Assessing risk of bias in included studies

Steps of a Cochrane review

1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. **assess studies for risk of bias**
8. analyse and present results
9. interpret results and draw conclusions
10. improve and update review

Outline

- **risk of bias in systematic reviews**
- assessing sources of bias
- putting it into practice: 'Risk of bias' tables
- incorporating findings into your review

See Chapter 8 of the Handbook

What is bias?

Systematic error or deviation from the truth

- systematic reviews depend on included studies
  - incorrect studies = misleading reviews
  - should I believe the results?
- assess each study for risk of bias
  - can’t measure the presence of bias
  - may overestimate or underestimate the effect
  - look for methods shown to minimise risk

Bias is not the same as

Imprecision

- random error due to sampling variation
- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies
- not all methodological flaws introduce bias

Reporting

- good methods may have been used but not well reported

Quality scales and checklists

- many scales available
- not supported by empirical evidence
- different scales, different conclusions
- may include criteria not related to bias
- numerical weighting not justified
- difficult for readers to interpret the score

Quality scales should not be used in Cochrane reviews

Cochrane 'Risk of bias' assessment

- 7 evidence-based domains
- review authors' judgement
  - ✓ **Low risk** of bias
  - ✘ **High risk** of bias
  - ? **Unclear**
- support for judgement
  - evidence/quotes from the paper or other sources
  - review author's explanation

Domains to address

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
- selective reporting
- other bias

You MUST consult the Handbook before completing your Risk of Bias assessment

Overview

- risk of bias in systematic reviews
- **assessing sources of bias**
- putting it into practice: ‘Risk of bias’ tables
- incorporating findings into your review

Sources of bias

Selection

Performance

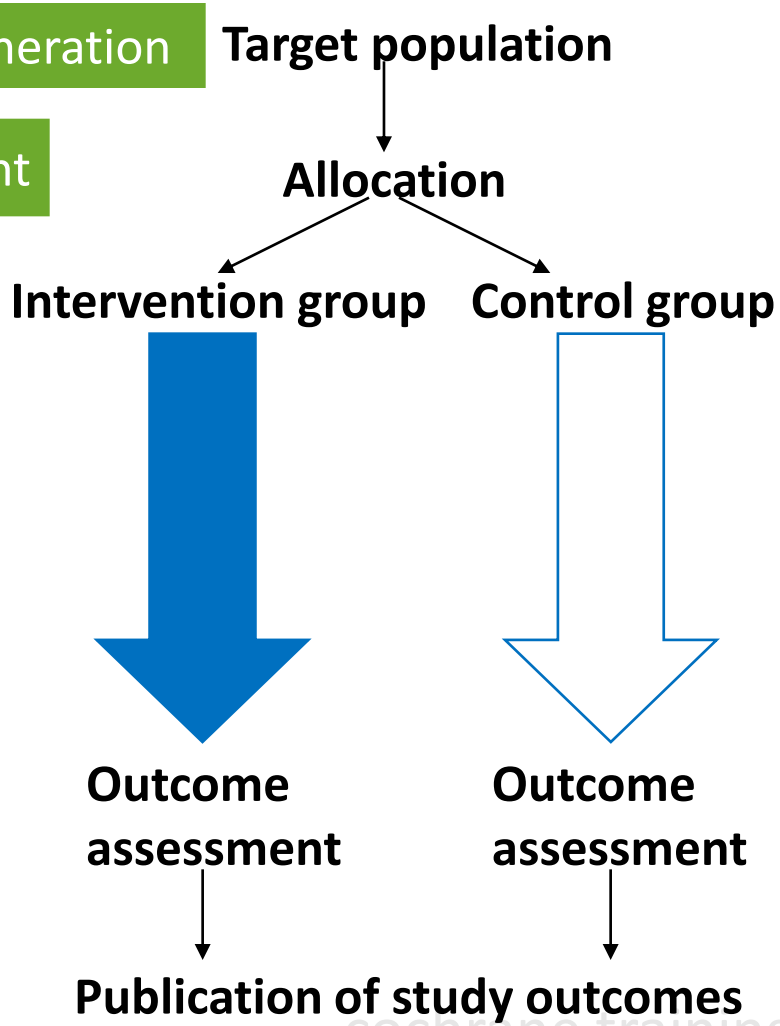
Detection

Attrition

Reporting

Random sequence generation

Allocation concealment



Random sequence generation

- occurs at the start of a trial before allocation of participants
- avoids **selection bias**
- determines a random order of assigning people into intervention and control groups
- avoids systematic differences between groups
- accounts for known and unknown confounders

Random sequence generation

Low risk – unpredictable

- random number table
- computer random number generator
- stratified or block randomisation
- minimisation
- low tech - coin toss, shuffling cards or envelopes, throwing dice, drawing lots

High risk – predictable

- quasi-random – date of birth, day of visit, ID or record number, alternate allocation
- non-random – choice of clinician or participant, test results, availability

See Section 8.9 of the Handbook

Allocation concealment

- occurs at the start of the trial during allocation of participants
- avoids **selection bias**
- when a person is recruited to the study, no-one can predict which group they will be allocated to
- ensures the strict implementation of the random sequence
  - prevents changing the order
  - prevents selecting who to recruit

Allocation concealment

Low risk – unpredictable

- central allocation (phone, web, pharmacy)
- sequentially numbered, sealed, opaque envelopes
- sequentially numbered, identical drug containers

High risk – predictable

- random sequence known to staff in advance
- envelopes or packaging without all safeguards
- non-random, predictable sequence

See Section 8.10 of the Handbook

Sources of bias

Selection

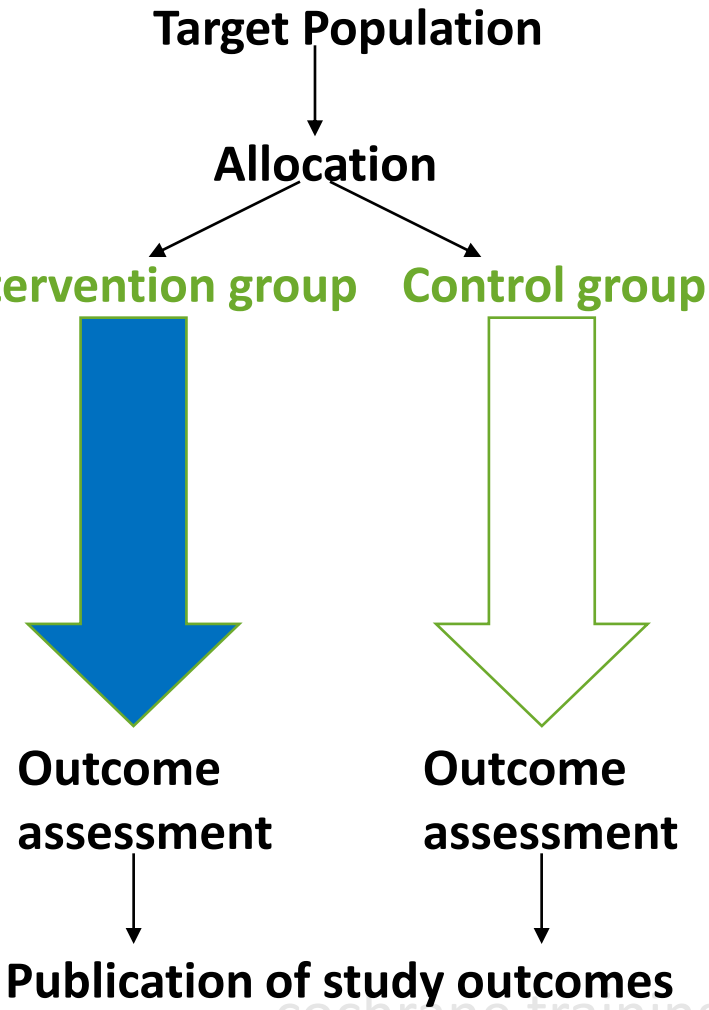
Performance

Blinding of participants, personnel

Detection

Attrition

Reporting



Blinding of participants & personnel

- avoids **performance bias**
  - different treatment of the intervention groups
  - different participant expectations
  - leads to changes in the actual outcomes
- assess carefully
  - avoid terms like “single blinding” and “double blinding”
  - is it likely that blinding was broken?
  - consider impact even if not feasible for this intervention

Blinding of participants & personnel

Low risk

- blinding, and unlikely that the blinding could have been broken
- no blinding or incomplete blinding, but outcome unlikely to be influenced

High risk

- no blinding, incomplete or broken blinding, and outcome likely to be influenced

See Section 8.11 of the Handbook

Sources of bias

Selection

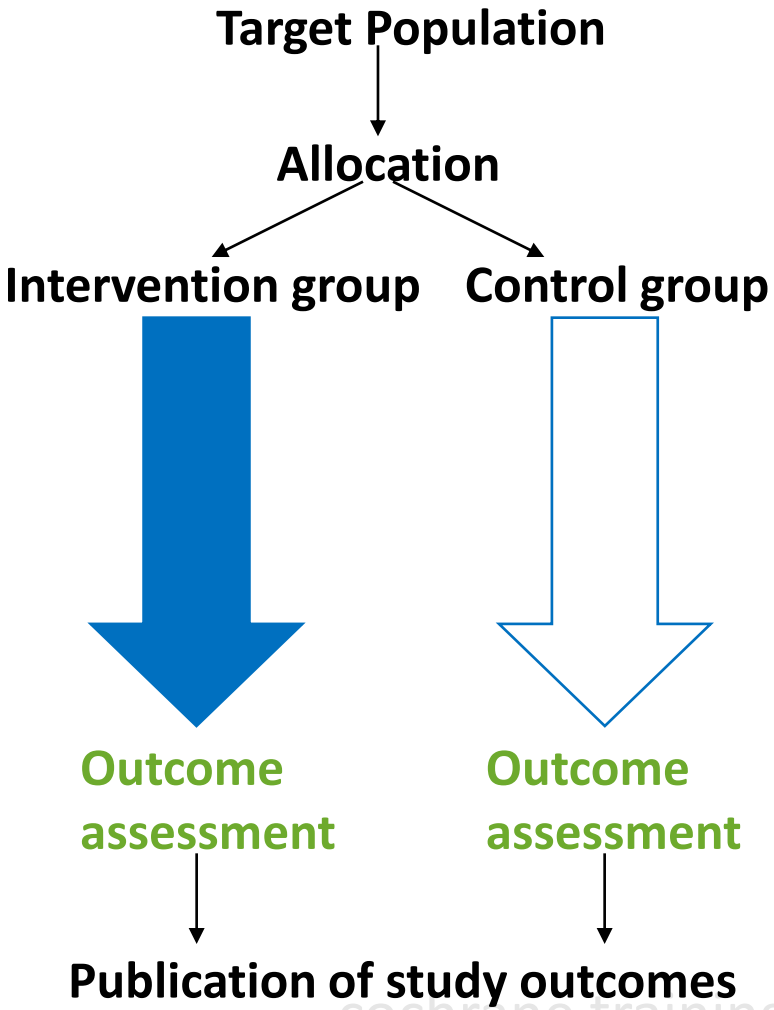
Performance

Detection

Blinding of outcome assessment

Attrition

Reporting



Blinding of outcome assessment

- avoids **detection bias**
  - measurement of outcomes affected by knowledge of the intervention received
- assess carefully
  - avoid terms like “single blinding” and “double blinding”
  - is it likely that blinding was broken?
  - may be feasible even where blinding of participants and care providers is not
  - remember that participants and personnel may also be outcome assessors

Blinding of outcome assessment

Low risk

- blinding, and unlikely that the blinding could have been broken
- no blinding, but measurement unlikely to be influenced

High risk

- no blinding or broken blinding, and measurement likely to be influenced

See Section 8.12 of the Handbook

Assessing blinding by outcome

- may reach different conclusions for different outcomes
  - measurement of only some outcomes may be blinded
  - subjective outcomes may be more vulnerable to bias
    e.g. death vs quality of life
- may apply to both **performance bias** and **detection bias**
- option to design your table with two or more outcome groups for these categories

Sources of bias

Selection

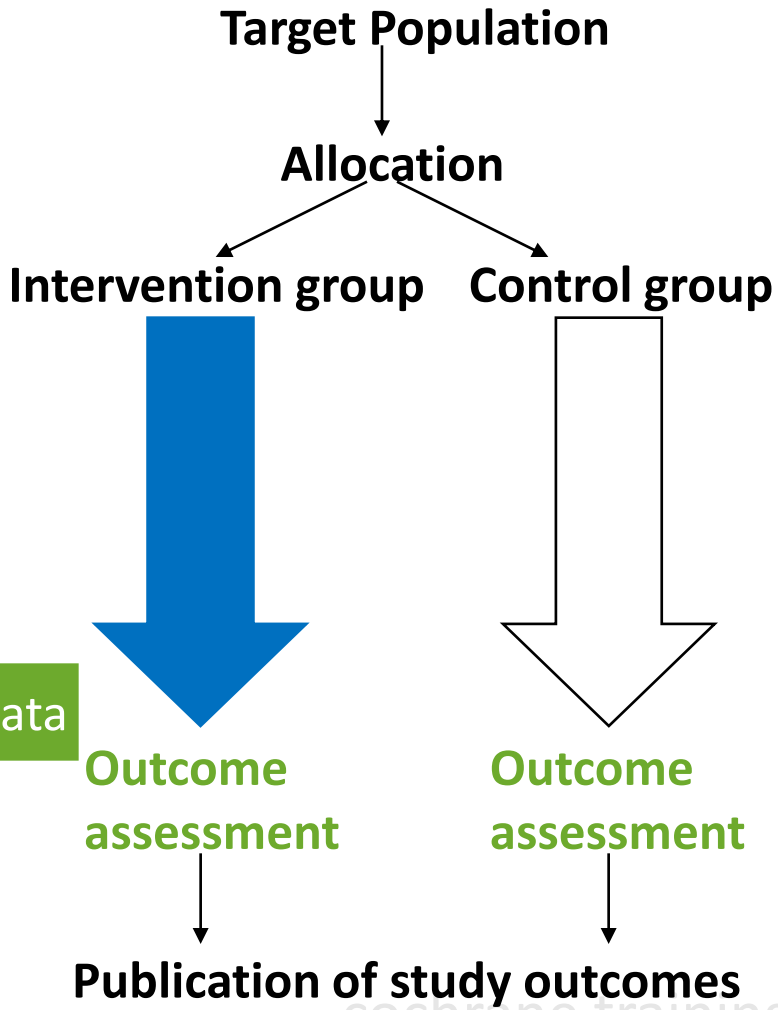
Performance

Detection

Attrition

Reporting

Incomplete outcome data



Incomplete outcome data

- when complete outcome data for all participants is not available for your review
  - attrition - loss to follow up, withdrawals, other missing data
  - exclusions – some available data not included in report
- can lead to **attrition bias**
- considerations
  - how much data is missing from each group? (include numbers in your description)
  - why is it missing?
  - how were the data analysed?

How much is too much missing data?

- **no simple rule**
- enough missing to meaningfully affect the results
  - overall proportion of missing data
  - event risk (dichotomous outcomes)
  - plausible effect size (continuous outcomes)
- reasons related to study outcomes
  - e.g. recovered, adverse event, refusal
  - reasons can have different meaning in each group
- missing data or reasons not balanced between groups

Intention-to-treat analysis

- all participants analysed in the groups randomised
  - regardless of what happened during the study
- issues that may arise
  - **per protocol** analysis
    - non-compliers excluded from analysis
  - **as-treated** analysis
    - non-compliers moved between groups
  - **imputation** of missing values
    - assumptions may be inappropriate - consult a statistician
- it may be possible to re-include some excluded data

Assessing incomplete data by outcome

- may reach different conclusions for different outcomes
  - may be more missing data at different time points
  - some outcomes may have more missing data
    e.g. sensitive questions, invasive tests
- option to design your table with two or more outcome groups for ‘incomplete data’

Incomplete outcome data

Low risk

- no missing data
- reasons for missing data not related to outcome
- missing data balanced across groups, and reasons similar
- proportion missing or plausible effect size not enough to have a clinically relevant effect

High risk

- reasons related to outcome, and imbalance in numbers or reasons
- proportion missing or plausible effect size enough to have a clinically relevant effect
- 'as-treated' analysis with substantial departure from allocation
- inappropriate use of imputation

See Section 8.13 of the Handbook

Sources of bias

Selection

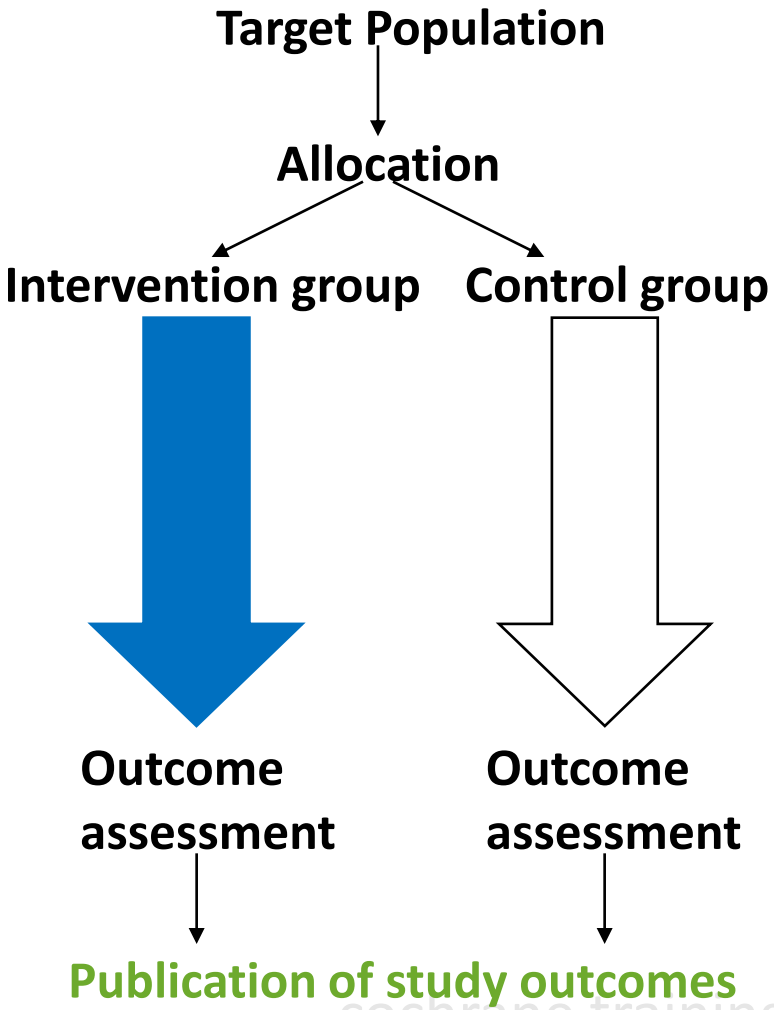
Performance

Detection

Attrition

Reporting

Selective reporting



Selective reporting

- can lead to **reporting bias**
- statistically significant results more likely to be reported
  - as planned
  - in detail
- difficult to determine
  - compare methods to results – look for:
    - outcomes measured (or likely to be measured) but not reported
    - outcomes added, statistics changed, subgroups only
    - reporting that cannot be used in a review
      (e.g. stating non-significance without numerical results)
  - refer to study protocol or trial register
- focus on outcomes of interest to your review

Selective reporting

Low risk

- protocol is available and all pre-specified outcomes of interest to the review reported in the pre-specified way
- protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported

Unclear risk

- **most studies will be judged in this category**

High risk

- outcomes not reported as pre-specified or expected
  - e.g. missing, added, subsets, unexpected measurements or methods
- outcomes reported incompletely so they cannot be entered in a meta-analysis

See Section 8.14 of the Handbook

Other sources of bias

- must be a clear rationale why a factor may cause bias
- do **not** include
  - imprecision (e.g. small sample size)
  - diversity (e.g. inadequate dose, unusual population)
  - other measures of quality (e.g. ethics approval, funding)
- if possible, identify important issues in your protocol
- option to add rows to your table for items to be assessed across all studies

Other sources of bias

Low risk

- study appears to be free of other sources of risk

High risk

- issues specific to the study design
  - carry-over in cross-over trials
  - recruitment bias in cluster-randomised trials
  - non-randomised studies
- baseline imbalance
- blocked randomisation in unblinded trials
- differential diagnostic activity
- other bias

See Section 8.15 of the Handbook

Overview

- risk of bias in systematic reviews
- assessing sources of bias
- **putting it into practice: 'Risk of bias' tables**
- incorporating findings into your review

Completing the assessments

- at least two assessors
  - ensure all understand the methodological issues
  - include content and methods experts
- pilot on 3-6 studies to check consistency of assessment
- look for missing information
  - study protocol
  - contact authors

‘Risk of bias’ tables

- one for each included study
- your judgement for each domain

  ✓ **Low risk**

  ✘ **High risk** - consider risk of **material** bias, not any bias

  ? **Unclear** = not enough information to make a clear judgement
- support for judgement
  - direct quotes from the paper or study author where possible
  - additional comments
  - rationale for any assumptions (e.g. “probably done”)
  - state explicitly if no information available

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...participants born on even days were assigned to the experimental group and participants born on odd days were assigned to the control group."
Allocation concealment (selection bias)	High risk	Comment: allocation by date of birth would allow prediction of the allocation sequence.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Caffeinated and decaffeinated coffee... was identical in appearance, colour and taste." Comment: it is likely that participants were blinded. Blinding of study personnel was not described.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: Blinding of outcome assessors was not described.
Blinding of outcome assessment (detection bias) Reaction time	Low risk	Comment: Blinding of outcome assessors was not described, but is unlikely to affect measurement of this outcome.
Incomplete outcome data (attrition bias)	High risk	Comment: outcome data for adverse events were only reported for 53 of 58 participants in the caffeine group. Reasons for loss to follow-up were not described.
Selective reporting (reporting bias)	High risk	Comment: alertness was the primary outcome of the study, but data were not reported. Study protocol was not available to identify any other unreported outcomes. Outcome data were presented for drowsiness although this was not listed as an outcome of interest in the study methods.
Other bias	Low risk	Comment: none were identified.

Overview

- risk of bias in systematic reviews
- assessing sources of bias
- putting it into practice: 'Risk of bias' tables
- **incorporating findings into your review**

Prioritise domains for your review

- all reviews address all domains, but you can select one or more as priorities for your review
  - specify in your protocol
- give a rationale, considering:
  - empirical evidence of impact
  - likely direction of impact
    - bias most likely to exaggerate effect
    - if likely to underestimate and a significant effect observed, may be ok
  - likely magnitude of impact in relation to observed effect

See Handbook Sections 8.5-8.14

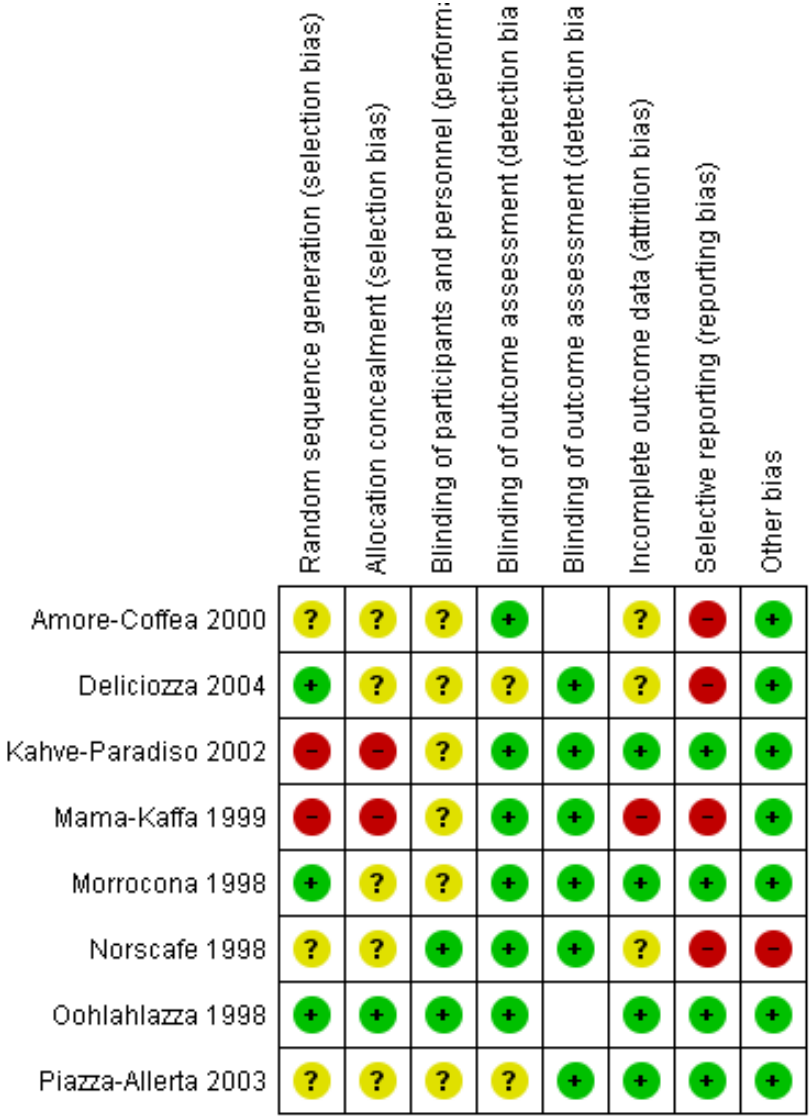
Incorporating findings into your review

- always give a narrative description
  - may be missed by readers
  - does not address impact on results
- may restrict primary analysis to studies at low risk
  - based on reasoned (but arbitrary) key domains
  - always conduct sensitivity analysis
- may present a stratified analysis
- may explore the impact further
  - subgroup analysis
  - meta-regression - get statistical advice

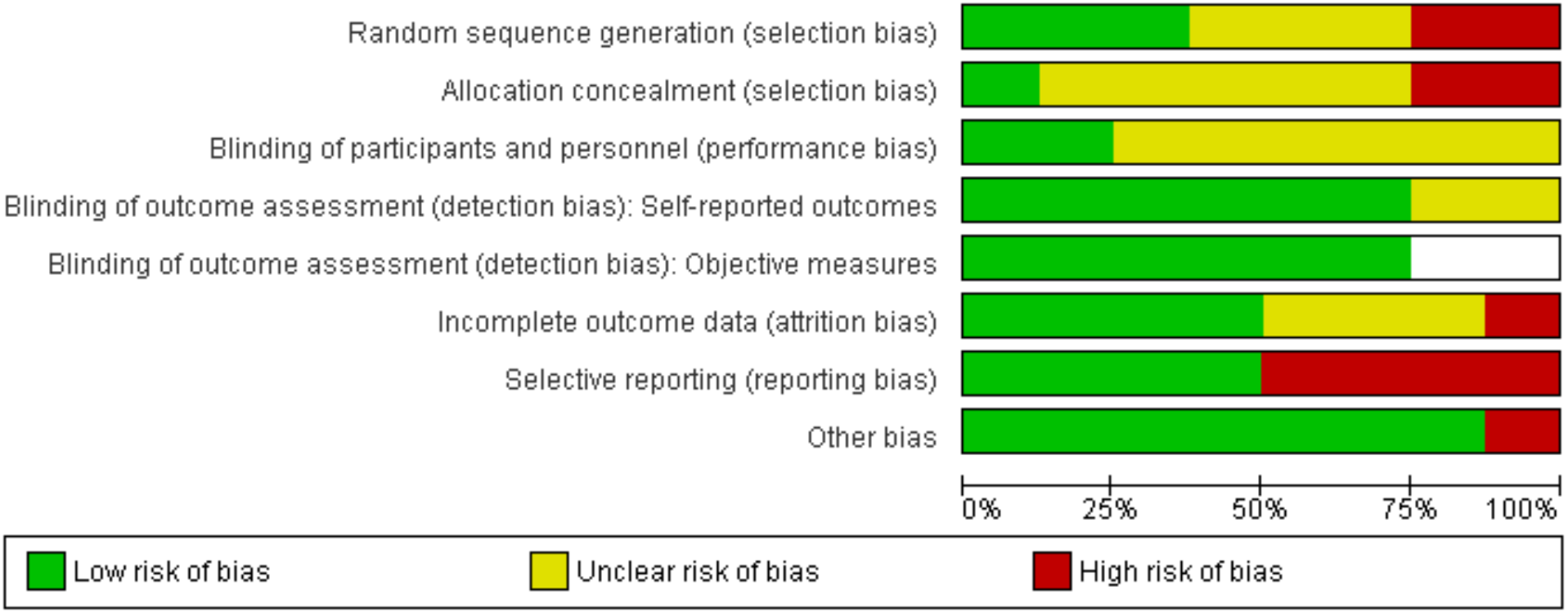
Reaching an overall interpretation

- don’t try to summarise all outcomes and all studies at once
- summarise by **outcome**
  - outcome may have different risk assessments (e.g. blinding, incomplete data)
  - not all studies contribute to each outcome
  - start by summarising **within a study**, then **across studies**
- studies at ‘unclear’ risk should not be grouped with ‘low risk’ without a rationale

Risk of bias summary

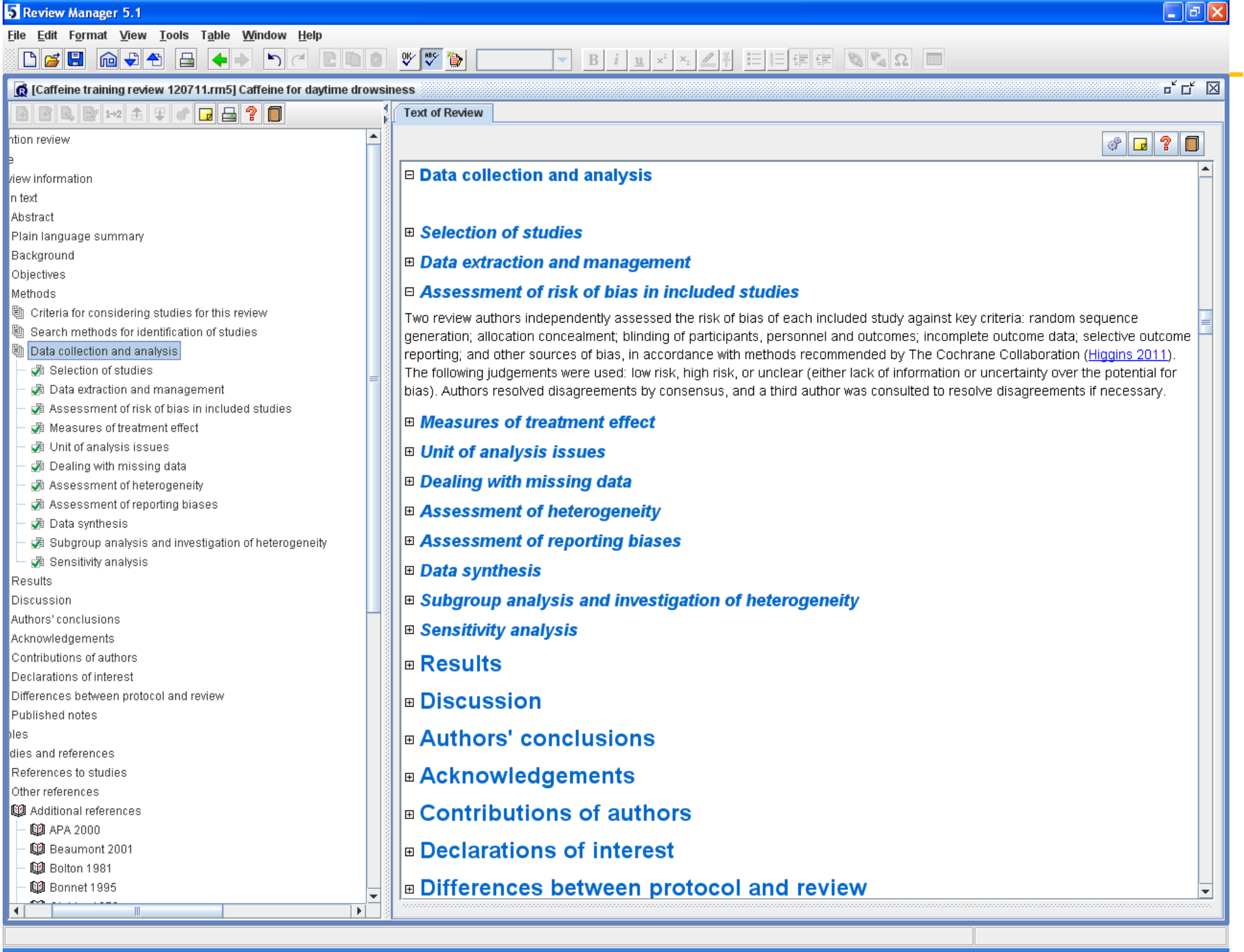


Risk of bias graph



What to include in your protocol

- check with your CRG for standard text
- brief description of risk of bias assessment tool
  - list domains
  - refer to Handbook Chapter 8
- more than one author will assess risk of bias
- how will disagreements will be resolved?
- are there specific domains you consider to be important for the review?
- how will you incorporate findings into your analysis?


Review Manager 5.1
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[Caffeine training review 120711.rm5] Caffeine for daytime drowsiness
Text of Review
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n text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Selection of studies
Data extraction and management
Assessment of risk of bias in included studies
Measures of treatment effect
Unit of analysis issues
Dealing with missing data
Assessment of heterogeneity
Assessment of reporting biases
Data synthesis
Subgroup analysis and investigation of heterogeneity
Sensitivity analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
bles
dies and references
References to studies
Other references
Additional references
APA 2000
Beaumont 2001
Bolton 1981
Bonnet 1995
Data collection and analysis
Selection of studies
Data extraction and management
Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias of each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by The Cochrane Collaboration (Higgins 2011). The following judgements were used: low risk, high risk, or unclear (either lack of information or uncertainty over the potential for bias). Authors resolved disagreements by consensus, and a third author was consulted to resolve disagreements if necessary.
Measures of treatment effect
Unit of analysis issues
Dealing with missing data
Assessment of heterogeneity
Assessment of reporting biases
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Sensitivity analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review

Take home message

- biased studies may lead to misleading reviews
- seven domains of bias to be assessed
- describe what happened in detail and give your judgement
- consider the possible effects and use appropriate caution in interpreting your results

References

- Higgins JPT, Altman DG, Sterne JAC (editors). **Chapter 8: Assessing risk of bias in included studies**. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Acknowledgements

- Compiled by Miranda Cumpston
- Based on materials by the Cochrane Bias Methods Group and the Australasian Cochrane Centre
- Approved by the Cochrane Methods Board