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

- 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
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 including 50,000 patients

Test for overall effect: Z = -3.55, p = 0.0004
Test for heterogeneity: p = 0.20, I^2 = 20%
Vitamin D and calcium

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69</td>
<td>36640</td>
<td>0.97 (0.92, 1.02)</td>
</tr>
<tr>
<td>70-79</td>
<td>12481</td>
<td>0.89 (0.82, 0.96)</td>
</tr>
<tr>
<td>80+</td>
<td>3504</td>
<td>0.76 (0.67, 0.87)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.88 (0.83, 0.95)</td>
</tr>
</tbody>
</table>
A: no credibility to sub-group analysis. Believe pooled estimate, don’t rate down for inconsistency
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.

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