Assessing risk of bias to non-randomised studies (NRS) [for systematic reviews]

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Non-randomised studies

Any quantitative study estimating the effects of an intervention (benefit or harm) that does not use randomisation to allocate interventions to participants or units of care such as general practices (including studies where 'allocation' occurs in the course of usual treatment decisions or people's choices, i.e. studies usually called 'observational') .

NRSMG chapter in Cochrane Collaboration handbook

- Chapter 13 in 'Part 3' of Handbook (additional topics)
  - www.cochrane.org/resources/handbook/
  - Also chapter 8 in 'Part 2': "Assessing risk of bias"
- Considers what's different when doing a systematic review that includes NRS
- This workshop focuses on what's different about NRS when assessing risk of bias

Validity and applicability

		Risk of bias: Low	Risk of bias: High
Applicability	Good	✓	?
	Poor	?	✗

Validity and applicability

How to have good applicability and low risk of bias?

- Pragmatic RCT, **or**
- Natural experiment with low risk of bias

Which natural experiments have a low risk of bias?

- Population-based interventions often target subjects in 'clusters' – complex designs
  - "[Cohort] controlled before-and-after studies" (CBA)
  - "[Controlled] interrupted time series" ([C]ITS)
- Other prospective studies (?)

Validity of NRS

- Comparisons of effect estimates from RCTs and NRS not helpful [Deeks et al., HTA 2003;7(27)]
- Features of NRS make them at greater risk of bias compared to RCTs – and at more or less risk of bias with respect to each other
- Different study design features associated with more or less bias, e.g.:
  - Prospective designs usually have less measurement error than retrospective designs
  - Allocation by researchers may lead to different selection bias than allocation by practitioners or people's preferences

Example: Poulstrop et al. 2000

Research question [review question?]:

P Elderly people living in the community

I Community health programme to prevent falls [causing injury]: (a) information [by post and through social clubs]; (b) home visits by district nurses to 70-74 year-olds, informing about and reducing risks; (c) home visits by GPs for all 75-79 year-olds; (d) information to [home helpers?]

C Absence of the intervention

O Falls causing injuries [sufficiently serious to cause attendance at a hospital for investigation]

Assessment of risk of bias

- NRS are at risk of same biases as RCTs (selection, performance, detection and attrition) – but more so
- RCTs and NRS differ primarily with respect to selection bias – but no method of assessing it
- Cochrane Collaboration "risk of bias" tool – most items apply to any cohort study; but need to supplement with item about confounding
- Judge on 5-point scale to differentiate studies at varying risk of bias – but also on 'level playing field' with RCTs (1 = low risk of bias in RCT)

Item	Judgement [a]	Description (quote from paper, or describe key information)
1. Sequence generation		
2. Allocation concealment		

- **Assess these items as giving risk to low or high risk of bias.**
- **Record "unclear" if inadequate reporting prevents a judgement being made.**

- **For all NRS, sequence generation gives risk to high risk of bias.**

3a. Confounding [b]	**Low extr. fracture**		
3b. Confounding [b]	**Hip fracture**		
4a. Blinding?	**Low extr. fracture**		
4b. Blinding?	**Hip fracture**		

- **Assess these items on a [5]-point scale as giving rise to: 1=low, …. 5=high risk of bias.**
- **Record "unclear" if inadequate reporting prevents a judgement being made.**

- **Confounding, blinding, incomplete outcome data and selective reporting are judged for each outcome considered in the review**

Confounding (selection bias)

- Compile an a priori list of “important” confounders – outcome specific?
- Which confounders on list were “considered”? Were the most important confounders considered?
- How precisely were confounders measured?
- Were confounders distributed similarly in intervention and control cohorts?
- How carefully were confounders “controlled for”?
- How did researchers control for confounding

Confounder	Considered	Precision	Imbalance	Adjustment
Age	☐	☐	☐	☐
Sex	☐	☐	☐	☐
Marital status	☐	☐	☐	☐
Living in home / institution	☐	☐	☐	☐
Living in rural / urban setting	☐	☐	☐	☐
Distance from home to hospital	☐	☐	☐	☐
Other:	☐	☐	☐	☐
Other:	☐	☐	☐	☐
Other:	☐	☐	☐	☐
Other:	☐	☐	☐	☐

8.	*A priori* protocol? [c]		
9.	*A priori* analysis plan? [d]		

- **Assess these items as giving rise to low (yes) or high risk (no) of bias.**
- **Record "unclear" if inadequate reporting prevents a judgement being made.**

- **Note: instrument is a checklist of items, NOT a 'scale'**

Data extraction in small groups

- Task: to extract relevant data from a NRS
  - Discuss items in a group, make decision / judgement individually
- Groups all extracting data from one paper
- Usual small group 'rules': appoint a spokesperson, stick to time
- Feedback session will focus on:
  - Distribution of participants' answers
  - Workshop leader's view, with justification

Assessing risk of bias

- Need additional information about method of allocation – details provided by study design checklist
- Need more information about confounding factors
- But not obvious that information about confounding can ever be complete
  - Possible to identify all relevant confounders? How?
  - Different confounders considered in different papers
  - Confounding factors measured in different ways
  - Confounding factors adjusted for in different ways
- Varying risk of bias contributes to heterogeneity

Assessment of confounding

- Unadjusted estimates very likely to be biased
- But adjusted estimates very unlikely to be 'equivalent' across studies
- Different methods for adjusting represents an additional source of variation between studies
- Not clear how much detail about confounding is required – time consuming to extract and not well reported

Summary

If you do a systematic review that includes NRS:

- DO extract detailed data carefully / systematically
- DO apply a checklist of "what researchers did"
- DO assess risk of bias appropriately
- DO draw forest plots to display results across studies; sort plots by key study design features
- Do NOT pool results across studies (if you do pool, do not pool across study designs)
- Case control studies?