GRADE and Sub-group analysis

- randomized trials begin as high quality evidence
- five limitations may reduce quality to moderate, low, or very low
  - high risk of bias
  - imprecision
  - inconsistency
  - indirectness
  - suspicion of publication bias

Sub-group analysis issue

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- five limitations may reduce quality to moderate, low, or very low
  - high risk of bias
  - imprecision
  - *inconsistency*
  - indirectness
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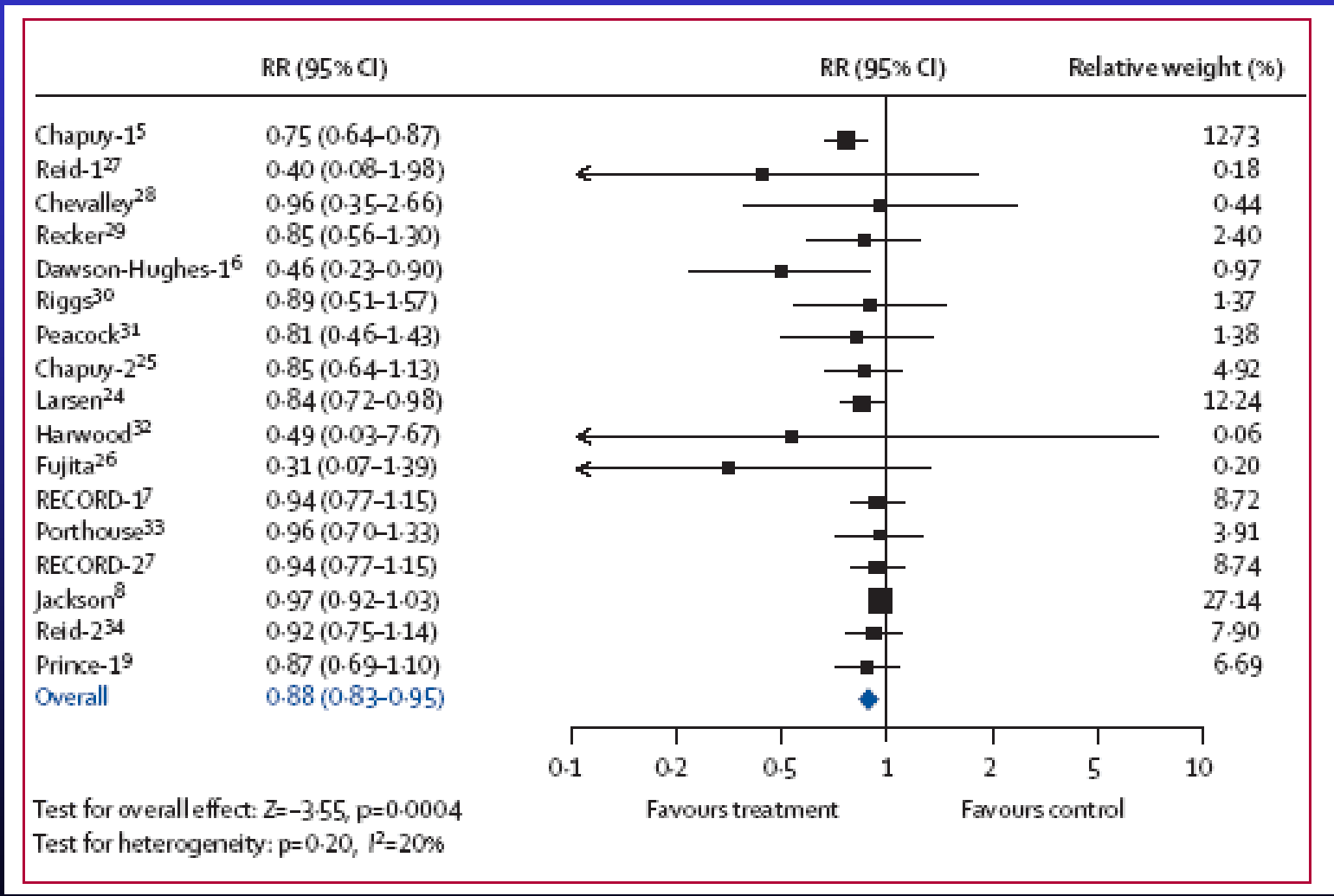
Results inconsistent (heterogeneous)

- search for explanation
  - patients
  - interventions
  - comparators
  - outcomes
  - methodology
- ideally a priori hypothesis
- apparent explanation: scepticism

Should we believe sub-group analysis?

- within rather than between study comparison?
- unlikely chance?
- a priori hypothesis?
- one of small number hypotheses?
- biologically compelling?

Calcium ± Vitamin D to prevent fractures, Lancet 2007
17 eligible trials incuding 50,000 patients



Vitamin D and calcium

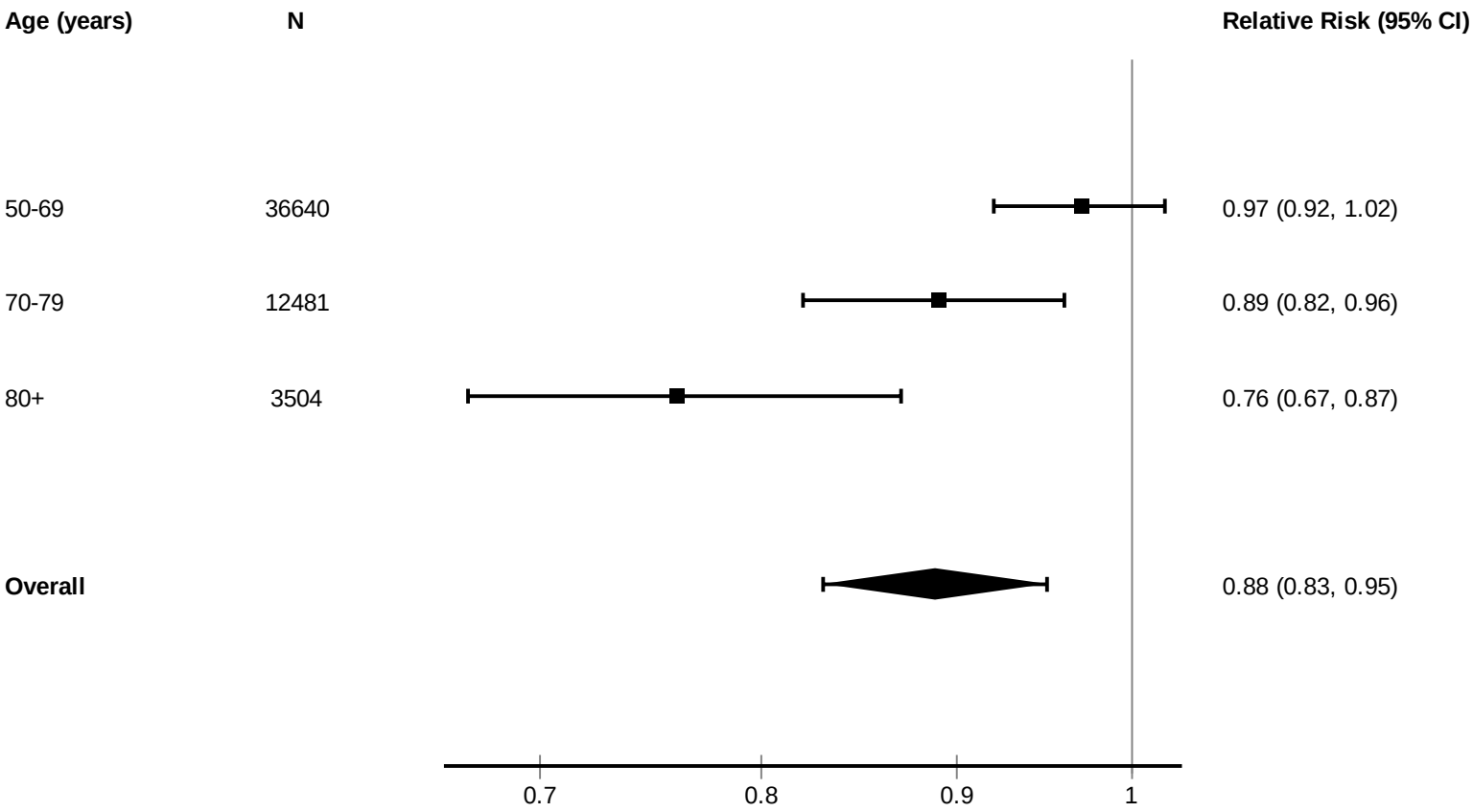


Figure 11: How to handle sub-group issue in rating quality of evidence?

A: no credibility to sub-group analysis.
Believe pooled estimate, don't rate down for inconsistency

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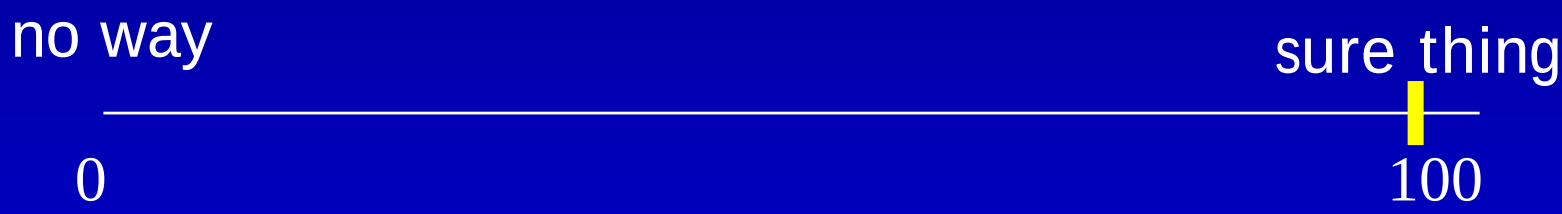
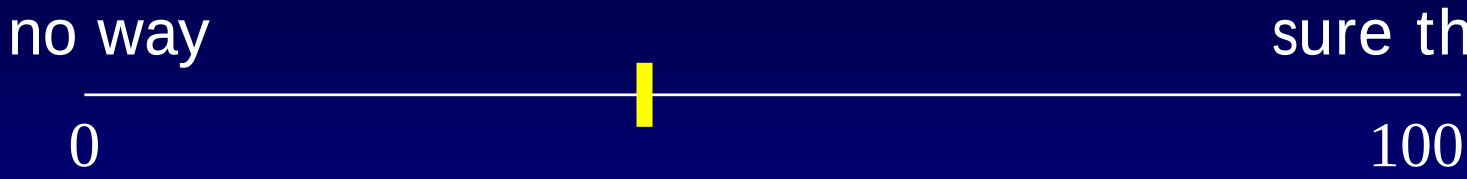


B: Sub-group analysis highly credible.
Believe subgroups, separate estimate for each subgroup, don't rate down for inconsistency

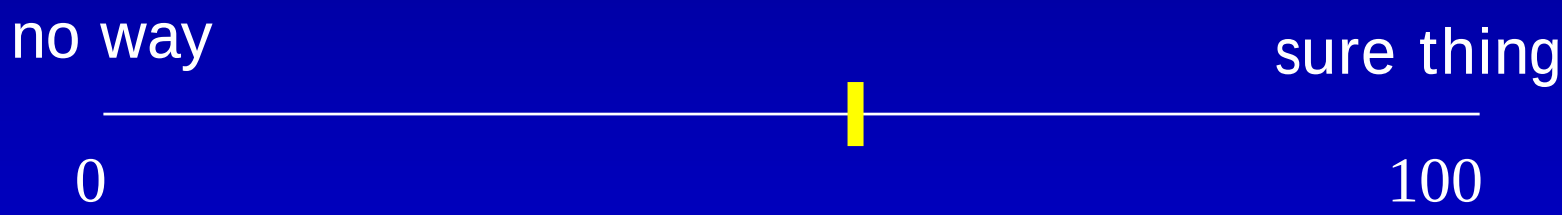
How to handle sub-group issue in rating quality of evidence?

C: Sub-group analysis plausible, but considerable doubt remains
Present pooled estimate, rate down for inconsistency

How to handle sub-group issue in rating quality of evidence?



C: Sub-group analysis plausible, but overall judged unlikely
Present pooled estimate, rate down for inconsistency



D: Sub-group analysis plausible, even likely
but considerable doubt remains
Present separate estimates for each subgroup,
rate down for inconsistency

Conclusions

- careful, limited a priori hypotheses to explain heterogeneity
- test hypotheses even if apparently limited heterogeneity
- criteria available to guide credibility of sub-group
- often not yes or no
- if uncertainty, whether decision to present, single or two or more estimates, rate down for inconsistency