Health Canada Santé Canada

Canada

From Science to Policy: Evaluating Nutrition Evidence for Informed Decision-Making

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Workshop on the Use of Meta-analysis in Nutrition Research and Policy: Interpretation and Application of Meta-analyses to evaluate the Totality of Evidence
National Academies Sciences Engineering and Medicine

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Disclosures and acknowledgments

My disclosures

- Core member of the NUQUEST Working Group that developed risk of bias assessment tools for nutrition studies

Acknowledgements

- I developed this presentation using published references (cited) and unpublished data
- Dr. Amanda MacFarlane for reviewing the presentation and providing slides

Outline

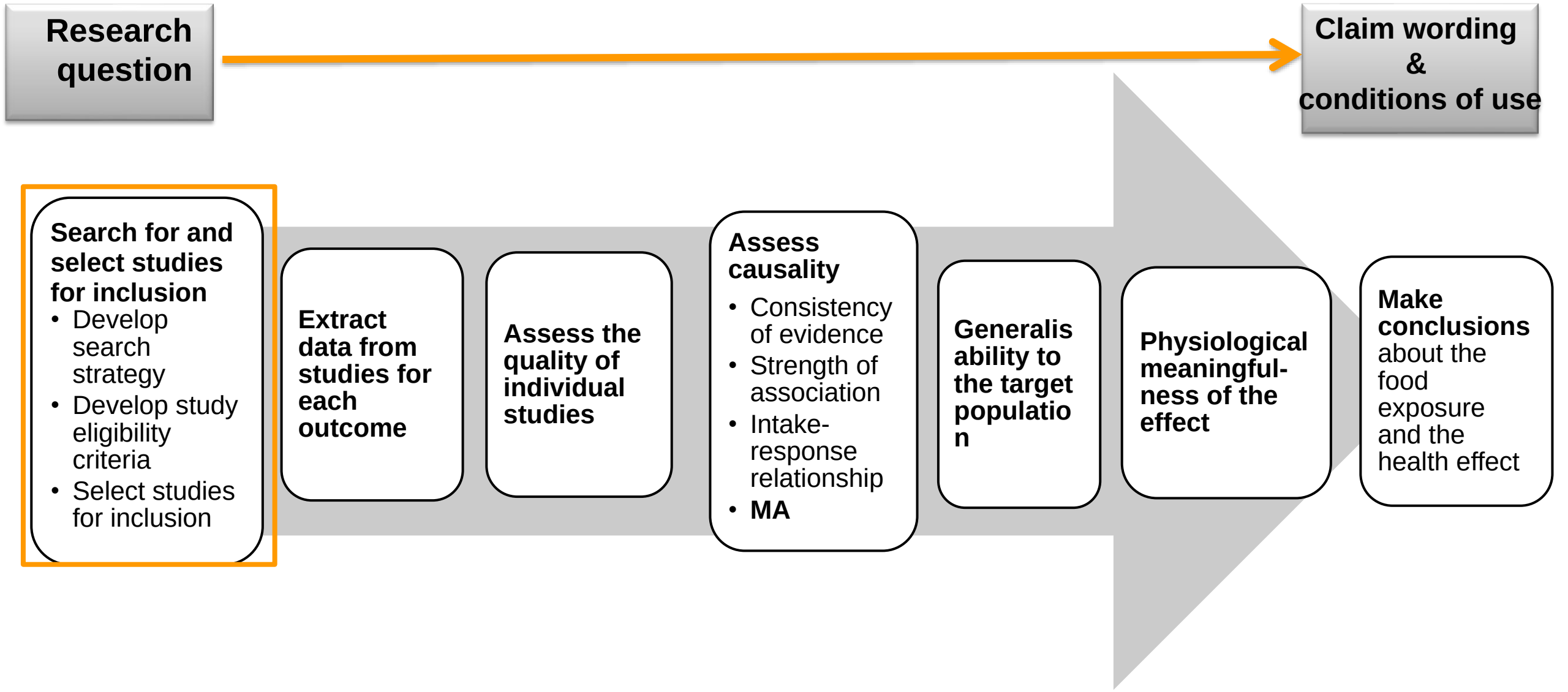
- Use of systematic reviews and meta-analyses for heath claims substantiation
  - Impact publication bias, heterogeneity and risk of bias on interpretation of results
  - Evaluating the totality of the evidence
- Other examples of application of meta-analysis in nutrition policy

Health Canada's Guidance for health claims substantiation

- A health claim is any representation in labelling or advertising that states, suggests, or implies that a relationship exists between consumption of a food or an ingredient in the food and a person's health.
  - Example: "A healthy diet low in saturated and trans-fat may reduce the risk of heart disease".

Guidance	Description
Guidance Document for Preparing a Submission for Food Health Claims	▪ Systematic review of the evidence with or without meta-analysis
Guidance Document for Preparing a Submission for Food Health Claims Using an Existing Systematic Review	▪ Eligible SR/MA types and regulatory or scientific organization specified
Questions and Answers about Preparing Submissions for Food Health Claims	▪ Addresses the most frequently asked questions

Systematic approach for health claims substantiation

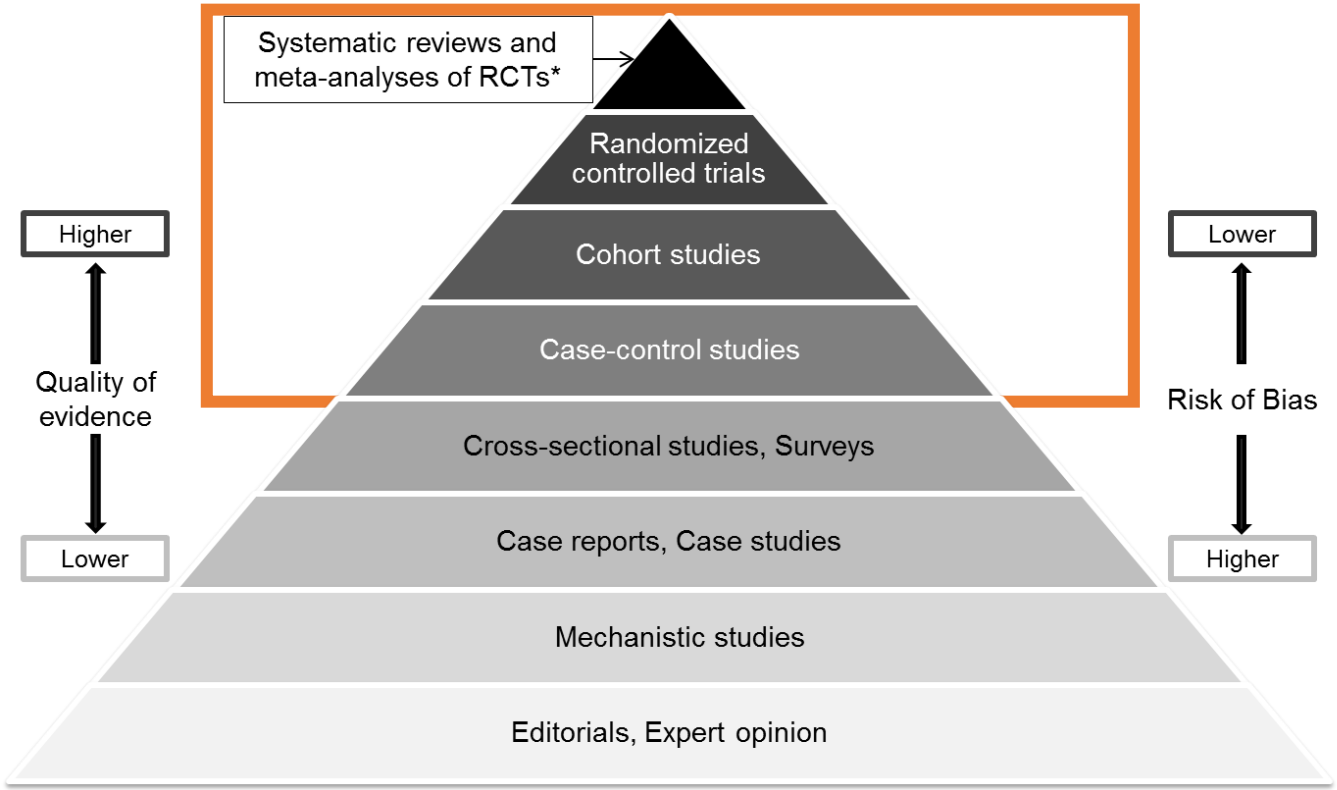


Health Canada (2009) Guidance Document for Preparing a Submission for Food Health Claims

Evidence requirements for health claims substantiation

Types of study designs included

- Intervention studies & meta-analysis
  - Establish causality
  - Intake-response
- Prospective observational studies (cohort and case-control studies)
  - Associations only
  - Confounding and selection bias
  - Self-reported intake



Yetley E.A., A.J. MacFarlane, L.S. Green-Finestone, B.G. Garza, et al. **Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: Report from a Joint US/Canadian-sponsored working group**. Am J Clin Nutr 105(1): 249S-285S. 2017.

Publication bias: impact of missing studies

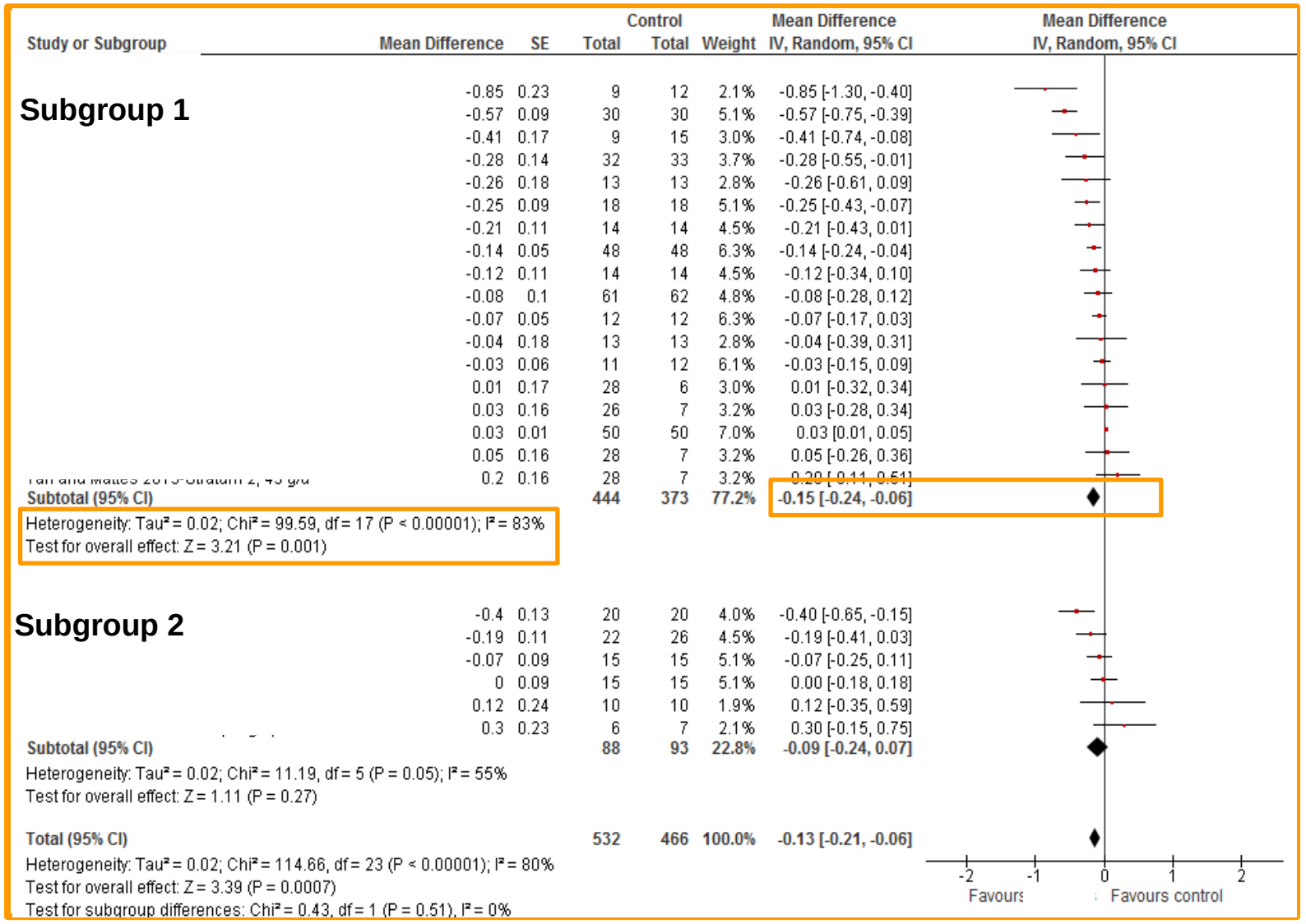
- Not unique to meta-analyses
- MA more likely to include studies with significant results or with large effects
- Various sources….
  - Relying only on electronic searches or not searching relevant databases
  - Not searching/excluding the grey literature sources and unpublished reports (e.g., proprietary data)
  - Limiting language…

- Is our set of studies biased?

AND

- What is the impact of the bias for decision making?

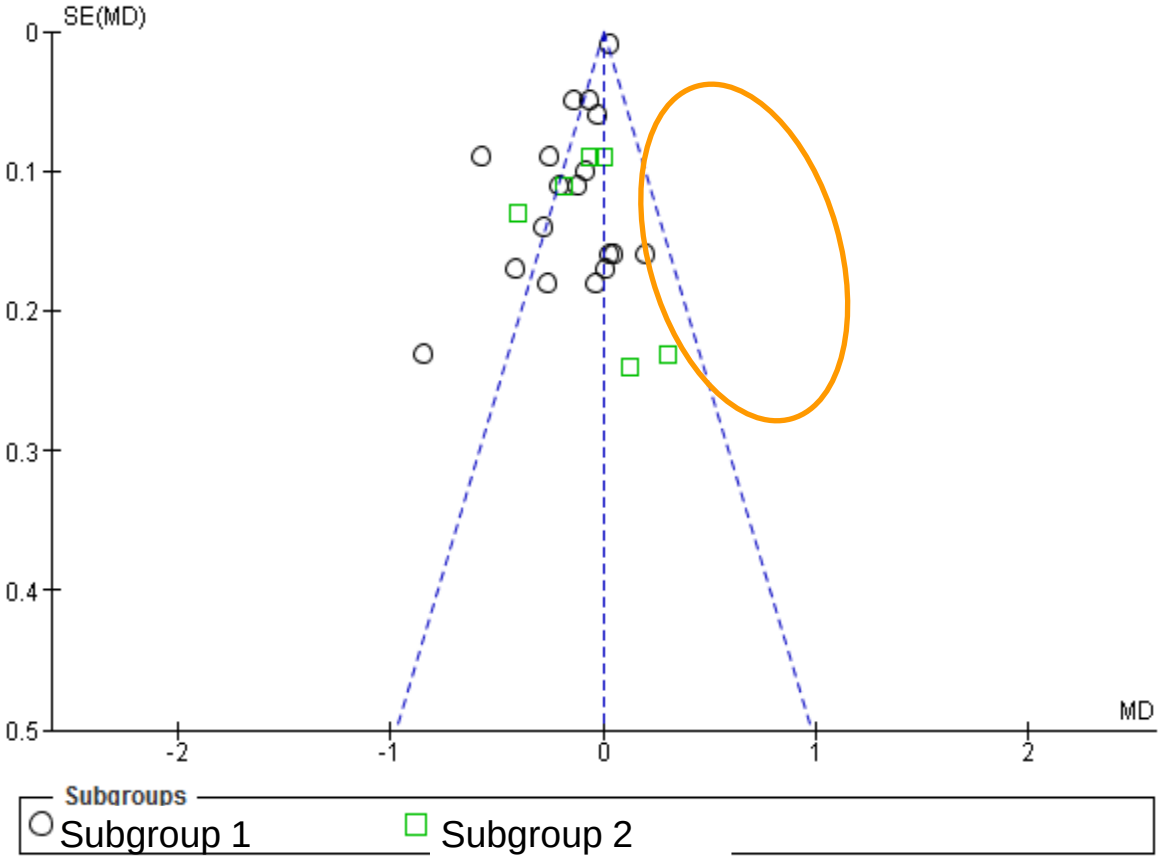
Publication bias: impact of missing studies (cont.)



Forest plot: Effects on LDL-C from RCTs (unpublished)

Is there evidence for missing studies?

Publication bias: impact of missing studies (cont.)



- Visual inspection of the funnel plot
- Methods exist for assessing/ estimating the effect size in the absence of bias
  - Some methods perform poorly in presence of heterogeneity

What is the impact of adjusted estimates on the interpretation of the results of the MA?

Impact of heterogeneity on conclusions

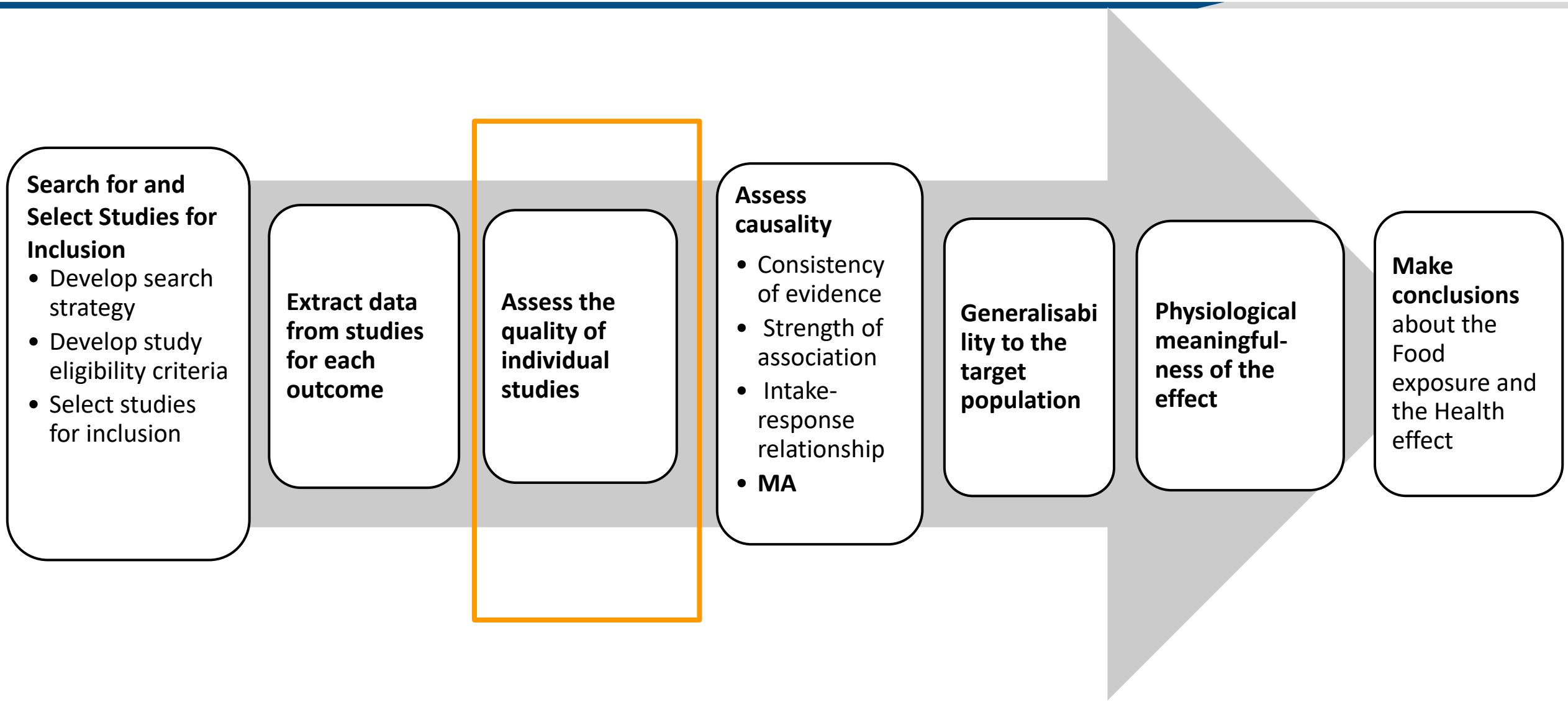
- Explored heterogeneity using sensitivity and subgroup analyses:
  - Influential studies
  - Baseline status
  - Gender
  - Intake
  - Study quality
  - Duration of intervention
  - Type of comparator

Question asked by sponsor:

- How do you consider statistical heterogeneity (e.g., I2) when evaluating diet and disease relationships? Are higher (substantial or considerable) levels of unexplained statistical heterogeneity acceptable for the field of nutrition?

Interpreting publication bias involves a combination of visual inspection, statistical tests, sensitivity analysis, and expert judgment.

Systematic approach for health claims substantiation



Health Canada (2009) Guidance Document for Preparing a Submission for Food Health Claims

Importance of assessing quality/Risk of Bias in nutrition studies

- Bias can lead to over-or underestimation of the effect
- Observational studies are particularly vulnerable to random and non-random intake errors
- Nutritional intake/exposure assessment can add major uncertainty to judgements
  - Intake/exposure
  - Intake–health relationships
- Different methods for assessing intake/exposure have different strengths and weaknesses
  - Impact interpretation and application, and must be considered in SR/MA

- Most Risk of Bias or quality assessment tools do not address issues specific to nutrition
- Some are adapted for nutrition studies

Bias domains in nutrition studies

Performance bias	Systematic differences between groups in the care provided or exposure to factors other than the interventions/exposure of interest.
Attrition bias	Systematic differences between groups in withdrawals from the study.
Detection bias	Systematic differences between groups in how exposure/status and outcomes are determined.
Selection bias	Systematic differences between groups on baseline characteristics.
Dietary exposure assessment bias	Error associated with the use of methodologies for assessing dietary intakes. A subcategory for self-reporting methodologies is **recall bias**, which refers to systematic error due to differences in completeness or accuracy of recall. Self-reported dietary intakes are at risk of this bias.
Misclassification bias	Systematic error due to inaccurate measurements or classifications of participants' exposure or outcome; error may be related to the risk of outcome. If the error is unrelated to the risk of outcome, the effect is usually biased to the null.

Kelly SE, Greene-Finestone LS, Yetley EA, Benkhedda K, Brooks SPJ, Wells GA, MacFarlane AJ. **NUQUEST—NUtrition QUality Evaluation Strengthening Tools: development of tools for the evaluation of risk of bias in nutrition studies**. The American Journal of Clinical Nutrition, Volume 115, Issue 1, January 2022, Pages 256–271.

Health Canada's quality appraisal tools

Table 13a. Quality appraisal tool for intervention studies

Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".

Reference (Author, year):			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?		
2. Group Allocation[1]	Was the study described as randomized?		
	Was the randomization method reported?		
	Was the randomization method appropriate?[2]		
	Was allocation concealed?[3]		
3. Blinding	Were the study subjects blinded to the intervention received?		
	Were the research personnel blinded to the intervention received by the subjects?		
4. Attrition	Was attrition numerically reported?		
	Were the reasons for withdrawals and dropouts provided?[4]		
5. Exposure/ Intervention	Was the type of food described (e.g., composition, matrix)?		
	Was the amount of food described (i.e., dose)?		
6. Health Effect	Was the methodology used to measure the health effect reported?		
7. Statistical Analysis	Was a between-group statistical analysis of the health effect conducted (*i.e.*, control vs. intervention)?		
	Was an intention-to-treat analysis conducted?[5]		
8. Potential Confounders	Were potential confounders of the food/health relationship considered?[6]		
TOTAL SCORE (maximum of 15):			
Higher quality (Score ≥ 8)		☐	
Lower quality (Score ≤ 7)		☐	

Table 13b. Quality appraisal tool for prospective observational studies

Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".

Reference (Author, year):			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?		
2. Attrition	Was attrition numerically reported?		
	Were the reasons for withdrawals and dropouts provided?[1]		
3. Exposure	Was the methodology used to measure the exposure reported?		
	Was the exposure assessed more than once?		
4. Health Outcome	Was the methodology used to measure the health outcome reported?		
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?		
5. Blinding	Were the outcome assessors blinded to the exposure status?		
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		
7. Statistical Analysis	Was the statistical significance of the trend reported?		
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]		
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]		
TOTAL SCORE (maximum of 12):			
Higher quality (Score ≥ 7)		☐	
Lower quality (Score ≤ 6)		☐	

Health Canada (2009) Guidance Document for Preparing a Submission for Food Health Claims

Documenting methods of assessmnent- Worksheet

Example: Relationship between sodium intakes and blood pressure.

Key Research Question	Among all adults, what is the relationship (benefits and harms) between dietary sodium intake and blood pressure?

Example: Relationship between sodium intakes and blood pressure.

Participants/Population	All adults excluding persons with end stage renal disease, heart failure, HIV, or cancer.
Intervention/Exposure	Interventions to reduce dietary sodium (e.g., lower sodium diet or salt substitute).
Comparator	Higher dietary sodium intakes (e.g., usual diet) vs. lower sodium intakes (e.g., dietary salt reductions or use of salt substitutes).
Outcome(s)	Blood pressure (e.g., systolic and/or diastolic blood pressure, percent participants meeting a blood pressure goal, or changes in blood pressure).

Example: Usual Sodium Intake.

Research objectives	Method of assessment	Risk of Bias[1]
Determining difference between 2 points in time or between 2 groups	One or more 24 hr urine collections with quality control on whole sample at each point in time	Low
	One or more 24 hr urine collections without quality control on whole sample at each point in time	Moderate
	One or more 24 hr diet recalls on whole sample at each point in time	Moderate
	FFQ on whole sample at each point in time.	High
Determining change between 2 points in time or between 2 groups over time, in proportion of individuals above/below some threshold	Multiple 24 hr urine collections with quality control on whole sample at each point in time	Low
	Multiple 24 hr urine collections without quality control on whole sample at each point in time	Moderate
	Multiple 24 hr diet recalls on whole sample at each point in time	Moderate
	Single 24 hr recall on whole sample plus repeat on large subsample	Moderate
	FFQ or single 24 hr recall without repeat subsample	High
Examining the association between diet as an independent variable and a dependent variable (outcome)	Multiple 24 hr urine collections with quality control on whole sample at each point in time	Low
	Multiple 24 hr diet recalls on whole sample at each point in time	Moderate
	Single 24 hr recall on whole sample plus repeat on large subsample	Moderate

Example: Blood pressure measurements.

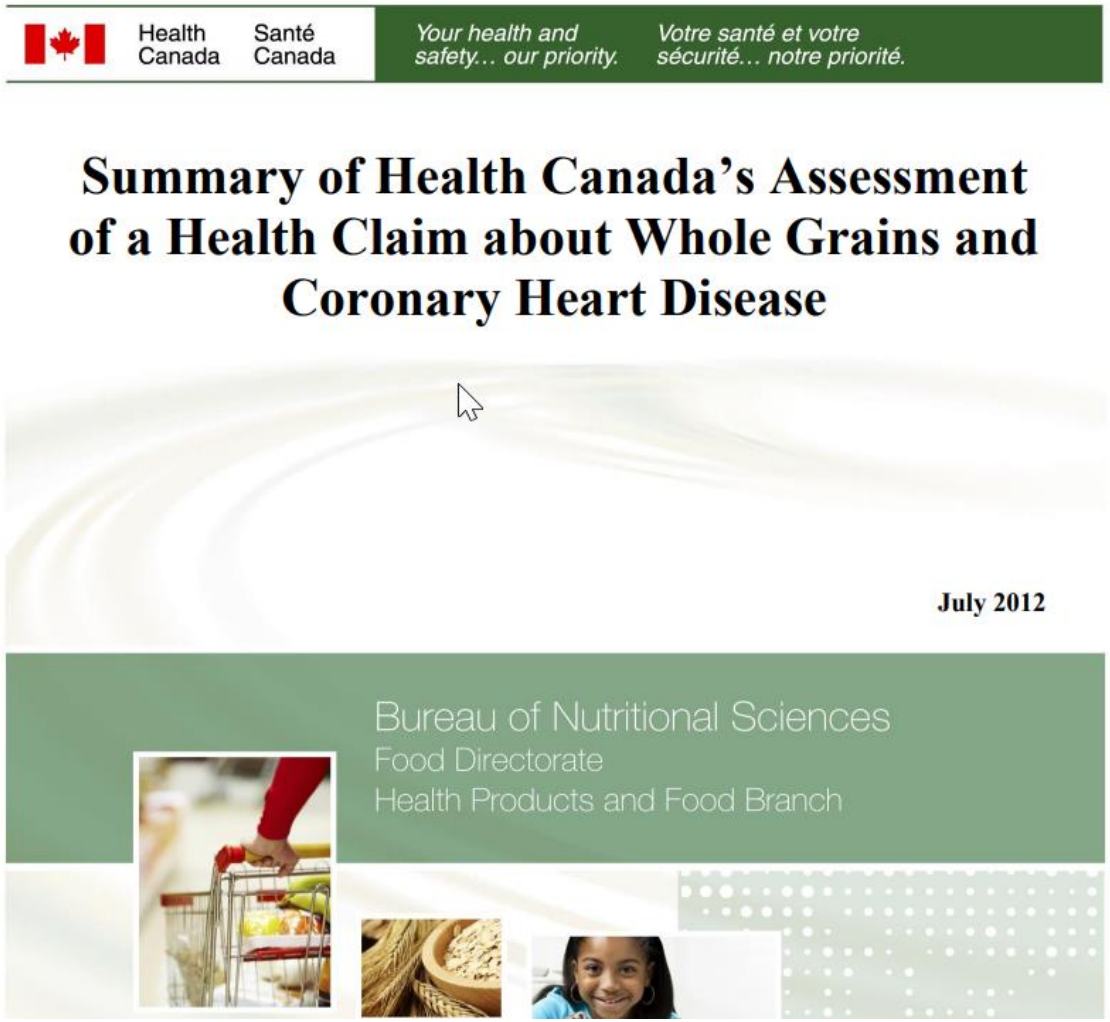
Research objectives	Method of assessment	Risk of Bias[1]
Systolic and diastolic blood pressure for classification of individuals	Multiple day, 3-repeat measure by trained personnel in clinic setting according to accepted and referenced guidelines.	Low
	Multiple day, 3-repeat measure at home with a validated automated sphygmomanometer with accepted guidelines (4).	Moderate
	Single measure at home with an automated sphygmomanometer without training or guidelines (5).	High

Example: Confounders related to the relationship between sodium intakes and blood pressure.

Key confounders	Method of assessment	Risk of Bias[1]
Sex	Self-reported	Low
Age	Birth certificate (documented)	Low
Use of blood pressure medication	Self-reported	Moderate
Changes in sodium intakes unrelated to the intervention	Dietary assessment method conducted more than once during study (see Table 1 on intake/exposure methods)	Low to High
Pre-existing medical conditions (e.g., hypertension, conditions that affect the relationship between intakes and outcome)	Self-reported	Moderate
Potassium intake	Dietary assessment method conducted more than once during study (see Table 1 on intake/exposure methods)	Low to High
Physical activity	Self-reported	High
Physical activity	Activity monitor	Moderate

Kelly SE, Greene-Finestone LS, Yetley EA, Benkhedda K, Brooks SPJ, Wells GA, MacFarlane AJ. **NUQUEST—NUtrition QUality Evaluation Strengthening Tools: development of tools for the evaluation of risk of bias in nutrition studies**. The American Journal of Clinical Nutrition, Volume 115, Issue 1, January 2022, Pages 256–271.

Evaluating the evidence: whole grains and coronary heart disease



Objectives:
To determine whether or not the evidence from intervention and prospective cohort studies supports a health claim about whole grains and CHD risk in generally healthy populations.

Population	Adults, excluding persons with diabetes mellitus or coronary artery disease
Intervention exposure	Whole grain foods, or diets high in whole grain foods
Comparator	Foods or diets low in whole grains
Outcomes	**Primary:** CHD mortality and incidence, change in CHD risk biomarkers (blood pressure, total blood cholesterol, and blood LDL cholesterol)

Types of study designs:
- RCTs: 26 (17 parallel, 9 cross over design)
- Prospective cohorts: 6

Sensitivity analysis- impact of study quality

Analysis description	Subgroup	# studies in analysis	# trial arms	# participants	Mean difference mmol/L (95% CI)	p-value
Overall	Parallel	11	15	1142	-0.12 (-0.20, -0.03)	0.008
	Crossover	6	8	285	-0.20 (-0.36, -0.04)	0.02
Lower quality/high risk of bias removed studies	Parallel	10	14	1099	-0.11 (-0.20, -0.01)	0.03
	Crossover	4	6	215	-0.13 (-0.31, 0.06)	0.17

LDL cholesterol-intervention studies

Analysis description	Subgroup	# studies in analysis	# trial arms	# participants	Mean difference mmol/L (95% CI)	p-value
Overall	Parallel	13	17	1517	-0.16 (-0.24, -0.07)	0.0004
	Crossover	6	8	285	-0.18 (-0.32, -0.07)	0.005
Lower quality/high risk of bias studies removed	Parallel	12	16	1494	-0.16 (-0.32, -0.11)	0.0004
	Crossover	4	6	215	-0.13(-0.33, 0.08)	0.22

Total cholesterol-intervention studies

Sinclair SE, Mansfield ED and GA Wells. **Evidence for a whole grains and coronary heart disease claim** (2013). International Food Risk Analysis Journal. Vol. 3, 1

Whole grains and coronary heart disease: evidence from cohort studies

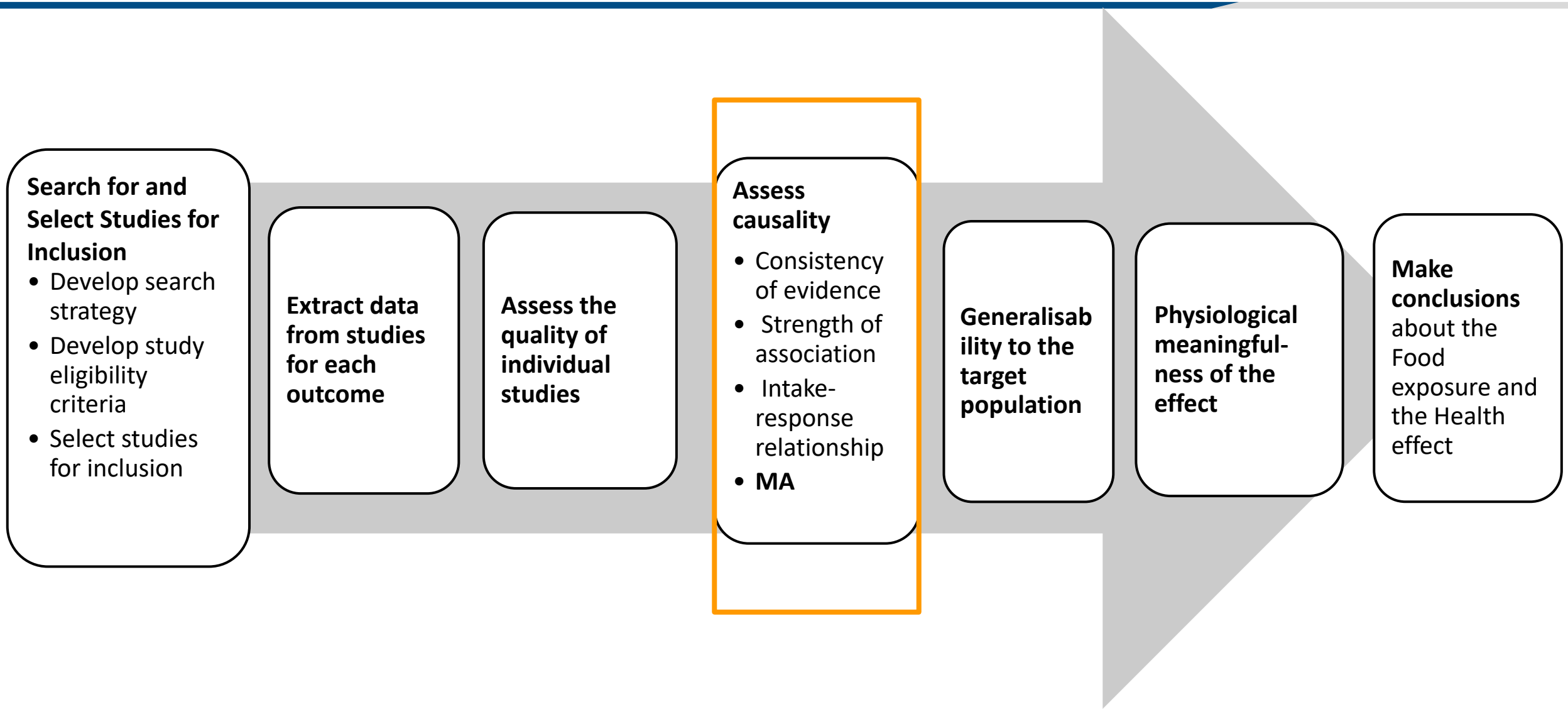
- Data was too heterogeneous to be pooled
- Most studies were of lower quality/higher risk of bias:
  - Lack of adjustment of confounding factors
  - Lack of control for a potential confounder, such as total energy intake or fruits and vegetables intake
  - Limited generalizability of the findings

Question asked by sponsor:

- How do you consider risk of bias when evaluating diet and disease relationships?

The evidence for an association between whole grains and CHD from observational studies was insufficient to support the claim.

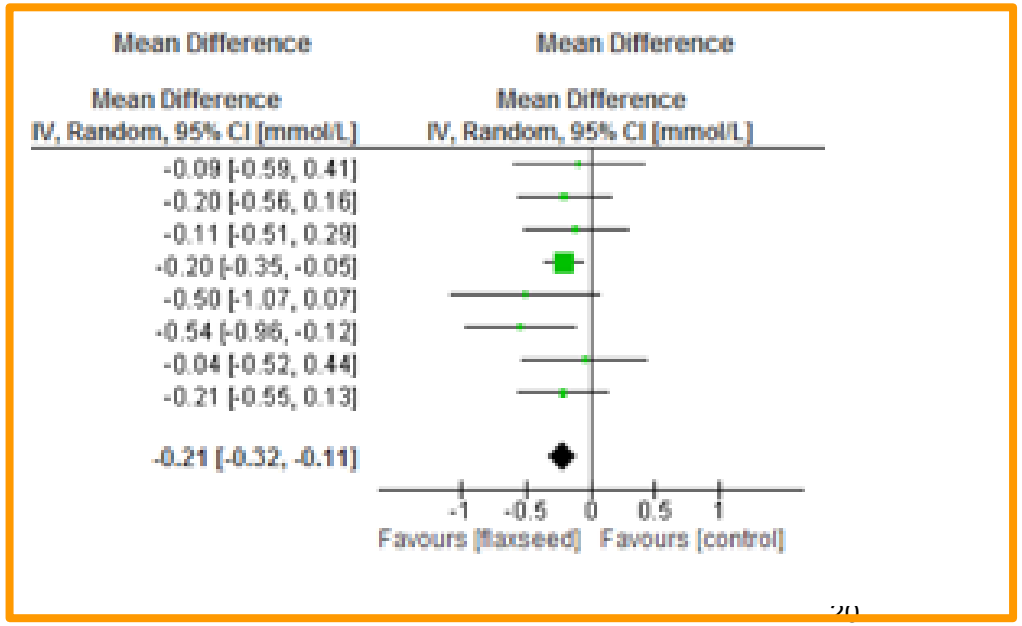
Systematic approach for health claims substantiation



Health Canada (2009) Guidance Document for Preparing a Submission for Food Health Claims

Consistency of the evidence

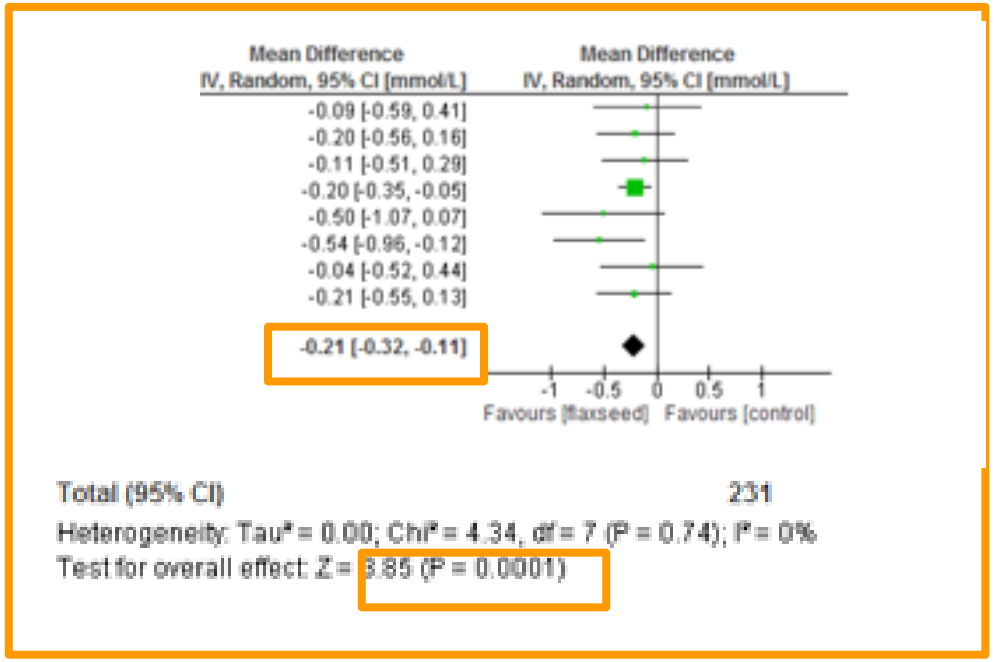
- Considering study quality, assessing consistency in direction of favourable effect for each outcome
- Consideration for study design
- Consistency rating:
  - High: ≥ 75%
  - Moderate: 60-74%
  - Low:< 60%
- **Meta-analysis:**
  - Use appropriate tests to quantify heterogeneity (chi-square test (Q test), I2 statistic)



Strength of the association

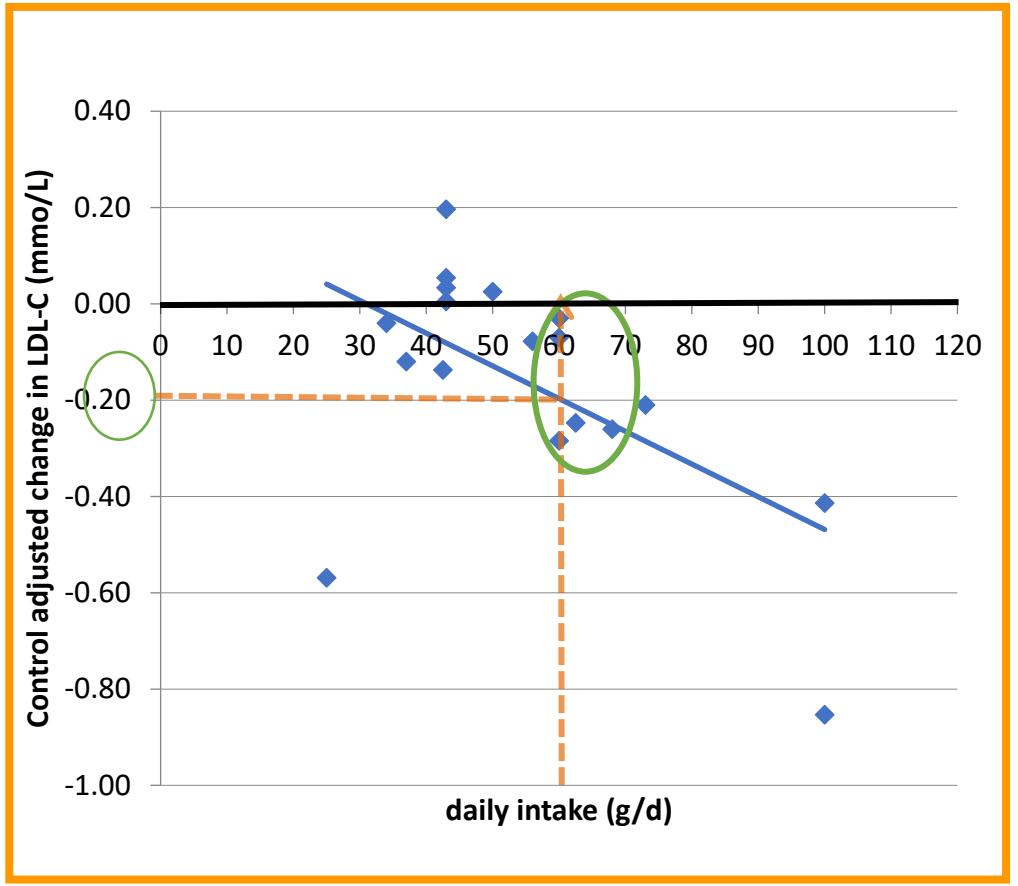
- Assessing the strength of the association between the food and the health outcome to determine if there is an effect
  - Statistically significant (SS) effects in individual studies
  - SS effects in higher quality studies
    - High: ≥ 75%
    - Moderate: 60-74%
    - Low:< 60%
  - Factors that may have contributed to lack of SS

- **Meta-analysis:**
  - Statistical significance of effect estimates
  - Confidence intervals for effect estimates



Intake-response relationship

- Assess existence of intake-response relationship
  - Whether a greater effect is observed with a greater food exposure, considering intake, duration, adherence
  - Minimum effective amount
  - For observational studies, whether statistical significance was achieved between highest and lowest dietary intake group



Generalizability of the data to the target population

- Demonstrate relevance of the effect to the target population for the claim
  - Impact of health (baseline) status of study population
  - Target population being represented in the studies
    - background diets, health status, age, gender
  - Applicability of the results of the meta-analysis to the target population

Physiological meaningfulness of the size effect

- To understand the impact of the food exposure on human health
  - Whether the effects observed with food exposure are meaningful (i.e., biologically relevant)
    - Most relevant outcome(s)
    - Relevant change in valid biomarker(s)
- Sustainability of effect based on study durations

Evaluating the totality of the evidence- health claims' approach

- Reflects an overall assessment of the evidence
  - Comprehensiveness
  - Most relevant outcomes (valid surrogate endpoints)
  - Causality (consistency, strength of the association intake-response relationship)
  - Quality
  - Meaningfulness of the size effect
  - Generalizability of the data
  - Consistency of effect across study designs
- Claim wording reflects the evidence
  - Disease outcome or change in risk biomarkers

Question asked by sponsor:

- How can meta-analyses be used to evaluate the strength of the totality of evidence when there is evidence from different nutrition study designs (e.g., both intervention and observational)?

Question asked by sponsor:

- How can meta-analyses be used to evaluate the strength of the evidence when different outcomes are reported in different studies (clinical outcomes vs. surrogate endpoints)?

Evaluating the totality of the evidence- health claims' approach

Two possible conclusions about the acceptability of the claim:

1) The evidence is sufficient. Reasons provided

Health Canada has concluded that **sufficient scientific evidence** exists to support a **health claim about vegetables and fruit consumption and a reduced risk of heart disease**. The claim is relevant and generally applicable to the Canadian population. Heart disease is a major public health concern in Canada. In 2011, heart disease was the second leading cause of death in Canada, accounting for 20% of all deaths.

2) The evidence is insufficient. Reasons provided

Health Canada concluded that the evidence to date from clinical trials and prospective cohort studies was **not sufficient to support a whole grains and coronary heart disease risk reduction claim** in Canada. …. were limited by potential bias due to confounding factors and poor applicability to the general population of Canada. There was an overall effect of whole grains on total and LDL cholesterol when the results from controlled clinical trials were pooled, **but sensitivity analysis showed that the effect was largely attributable to trials that tested single grains high in beta-glucan fibre and trials judged to be of poor quality**

Health Canada: Health Claims assessments

Considerations for application of MA in policy

- Nutrition Guidance and policies are based on the best available evidence
- Evidence may include SR/MA and other relevant individual studies
- Consideration given to:
  - Relevance of SR/MA to the policy question
  - Overall quality of evidence
  - Level of certainty appropriate for decision-making
    - Standard of evidence applied, approaches used to assess the quality of the evidence, transparency in reporting, uncertainties, limitations
  - Applicability of the results of a SR/MA to the national context

From research to dietary guidance and nutrition labelling

1. **Dietary Guidance: Canada's Food Guide**

2. **Nutrition labelling: Front-of-pack**

Examples of SR/MA

- Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization; 2016.
- Souza RJ, Mente A, Maroleanu A, Cozma A I, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all-cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015;351:h3978.
- Hooper L, Martin N, Abdelhamid A, Smith GD. Reduction in saturated fat intake for cardiovascular disease (Review). Cochrane Database Syst Rev. 2015;11(6):CD011737.
- Dietary Guidelines Advisory Committee. Scientific report of the 2015 Dietary Guidelines Advisory Committee: advisory report to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington: U.S. Department of Agriculture, Agricultural Research Service; 2015.
- Newberry SJ, Chung M, Anderson C, Fu W, Chen C, Tang A, et al. Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors. Rockville: Agency for Healthcare Research and Quality. 2018. Systematic Review No. 206. AHRQ Publication No. 18-EHC009-EF.

Food, Nutrients and Health: Interim Evidence Update 2018
Front-of-package nutrition labelling

THANK YOU FOR YOUR TIME!