Use of Meta-Analyses in Nutrition Research and Policy:
Planning of Meta-Analysis

The First in the Series

Systematic reviews & meta-analysis for developing nutrition guidance:

The core pillars of planning and methods to deliver high quality, useful synthesised evidence

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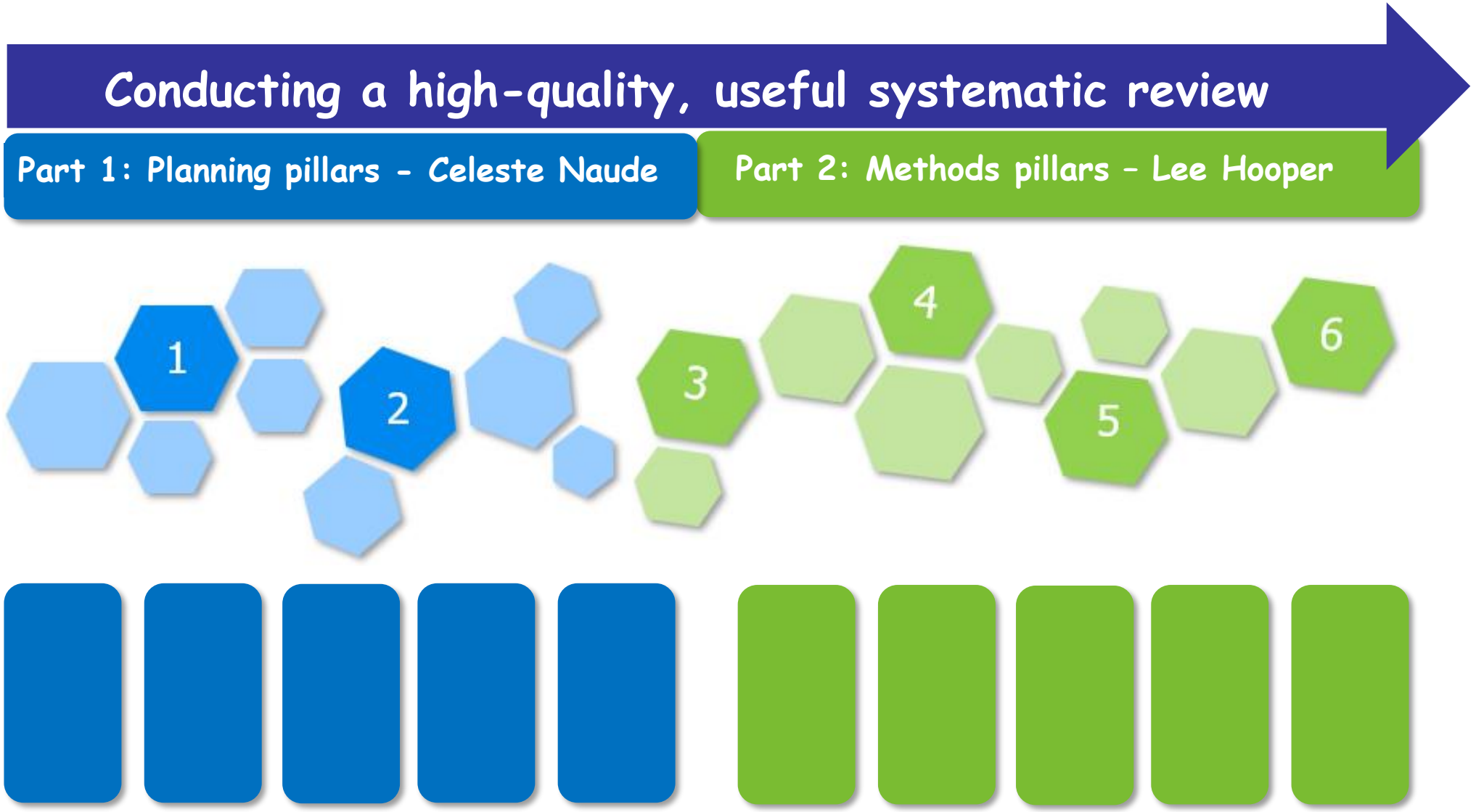
Systematic reviews & meta-analysis for developing nutrition guidance



Systematic reviews & meta-analysis for developing nutrition guidance:

The core pillars of planning and methods to deliver high quality, useful synthesised evidence

Part 1: The planning pillars

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Centre for Evidence Based Health Care

Disclosures and Acknowledgements

My Disclosures

- No funding from industry sources
- Co-director: Cochrane Nutrition; involved in other Cochrane groups
- Founding member South African GRADE Network
- WHO Guideline Methodologist
- Member past and current WHO Guideline Development Groups
- Past member: Ministerial Committee on Morbidity and Mortality in under-5s, South Africa
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- Taryn Young, Director of Centre for Evidence-based Health Care, Stellenbosch University, South Africa
- Content guided largely by latest online version of Cochrane Handbook [Higgins JPT et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. www.training.cochrane.org/handbook]

Systematic reviews & meta-analysis for developing nutrition guidance

What will I cover in Part 1?

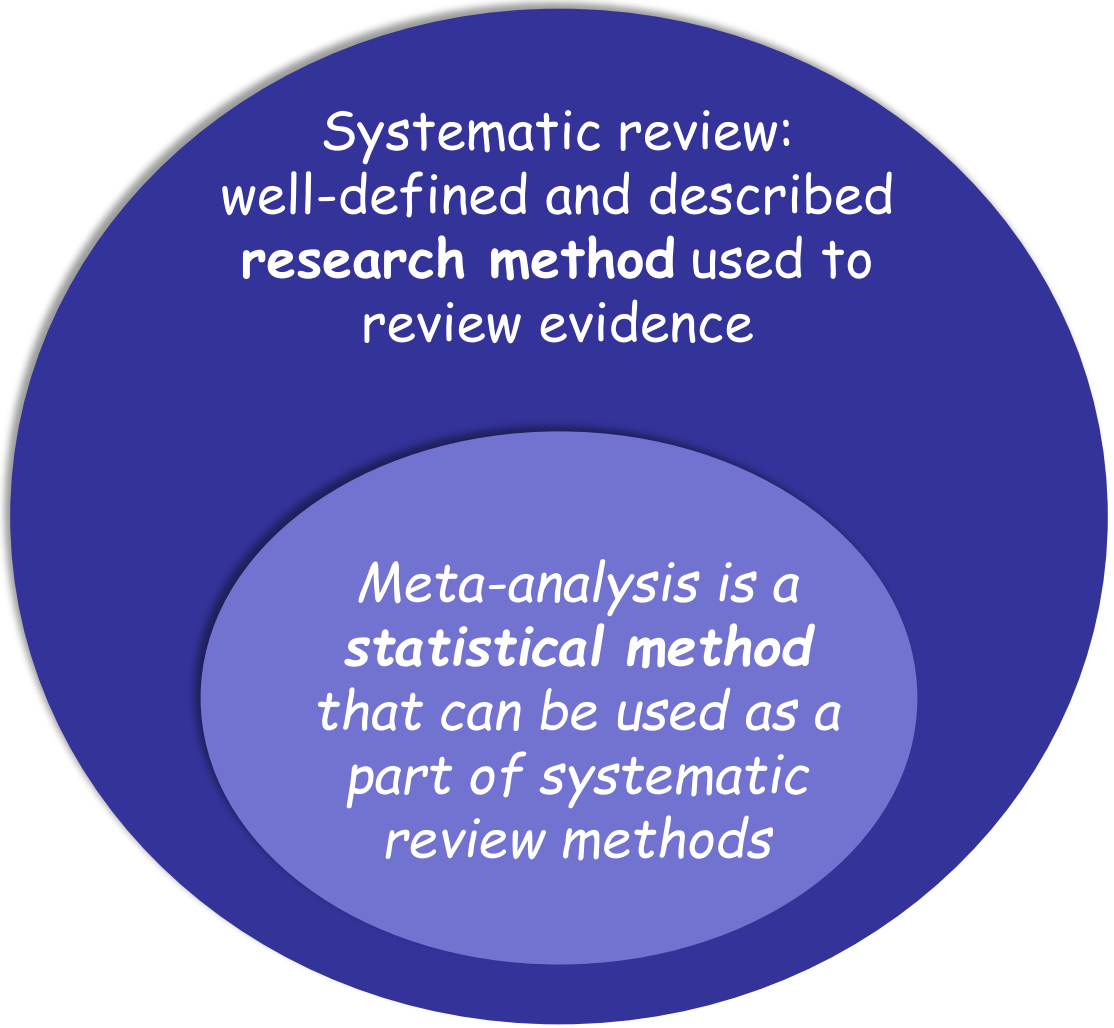
- Introduction: definitions and 'setting the scene'

- The pillars of planning a systematic review (SR)

1. Background information
2. The author team
3. Resources and reliability
4. The systematic review question

Introduction: Systematic reviews versus meta-analysis

- Mistake often made is confusing systematic reviews and meta-analysis
- Very important differences



What is a systematic review (SR)?

Research method that **collates** results of **multiple primary studies** that fit **pre-specified criteria** to answer a specific **research question**

Uses strategies to **minimise bias** when reviewing the evidence, including specific, transparent methods detailed in a **protocol** that is prospectively registered

Analyses and **interpretations consider risk of bias** and **other factors affecting certainty** of the evidence (e.g. by using GRADE)

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

What is a meta-analysis (MA)?

Statistical method to **combine numerical results** from 2 or more separate studies

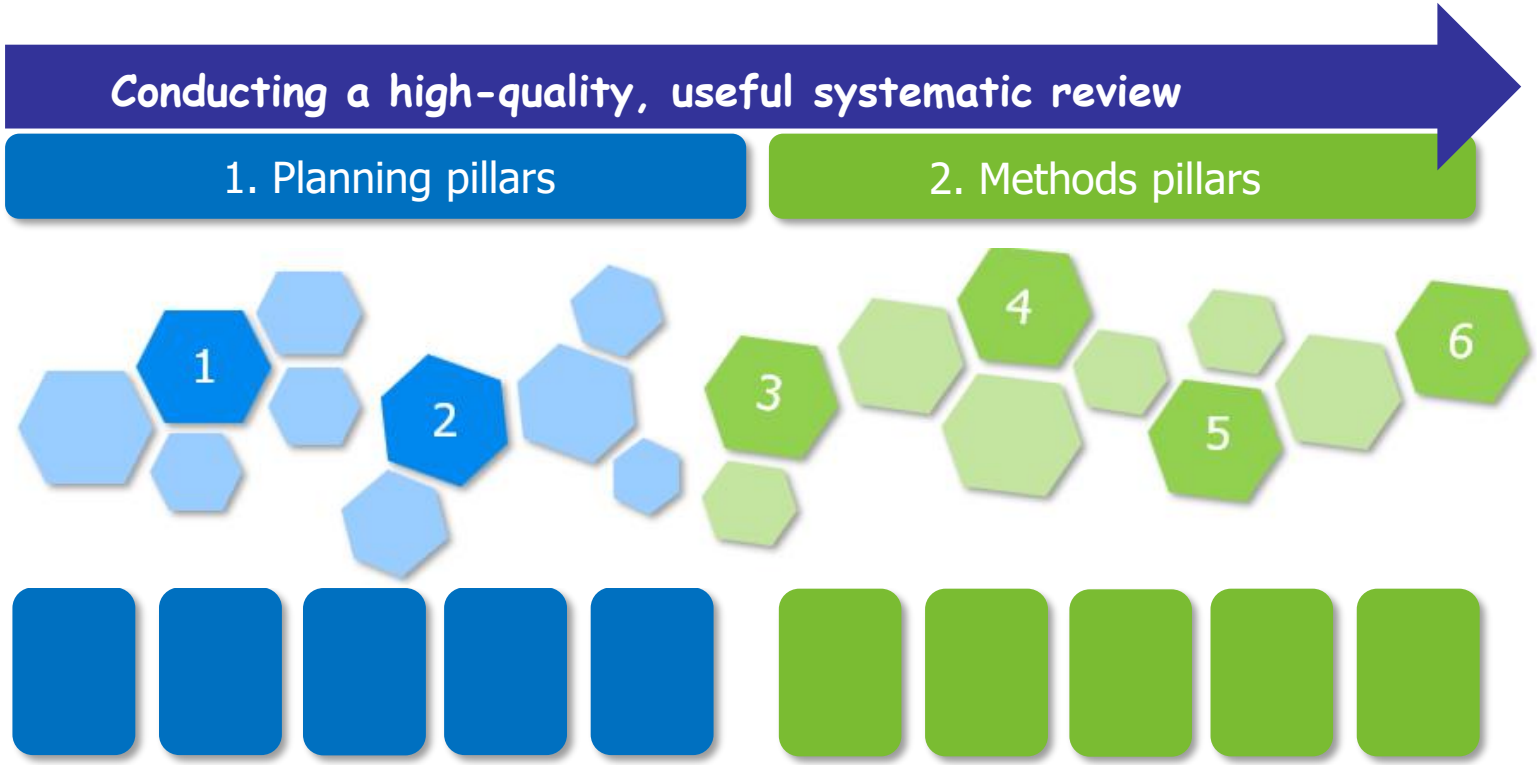
- **should be informed by a rigorous SR** that searches for both published and unpublished studies
- if not informed by a SR, **reviewer selection bias** is a **real concern** i.e.
  - identification and inclusion of relevant studies not pre-determined & clearly reported, or
  - based on a selective, non-systematic approach to 'engineer' the findings

A sound MA requires **thoughtful, transparent consideration** of whether it is **appropriate** to **statistically combine numerical results** from multiple studies

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

SRs and meta-analysis

- Use of **statistical synthesis methods** does not guarantee valid SR results
- Results of SRs and MAs can be very misleading if suitable attention has not been given to **planning** and **methods** that **underpin a high-quality SR**



Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

Not all SRs are created equal

SRs are **complex and time-consuming**

- Extent to which a SR can draw **valid conclusions depends on** whether the data and results from the **included studies** are valid
- Meta-analysis of invalid studies produces a precisely wrong result
- Quality: ***the likelihood that the design of a SR will generate unbiased results***

  Moher *et al*, 1995
- High methodological quality is a pre-requisite for valid interpretation and application of SR findings

  Shea *et al*, 2009

- A **well-planned** SR using **best practice methods** increases **quality** and **utility**
  - Interpret and reach conclusions by considering both the findings and how confident we are in the findings

Introduction: Developing nutrition guidance (policies, guidelines)

"It is the business of policy-makers and practitioners to intervene in other people's lives. Although they usually act with the best of intentions, ***their policies and practices sometimes have unintended, unwanted effects, and they occasionally do more harm than good."***

"This reality should be their main motivation for ensuring that ***their prescriptions and proscriptions for others are informed by reliable research evidence."***

Chalmers I. The Annals of the American Academy, 589, Sept 2003, pp 22-40

- **Decisions informing nutrition policy and practice** should always be informed by **best available research evidence**

Introduction: SRs for developing guidance (policies, guidelines)

Challenges to reviewing evidence:

- **Volume** of research is overwhelming and ever-increasing
- **Design & quality** of research **vary widely**
- **Access** to research is haphazard and often biased
- Conflicts of interest

Impossible for decision-makers to assess vast quantity of primary research to enable them to make most appropriate decisions that do more good than harm

- **High-quality SRs: important tool** and '**gold standard**' for **reviewing evidence** across many disciplines and informing guidance
  - critical examination and synthesis of current state of knowledge
  - 'take stock' of existing knowledge to make informed choices

High-quality SRs for developing nutrition guidance: advantages

- **Transparent**, repeatable and objective, **reduce bias** and **maximise reliability**
- SRs include the **totality of the evidence** around a particular question: no place for *cherry-picking/'document folder'* bias
- Most primary studies small, **combining** studies appropriately can give more **precise** results

- Not just a 're'-view or 'further look' at previous research
  - **Systematic documentation of current state of knowledge** with clear **considerations of strengths and limitations** of underlying research (risk of bias and other factors affecting certainty)
  - **Best practice methods** aim to **reduce risk of bias** that may occur **in process of reviewing evidence**

High-quality SRs for developing nutrition guidance: advantages

- **Aligned with best practice standards for developing trustworthy guidance**

Some **key components** of standards for high-quality, trustworthy guidance:

- Recommendations informed by **systematic, comprehensive, objective assessment** of balance of **totality of evidence** on potential **benefits and harms** and explicit consideration of **other relevant factors**
- **Process and methods** used to develop recommendations:
  - **Transparent** evidence-to-decision process
  - Aim to **minimize risk of bias** in the recommendations
  - Management of interests

Importantly, **evidence is necessary but not sufficient** for making sound decisions; final decisions may incorporate **non-evidence-driven** judgements

WHO 2012; Schünemann 2014, GIN 2012

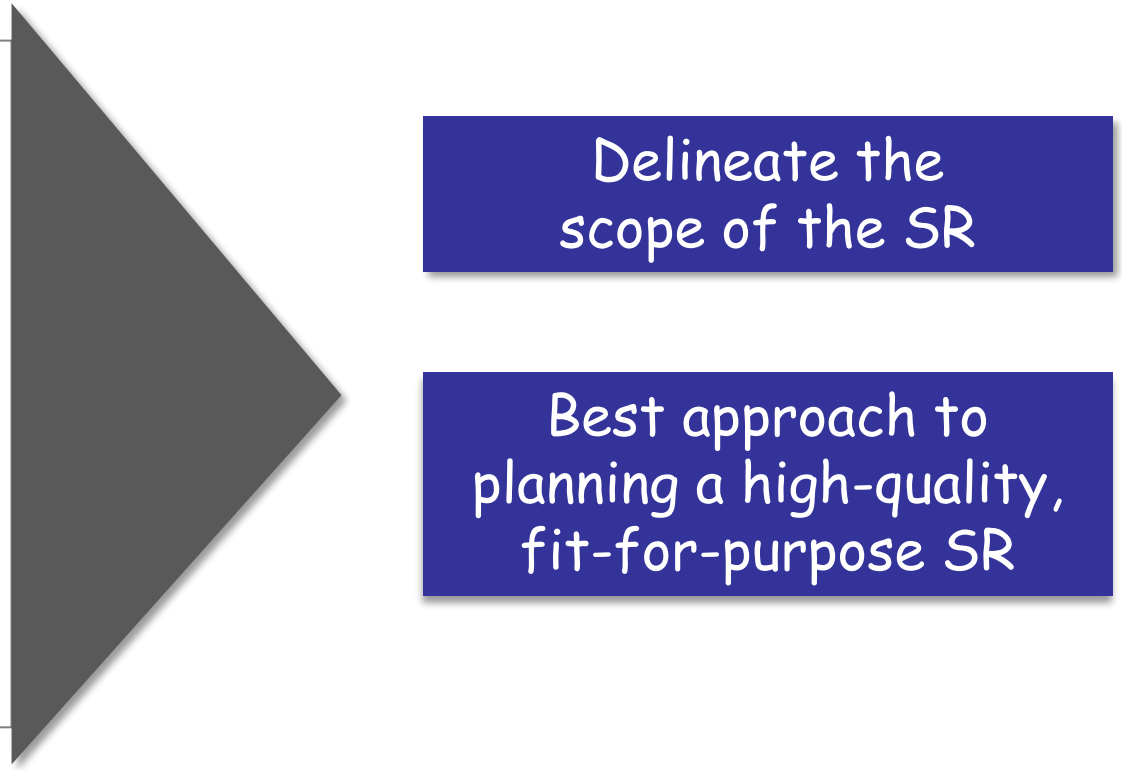
The pillars of planning a systematic review (SR)

1. Background information
2. The author team
3. Resources and reliability
4. The SR question

1. Background information: more is better

Engage with the users to obtain key information helpful for planning SRs for developing nutrition guidance:

- **Scope** of the specific **nutrition guidance** (policy, guideline) and guidance gap
- **End-product** of guidance process
- **Processes and methods** to be used by guidance developer
- **Target audience** and perspective(s)
- Timelines and pragmatic details



2. The author team: use a 'dream team'

- Team members and contributors must include:
  - Content/topic expertise and experience with SRs
  - Methods expertise and experience
  - Biostatistical expertise and experience
  - Information specialist with SR experience
  - Perspectives of key stakeholders (users, public, patients)
- ICMJE 2018 criteria for authorship recommended
- **SR lead** needs strong **project management and relational skills**
- Authors should not have a real or potential vested interest in the SR findings (**objectivity**)

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

2. The author team: use a 'dream team'

Conflict of interest in funding and authorship of SRs gives rise to **serious issues**

A SR for developing nutrition guidance:

- should **not be funded or conducted by commercial sponsors or commercial sources** with a real or potential vested interest in its findings

- should include **explicit efforts** to remove or **reduce influences** of personal beliefs and theories, vested interests (e.g. commercial, intellectual), values and ideologies, structural, cultural and financial constraints in its conduct

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

3. Resources and reliability: detailed preparation is essential

- Workload very variable, dependant on question, search yield, included studies etc. – need **adequate resources**
- **Many key tasks** to be completed to deliver high-quality SR
- Consider timelines and pragmatic information
- Time chart with target dates and responsible persons for key tasks

- Good data management and quality assurance processes are essential for replicability and credibility - secure and retrievable audit trail
- Review management software & sophisticated information technology
- **Transparent reporting and audit trail of SR decisions** enables readers to **assess** the **reliability** of the review for themselves

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

4. The SR question: informs and guides nearly everything, so spend the time to get it right

A **well-developed**, **clearly framed** question:

- is **critical** to SR success
- will inform and guide most aspects of the review process

Typically, guidance developers undertake **prioritisation** processes (scoping, stakeholder engagement, guidance gaps etc.) which yields **initial question(s):**

- problem statement, composite/broad/narrow/detailed/vague question

4. The SR question

Many types of questions

- Focus on subset - **impact of intervention(s)/ exposures** (prevention, treatment, screening) on specified human population

Establishing the **aim of the SR** is important, examples:

- single intervention/exposure compared with a specific alternative
- range of different interventions/exposures compared to each other
- comparing multi-component interventions/strategies implemented in different ways
- interventions as part of systems

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

4. The SR question

Formulate a clear answerable intervention question

Look at how these 2 questions differ?

1. *What are the effects of school food and nutrition policies on improving health?*

2. *What are the effects of implementing policies or interventions that influence the school food environment compared to not implementing them on children's health and nutrition outcomes?*

Using the mnemonic PI/ECO			
Population or problem (P)	**Intervention (I) or Exposure (E)**	**Comparator (C)**	**Outcomes (O)**
School-going children	Implementing policies or interventions that influence the school food environment	Not implementing these policies	Health and nutrition outcomes

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook; https://www.who.int/publications/i/item/9789240025646

4. The SR question

Broad vs narrow questions, influenced by:

- scope of guidance, **user needs** & **context**(s) of review use (background information)
- perspectives regarding **relevance** and **potential impact**
- supporting theoretical, biologic and epidemiological information
- potential generalizability and validity of answers to the questions
- available resources

PI/ECO elements of **most nutrition questions** need **further development** to unpack complexity and refine them for a SR(s)

- Conceptual frameworks and logic models can help

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

4. The SR question

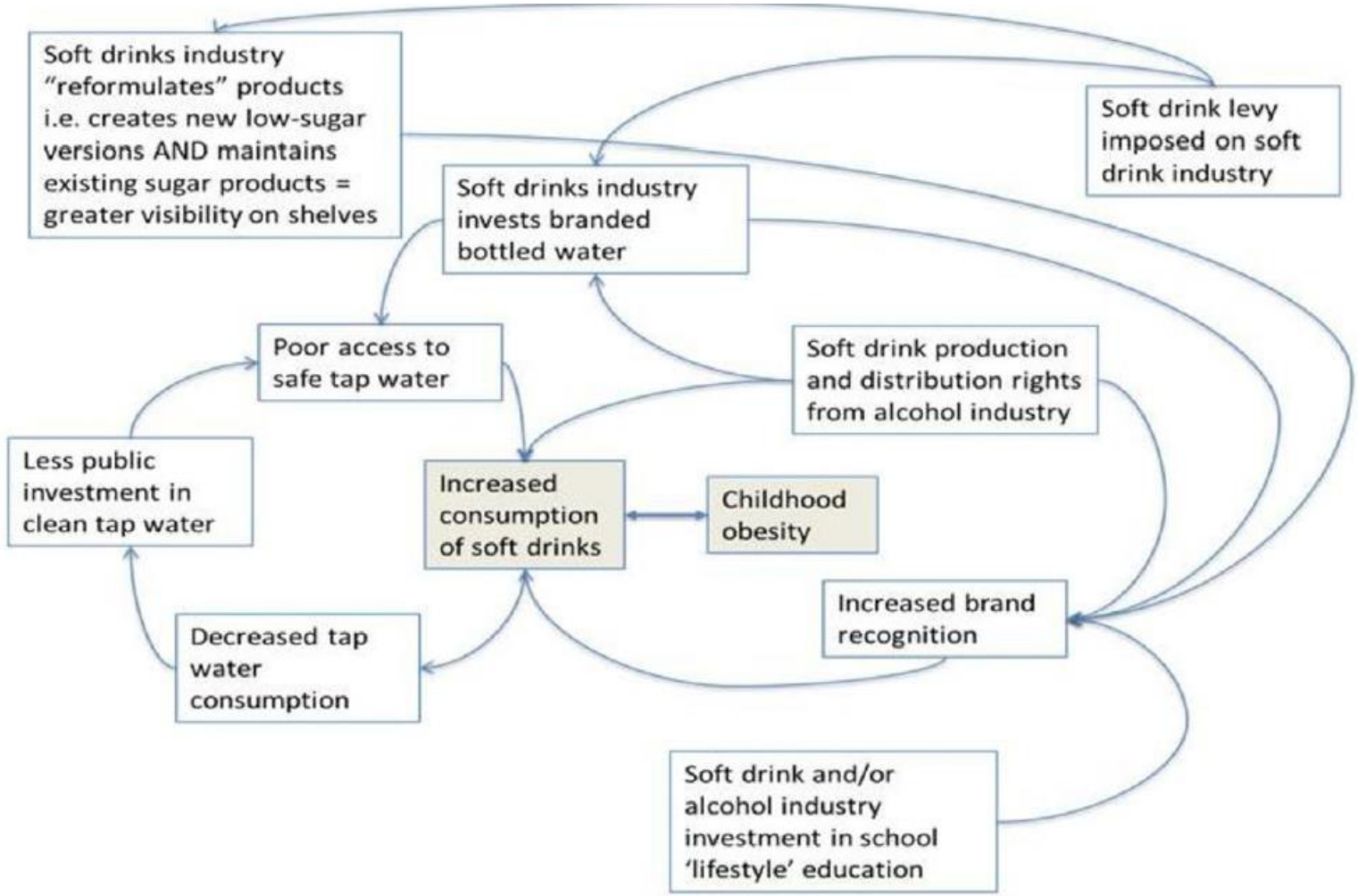
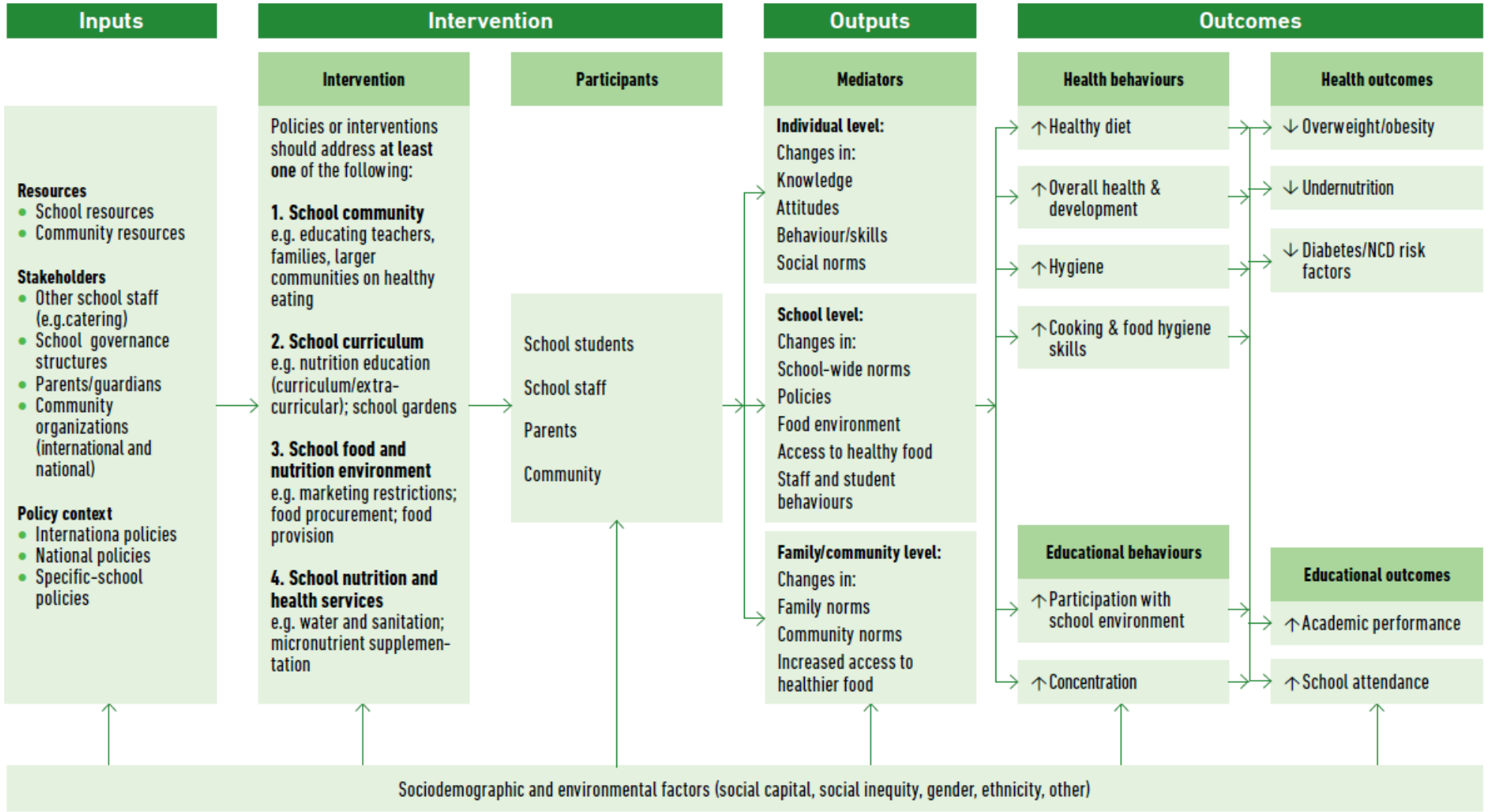


Figure 2 Conceptual framework: soft drinks consumption and childhood obesity in countries with limited access to safe drinking water.

Petticrew et al. BMJ Glob Health. 2019 Jan 25;4(Suppl 1):e000899.

4. The SR question

Fig. 1 Logic model depicting pathways from school food and nutrition policies to health and educational outcomes



https://www.who.int/publications/i/item/9789240025646

4. The SR question

3 different stages at which the **PI/ECO construct** might be used; helpful for understanding the decisions that need to be made:

1. The **review PICO** (planned at protocol stage): PICO on which **eligibility of studies** is based (inclusion and exclusion from SR)

2. The PICO for each synthesis (also planned at the protocol stage): defines the question that each specific synthesis aims to answer, determining how the synthesis will be structured, specifying planned comparisons (including intervention and comparator groups, any grouping of outcome and population subgroups).

3. The PICO of the included studies (determined at the review stage) is what was actually investigated in the included studies

Higgins et al. Cochrane Handbook V6.4 2023; www.training.cochrane.org/handbook

4. The SR question

Outcomes:

Choosing outcomes of interest **and rating their importance** is a **fundamental part** of **SRs for developing nutrition guidance**

What outcomes are critically important/important/not important for decision-making?

See GRADE guidance for further details

- GRADE Handbook
- GRADE guidance papers in J Clin Epi

GRADE guidelines: 2. Framing the question and deciding on important outcomes

Question asked by committee:

- 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)?

4. The SR question

Some **key issues** to consider when **developing PI/ECO question elements & protocols** of **nutrition SR questions – <u>anticipate & specify transparent, justified approaches</u>**:

- **Variations in** methods in same study design, analytical approaches, samples of people in nutrition studies, ways to measure same outcome
- **Quantifying** foods & nutrient **intake** is challenging + different measurement methods
- **Clear comparator** is 'critical' in nutrition SRs- effects of specific dietary element depends on what it is compared against; need adequate number of studies focusing on a single "comparator"
- **Baseline nutritional status** and contexts
- **Substitution effects** of specific dietary substitutions mostly more robust and useful
- **Multiplicity of results** in nutrition studies
- **Influences of industry** and other conflicts

End of Part 1

Thank you very much

Systematic reviews & meta-analysis for developing nutrition guidance:

The core pillars of planning and methods to deliver high quality, useful synthesised evidence

Part 2: The pillars: methods to reduce the risk of bias

Lee Hooper, RD, PhD

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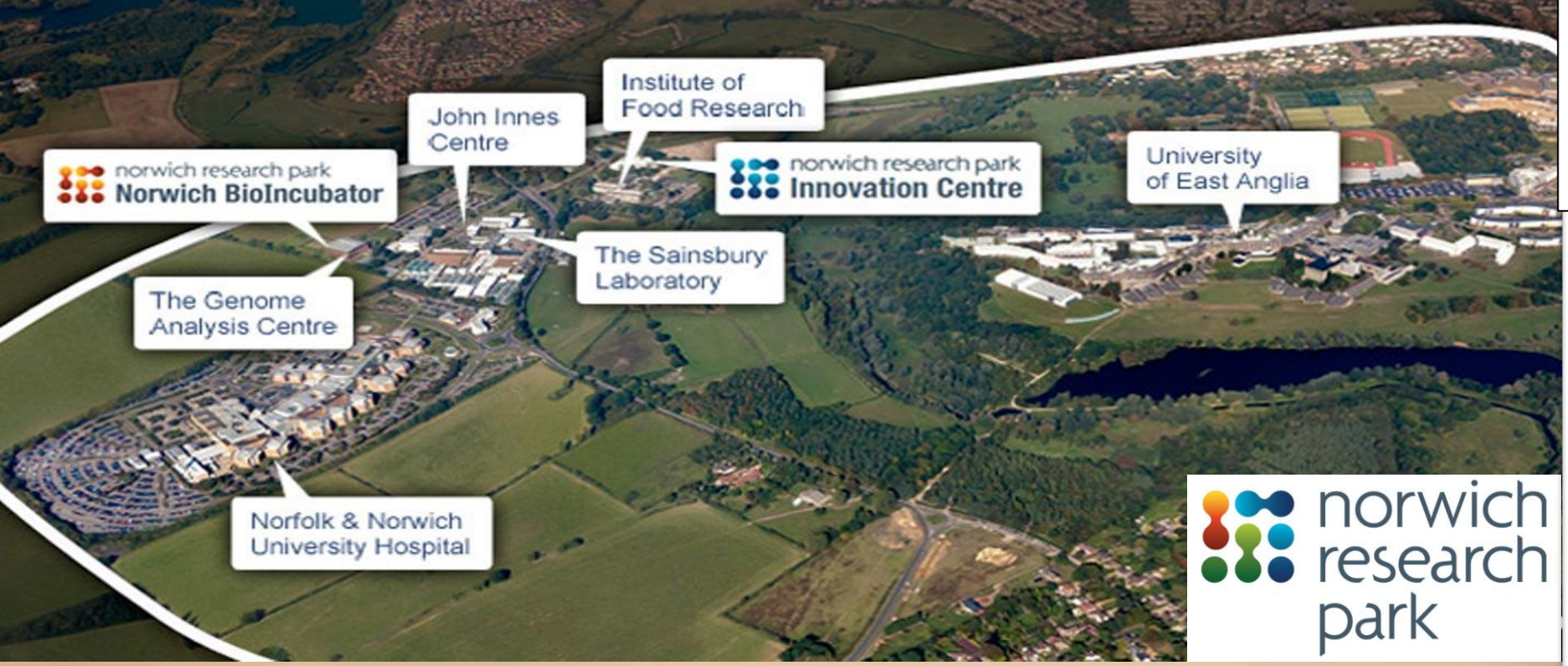
NORWICH MEDICAL SCHOOL



UEA University of East Anglia

norwich research park

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My Disclosures

- No funding from industry sources
- Over the past 10 years research funding has come from
  - Age UK Norwich
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  - Dunhill Medical Trust
  - European Regional Development Fund
  - Economic and Social Research Council
  - NHS England
  - University of East Anglia Impact Funding
  - NHS Norfolk & Waveney Integrated Care Board
- Was an editor of the Cochrane Heart Group for almost 20 years
- Was an editor of the Cochrane Oral Health Group for 5 years
- Member of the WHO Nutrition Guidance Expert Advisory Group (NUGAG) – subgroup on Diet & Health (since 2013)
- WHO systematic review methodologist
- Member of several ESPEN guidelines groups

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I developed this presentation using published references (cited) and structure and ideas used in Cochrane Training

The pillars: methods to reduce the risk of bias in systematic reviews

The pillars:

1. Writing the protocol
2. Searching for studies
3. Selecting studies and collecting data
4. Assessing risk of bias of included studies
5. Analysing the data
6. Interpreting the findings
7. Reporting the review

Plus: Assessing risk of bias in published systematic reviews

The pillars: methods to reduce the risk of bias in systematic reviews

- Further details are available from:
  - Cochrane Handbooks (SRs of interventions; DTA)
  - MECIR manual (Methodological Expectations for Cochrane Intervention Reviews)
  - JBI manuals (variety of types of reviews)
- Training is available from:
  - Cochrane Interactive Learning
  - WHO / Cochrane / Cornell Summer Institute

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The pillars: methods to reduce the risk of bias in systematic reviews

Writing the protocol

- "protocols ensure transparency in how reviews are prepared and allow the planned methods to be critiqued" Julian Higgins

Protocols

- Help establish & clarify the research question
- Plan review methods in advance to minimise bias in the review process
- Make the protocol publicly available to
  - Enable peer review and improvement of the question & methods
  - Allow others to assess changes to the review methods during the review – where any changes justified?
  - Prevent duplication of effort

The pillars: methods to reduce the risk of bias in systematic reviews

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The pillars: methods to reduce the risk of bias in systematic reviews

Searching for studies

- The search is the basis for ensuring that a full and representative sample of all the most relevant studies is included within the review
- Selection bias: easier to find studies in English, in Medline, in high impact journals, with positive findings BUT these are likely to be
  - a biased sample of the full set of research, and
  - less generalisable to all participants and settings
- Collect all info on potential studies:
  - Published papers (all)
  - Registration documents
  - Corrections and retractions
  - Replies to letters
  - Conference abstracts

The pillars: methods to reduce the risk of bias in systematic reviews

Searching for studies

- Search should be across
  - Years, settings, countries, languages
  - Sources
    - Databases of published literature (different paradigms eg nursing, education, medicine)
    - Trials registries
    - Grey literature (eg theses, government websites)
- Use a search expert to get this right
  - Sensitive approach: high % of relevant studies
  - Reproducible
- Peer review of search strategy by search & topic experts

The pillars: methods to reduce the risk of bias in systematic reviews

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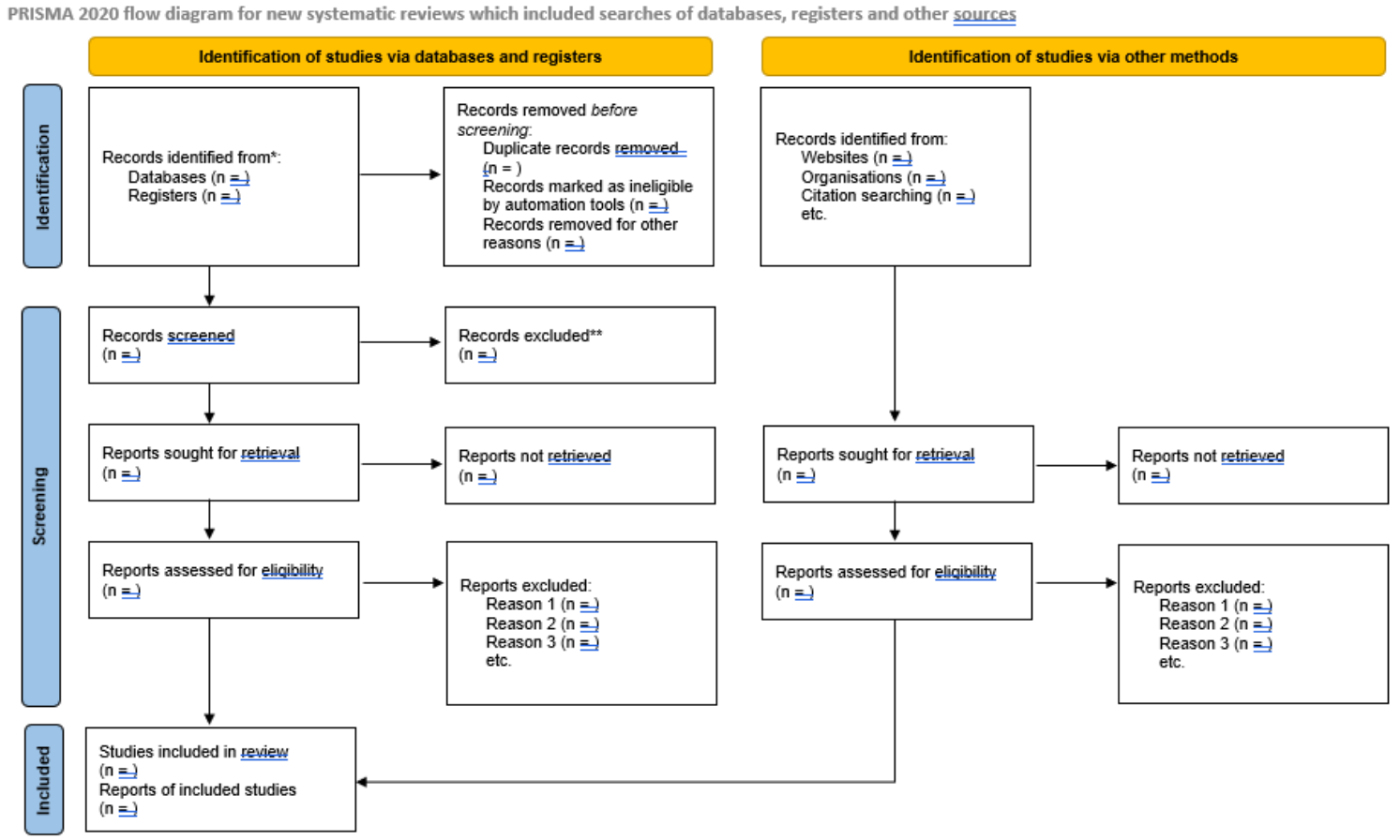
The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and collecting data

- Assess which studies collected in searches meet pre-specified criteria (so included)
- Process needs to be systematic & fair
- Recorded in enough detail to complete PRISMA flow chart



The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and collecting data

- Minimising bias during study selection:
- Use your pre-specified inclusion criteria (PICO or PECO plus study design) – to be included a study has to satisfy ALL criteria (except outcome measures)
- Independent duplication of
  - assessment of inclusion of titles & abstracts
  - assessment of inclusion of full texts
  - Data extraction
  - Risk of bias assessment
- Have rules on how to proceed with disagreements
- Record any refinements in inclusion/exclusion criteria

The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and collecting data

- Carry out data collection independently in duplicate, discuss disagreements as a team
- Prespecify info to collect (trial data collection sheet)
  - Include measures of baseline nutritional status or intake
  - Include study flow (no. randomised, dropped out, analysed)
  - Outcome data

The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and collecting data

- Outcome data can be in a large variety of formats, collected at different time points, may be difficult to understand, and may include errors of data
  - The original authors may be able to clarify
  - Talk through and agree your data extraction as a team
  - Review Manager software includes a super useful tool to convert some types of data to others for combining
  - Look out for fraudulent data and studies, to learn more (& checklist) see Parker 2022; INSPECT-SR tool

The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and col

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  - Talk through …
  - Include studies that fu… utcomes

NASEM question:

Extraction errors and errors in calculating mean differences and confidence intervals (CI) from the primary studies that are included in a meta-analysis published in the literature are common. What are best practices to avoid/identify these types of errors?

The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and colle

- Carry out data e… …reements as a team
- Prespe…
  - In…
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- Outc… points,
  - The ori…
  - Talk through…
  - Include studies that re… …tcomes

NASEM question:

How should a meta-analysis be evaluated for methodological quality when extraction and/or data errors are present? At what point do data errors (in kind and number) reach a level that invalidates the conclusions of the meta-analysis?

The pillars: methods to reduce the risk of bias in systematic reviews

Selecting studies and collecting data

- Tools
  - Covidence – enables assessment of inclusion, data extraction and risk of bias assessment in duplicate online
  - Rayyan – enables assessment of inclusion in duplicate, free
  - EPPI reviewer – supports a range of reviews, including meta-ethnographies
  - Software to obtain numbers from a visual plot (Plot Digitizer or Microsoft Paint)

The pillars: methods to reduce the risk of bias in systematic reviews

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The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

- The quality [or risk of bias of included studies] is of obvious relevance to systematic reviews. If the 'raw material' is flawed then the conclusions of systematic reviews cannot be trusted. Jüni et al in BMJ (2001; 323, 42-46)
- Garbage in: garbage out
- Bias is where the results of a study do not represent the “truth”
- Meta-analysis of biased studies can lead to a precise estimate of the wrong answer

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

- Handle risk of bias of included studies by:
  - Excluding studies at highest risk of bias (so might exclude non-randomised studies, or observational studies that did not adjust for key confounders)

The pillars: methods to reduce the risk of bias in systematic reviews

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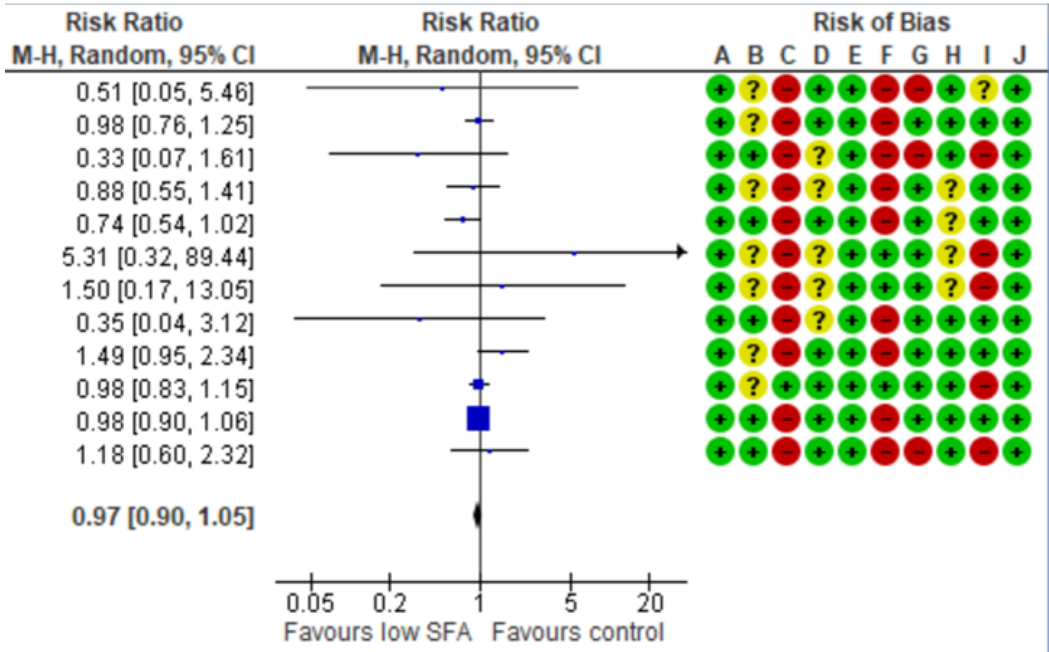
  - Assess and report remaining risks of bias study by study (represent in meta-analysis)



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  - Assess effects including and excluding studies at higher risk of bias (assess risk of bias and plan meta-analytic sensitivity analyses excluding those at highest risk of bias)

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

- Handle risk of bias of included studies by:
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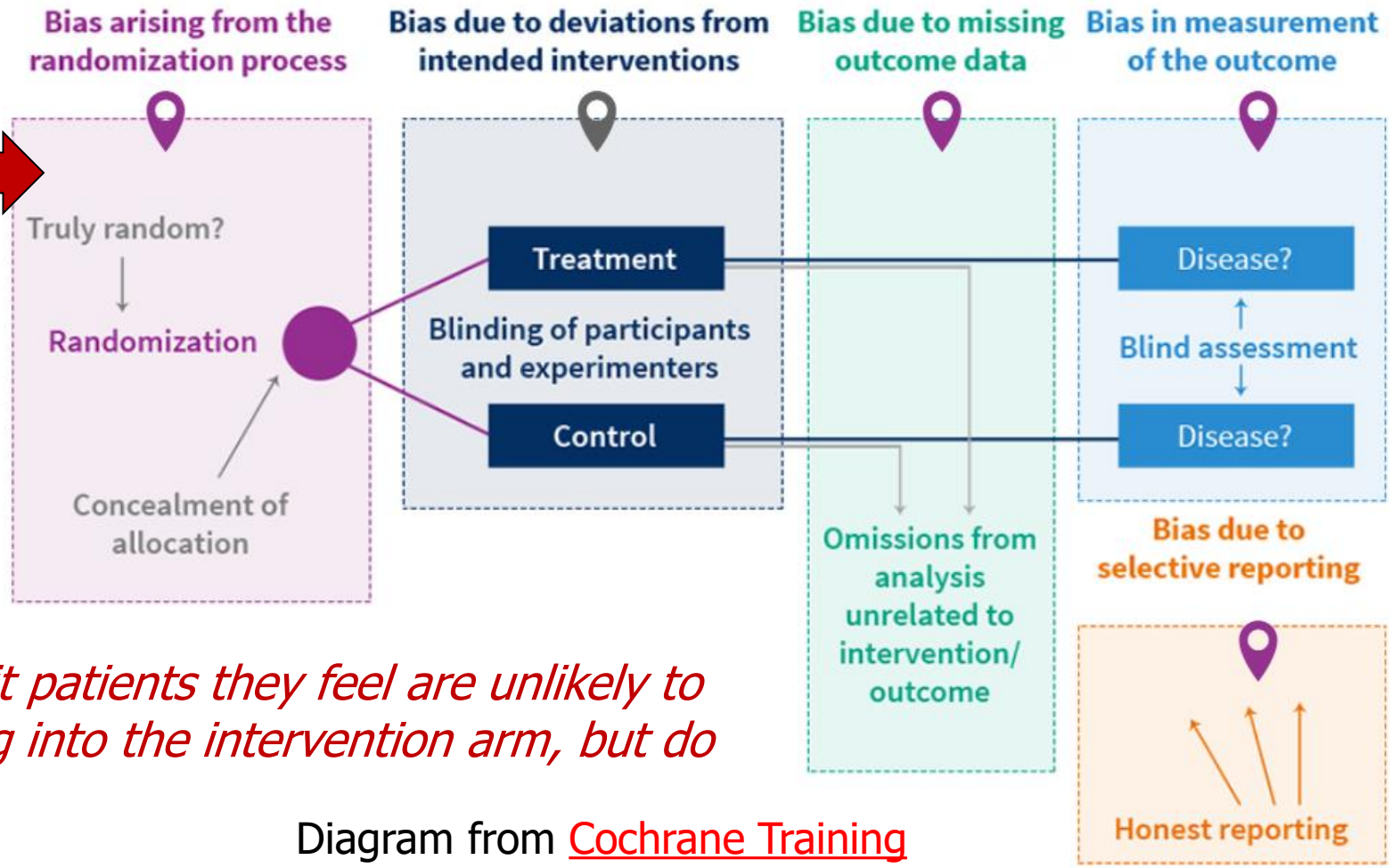
  - Assess effects including and excluding studies at higher risk of bias (assess risk of bias and plan meta-analytic sensitivity analyses excluding those at highest risk of bias)
  - Assess and report remaining risks of bias study by study (represent in meta-analysis)
  - Assess and discuss risk of bias across studies for each review question (each outcome) using tools like GRADE (see later)

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if…..
participants allocated to 2 arms are not equivalent (via allocation not random OR allocation not concealed).
The two arms are non-equivalent at baseline, so differences in outcome may be due to initial differences, rather than differences in intervention.



Example: clinicians don't recruit patients they feel are unlikely to manage dietary change if going into the intervention arm, but do recruit them for the control

Diagram from Cochrane Training

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if…..
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Example: clinicians don't recruit p
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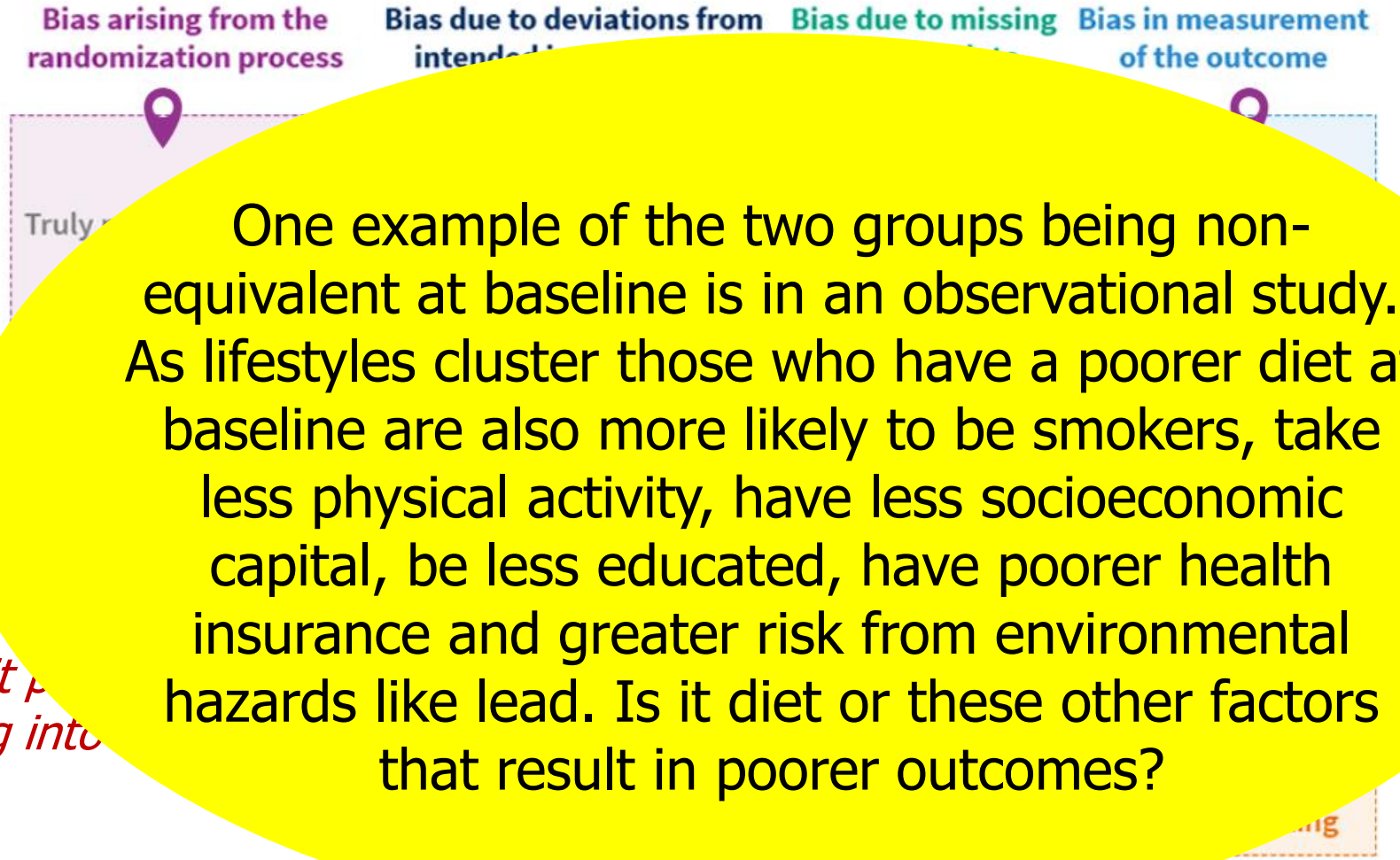
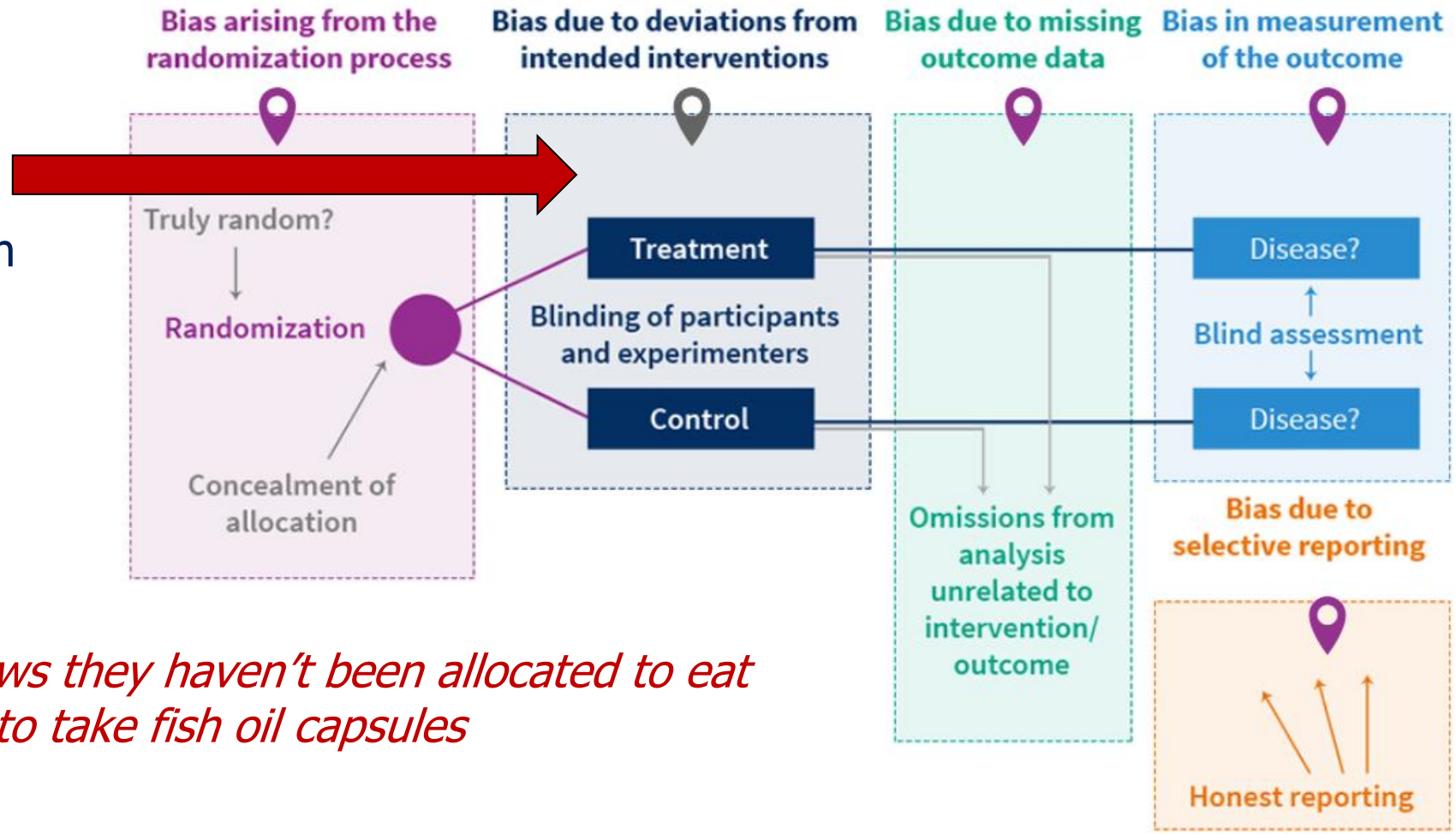


One example of the two groups being non-equivalent at baseline is in an observational study. As lifestyles cluster those who have a poorer diet at baseline are also more likely to be smokers, take less physical activity, have less socioeconomic capital, be less educated, have poorer health insurance and greater risk from environmental hazards like lead. Is it diet or these other factors that result in poorer outcomes?

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if….. there are deviations from intended intervention or control conditions as participants, carers, health professionals and/or researchers are aware of allocation

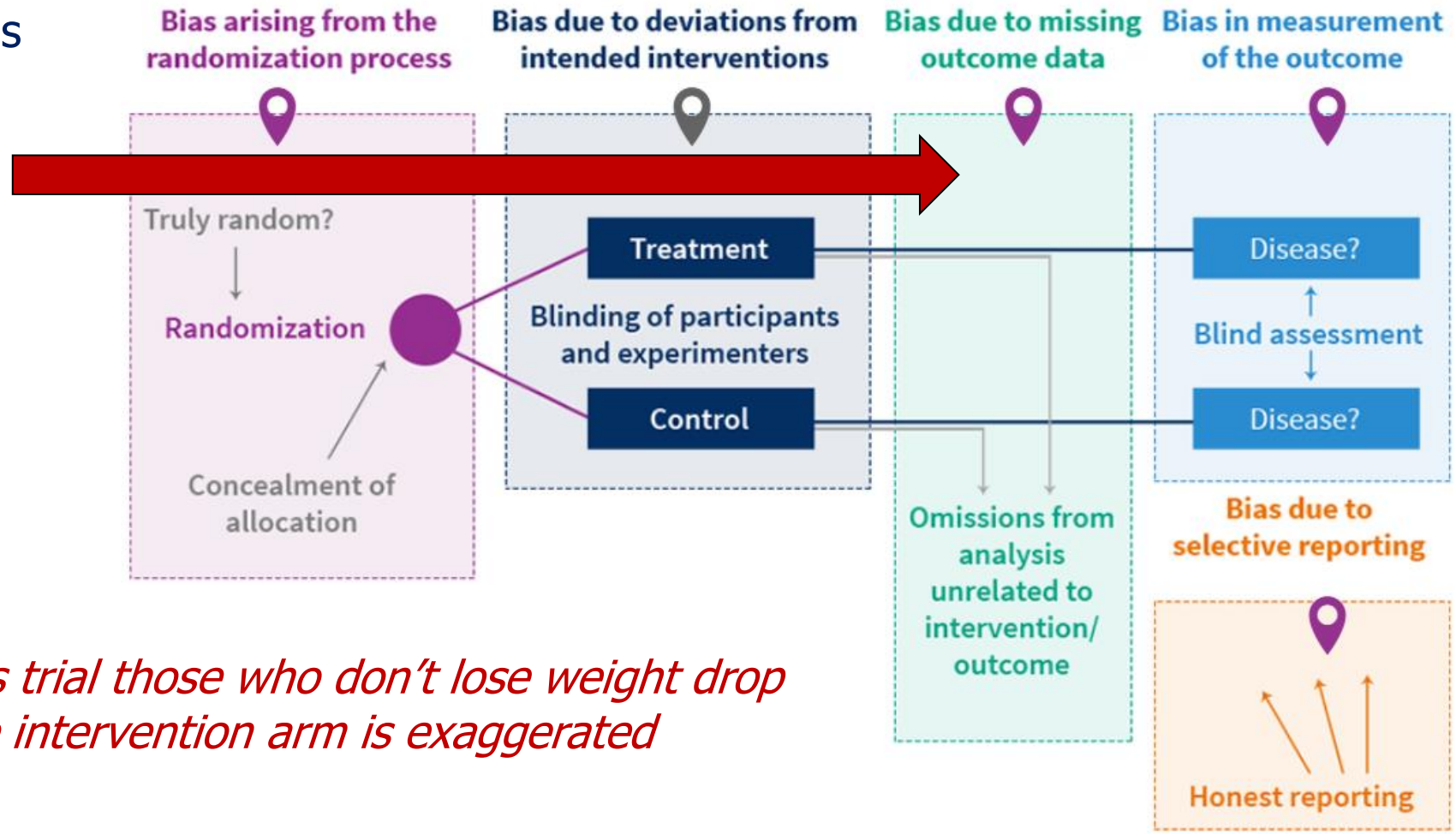


Example: participant knows they haven't been allocated to eat more oily fish, so decide to take fish oil capsules

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if….. there is substantial loss of participants from one or both arms.
The true effect of the intervention across participants is difficult to see

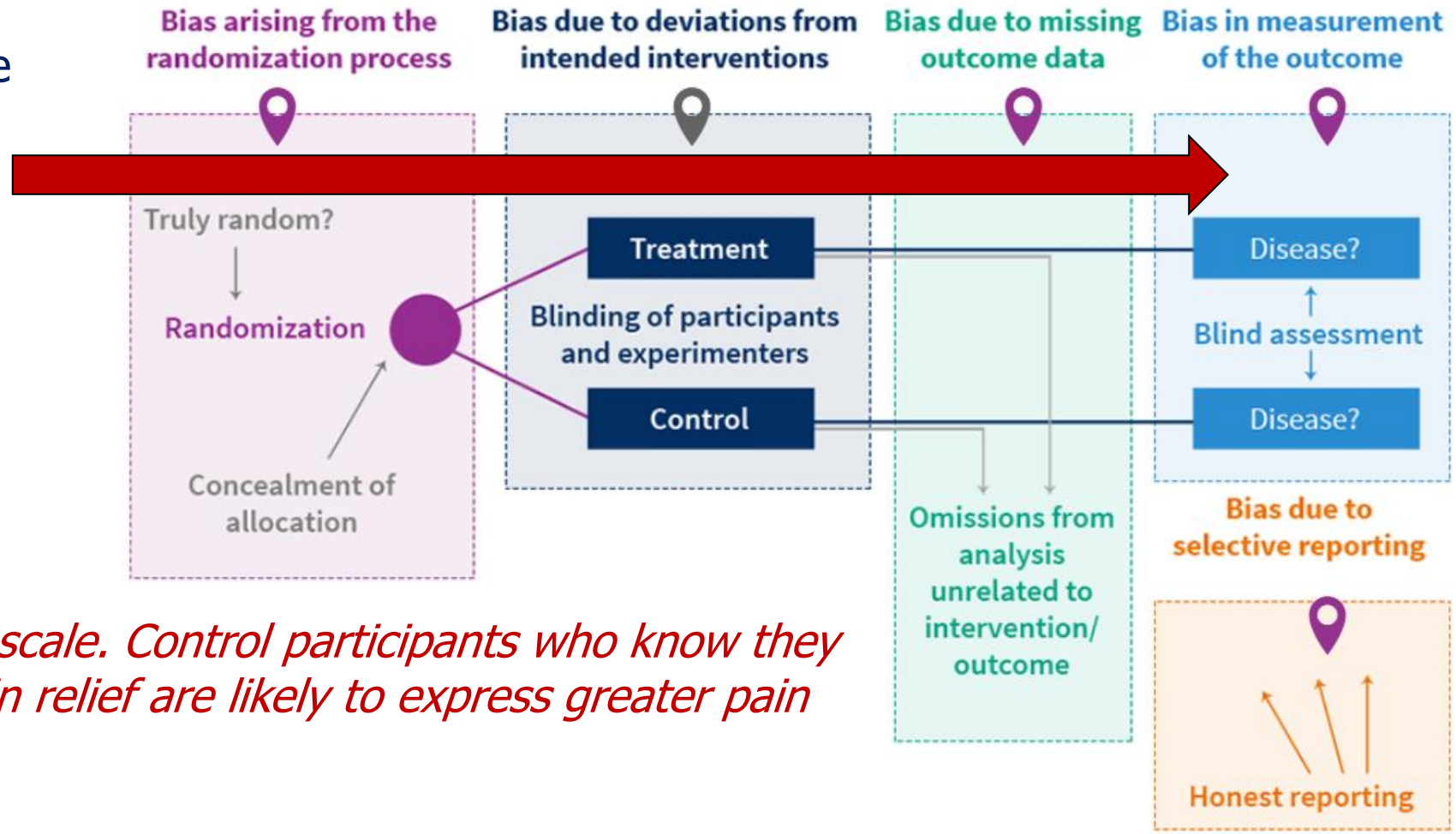


Example: in a weight loss trial those who don't lose weight drop out, so weight loss in the intervention arm is exaggerated

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if….. people involved in outcome assessment are not masked to intervention arm

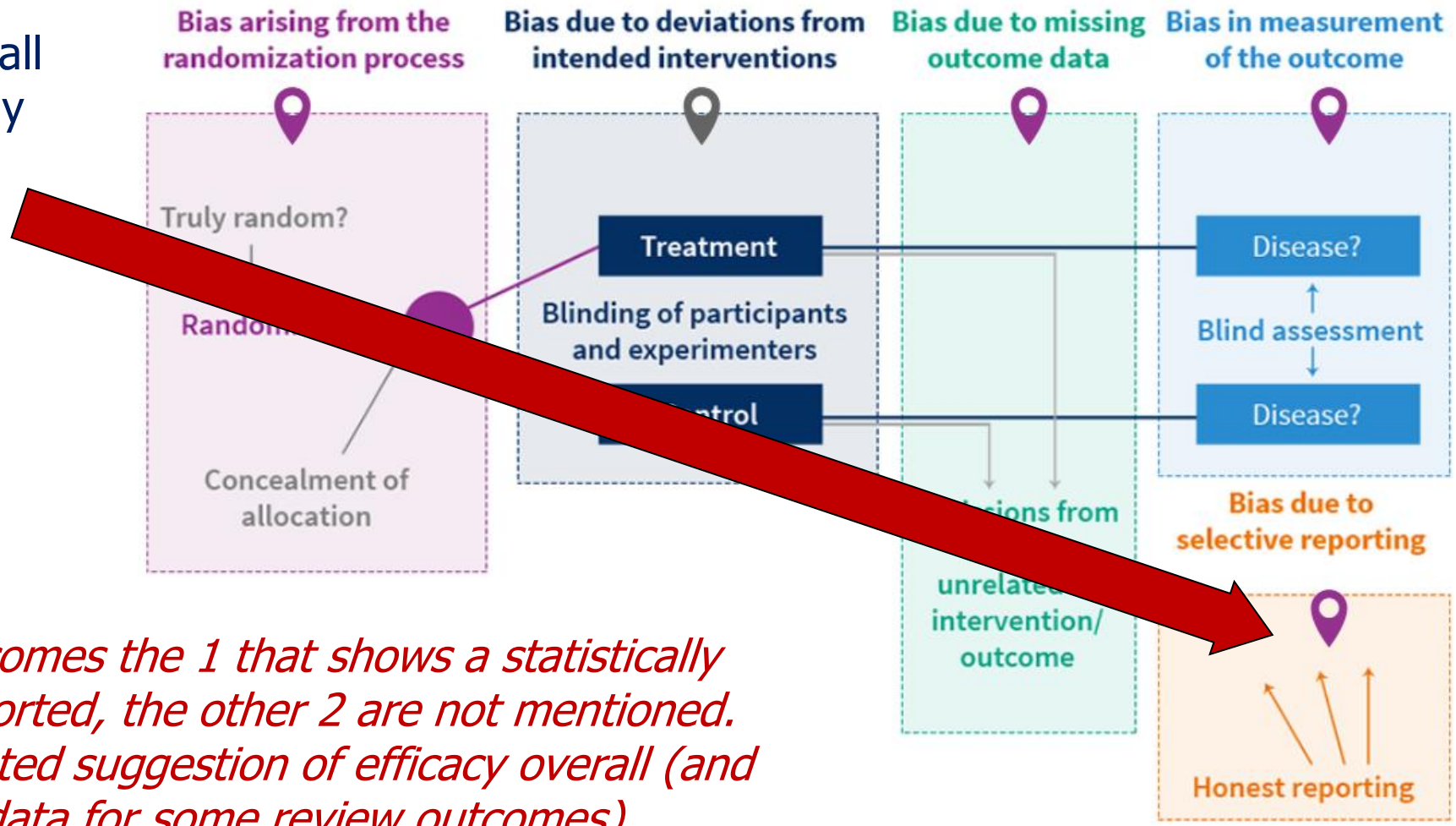


Example: outcome -pain scale. Control participants who know they did not receive active pain relief are likely to express greater pain than if unaware.

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included studies

Bias can arise if….. Not all outcomes are completely reported



Example: of 3 key outcomes the 1 that shows a statistically significant effect is reported, the other 2 are not mentioned. This gives an exaggerated suggestion of efficacy overall (and there may be missing data for some review outcomes)

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of included **observational** studies

These are the domains used for assessing study limitations in observational studies (taken from GRADE Handbook, Table 5.5)

Table 5.5: Study limitations in observational studies

	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	• Under- or over-matching in case-control studies • Selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	• Differences in measurement of exposure (e.g. recall bias in case-control studies) • Differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	• Failure of accurate measurement of all known prognostic factors • Failure to match for prognostic factors and/or adjustment in statistical analysis
Incomplete or inadequately short follow-up	Especially within prospective cohort studies, both groups should be followed for the same amount of time.

The pillars: methods to reduce the risk of bias in systematic reviews

Assessing risk of bias of includ

These are the domains used for assessing study limitations in observati studies (taken from G Handbook, Table 5.5

NASEM question: How do you consider risk of bias when evaluating diet and disease relationships? – reporting of risk of bias, and use of relevant sensitivity analyses

	hing in case-
	l unexposed in t populations
	nt of ase-control
	or outcome in cohort studies
	asurement of all ors
	for prognostic factors ent in statistical analysis
	prospective cohort studies, both uld be followed for the same amount time.

The pillars: methods to reduce the risk of bias in systematic reviews

- **Selective reporting/ Publication bias**
- Studies may be unpublished, partially published or fully published:
  - No results appear
  - Conference abstract of early or full analysis
  - Full publication of some planned outcomes
  - Full publication of all outcomes
- Details of a study may be omitted depending on:
  - Author beliefs about what is important or interesting
  - Word restrictions
  - Editor and peer reviewer ideas

A concise summary of all the best evidence on a specific question

- **Selective reporting/ Publication bias**
- RCTs:
  - pre-registration now obligatory for publication.
  - "Negative" trials can be identified even if not published
  - Analysis methods, subgrouping and outcomes prespecified (can check if adhered to)
- Cohorts & case-control studies:
  - potential for databases to be trawled for "significant" associations – these are published but non-significant ones aren't
  - Significant associations can also be found if you create post-hoc subgroups, manipulate the method of analysis or choose to report particular outcomes
  - So lots of "positive" associations are published, and the "negative" studies are invisible – we don't even know they existed

A concise summary of all the best evidence on a specific question

- **Selective reporti**
- RCTs:
  - pre-registrat
  - "Negative"
  - Analysis m
- Cohorts & c
  - potential f
    published bu
  - Significant as
    manipulate the
  - So lots of "positive
    invisible – we don't even

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NASEM question:

What are best practices for addressing publication bias?

1. Note missing outcome data at every stage: registered but unpublished, published but missing outcomes, outcome data not usable.
2. Qualify all 'answers' by degree of missing data
3. Impute if appropriate BUT run sensitivity analyses

The pillars: methods to reduce the risk of bias in systematic reviews

1. Writing the protocol
2. Searching for studies
3. Selecting studies and collecting data
4. Assessing risk of bias of included studies
5. Analysing the data - will primarily be discussed in the meeting on meta-analysis and pooling.
6. Interpreting the findings
7. Reporting the review

- "*Doing a meta-analysis is easy, doing one well is hard.*" Ingram Olkin, Professor of Statistics and Education, University of Stanford

The pillars: methods to reduce the risk of bias in systematic reviews

Analysing the data – to specify in your protocol (decide up front):

- Pre-specify levels clinical relevance
- Meta-analysis options:
  - What comparisons will you make?
  - Effect measures used for dichotomous data, continuous data, other data types
  - How you will decide whether meta-analysis is appropriate
  - Meta-analytical methods to be used, and fixed or random effects
- Which study designs to include (cluster randomised, prospective cohort etc)
  - How different designs will be analysed (never pool RCTs and observational)
  - Unit of analysis error issues

The pillars: methods to reduce the risk of bias in systematic reviews

Analysing the data – to specify in your protocol (decide up front):

- Heterogeneity
  - Assessment (study comparability, visual inspection of forest plots, I^2)
  - Investigation (planned subgroup analyses, meta-regression) – for example subgroup by baseline nutritional status
- Sensitivity analyses (to assess robustness of results) – exclude studies at highest risk of bias, imputed data or where there were borderline decisions

The pillars: methods to reduce the risk of bias in systematic reviews

Analysing the data – to specify in your protocol (decide up front):

NASEM question:
What criteria should be used to determine if individual nutrition studies have too many clinical or methodological differences (e.g., treatment, dose, population, mean BMI, duration, comparators/diets, results) to be combined into the same meta-analysis?

1. Include only studies that answer your main review question and include them all in your answer
2. Do not combine data from different methodologies
3. Use subgrouping to answer sub-questions: eg effects in those with low or high baseline status

The pillars: methods to reduce the risk of bias in systematic reviews

Analysing the data – to specify in your protocol (decide up front):

NASEM question:
What are best practices for planning appropriate subgroup and sensitivity analyses a priori?

❖ Set up main question and sub-questions eg

- What is the effect of increasing selenium on cognition?
  - Does this effect differ by baseline selenium status?
  - Does this effect differ by baseline cognitive status?
  - Does this effect differ with selenium source?

Baseline selenium status, cognitive status and selenium source are your subgroups (include in data collection).

The pillars: methods to reduce the risk of bias in systematic reviews

1. Writing the protocol
2. Searching for studies
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6. Interpreting the findings
7. Reporting the review

The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

- [Often] “information is incomplete and decision makers must wrestle with an irreducible core of uncertainty. How we take account of and express that uncertainty within the specific context of care is the crux of the issue.” Mike Bedford et al, Journal of Clinical Epidemiology (2011, 64, 1272-74)

The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

- GRADE: Assessing certainty of evidence for each main question in a review
- Consistent framework to present certainty of evidence in reviews across health
  - Risk of bias: springs from study-level risk of bias assessment for each question & sensitivity analyses
  - Inconsistency: if there is inconsistency (heterogeneity) across study results can it be explained via subgrouping or meta-regression?
  - Imprecision: does the meta-analytical pooling include both no effect and an important clinical effect?
  - Indirectness: does the evidence found address the original PICO question?

The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

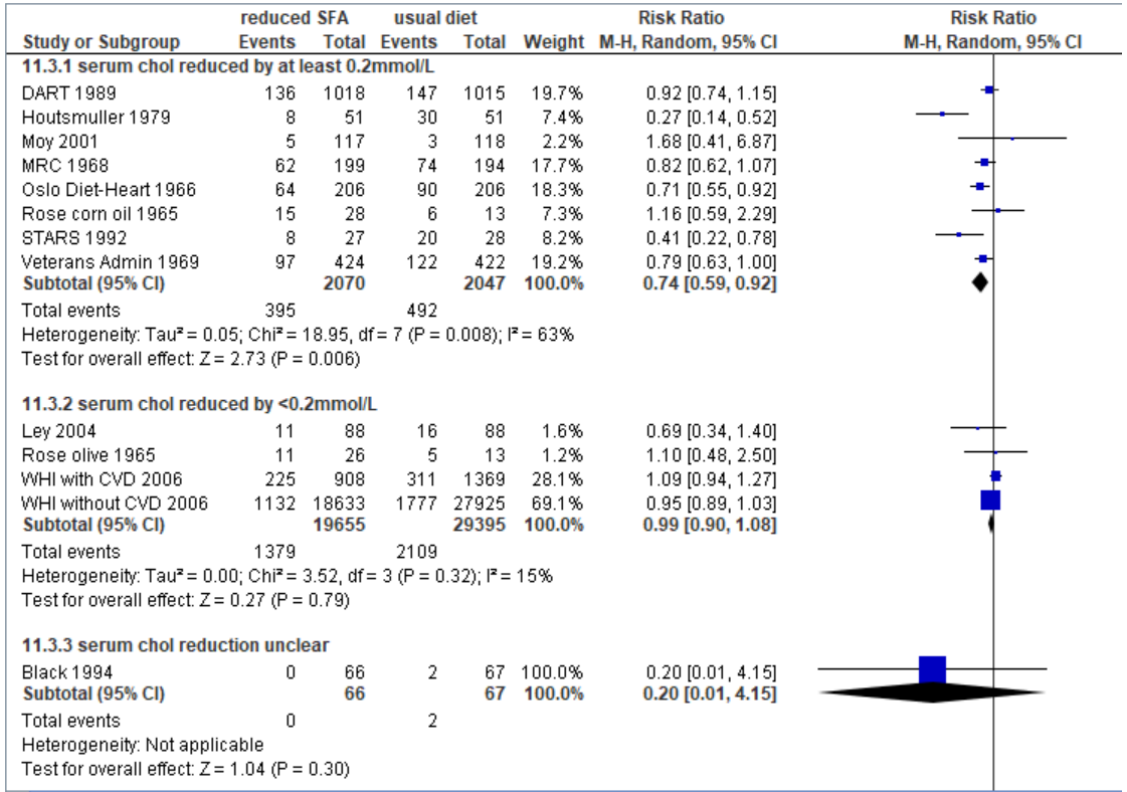
- GRADE: Assessing certainty of evidence for each main question in a review
  - Risk of bias: springs from study-level risk of bias assessment for each question
    - *In assessing risk of bias results of sensitivity analyses omitting studies at highest risk of bias are helpful– downgrade if omitting the higher risk of bias studies alters the outcome*

The pillars: methods to reduce the risk of bias in systematic reviews

GRADE

Interpreting the findings

- Inconsistency: if there is inconsistency (heterogeneity) across study results can it be explained via subgrouping or meta-regression?
  - *Here I^2 is 71% but largely explained by the difference in cholesterol-lowering, so not downgraded*



Study or Subgroup	reduced SFA Events	Total	usual diet Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.3.1 serum chol reduced by at least 0.2mmol/L						
DART 1989	136	1018	147	1015	19.7%	0.92 [0.74, 1.15]
Houtsmuller 1979	8	51	30	51	7.4%	0.27 [0.14, 0.52]
Moy 2001	5	117	3	118	2.2%	1.68 [0.41, 6.87]
MRC 1968	62	199	74	194	17.7%	0.82 [0.62, 1.07]
Oslo Diet-Heart 1966	64	206	90	206	18.3%	0.71 [0.55, 0.92]
Rose corn oil 1965	15	28	6	13	7.3%	1.16 [0.59, 2.29]
STARS 1992	8	27	20	28	8.2%	0.41 [0.22, 0.78]
Veterans Admin 1969	97	424	122	422	19.2%	0.79 [0.63, 1.00]
Subtotal (95% CI)		**2070**		**2047**	**100.0%**	**0.74 [0.59, 0.92]**
Total events	395		492			
Heterogeneity: Tau² = 0.05; Chi² = 18.95, df = 7 (P = 0.008); I² = 63%						
Test for overall effect: Z = 2.73 (P = 0.006)						
11.3.2 serum chol reduced by <0.2mmol/L						
Ley 2004	11	88	16	88	1.6%	0.69 [0.34, 1.40]
Rose olive 1965	11	26	5	13	1.2%	1.10 [0.48, 2.50]
WHI with CVD 2006	225	908	311	1369	28.1%	1.09 [0.94, 1.27]
WHI without CVD 2006	1132	18633	1777	27925	69.1%	0.95 [0.89, 1.03]
Subtotal (95% CI)		**19655**		**29395**	**100.0%**	**0.99 [0.90, 1.08]**
Total events	1379		2109			
Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 0.27 (P = 0.79)						
11.3.3 serum chol reduction unclear						
Black 1994	0	66	2	67	100.0%	0.20 [0.01, 4.15]
Subtotal (95% CI)		**66**		**67**	**100.0%**	**0.20 [0.01, 4.15]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						

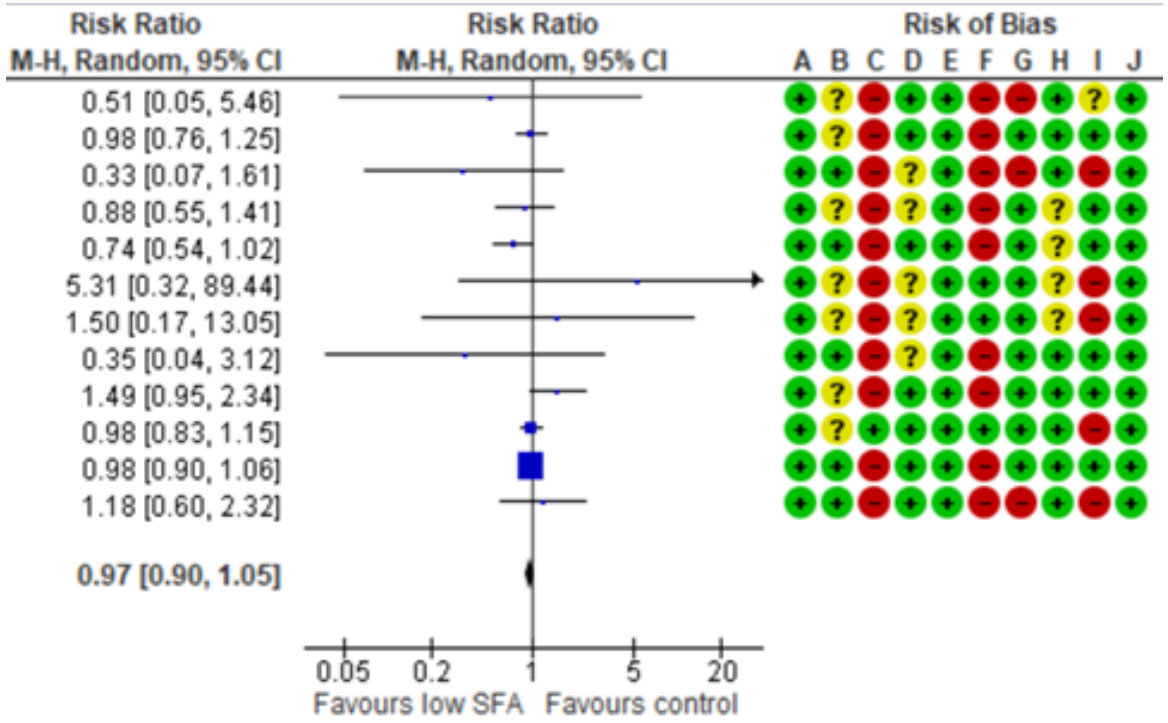
The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

- Imprecision: are there too few small studies to estimate the answer? Or does the meta-analytical pooling include both no effect and an important effect?

- Here RR 0.97 (95% CI 0.90 to 1.05)
- CI interval includes "no effect" and "small benefit"
- Downgraded by 1
- Depends on a pre-specified clinical effect

GRADE



The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

- GRADE: Assessing certainty of evidence for each main question in a review
  - Indirectness: does the evidence found address the original PICO question?
    - Issues here could include whether data comes from relevant parts of the world, includes both men and women, and includes both healthy people and those with existing CVD, younger and older people
    - Would downgrade if important areas are missing

The pillars: methods to reduce the risk of bias in systematic reviews

Interpreting the findings

- GRADE: Assessing certainty of evidence for each main question in a review
  - For a systematic review of RCTs you start by assuming high quality evidence, and downgrade for problems from risk of bias, inconsistency, imprecision and indirectness.
  - For a systematic review of observational data you start by assuming low quality evidence but can either downgrade (for same issues) or upgrade (for strong relationship, dose response, residual confounding works against)
  - If you have systematic review of both interventional and observational evidence carry out GRADE for each and use the higher rating overall.

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The pillars: methods to reduce the risk of bias in systematic reviews

Reporting the review

- “the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews” Moher et al 2009, PRISMA Statement.
- Use PRISMA to ensure that your systematic review is well reported.
- PRISMA includes
  - a flow diagram of potential studies for the review, and
  - a check list of key components to report

The pillars: methods to reduce the risk of bias in systematic reviews

- Specific issue: how to combine data from RCTs and cohort studies?

Questions asked by committee:

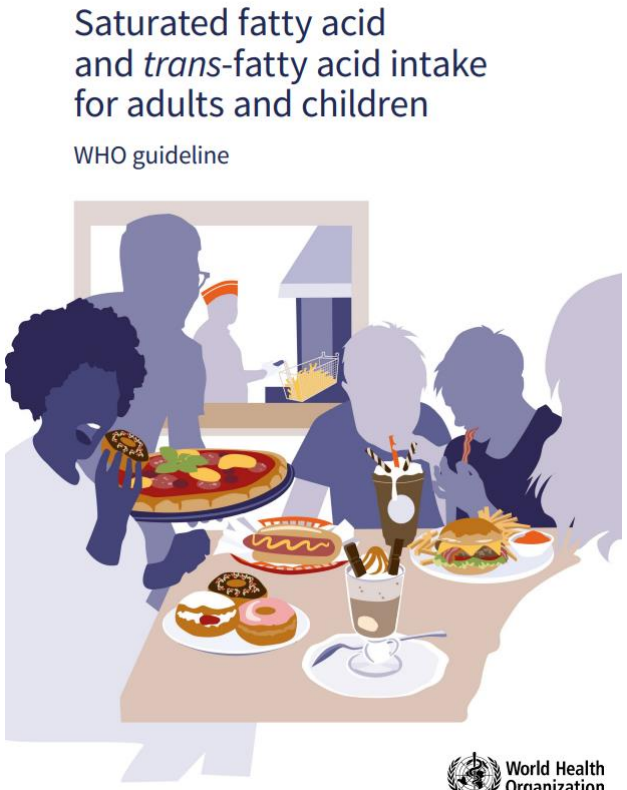
- How can meta-analyses be used to evaluate the strength of the evidence when different outcomes are reported in different studies (clinical outcomes vs. surrogate endpoints)?
- How can meta-analyses be used to evaluate the strength of the totality of evidence when there is evidence from different nutrition study designs (e.g., both intervention and observational)?

Combining evidence from different methodological types of study

Always systematically review the interventional data if you are reviewing observational data, and use this evidence together to understand the answer to your key questions (but never pool in a single forest plot!)

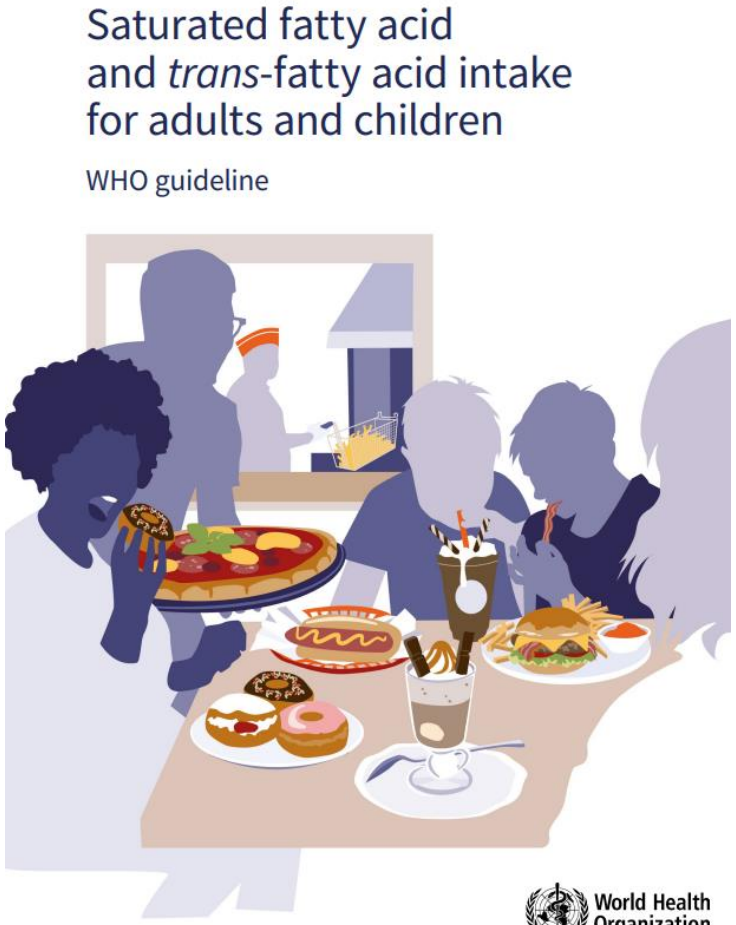
WHO NUGAG has overcome some of the issues of scarcity of trials on effects of reducing saturated fats on CVD & other NCDs by carrying out 3 separate systematic reviews:

1. SR of RCTs of reducing saturated fats (duration ≥ 2 years) on health (CVD, mortality, cancers, diabetes, lipids etc)
2. SR of prospective observational studies of saturated fat intake & health
3. SR & regression analysis of SFA intake and lipids in highly controlled metabolic studies



Combining evidence from different methodological types of study

- WHO NUGAG
  - Assessed the certainty of evidence via GRADE for each outcome for each type of evidence (SR of RCTs, SR of cohort studies, SR of metabolic studies)
  - GRADE for each outcome comes from the strongest evidence of the three reviews
  - Consistency in evidence across the 3 reviews strengthens overall GRADE assessment



World Health Organization

Assessing the validity of completed SRs & MAs

- How to assess risk of bias of existing systematic reviews? One useful tool is ROBIS
- Target audience:
  - guideline developers, authors of overviews of systematic reviews
  - others may assess your review
- ROBIS phases:

1. assess relevance
2. identify concerns
   1. Study eligibility criteria;
   2. Identification & selection of studies;
   3. Data collection & study appraisal;
   4. Synthesis & findings.

i. Judge overall risk of bias
   - Signalling questions help judge concerns

Table 1. Summary of phase 2 ROBIS domains, phase 3, and signaling questions

	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Signaling questions	1.1 Did the review adhere to predefined objectives and eligibility criteria?	2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	3.1. Were efforts made to minimize error in data collection?	4.1. Did the synthesis include all studies that it should?	A. Did the interpretation of findings address all of the concerns identified in domains 1 to 4?
	1.2 Were the eligibility criteria appropriate for the review question?	2.2 Were methods additional to database searching used to identify relevant reports?	3.2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	4.2. Were all predefined analyses reported or departures explained?	B. Was the relevance of identified studies to the review's research question appropriately considered?
	1.3 Were eligibility criteria unambiguous?	2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	3.3. Were all relevant study results collected for use in the synthesis?	4.3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs, and outcomes across included studies?	C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?
	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	2.4 Were restrictions based on date, publication format, or language appropriate?	3.4. Was risk of bias (or methodologic quality) formally assessed using appropriate criteria?	4.4. Was between-study variation minimal or addressed in the synthesis?	
	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	2.5 Were efforts made to minimize error in selection of studies?	3.5. Were efforts made to minimize error in risk of bias assessment?	4.5. Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses?	
				4.6. Were biases in primary studies minimal or addressed in the synthesis?	
Judgment	Concerns regarding specification of study eligibility criteria	Concerns regarding methods used to identify and/or select studies	Concerns regarding methods used to collect data and appraise studies	Concerns regarding the synthesis	Risk of bias in the review

Thank you for your time

- Any questions?
- email Lee: l.hooper@uea.ac.uk