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

<u>Sub-group analysis issue</u>

- randomized trials begin as high quality evidence
- five limitations may reduce quality to moderate, low, or very low
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<u>Results inconsistent</u> (heterogeneous)

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

<u>Should we believe sub-group</u> <u>analysis?</u>

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

Calcium <u>+</u> Vitamin D to prevent fractures, Lancet 2007 17 eligible trials incuding 50,000 patients

	RR (95% CI)			F	RR (95% C	I)	Relative	weight (%)
hapuy-15	0.75 (0.64-0.87)							1273
leid-1 ²⁷	0.40 (0.08-1.98)	←		_				0.18
hevalley ²⁸	0.96 (0.35-2.66)							0.44
lecker ²⁹	0.85 (0.56-1.30)			_				2.40
awson-Hughes-1 ⁶	0.46 (0.23-0.90)							0.97
iggs ³⁰	0.89 (0.51-1.57)					_		1-37
eacock ³¹	0.81 (0.46-1.43)							1.38
hapuy-2 ²⁵	0.85 (0.64-1.13)							4.92
arsen ²⁴	0.84 (0.72-0.98)							12.24
arwood ³²	0.49 (0.03-7.67)	<i>←</i>						0.06
ujita ²⁶	0.31 (0.07-1.39)	-						0.20
ECORD-17	0.94 (0.77-1.15)							8.72
orthouse ³³	0.96 (0.70-1.33)							3.91
ECORD-2 ⁷	0.94 (0.77-1.15)							8.74
ckson ⁸	0.97 (0.92-1.03)							27.14
eid-234	0.92 (0.75-1.14)							7.90
rince-1 ⁹	0.87 (0.69-1.10)							6.69
verall	0.88 (0.83-0.95)				•			-
			I	I		1	1	
		0-1	0-2	0.5	1	2	5	10

Test for overall effect: Z=-3.55, p=0.0004 Test for heterogeneity: p=0.20, 1²=20%

Vitamin D and calcium

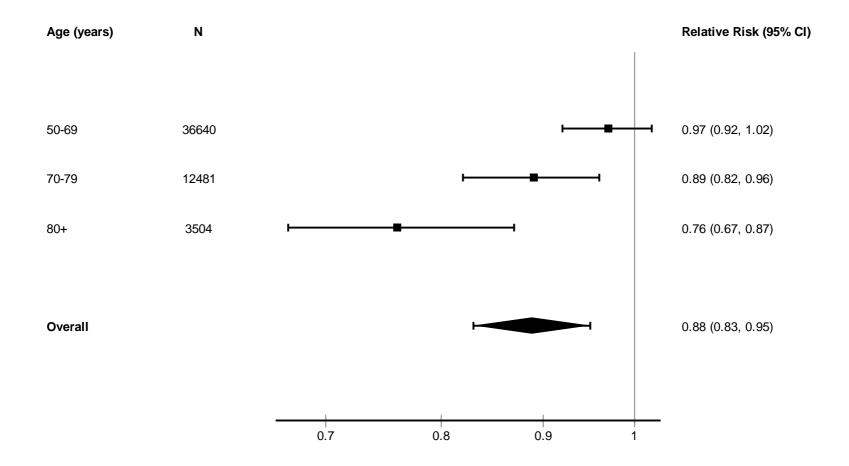


Figure 11: How to handle sub-group issue in rating quality of evidence?

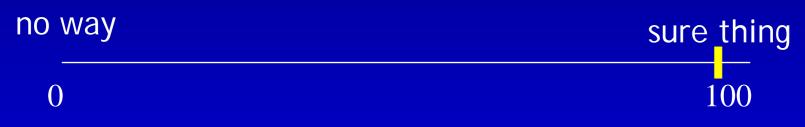


A: no credibility to sub-group analysis. Believe pooled estimate, don't rate down for inconsistency



100

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?



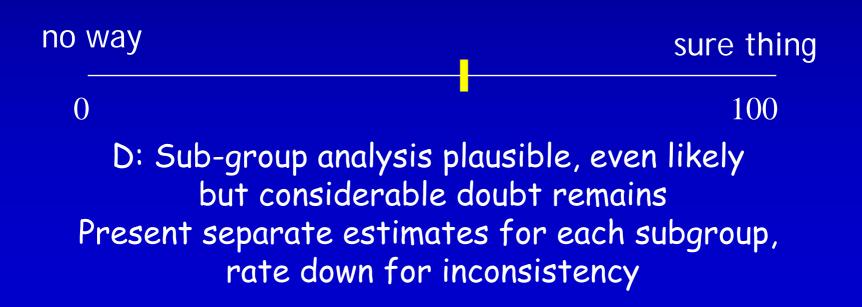
C: Sub-group analysis plausible, but considerable doubt remains Present pooled estimate, rate down for inconsistency

How to handle sub-group issue in rating quality of evidence? no way sure thing

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

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<u>Conclusions</u>

- 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