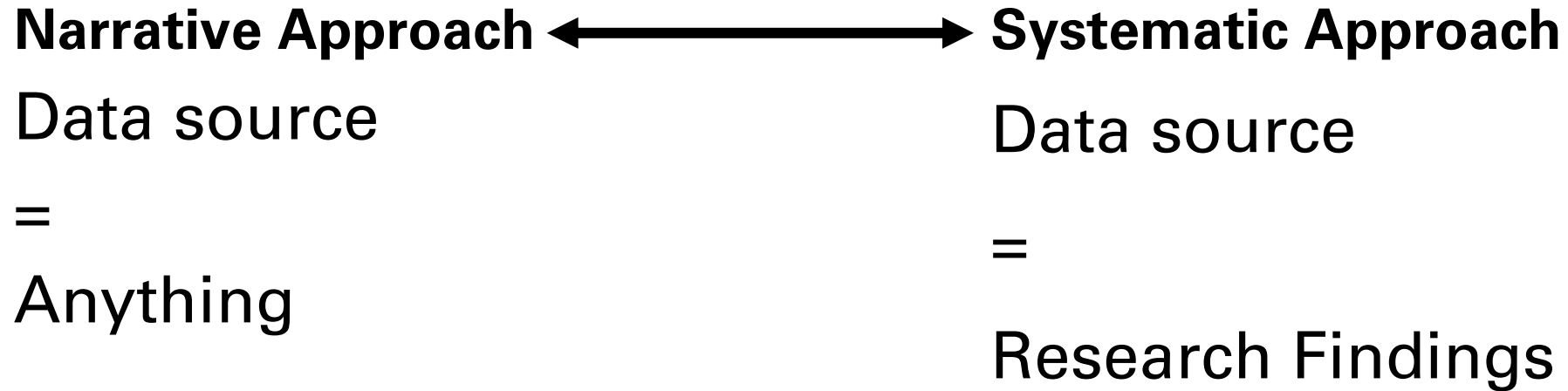
# Literature Review: Objectives

**Narrative Approach** ⟷ **Systematic Approach**

- Describe what is going on

- Explore ideas

- Find alternatives

- Develop hypothesis

- Support/deny an argument

- Explore ideas

- Find alternatives

- Develop hypothesis

- Test theories

- Evaluate effectiveness of solutions

- Do the solutions work better?

- How does it influence outcomes?

# Literature Review: Process
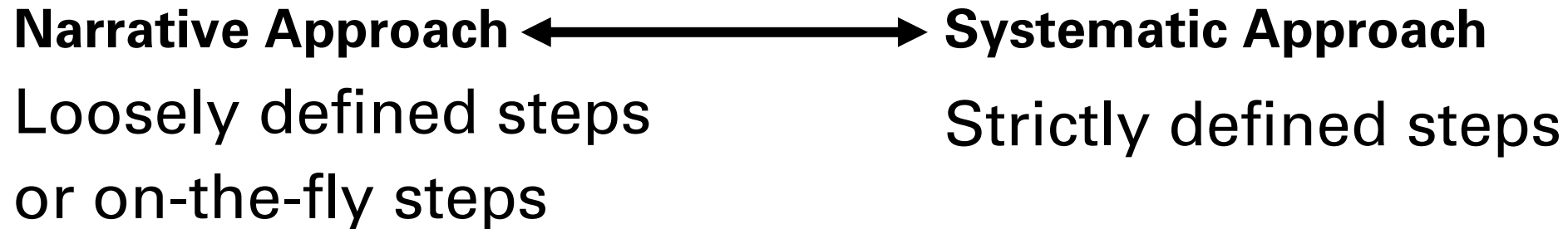
**Narrative Approach** ←————————→ **Systematic Approach**

Loosely defined steps
or on-the-fly steps

Strictly defined steps

# Literature Review: Data sources

**Narrative Approach**

Data source

=

Anything

**Systematic Approach**

Data source

=

Research Findings

# Literature Review: Data sources

**Narrative Approach**  ←——————————→  **Systematic Approach**

Data source

=

Anything

Data source

=

Research Findings

For example, FDA (2009)
- Human interventions
- Observational studies

Animal model studies
Ecology studies

US Food and Drug Administration. (2009). Guidance for industry: evidence-based review system for the scientific evaluation of health claims. *Office of Nutrition Labeling and Dietary Supplements*. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims

# Literature Review: Synthesis

**Narrative Approach** ←————————→ **Systematic Approach**

Synthesis

=

Reorganization

Synthesis

=

Critical appraisals

# Literature Review: Synthesis

**Narrative Approach**

Synthesis

=

Reorganization

**Systematic Approach**

Synthesis

=

Critical appraisals

For example, FDA (2009)
-Certainty of conclusion
-Quality of methodology
-Totality of scientific evidence
-Significant scientific agreement

US Food and Drug Administration. (2009). Guidance for industry: evidence-based review system for the scientific evaluation of health claims. *Office of Nutrition Labeling and Dietary Supplements*. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims

**Systematic review as a research method**

Quantitative method

Mixed method

Qualitative method

Process

Step 0
Does the review
exist?

Follow-up &
Update

Question
Formulation

Framework
Development

Protocol
Development

Searching,
Screening &
Organizing
Data

Data
Extraction

Critical
Appraisal

Synthesis &
Reporting
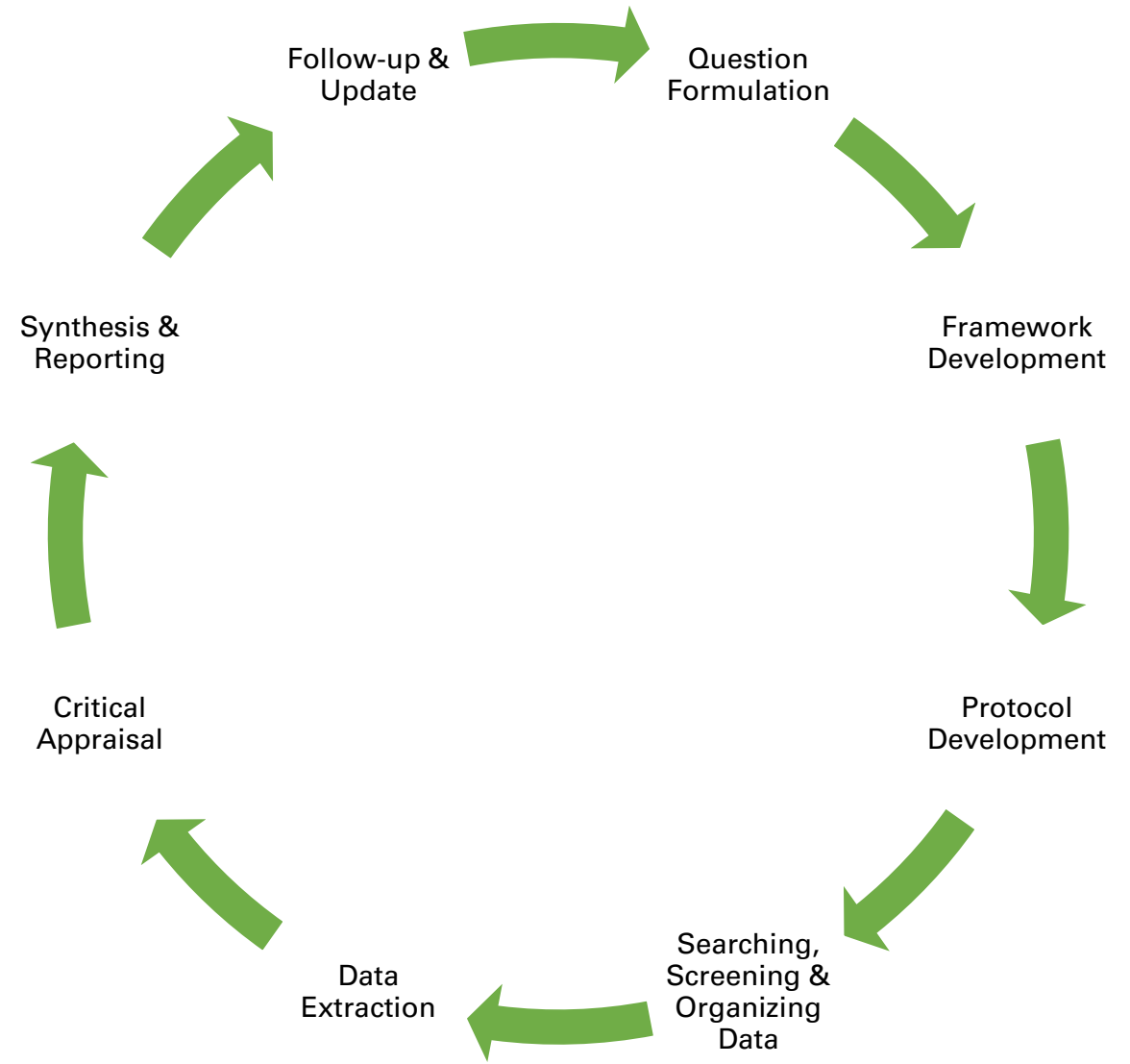
# Overview of reviews

- To summarize evidence from *systematic reviews*

- Describe clinical and methodological inclusion and exclusion criteria. The study design of interest is the *systematic review*

- Comprehensive search for relevant *systematic reviews*

- Assess methodological quality/risk of bias of included *systematic reviews*. Also report risk of bias assessments for primary studies contained within included systematic reviews.

Figure 1. Overview of the process for conducting a systematic review to self-substantiate a food-health relationship

New Zealand Ministry of Primary Industries, Biosecurity Science, Food Science & Risk Assessment Directorate, Regulation and Assurance Branch. (2016). *Systematic review of a food-health relationship*. https://www.mpi.govt.nz/dmsdocument/11263/direct

# Food-health relationship

**Health effect** means an effect on the human body, including an effect on one or more of the following –
(a) a biochemical process or outcome;
(b) a physiological process or outcome;
(c) a functional process or outcome;
(d) growth and development;
(e) physical performance;
(f) mental performance;
(g) a disease, disorder or condition.

New Zealand Ministry of Primary Industries, Biosecurity Science, Food Science & Risk Assessment Directorate, Regulation and Assurance Branch. (2016). *Systematic review of a food-health relationship*. https://www.mpi.govt.nz/dmsdocument/11263/direct

# Food health relationship

**Health claim** (FAO, 2009)

- Nutrient function claims
  "Food X is a source of/high in A."

- Other function claims
  "Food Y contains x grams of substance A."

- Reduction of disease risk claims
  "A healthy diet low in nutrient or substance A may reduce the risk of disease D.
  Food X is low in nutrient or substance A."

# FDA (2009)

- Have the studies specified and measured the substance that is the subject of the claim?
- Have the studies appropriately specified and measured the specific disease or health-related condition that is the subject of the claim?

# FDA (2009)

- Are the studies use appropriate surrogate endpoints of disease risk?

  For example:

  (1) serum low-density lipoprotein (LDL) cholesterol concentration, total serum cholesterol concentration, and blood pressure for cardiovascular disease;
  (2) bone mineral density for osteoporosis;
  (3) adenomatous colon polyps for colon cancer; and
  (4) elevated blood sugar concentrations and insulin resistance for type 2 diabetes.

Process

Follow-up & Update

Question Formulation

Framework Development

Protocol Development

Searching, Screening & Organizing Data

Data Extraction

Critical Appraisal

Synthesis & Reporting

# Question Types

- Etiology/causation/origination/risk factor
- Diagnosis/analytical method/evaluation tool
- Intervention/therapy/solution
- Prevention/prophylaxis
- Prognosis/prediction
- Meaning/interpretation/perception

# Question Elements

**P**    OPULATION/CONDITION

**I**    NTERVENTION

**C**    OMPARISON

**O**    UTCOME
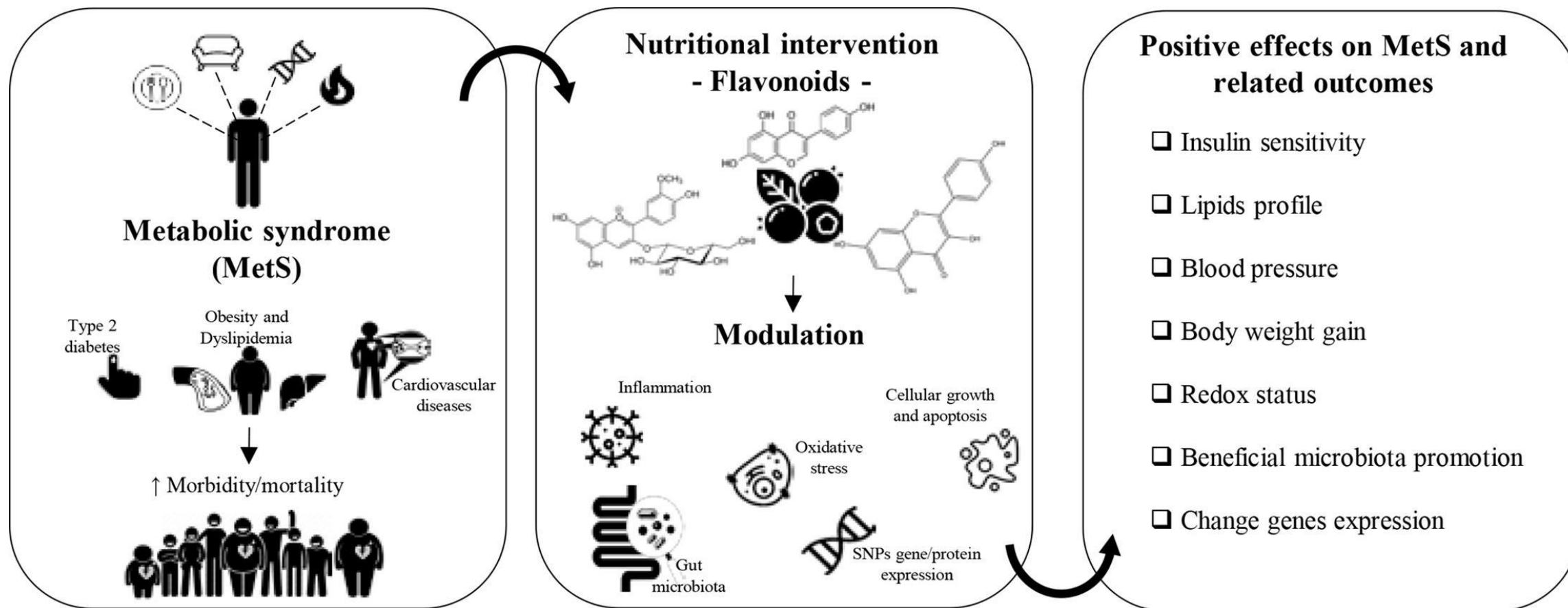
***T***    *IME*

***S***    *STUDY*
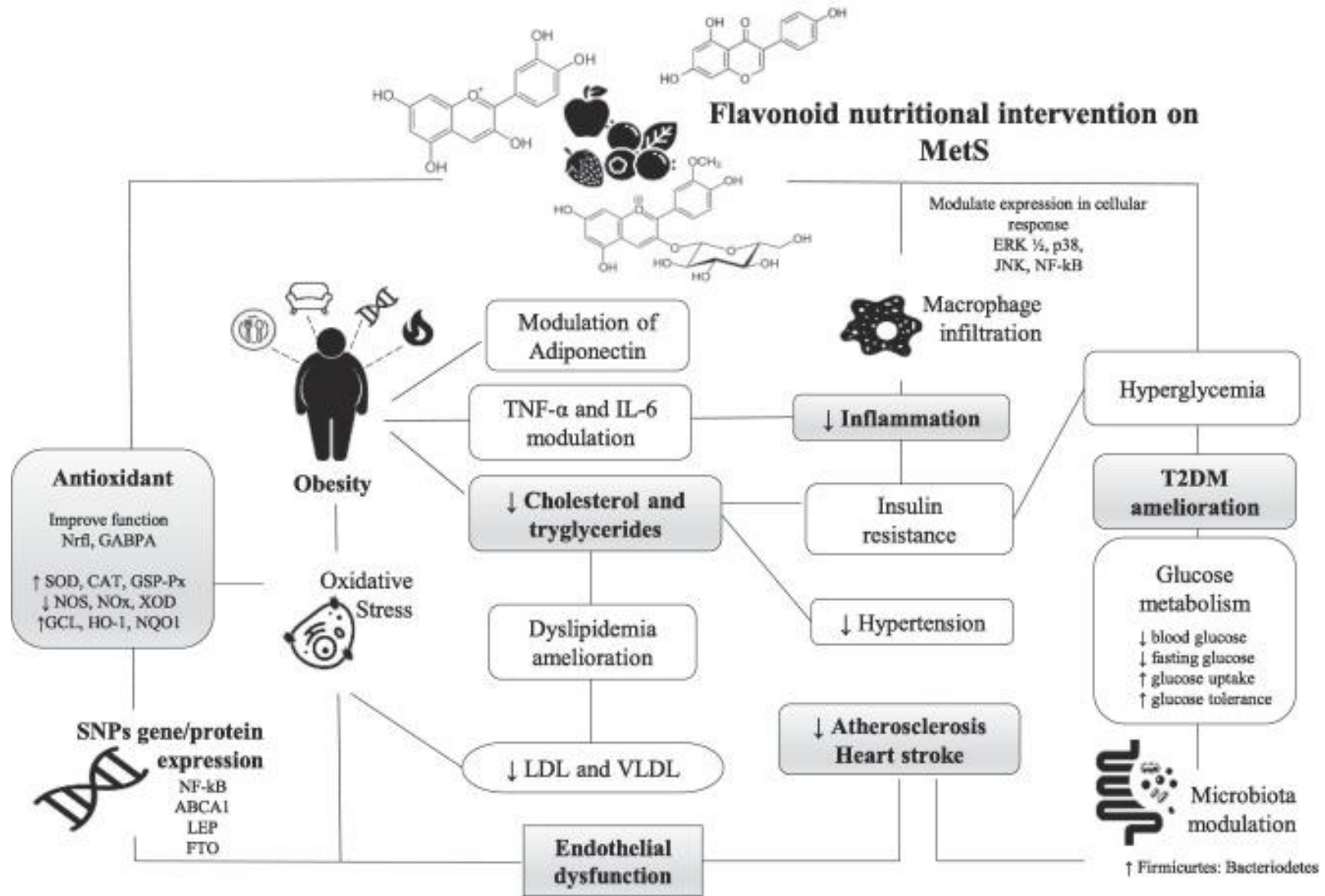
# Templates and Definitions for PICOT Questions[5, 6]

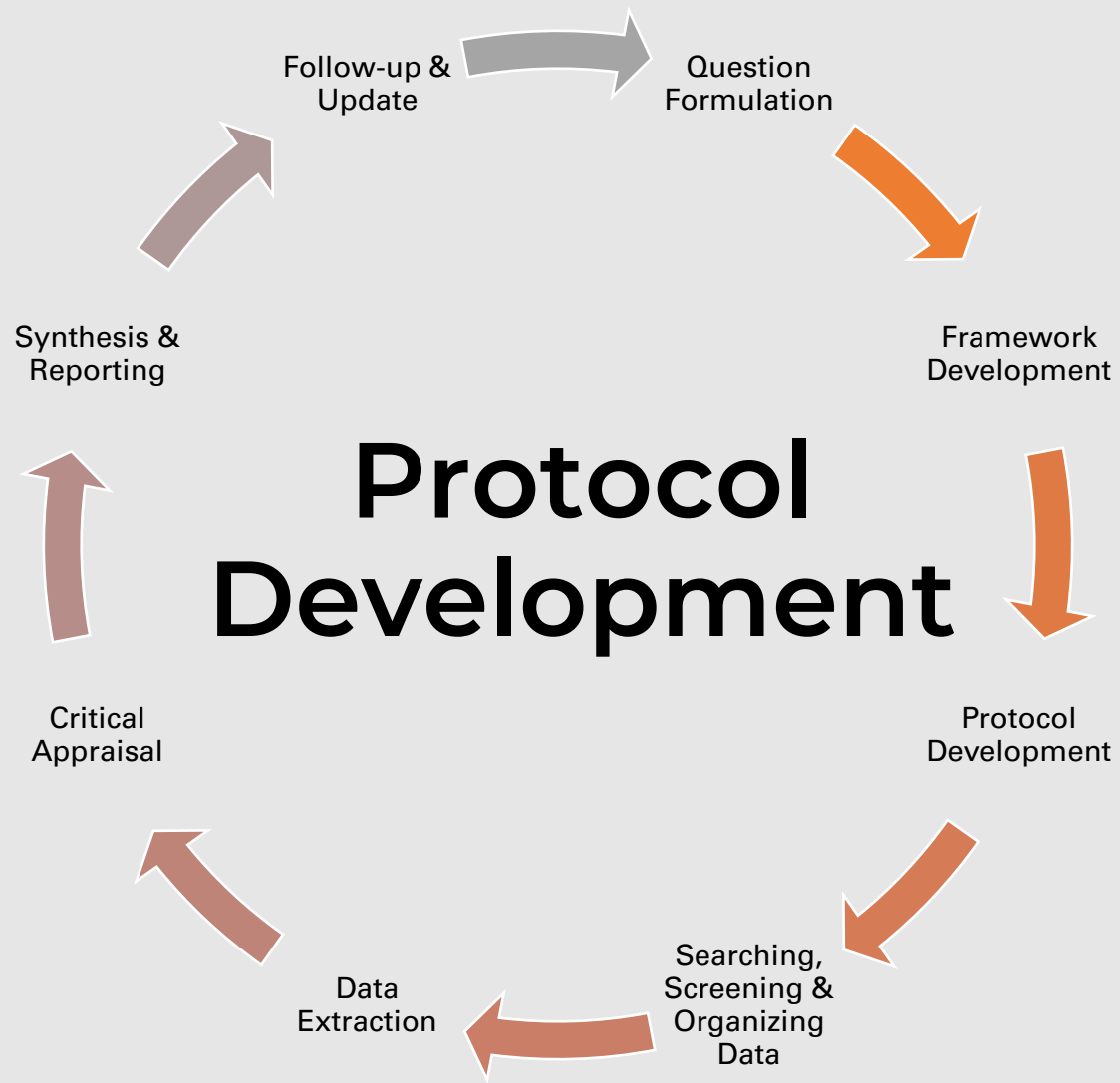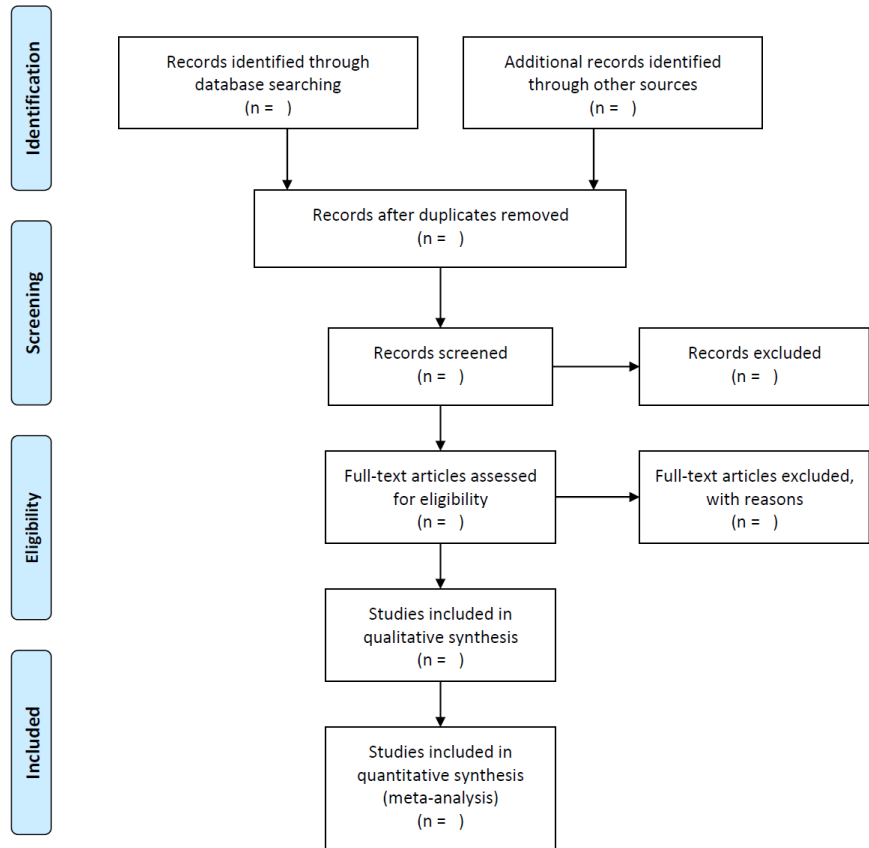| Question type | Definition | Template |
|---|---|---|
| Intervention or therapy | To determine which treatment leads to the best outcome | In _____ (P), how does _____ (I) compared with _____ (C) affect _____ (O) within _____ (T)? |
| Etiology | To determine the greatest risk factors or causes of a condition | Are _____ (P) who have _____ (I), compared with those without _____ (C), at ____ risk for _____ (O) over _____ (T)? |
| Diagnosis or diagnostic test | To determine which test is more accurate and precise in diagnosing a condition | In _____ (P), are/is _____ (I) compared with _____ (C) more accurate in diagnosing _____ (O)? |
| Prognosis or prediction | To determine the clinical course over time and likely complications of a condition | In _____ (P), how does _____ (I) compared with _____ (C), influence _____ (O) over _____ (T)? |
| Meaning | To understand the meaning of an experience for a particular individual, group, or community | How do _____ (P) with _____ (I) perceive _____ (O) during _____ (T)? |

Stillwell, S. B., Fineout-Overholt, E., Melnyk, B. M., & Williamson, K. M. (2010). Evidence-based practice, step by step: asking the clinical question: a key step in evidence-based practice. AJN The American Journal of Nursing,110(3), 58-61.

Neri-Numa, I. A., Cazarin, C. B. B., Ruiz, A. L. T. G., Paulino, B. N., Molina, G., & Pastore, G. M. (2020). Targeting flavonoids on modulation of metabolic syndrome. *Journal of Functional Foods*, *73*, 104132.

**Flavonoid nutritional intervention on MetS**

Modulate expression in cellular response
ERK ½, p38, JNK, NF-kB

Macrophage infiltration

**Antioxidant**

Improve function
Nrf1, GABPA

↑ SOD, CAT, GSP-Px
↓ NOS, NOx, XOD
↑GCL, HO-1, NQO1

Obesity

Oxidative Stress

Modulation of Adiponectin

TNF-α and IL-6 modulation

↓ Cholesterol and tryglycerides

Dyslipidemia amelioration

**SNPs gene/protein expression**

NF-kB
ABCA1
LEP
FTO

↓ LDL and VLDL

↓ Inflammation

Insulin resistance

↓ Hypertension

↓ Atherosclerosis Heart stroke

**Endothelial dysfunction**

Hyperglycemia

**T2DM amelioration**

Glucose metabolism

↓ blood glucose
↓ fasting glucose
↑ glucose uptake
↑ glucose tolerance

Microbiota modulation

↑ Firmicurtes: Bacteriodetes

Neri-Numa, I. A., Cazarin, C. B. B., Ruiz, A. L. T. G., Paulino, B. N., Molina, G., & Pastore, G. M. (2020). Targeting flavonoids on modulation of metabolic syndrome. *Journal of Functional Foods*, *73*, 104132.

**PRISMA 2009 Flow Diagram**

| | |
|---|---|
| Identification | Records identified through database searching (n = ) · Additional records identified through other sources (n = ) |
| Screening | Records after duplicates removed (n = ) → Records screened (n = ) → Records excluded (n = ) |
| Eligibility | Full-text articles assessed for eligibility (n = ) → Full-text articles excluded, with reasons (n = ) |
| Included | Studies included in qualitative synthesis (n = ) → Studies included in quantitative synthesis (meta-analysis) (n = ) |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

# PRISMA
http://www.prisma-statement.org/

Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**A**

Records identified through
database searching
(n = 1498)

Additional records identified through
other sources
(n = 26)

**Screening**

Records screened
(n = 1524)

Records excluded
(n =1324)

**Eligibility**

Full-text articles assessed
for eligibility
(n = 200)

Full-text articles excluded,
with reasons
(n = 92)

- n = 69 not
systematic review
with low risk of
bias
- n= 10 not reported
LDL cholesterol
- n = 7 not food-
specific
- n = 4 newer
version available
- n = 2 not in adults

**Included**

Studies included in
qualitative synthesis
(n = 108)

**B**

**Identification**

Records identified through
database searching
(n = 119)

Additional records identified through
other sources
(n = 4)

**Screening**

Records screened
(n = 123)

Records excluded
(n = 87)

**Eligibility**

Full-text articles assessed
for eligibility
(n = 36)

Full-text articles excluded,
with reasons
(n = 16)

- n= 11 not
reported LDL
cholesterol
- n = 2 not >13
days duration
- n = 2 not RCT
- n = 1 published
abstract only

Studies included in
qualitative synthesis
(n = 20)

**Included**

Studies included in
quantitative synthesis
(meta-analyses)
(n = 19)

# Review criteria

- Eligibility criteria
- Search strategies
- Screening and selection
- Data extraction
- Statistical analysis and treatment of qualitative data
- Critical appraisal

# Eligibility Criteria for Health Claims

- Example

https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidance-document-preparing-submission-food-health-claims-2009-1.html#tbl8b
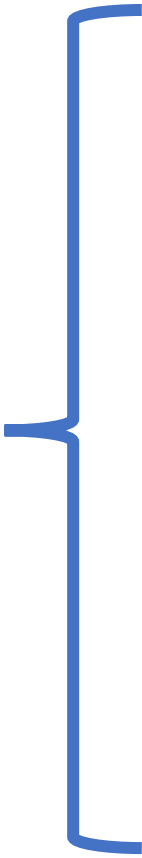
# Principles

- Comprehensiveness
- Transparency
- Strict to the protocol

1. Search strategy
2. Multiple rounds of searching
3. Data management
   - Deduplication
   - Document ID
   - Document storage and retrieval
4. Title/abstract screening
5. Full-text screening

**Search no. 1 (PubMed and Cochrane Database of Systematic Reviews, 4 June 2019):**

Filters: Systematic Reviews; Guideline
Title/Abstract:
Lipidemia* OR Dyslipidemia* OR Hyperlipidemia* OR Cholesterol* OR Lipoprotein*
OR
MeSH Terms:
Dyslipidemias OR Hyperlipidemias OR Cholesterol OR "Cholesterol, LDL" OR
Lipoproteins
AND
Title/Abstract:
Food OR Foods OR Diet OR Diets OR Dietary OR Garlic OR "Allium sativum" OR
Coffee OR Tea OR Chocolate OR Cacao OR Cocoa OR Spinach OR Spinacia OR
Grapefruit* OR "Citrus Paradisi" OR Probiotic* OR Yoghurt OR Yogurt OR Malus OR
Apple* OR Vitis OR Grape OR Grapes OR Wine OR Nut OR Nuts OR "Soy protein" OR
"Soy proteins" OR "Soybean Proteins" OR "Soybean Protein"
OR
MeSH Terms:
Food OR Diet OR Garlic OR Coffee OR Tea OR Chocolate OR Cacao OR "Spinacia
oleracea" OR "Citrus paradisi" OR Probiotics OR Yogurt OR Malus OR Vitis OR
"Soybean Proteins" OR Nuts

**Search no. 2 (PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), 4 June 2019):**

Coffee[Title/Abstract] OR coffee[MeSH Terms]
AND
lipidemia*[Title/Abstract] OR dyslipidemia*[Title/Abstract] OR hyperlipidemia*[Title/Abstract] OR cholesterol*[Title/Abstract] OR lipoprotein*[Title/Abstract] OR dyslipidemias[MeSH Terms]) OR hyperlipidemias[MeSH Terms] OR cholesterol[MeSH Terms] OR cholesterol, LDL[MeSH Terms] OR lipoproteins[MeSH Terms]
AND
randomised controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract]) OR placebo[Title/Abstract] OR clinical trials as topic[MeSH Terms] OR controlled clinical trials as topic[MeSH Terms] OR randomised controlled trials as topic[MeSH Terms] OR randomly[Title/Abstract] OR trial[Title] OR "random allocation"[Title/Abstract]

# Data Filtering

- Title Filter
- Abstract Filter
- Full text Filter

# Process

Identifying data to be extracted → Developing a form → Pilot testing → Extracting data
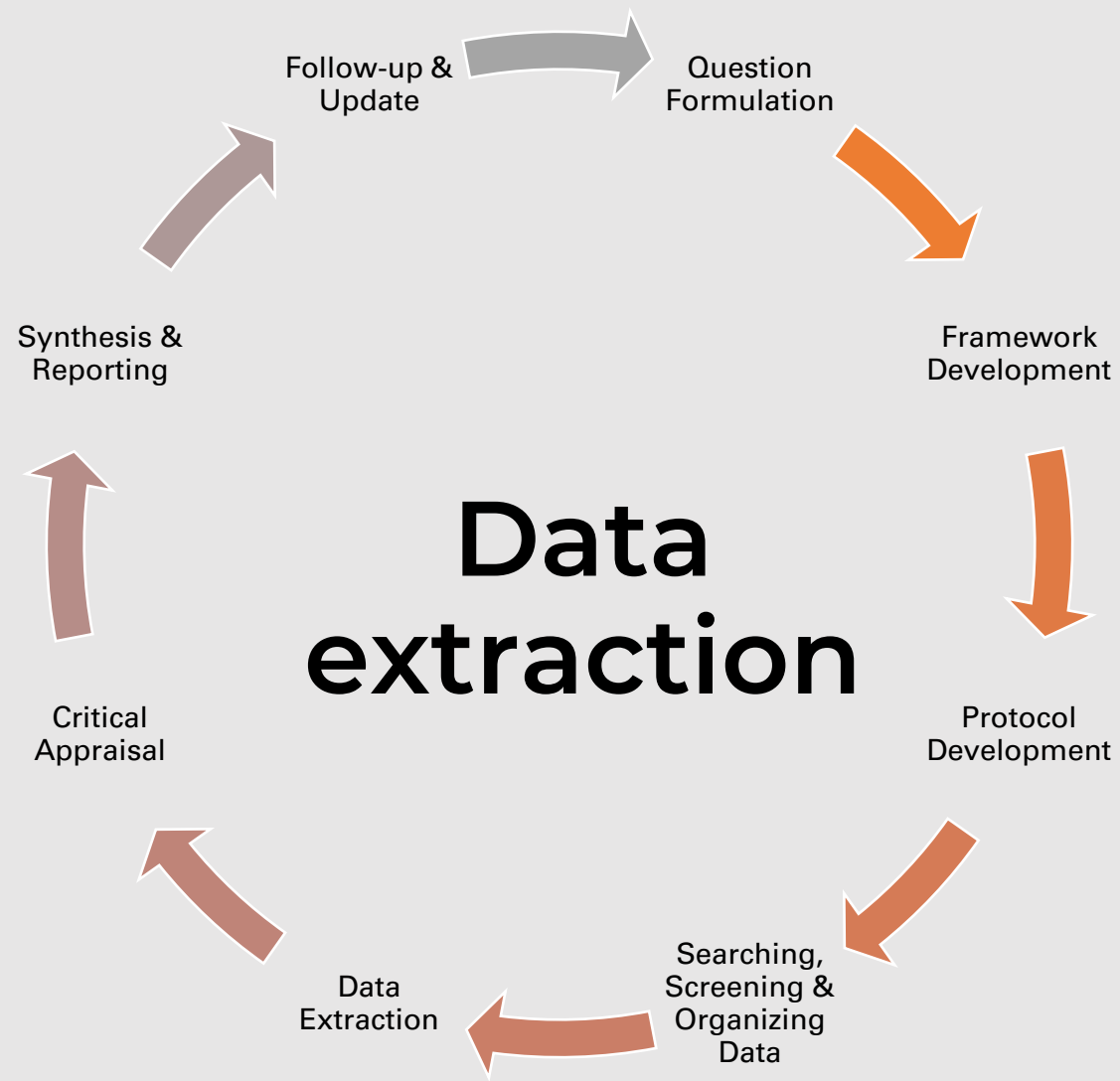
**Food Health Claims Submission Form**
**Food Directorate**

**Formulaire de demande d'approbation d'allégations santé relatives aux aliments**
**Direction des aliments**

**Table 12a.** Summary of intervention studies addressing the food/health relationship (*e.g.*, oats beta glucan fibre and heart disease risk).

| Reference and Quality Rating (Author, year) | Aim of Study | Design • R (Randomized) • NR (Non-randomized) • C (Control group) • SB (Single-blind) • DB (Double-blind) • P (Parallel) • CO (Crossover) | Sample Characteristics • Country • Health status • Setting (metabolic unit, free-living subjects) • Age range • Gender (M, F) • No. recruited • No. randomized • No. in final sample | Exposure and Duration • Food matrix • Food dose; method and frequency of consumption • Duration of intervention • Design and/or duration of stabilization period, washouts, follow-ups | Background Diet & Assessment Tool | Results & Statistics • Changes in health effect • Adverse effects | Relevant Authors' Conclusions |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

# Data extraction

| Article | Study design | Parameters | Results | Remarks |
|---|---|---|---|---|
| ID: #XXX<br>Author: XXX<br>Journal: XXX<br>Year: XXX<br>Affiliation: XXX | Method: XXX<br>Population: XXX<br>Sample size: XX<br>Instrument: XX<br>Study site: XX<br>Validity and reliability testing: XX<br><br>Group:<br>Intervention: XX<br>Control: XX | Demographic:<br>…<br>…<br>…<br><br>Observed variables:<br>Factor A: XX<br>Factor B: XX<br>Factor C: XX | Result A (Unit): XX<br>Result B (Unit): XX<br>Result C (Unit): XX<br><br>Side effects/Harms<br>…<br>…<br>… | ▪ Reasons for incompletion<br>▪ Conflict of interest<br>▪ Conflict of results reported<br>▪ Quality of study (in general) |

# Example

**Intervention Studies**

https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidance-document-preparing-submission-food-health-claims-2009-1.html#tbl13a

**Observational Studies**

https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidance-document-preparing-submission-food-health-claims-2009-1.html#tbl13b
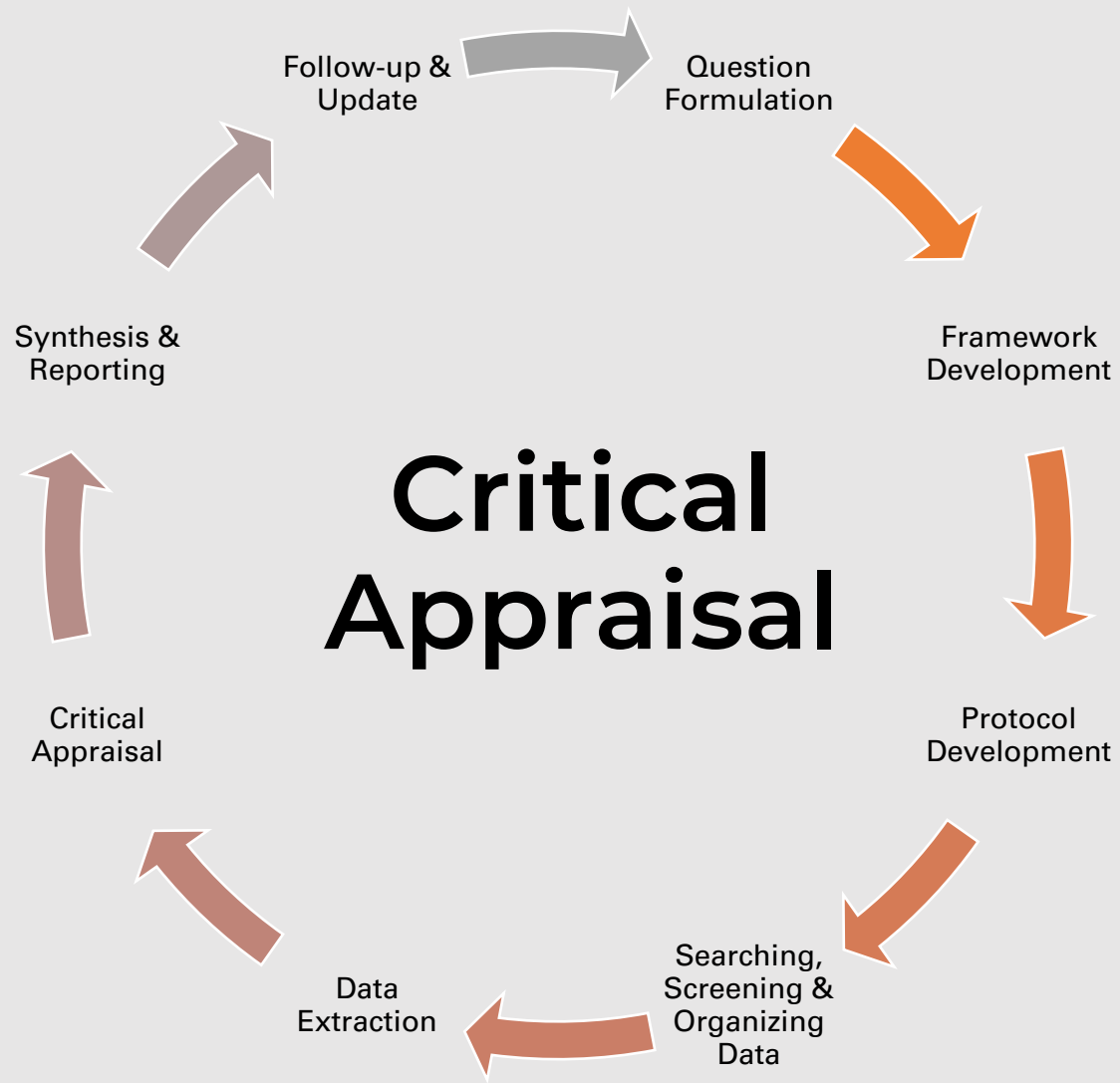
# Critical Appraisal

Evaluation of the quality of evidence
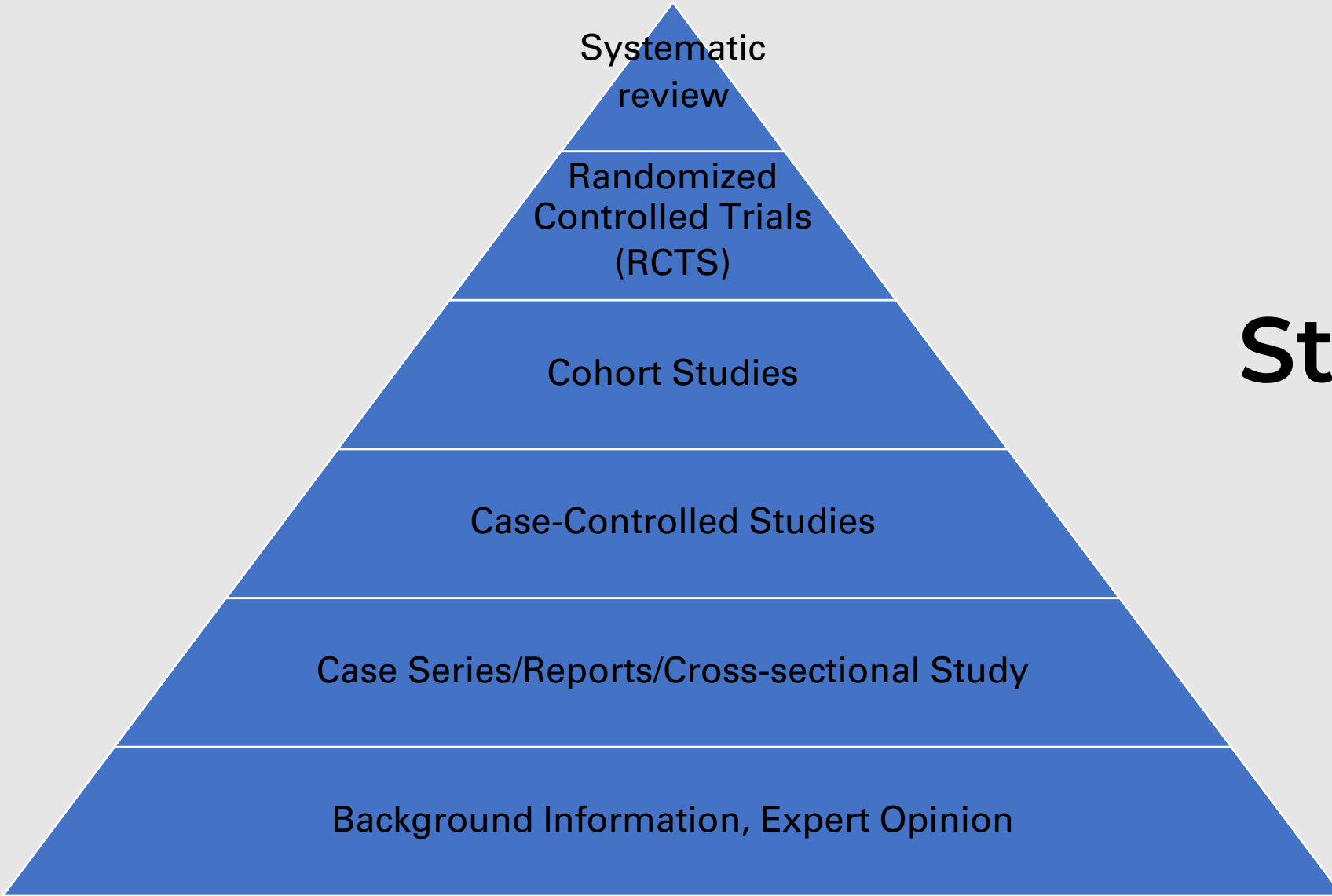
# Example

| Quality of evidence | Study design | Lower if [a] | Higher if [a] |
|---|---|---|---|
| High (4) | Randomized trial | Study limitations<br>– 1 serious<br>– 2 very serious | Large effect<br>+ 1 large<br>+ 2 very large |
| Moderate (3) | | Inconsistency<br>– 1 serious<br>– 2 very serious | Dose response<br>+ 1 evidence of<br>  a gradient |
| Low (2) | Observational study | Indirectness<br>– 1 serious<br>– 2 very serious | All plausible confounding<br>+ 1 would reduce<br>  a demonstrated<br>  effect, or |
| Very low (1) | | Imprecision<br>– 1 serious<br>– 2 very serious | + 2 would suggest<br>  a spurious effect<br>  when results<br>  show no effect |
| | | Publication bias | |

# Example

| Assessment | Type of evidence |
|---|---|
| **Strength of recommendation** | |
| Grade A | Good evidence to support a recommendation for use |
| Grade B | Moderate evidence to support a recommendation for use |
| Grade C | Poor evidence to support a recommendation |
| **Quality of evidence** | |
| Level I | Evidence from at least 1 properly designed randomized, controlled trial |
| Level II | Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments |
| Level III | Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees |

**NOTE.** Adapted from the Canadian Task Force on the Periodic Health Examination [11].

# QUALITY OF EVIDENCE

1. Is the study question relevant?

2. Does the study add anything new?

3. What type of research question is being asked?

4. Was the study design appropriate for the research question?

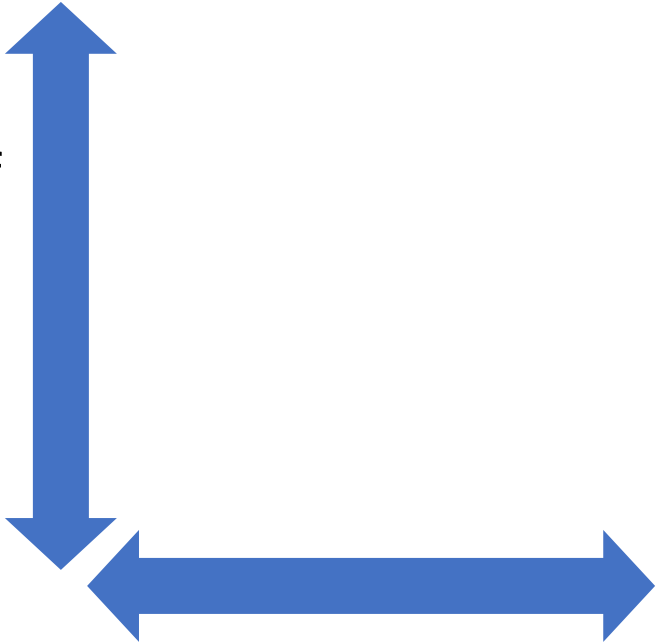5. Did the study methods address the most important potential sources of bias?

# QUALITY OF EVIDENCE

6. Was the study performed according to the original protocol?

7. Does the study test a stated hypothesis?

8. Were the statistical analyses performed correctly?

9. Do the data justify the conclusions?

10. Are there any conflicts of interest?

Young, J. M., & Solomon, M. J. (2009). How to critically appraise an article. *Nature Clinical Practice Gastroenterology & Hepatology, 6*(2), 82-91.

1. Immediate Outcomes
2. Long-term Outcomes
3. Harms

Balance of Benefits to Harms

Strength of Evidence/ Risks of Bias

Systematic review

Randomized Controlled Trials (RCTS)

Cohort Studies

Case-Controlled Studies

Case Series/Reports/Cross-sectional Study

Background Information, Expert Opinion
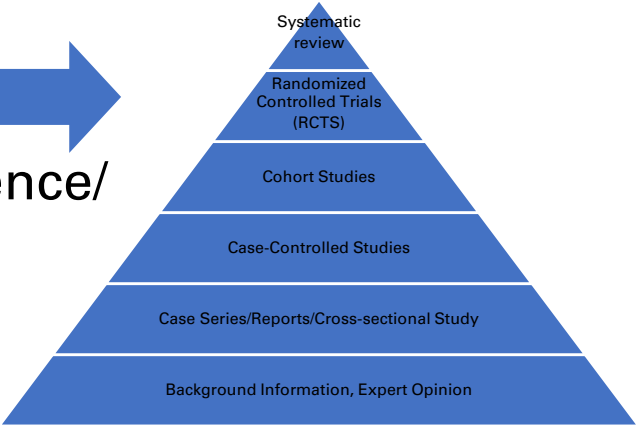
**Table 2** GRADE table for the effects of foods on LDL cholesterol.

| Food | Effect on LDL cholesterol[a] | GRADE evidence |
|---|---|---|
| Foods high in n-6 PUFA and/or MUFA and low in SFA; e.g. canola oil | Moderate to large reduction[b] | High ●●●● |
| Foods high in soluble fiber; e.g. psyllium, oats, and barley | Moderate reduction | High ●●●● |
| Foods with added plant sterols or stanols | Moderate reduction | High ●●●● |
| Flaxseeds (whole) | Small to moderate reduction | High ●●●● |
| Soy protein | Small to moderate reduction | High ●●●● |
| Tomatoes | Small to moderate reduction | High ●●●● |
| Almonds | Small reduction | High ●●●● |
| Fish | No clear effect | High ●●●● |
| Decaffeinated coffee (in place of regular coffee) | No effect | High ●●●● |
| Filtered coffee | No effect | High ●●●● |
| Foods high in SFA or *trans* fatty acids (i.e. solid and tropical fats) | Moderate to large increase[b] | High ●●●● |
| Unfiltered coffee (in place of filtered coffee) | Moderate to large increase | High ●●●● |
| Avocados | Moderate to large reduction | Moderate ●●●○ |
| Turmeric | Moderate to large reduction | Moderate ●●●○ |
| Hazelnuts | Small to moderate reduction | Moderate ●●●○ |
| Pulses | Small to moderate reduction | Moderate ●●●○ |
| Green tea | At least small reduction | Moderate ●●●○ |
| Fiber, whole grains | Small reduction | Moderate ●●●○ |

# Quality of Evidence Grades (GRADE Approach)

| Grade | Definition |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very Low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

# Factors that can reduce the quality of the evidence

| Factor | Consequence |
|---|---|
| Limitations in study design or execution (risk of bias) | ↓ 1 or 2 levels |
| Inconsistency of results | ↓ 1 or 2 levels |
| Indirectness of evidence | ↓ 1 or 2 levels |
| Imprecision | ↓ 1 or 2 levels |
| Publication bias | ↓ 1 or 2 levels |

# Factors that can increase the quality of the evidence

| Factor | Consequence |
|---|---|
| Large magnitude of effect | ↑ 1 or 2 levels |
| All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed | ↑ 1 level |
| Dose-response gradient | ↑ 1 level |

# Synthesis

RCT & Meta-analysis

Qualitative

**PRISMA**

**ENTREQ**

Preferred Reporting
Items for Systematic
Reviews and Meta-
Analyses

Enhancing
transparency in
reporting the
synthesis of
qualitative research

http://www.prisma-statement.org/

https://dx.doi.org/10.1186/1471-2288-12-181
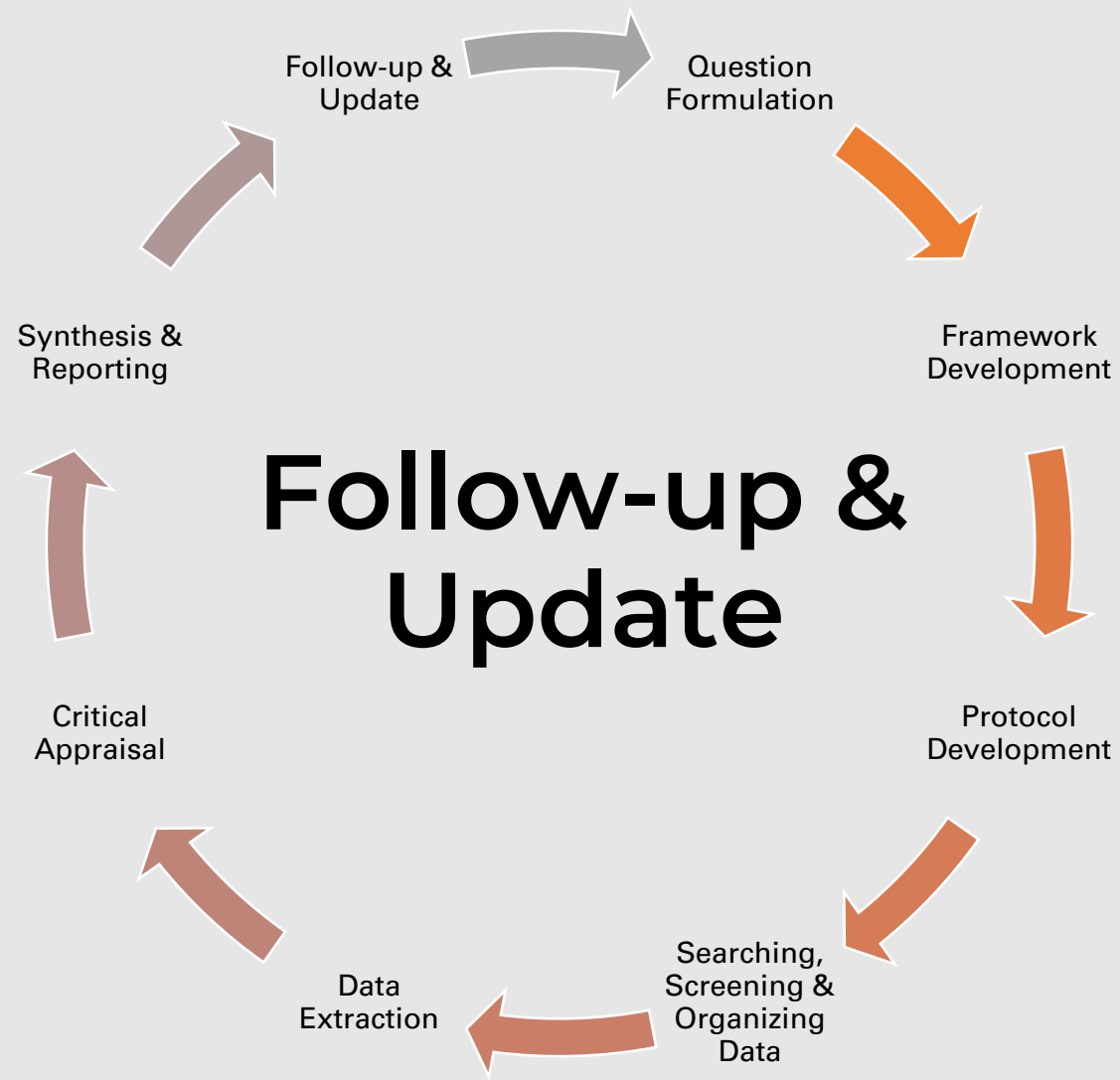
# Follow-up & update

Update search results

Reconsider research questions

Reconsider analytical frameworks

# Tools

**Systematic Review Toolbox**

http://systematicreviewtools.com

**Covidence**

https://www.covidence.org/home

**EPPI-Reviewer**

http://eppi.ioe.ac.uk/CMS/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4&

**DistillerSR**

http://distillercer.com/products/distillersr-systematic-review-software/

**SUMARI**

https://www.jbisumari.org/

**Sysrev**

https://sysrev.com/

**Abstrackr**

http://abstrackr.cebm.brown.edu/

**Rayyan**

https://rayyan.qcri.org/welcome

# Critiques of systematic review

Time consuming

Laborious

Resource burden

Time-sensitive