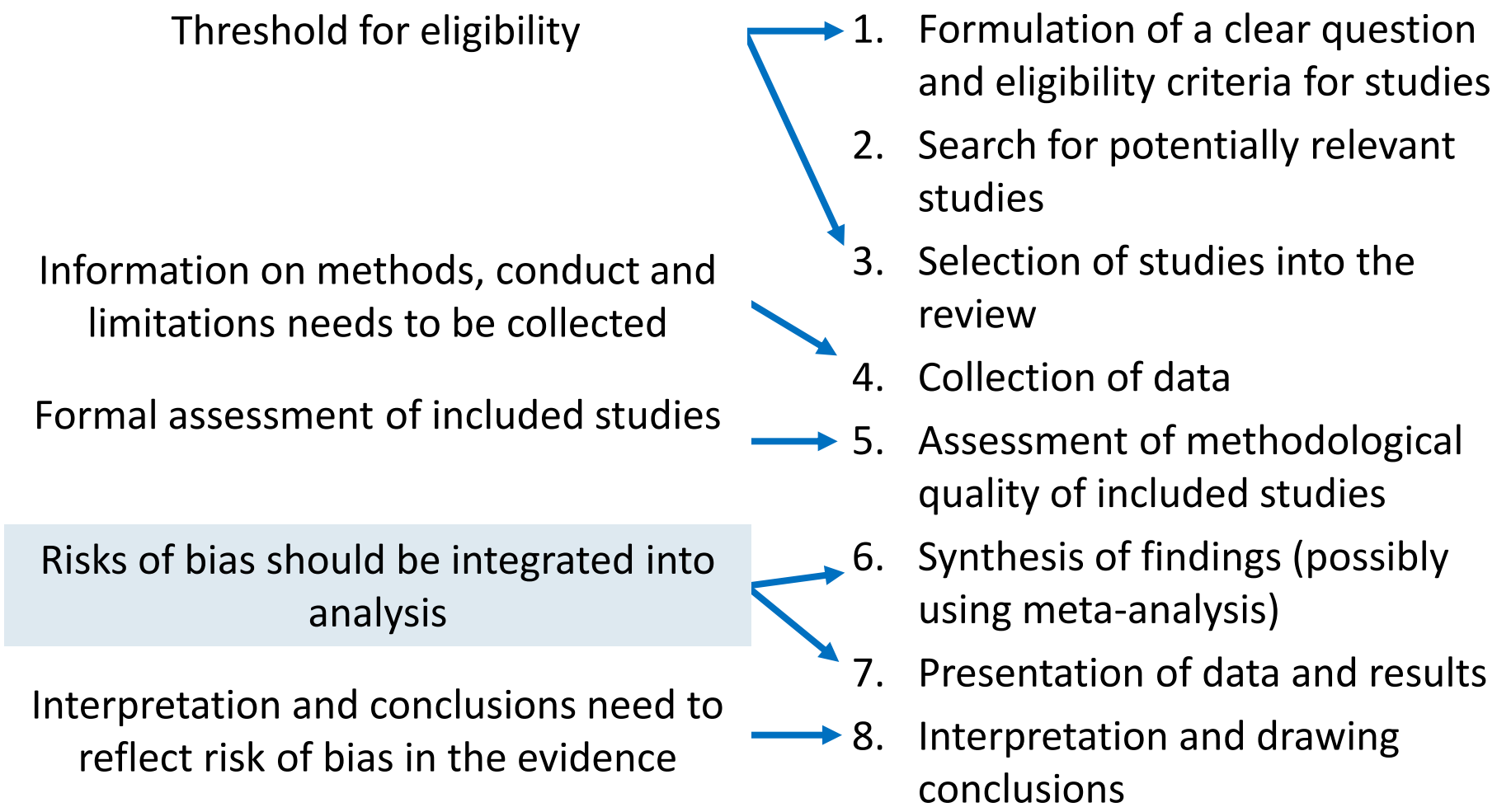
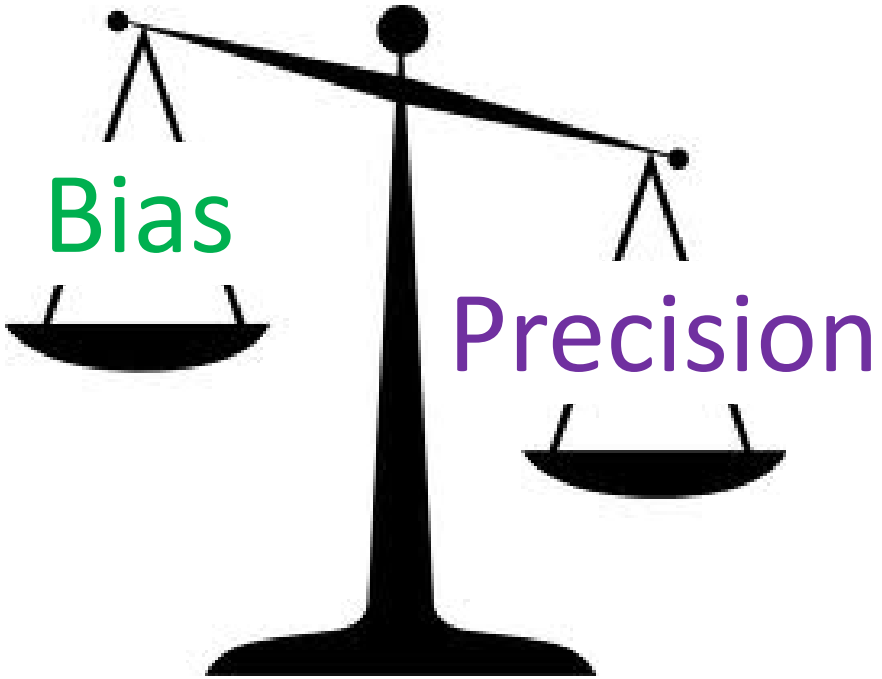
Incorporating 'risk of bias' assessments into meta-analyses

Julian Higgins

Where risk of bias might be addressed in a systematic review



Incorporating assessments into analyses



Only the studies at low risk of bias:
Low risk of bias, but
may be imprecise (wide confidence interval) because of limited information

All the studies:
High precision, but
may be seriously biased because of flaws in the conduct of some of the studies.

Comparison of subgroups, and meta-regression

- Explore the relationship between component(s) of study quality (e.g. blinding) and overall result
- Avoid using scales

What is meta-regression?

- A method for investigating possible causes of heterogeneity in a meta-analysis
- Relates study characteristics to their sizes of effect

- Problems we can address using meta-regression:
  - Does the intervention work better if given for longer?
  - Are smaller odds ratios observed in high-risk populations?
  - Is inadequate allocation concealment associated with a larger effect estimate?
  - Is there a relationship between sample size and effect size (e.g. due to publication bias)?

Limitations of meta-regression

- Low power in most Cochrane reviews:
  - unable to detect relationships that are there
  - typically cannot learn reliably about biases within one review or meta-analysis
- Spurious findings
  - high risk of false positive results by chance
- Confounding
  - cannot conclude causality
  - since associations are observational
- Can't be done in RevMan

Sensitivity analysis

- Are results sensitive to decisions and assumptions made to obtain them
- e.g.
  - Same result in ‘better’ studies?
  - Same result if [unblinded/short/high drop-out] studies excluded?

- the major approach to incorporating risk of bias assessments in Cochrane reviews is to **restrict** meta-analyses to studies at low (or lower) risk of bias, or to **stratify** studies according to risk of bias.

Options

- Primary analysis restricted to studies at low (or low and unclear) risk of bias
  - always conduct sensitivity analysis
- Present multiple (stratified) analyses
- Present all studies and provide a narrative discussion of risk of bias
  - be missed by readers
  - does not address impact on results

Primary analysis restricted to studies at low (or low and unclear) risk of bias

- Exclude studies with high risk of bias from the synthesis
- Based on summary judgements or one or more key domains
- All thresholds are arbitrary
  - spectrum from ‘free of bias’ to ‘undoubtedly biased’
- Problematic if few trials
- Perform sensitivity analyses showing how conclusions might be affected if studies at high risk of bias were included

What about ‘Unclear risk of bias’?

- It is recommended that review authors do not combine studies at ‘low’ and ‘unclear’ risk of bias in analyses, unless they provide specific reasons for believing that these studies are likely to have been conducted in a manner that avoided bias. In the rest of this section, we will assume that studies assessed as at low risk of bias will be treated as a separate category.

Present multiple (stratified) analyses

- May produce at least three estimates of the intervention effect
  - high risk of bias
  - low risk of bias
  - all studies
- Present two or more with equal prominence?
- May be confusing for readers
- Stratified *forest plots* present all information transparently
-

Restrict or stratify?

- Based on
  - context of the review
  - balance between the potential for bias and the loss of precision when studies at high or unclear risk of bias are excluded

- Recall, lack of a statistically significant difference between studies at high and low risk of bias should not be interpreted as implying absence of bias
  - because meta-regression analyses typically have low power

SoF elements

Summary of findings table

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Glucosamine versus placebo for treating osteoarthritis						
Patient or population: patients with treating osteoarthritis **Settings:** **Intervention:** Glucosamine versus placebo (adequate allocation concealment)						
Outcomes 1	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)** 3b	**No of Participants (studies)** 4	**Quality of the evidence (GRADE)** 5	**Comments** 6
	Assumed risk 2	**Corresponding risk** 3a				
	Control	Glucosamine versus placebo (adequate allocation concealment)				

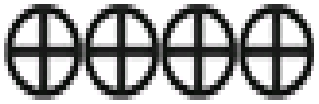
1. List of all important outcomes (desirable and undesirable)
2. A measure of the typical burden of these outcomes on control group
3. Absolute and relative magnitude of effect (if both are appropriate)
4. Numbers of participants in studies addressing these outcomes
5. Rating of quality of evidence for each outcome
6. Space for comments

What is GRADE?

- Judgment about the quality of evidence for each main outcome

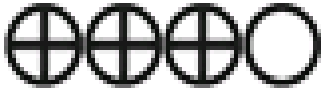
- Within the context of a systematic review, GRADE reflects how confident we are that an estimate is close to the truth

GRADE in a nutshell



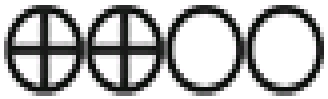
High

Further research is very unlikely to change our confidence in estimate of effect



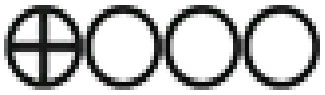
Moderate

Further research likely to have impact on confidence in the estimate of effect and may change the estimate



Low

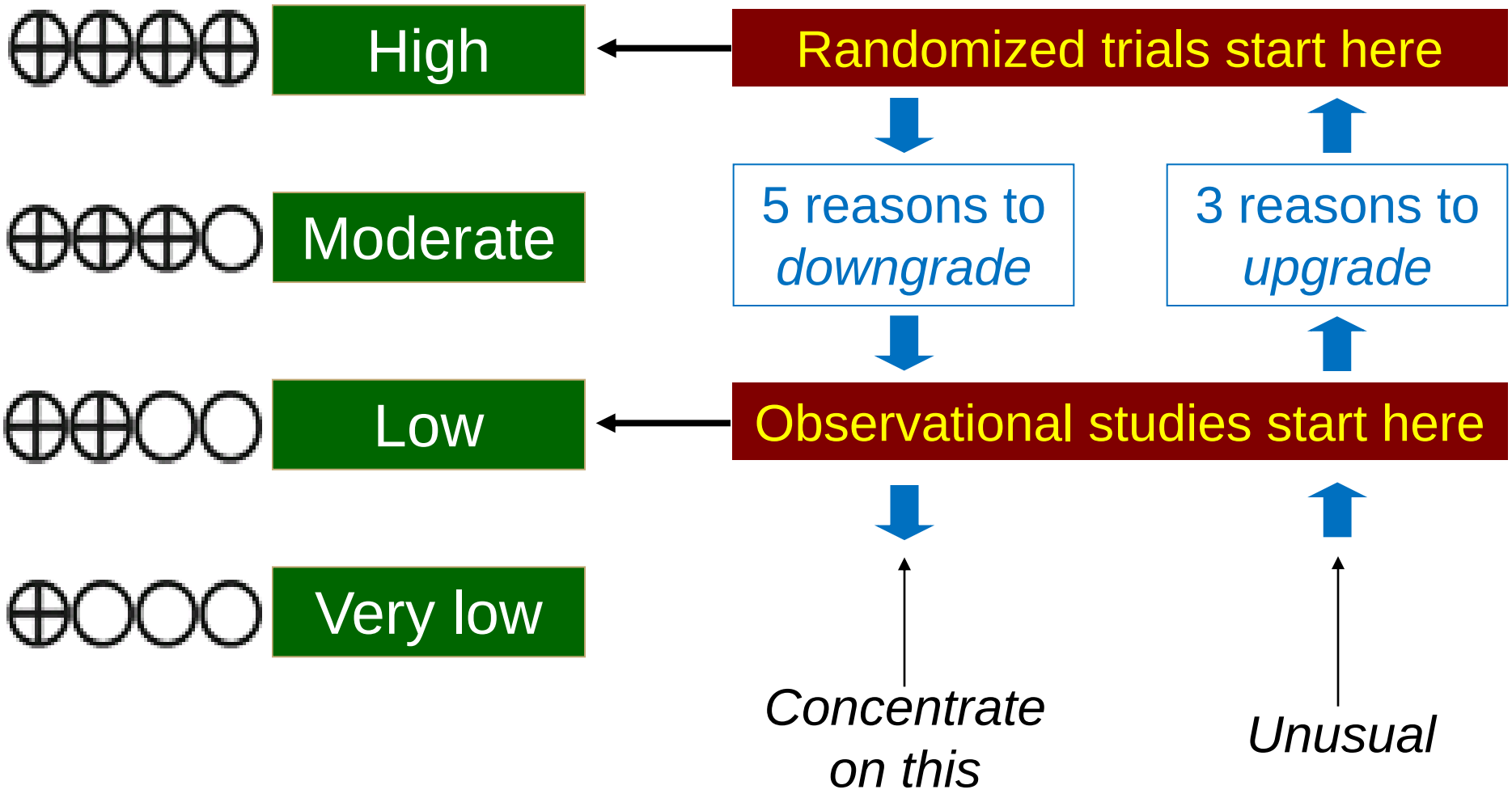
Further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate



Very low

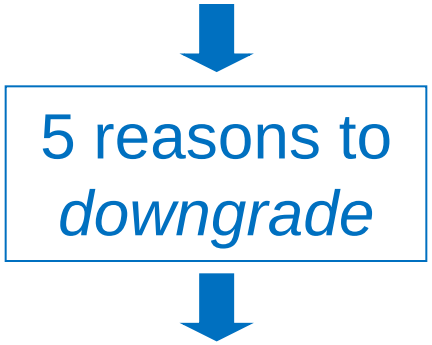
Any estimate of effect is very uncertain

GRADE in a nutshell



What might decrease quality of evidence

1. Study limitations (risk of bias)
2. Indirectness of evidence
3. Inconsistency of results
4. Imprecision
5. Publication bias



- Each category for factors that might *decrease* quality of evidence has 3 scoring options:
  - No concerns
  - Serious −1 level
  - Very serious −2 levels

Summary risk of bias by outcome

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key items	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key items	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key items	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

Risk of bias	Across studies	Considerations	**GRADE assessment**
Low risk of bias	Most information is from studies at low risk of bias	No apparent limitations	No serious limitations, do not downgrade
Unclear risk of bias	Most information is from studies at low or unclear risk of bias	Potential limitations are unlikely to lower confidence in the estimate of effect.	No serious limitations, do not downgrade
		Potential limitations are likely to lower confidence in the estimate of effect	Serious limitations, downgrade one level
High risk of bias	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results	Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect.	Serious limitations, downgrade one level
		Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect	Very serious limitations, downgrade two levels

Weighting by quality scores

- Weights based purely on quality scores are arbitrary, have little statistical justification and are *not recommended*

Adjusting for bias

- Bayesian analysis
  - Incorporate prior distributions on likely bias for each individual study
- Prior based on
  - empirical research (e.g. meta-epidemiology): Welton et al
  - plausible ranges
  - formal elicitation from experts: Turner et al
- These are perhaps the ‘state of the art’, but not likely to be feasible for most review teams
  - Save for the most important reviews

Concluding remarks

- Restrict or stratify
- Do sensitivity analyses
- Don’t expect to find evidence of bias within a meta-analysis
- Summary of findings tables and GRADE offer a convenient way to provide risk of bias assessments alongside results