How to interpret a meta-analysis

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Evidence synthesis

Answer a research question based on existing data of multiple studies

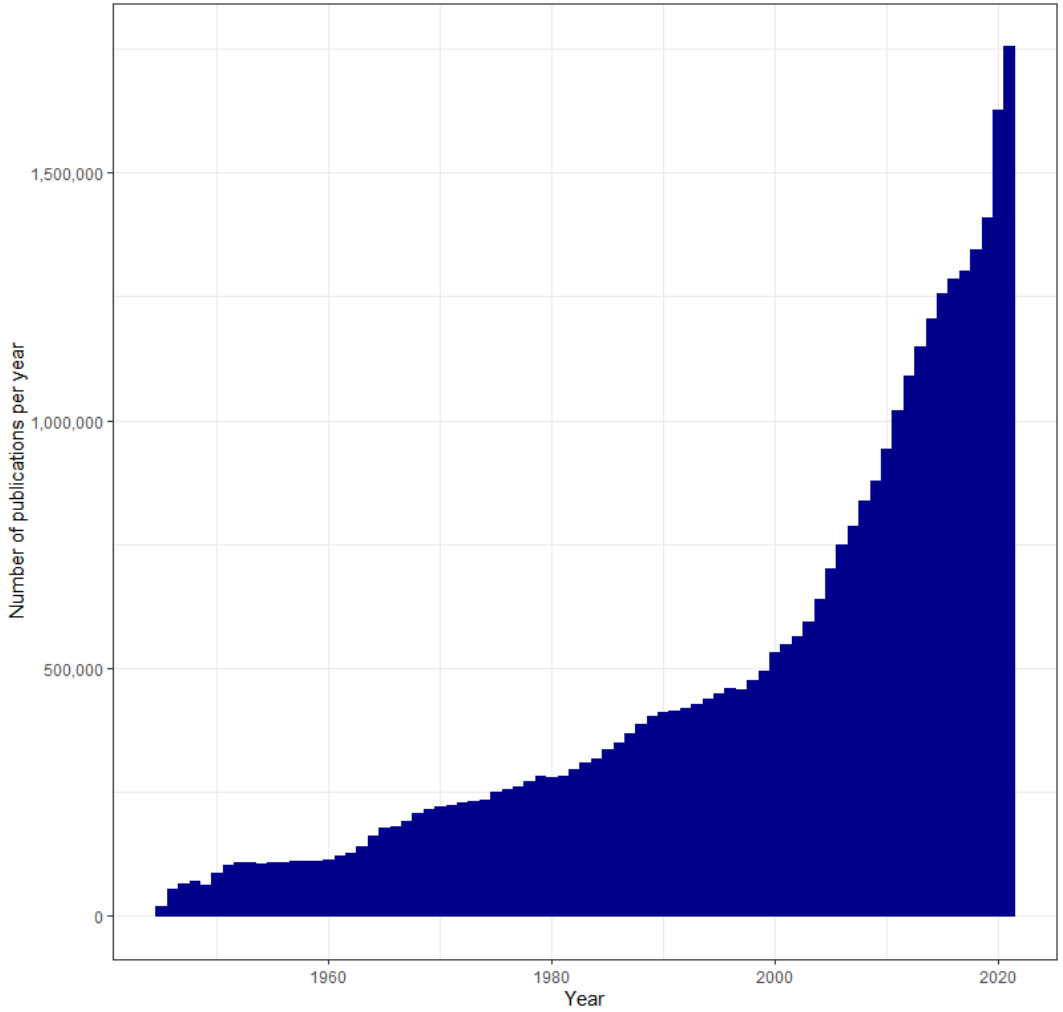
<u>Why?</u>

Large amount of data

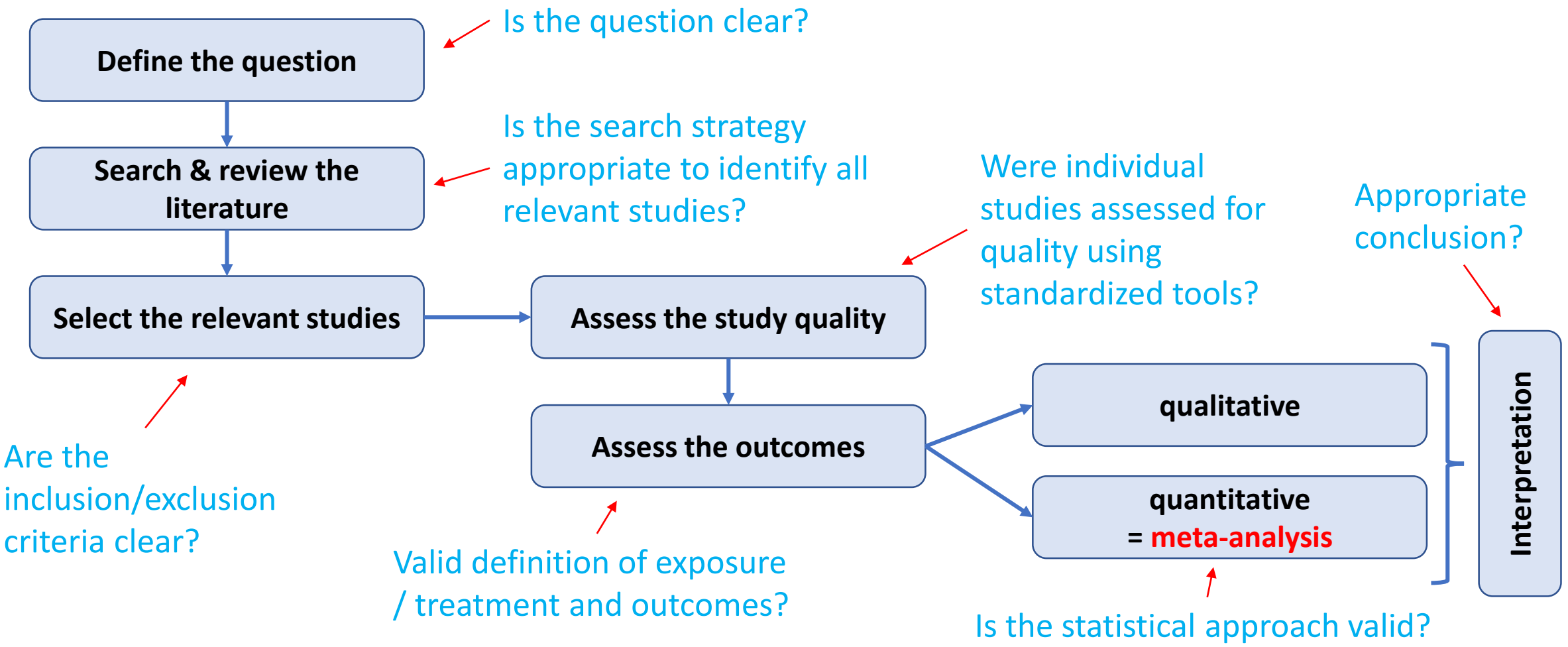
→ systematic assessment of available evidence

→ summarize existing information

→ support rational decision making (evidence-based medicine)



Systematic review process



Meta-analysis

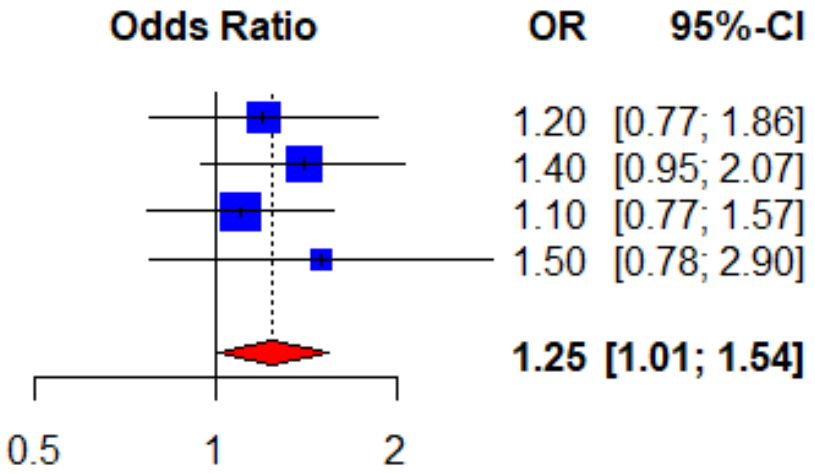
The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings

Ideally, the individual studies are obtained through a systematic review of the available literature

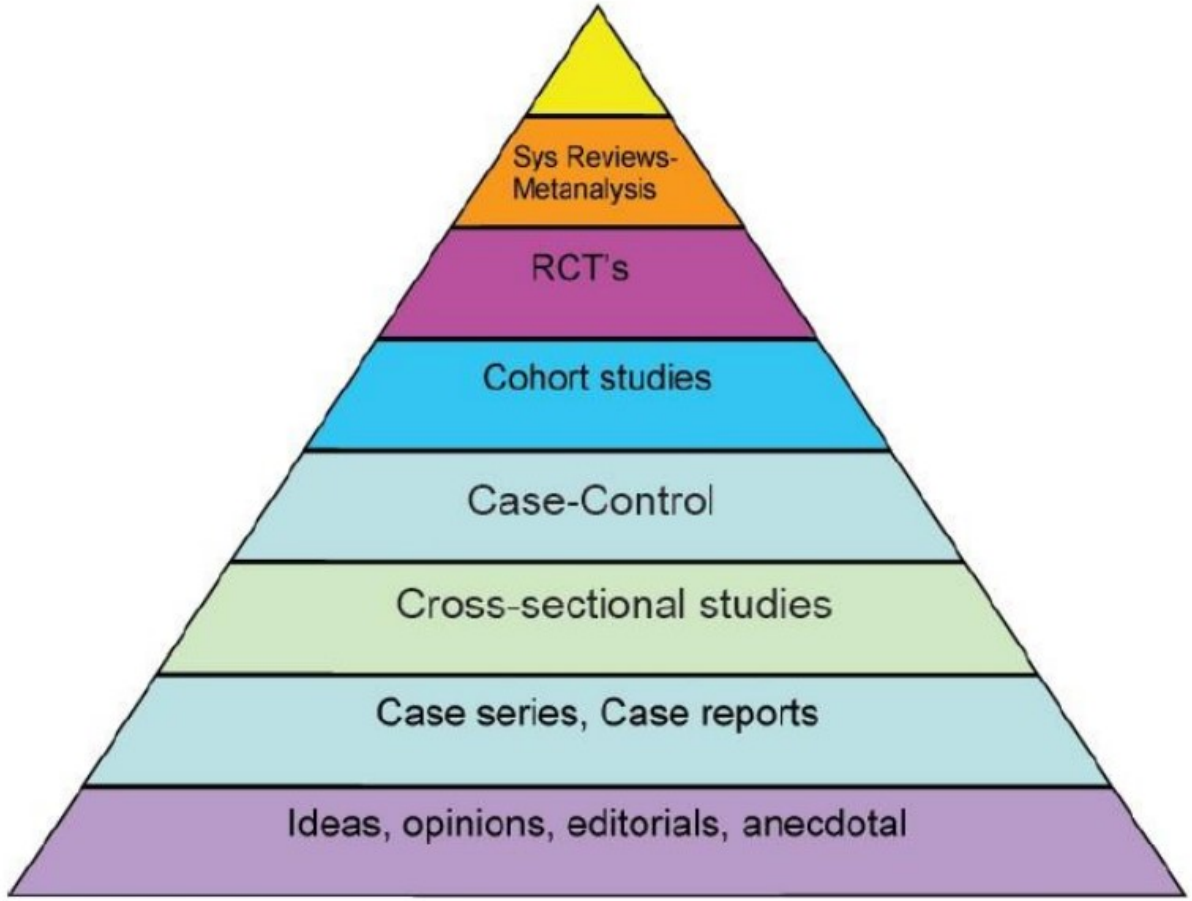
A clear, well formulated research question is at the start

Why perform meta-analysis?

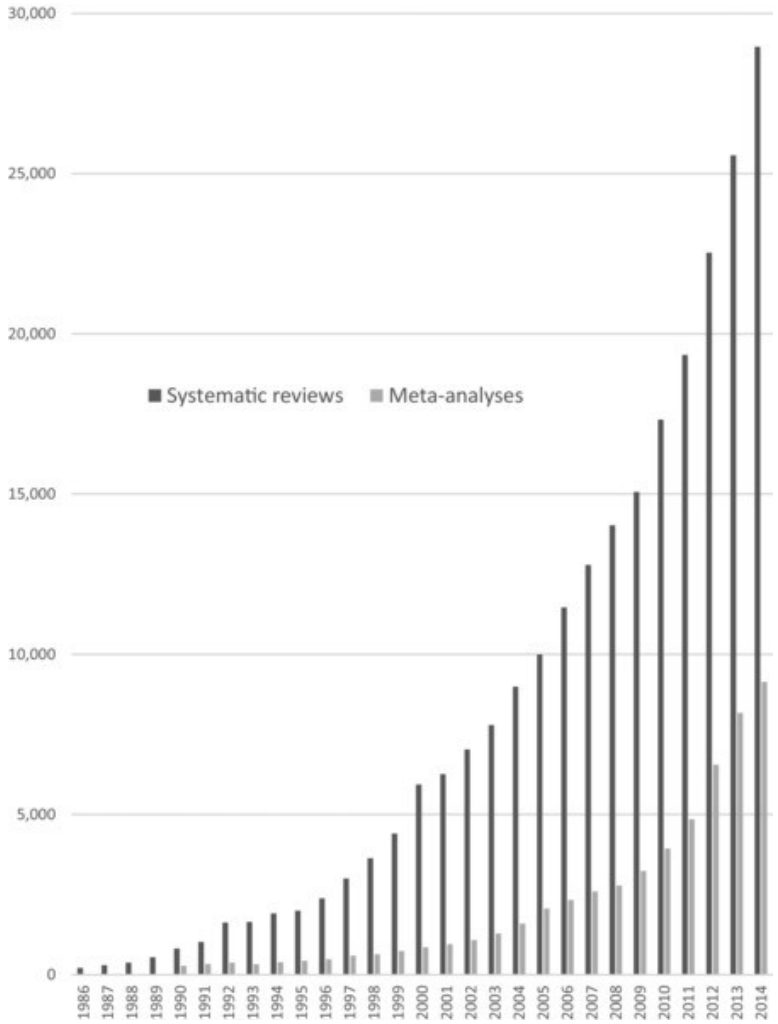
- Power and precision
- Comparative effectiveness research
- Investigate conflicting results from different studies
- Results may form basis of future research or generate hypotheses to be tested

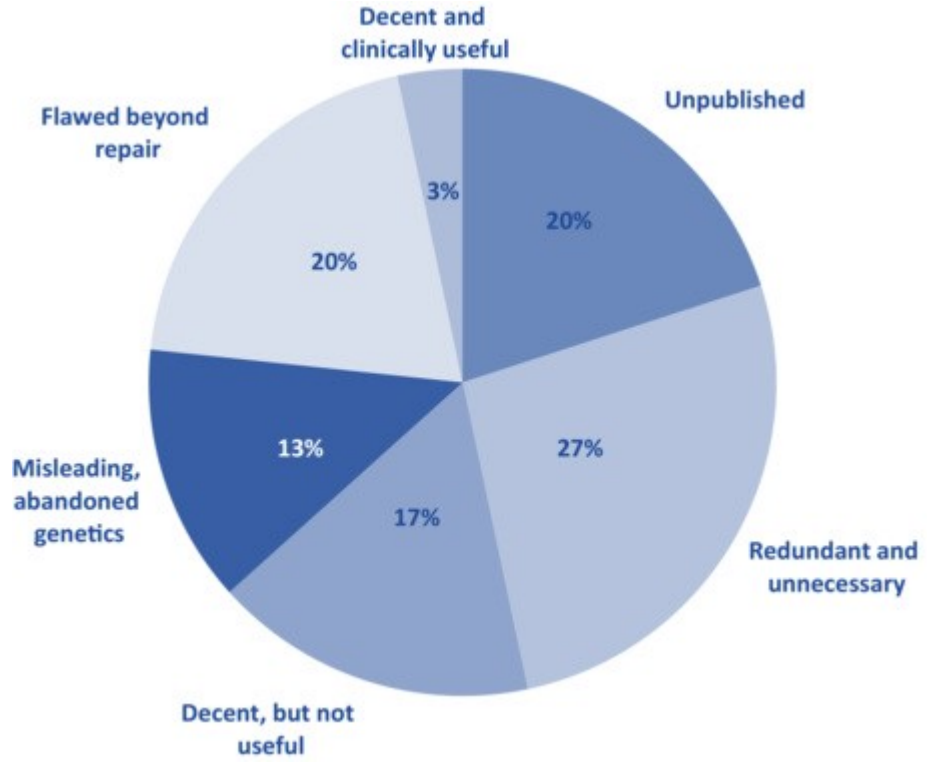


Evidence hierarchy?



Is it important to critically assess meta-analysis?





Ioannidis 2016 Milbank Q

Common issues with meta-analysis

- Should the analysis include all available studies, or only published studies?
- Aggregated studies may vary considerably in quality (“garbage in, garbage out”)
- When the relative risks or odds ratios from various studies differ, meta-analysis may mask important differences among individual studies.
- Reproducibility issues
- Publication bias issues
- Over-confidence in numerical result (ignoring the issues of meta-analysis)

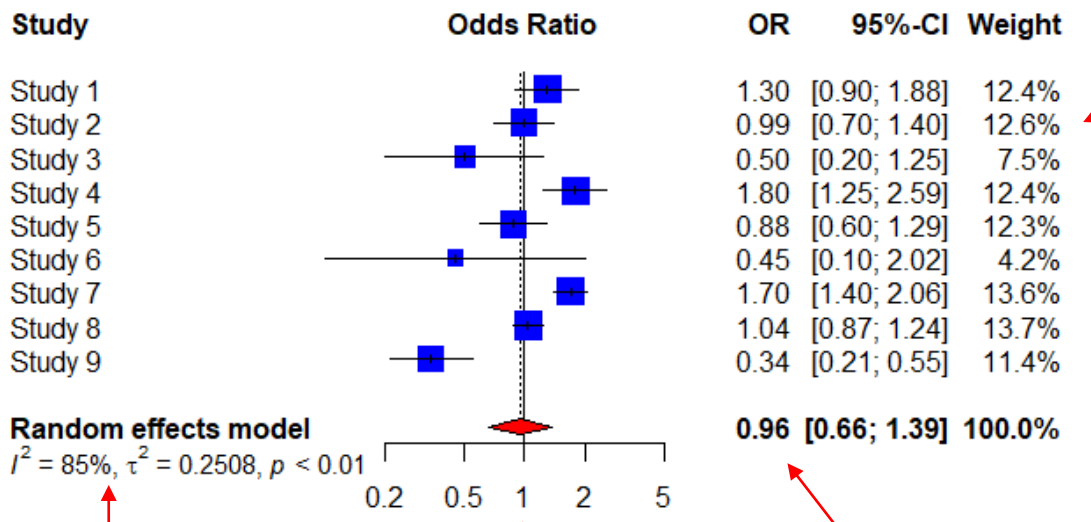
The forest plot

Included studies

Effect measure

Effect size with confidence interval

‘Influence’ of study on overall result

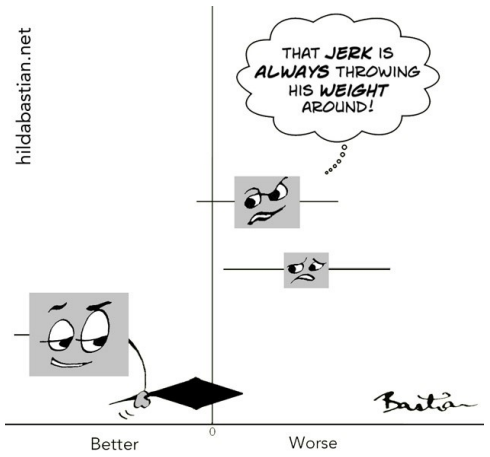


Used model

Measure(s) of heterogeneity

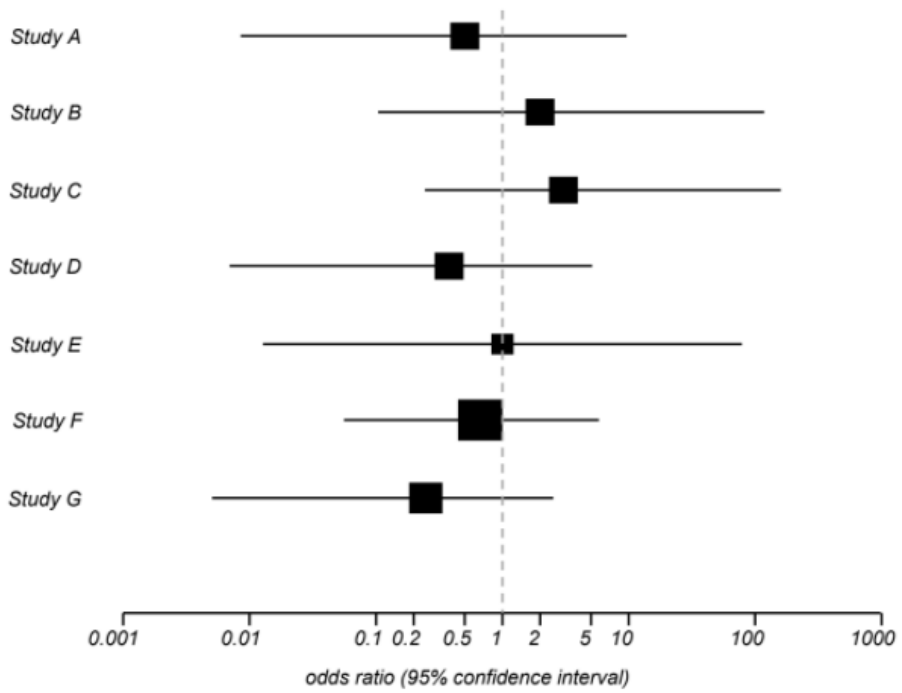
Null line

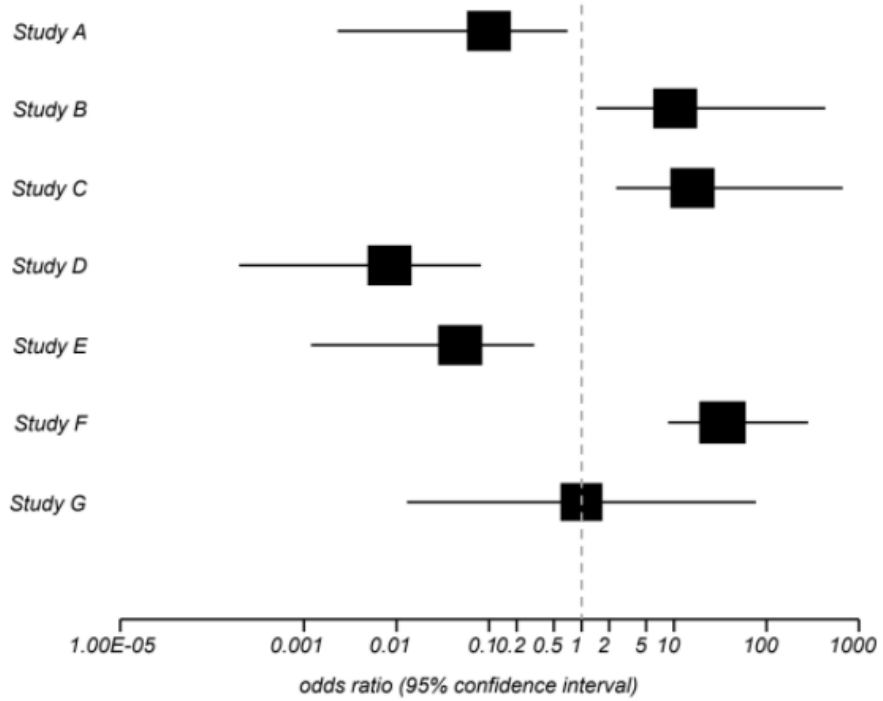
Overall = aggregated effect



Heterogeneity

How much does the **true effect** vary with different populations, patient characteristics, treatment characteristics, study characteristics?





What to do with heterogeneity?

- Ignore it → use a fixed-effect model
- Incorporate it → use a random-effects model
- **Explain it** → do subgroup analyses, do meta-regression

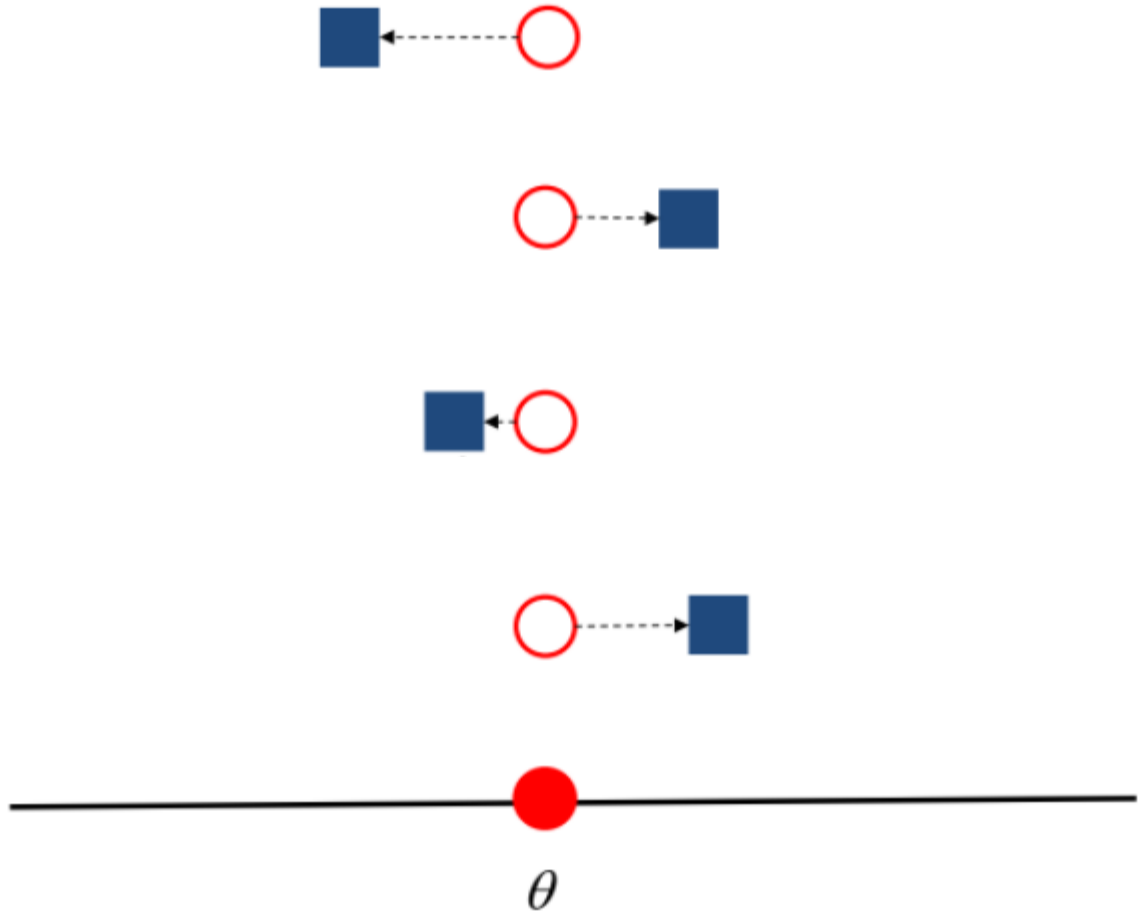
- (Test for it → do not pool studies if heterogeneity is present)

Fixed effect meta-analysis

Assumption:

All studies have one true underlying effect size

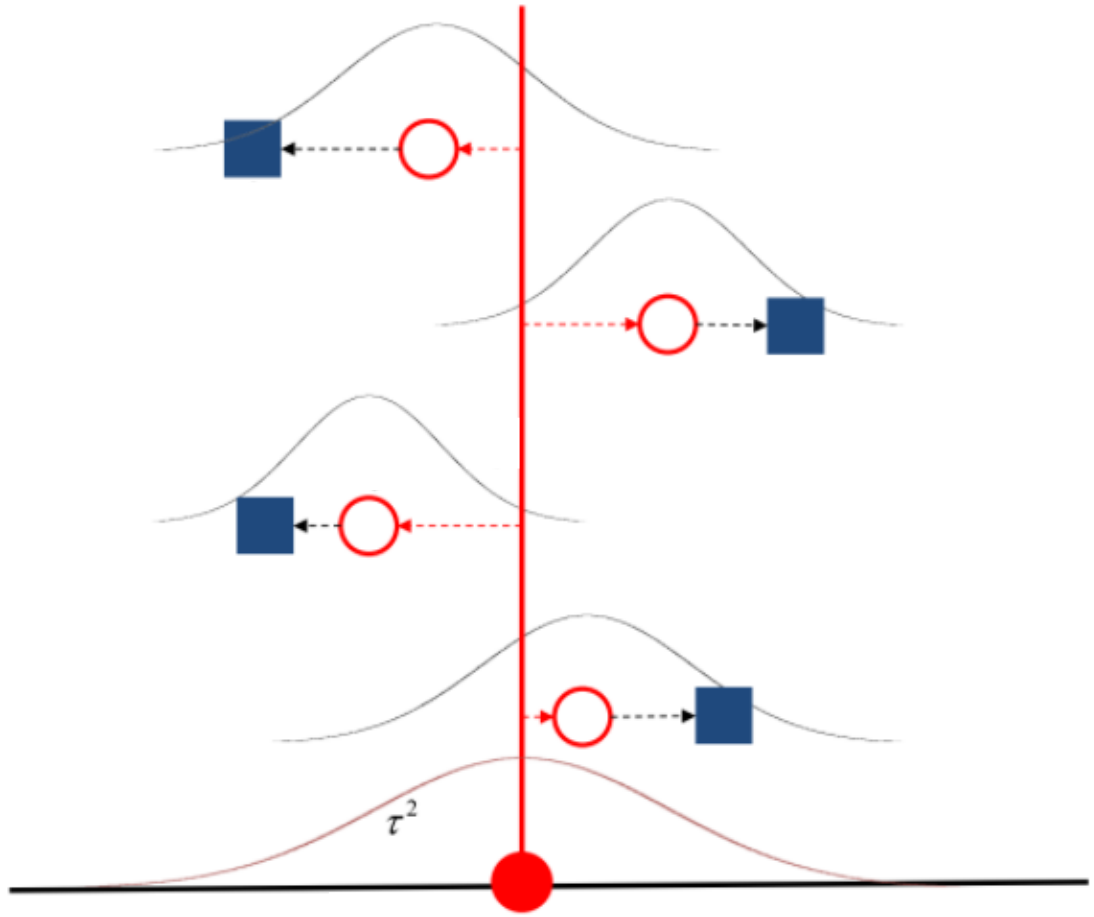
Observed variation between studies is either due to chance or due to sampling error



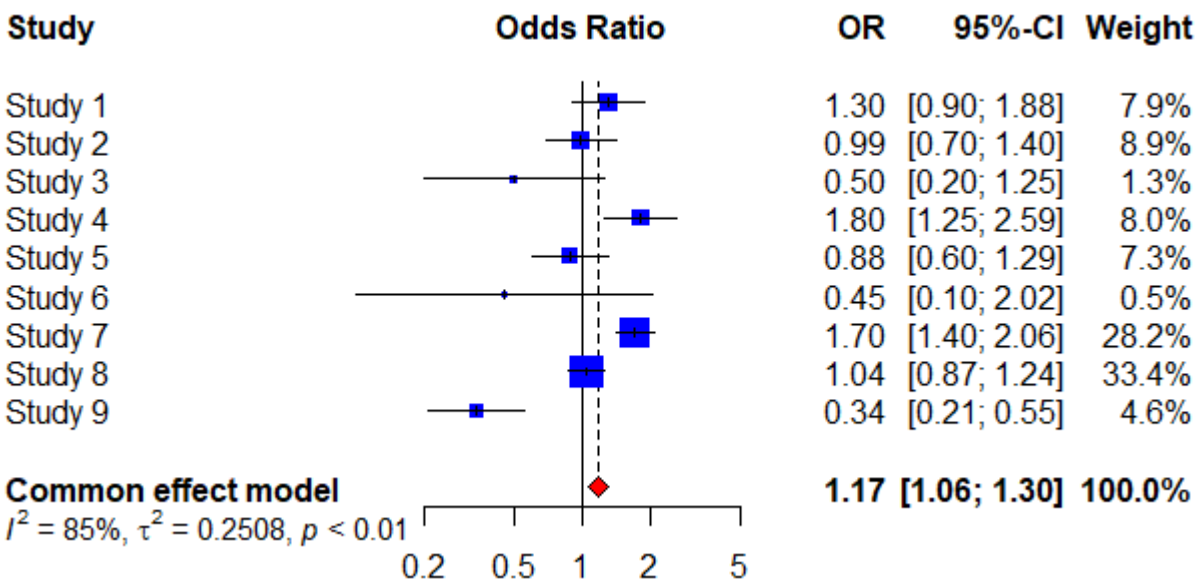
Random effects meta-analysis

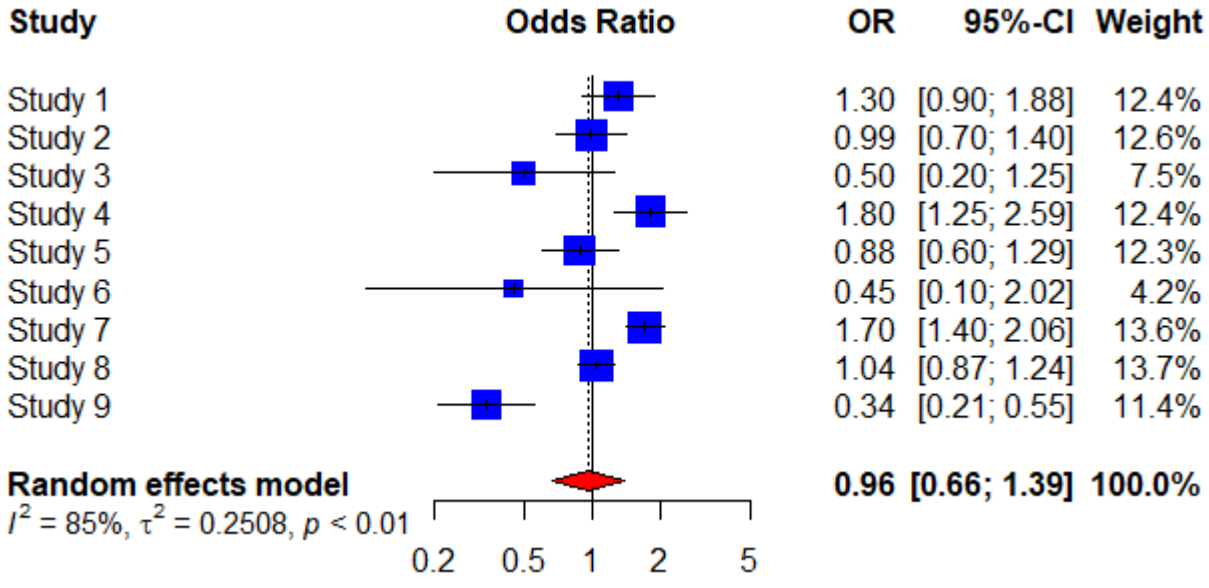
Assumption:

True effect size varies from study to study

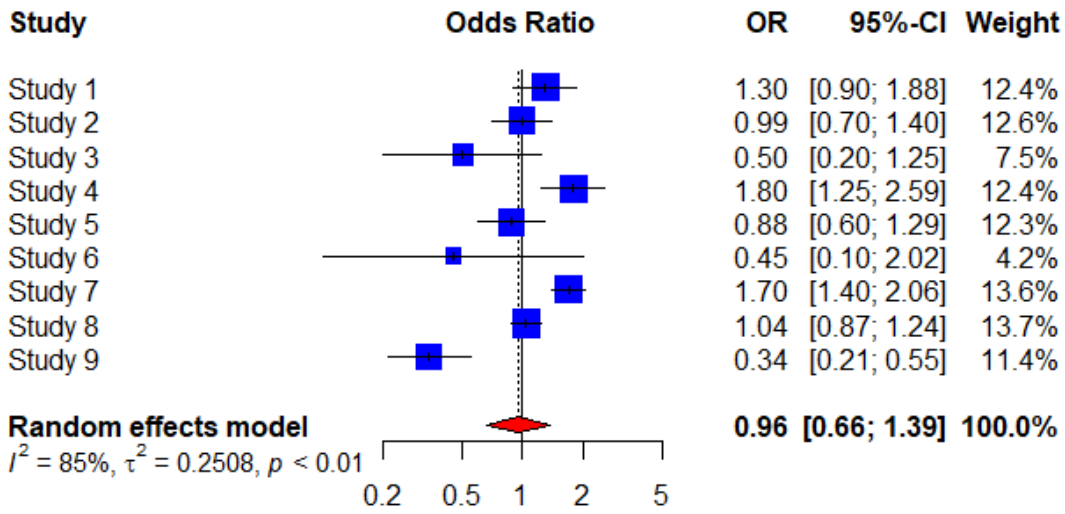


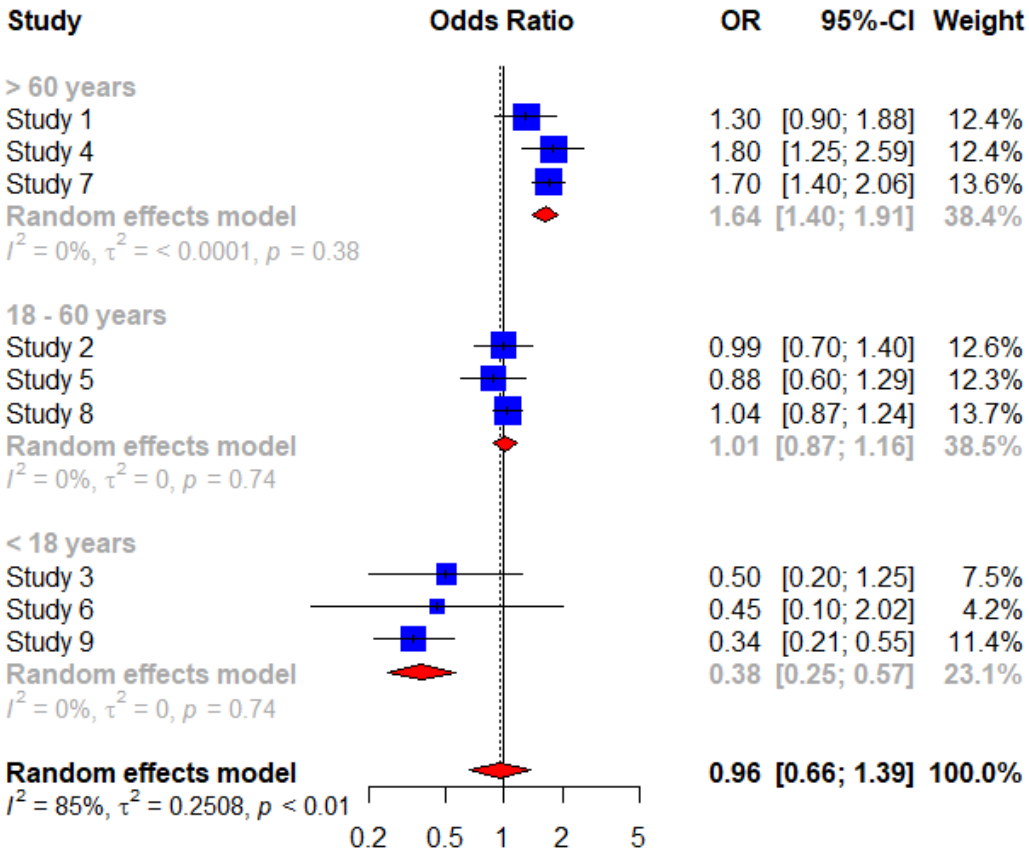
Fixed vs. random



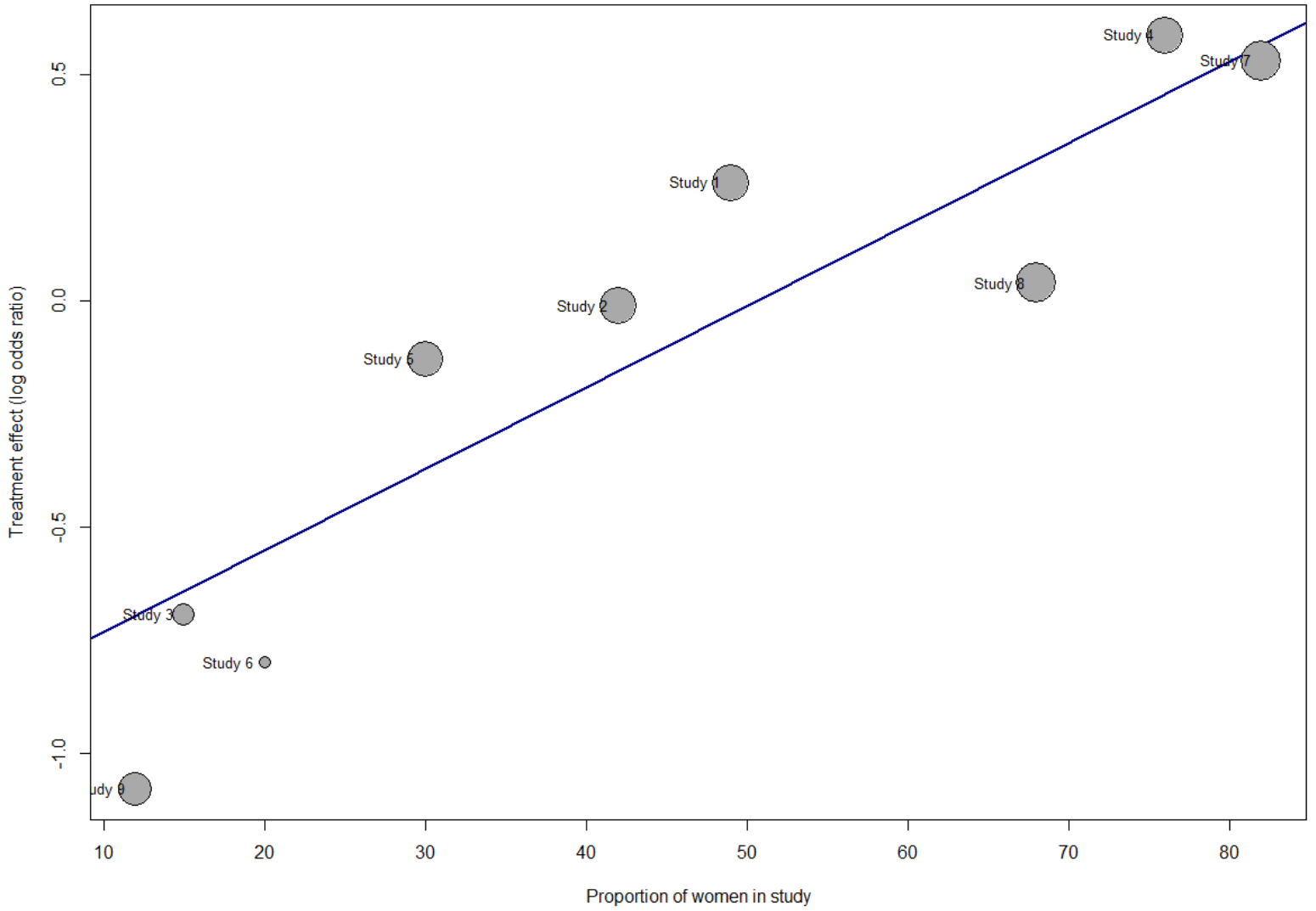


Explain it


Study
Odds Ratio
OR
95%-CI
Weight
Study 1 1.30 [0.90; 1.88] 12.4%
Study 2 0.99 [0.70; 1.40] 12.6%
Study 3 0.50 [0.20; 1.25] 7.5%
Study 4 1.80 [1.25; 2.59] 12.4%
Study 5 0.88 [0.60; 1.29] 12.3%
Study 6 0.45 [0.10; 2.02] 4.2%
Study 7 1.70 [1.40; 2.06] 13.6%
Study 8 1.04 [0.87; 1.24] 13.7%
Study 9 0.34 [0.21; 0.55] 11.4%
Random effects model 0.96 [0.66; 1.39] 100.0%
I^2 = 85%, τ^2 = 0.2508, p < 0.01
0.2 0.5 1 2 5

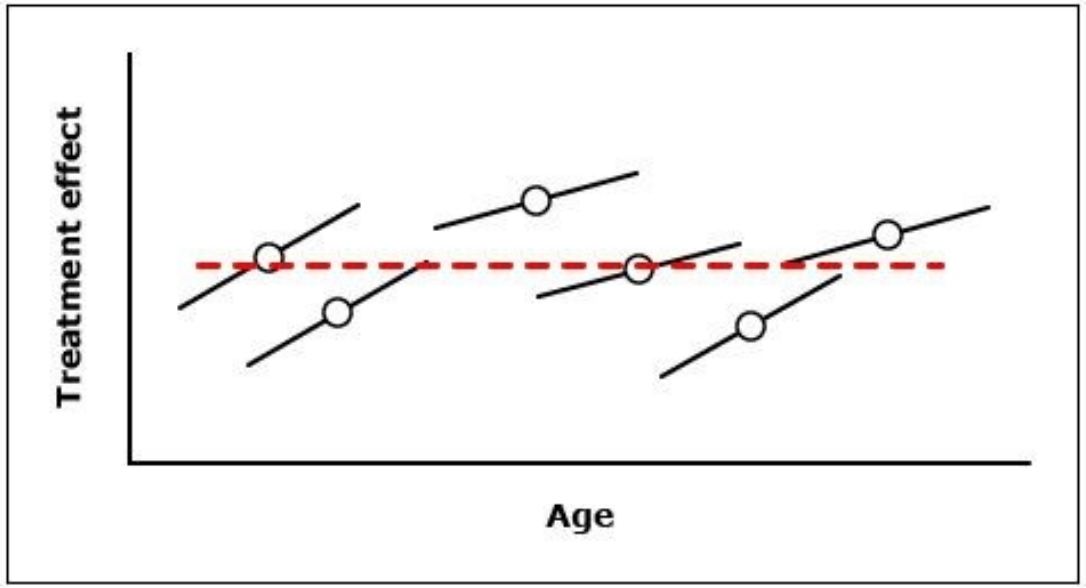

Study
Odds Ratio
OR
95%-CI
Weight
> 60 years
Study 1 1.30 [0.90; 1.88] 12.4%
Study 4 1.80 [1.25; 2.59] 12.4%
Study 7 1.70 [1.40; 2.06] 13.6%
Random effects model 1.64 [1.40; 1.91] 38.4%
I^2 = 0%, τ^2 = < 0.0001, p = 0.38
18 - 60 years
Study 2 0.99 [0.70; 1.40] 12.6%
Study 5 0.88 [0.60; 1.29] 12.3%
Study 8 1.04 [0.87; 1.24] 13.7%
Random effects model 1.01 [0.87; 1.16] 38.5%
I^2 = 0%, τ^2 = 0, p = 0.74
< 18 years
Study 3 0.50 [0.20; 1.25] 7.5%
Study 6 0.45 [0.10; 2.02] 4.2%
Study 9 0.34 [0.21; 0.55] 11.4%
Random effects model 0.38 [0.25; 0.57] 23.1%
I^2 = 0%, τ^2 = 0, p = 0.74
Random effects model 0.96 [0.66; 1.39] 100.0%
I^2 = 85%, τ^2 = 0.2508, p < 0.01
0.2 0.5 1 2 5

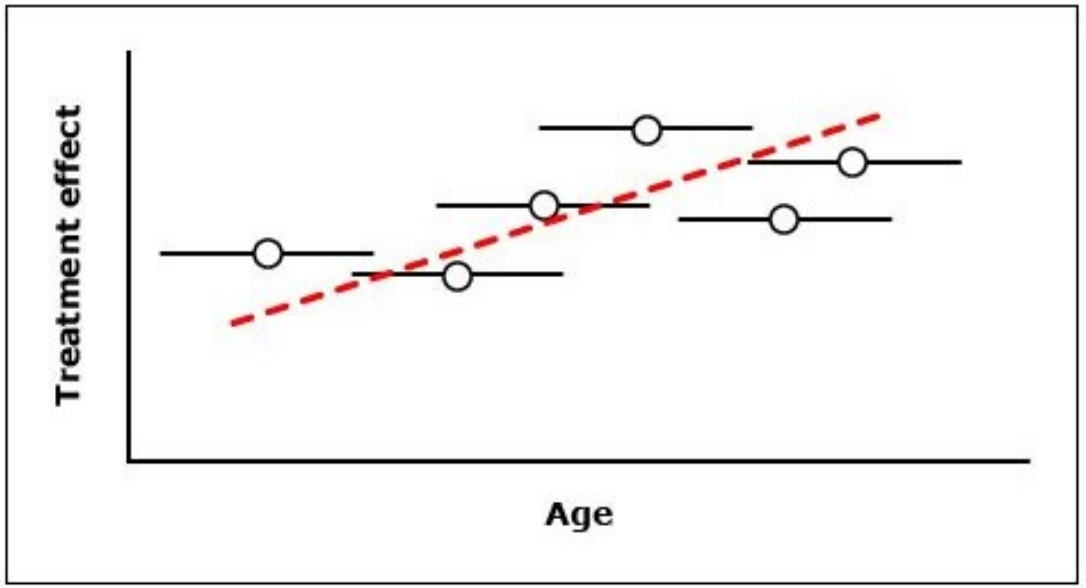
Meta-regression



Beta = 0.02 (95%CI 0.01 to 0.03)
p < 0.0001

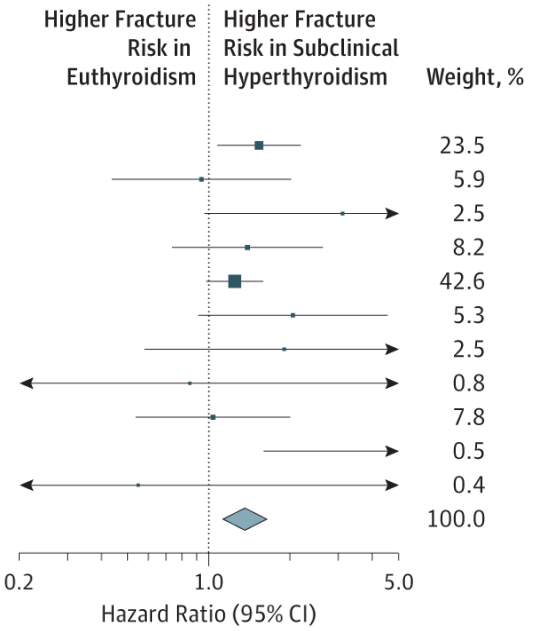
Ecological fallacy



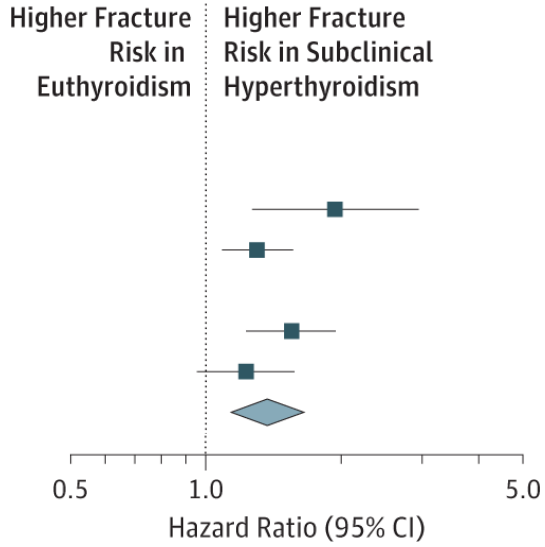


IPD meta-analysis

Fracture Outcome by Study	Hazard Ratio (95% CI)	Weight, %
Hip fracture		
Cardiovascular Health Study[8]	1.52 (1.07-2.17)	23.5
Health, Aging, and Body Composition Study[37]	0.94 (0.44-2.00)	5.9
Osteoporotic Fractures in Men Study (MrOS)[7]	3.09 (0.96-9.94)	2.5
EPIC-Norfolk Study[38]	1.38 (0.73-2.61)	8.2
HUNT Study[39]	1.24 (0.98-1.58)	42.6
Invecchiare in Chianti Study (InCHIANTI)[21]	2.03 (0.91-4.52)	5.3
Leiden 85-Plus Study[40]	1.89 (0.58-6.15)	2.5
Osteoporosis and Ultrasound Study (OPUS)[41]	0.85 (0.10-7.06)	0.8
Rotterdam Study[42]	1.03 (0.54-1.99)	7.8
Sheffield Study[6]	21.43 (1.59-289)	0.5
Busselton Health Study[19]	0.55 (0.03-9.20)	0.4
Overall ($\tau^2 = 0.01$)	1.36 (1.13-1.64)	100.0



Fracture Outcome by Age and Sex	Hazard Ratio (95% CI)
Hip fracture[a]	
Sex	
Men	1.92 (1.26-2.94)
Women	1.29 (1.08-1.55)
Age, y[b]	
<75	1.54 (1.22-1.93)
≥75	1.22 (0.95-1.56)
Overall	1.36 (1.13-1.64)



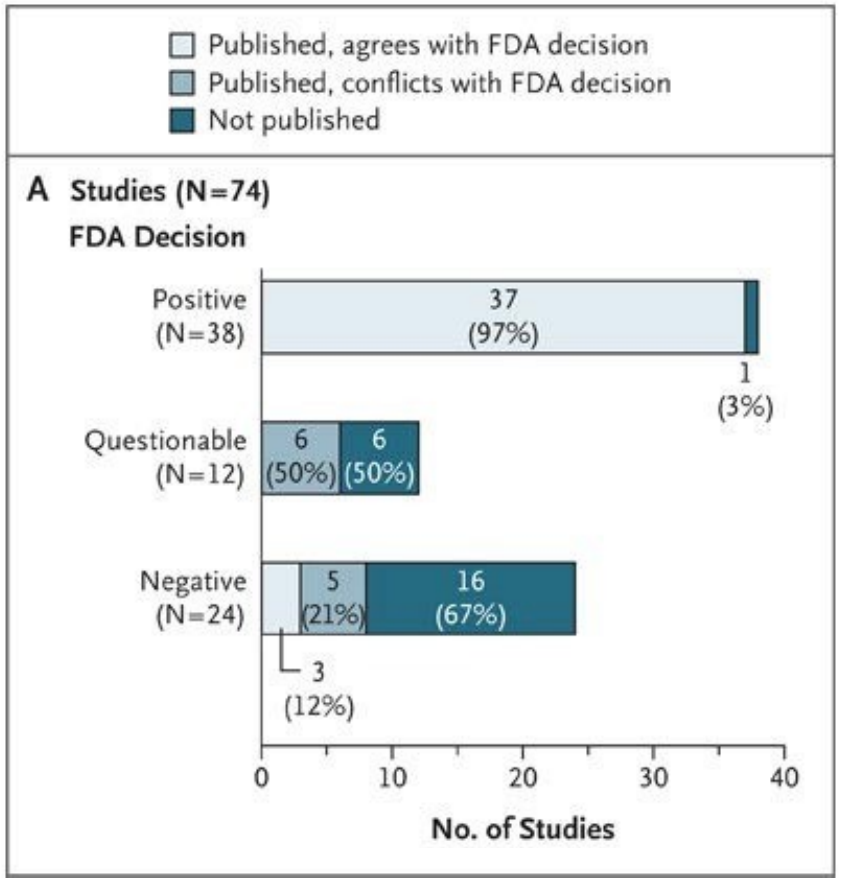
Blum 2015 JAMA

Publication bias

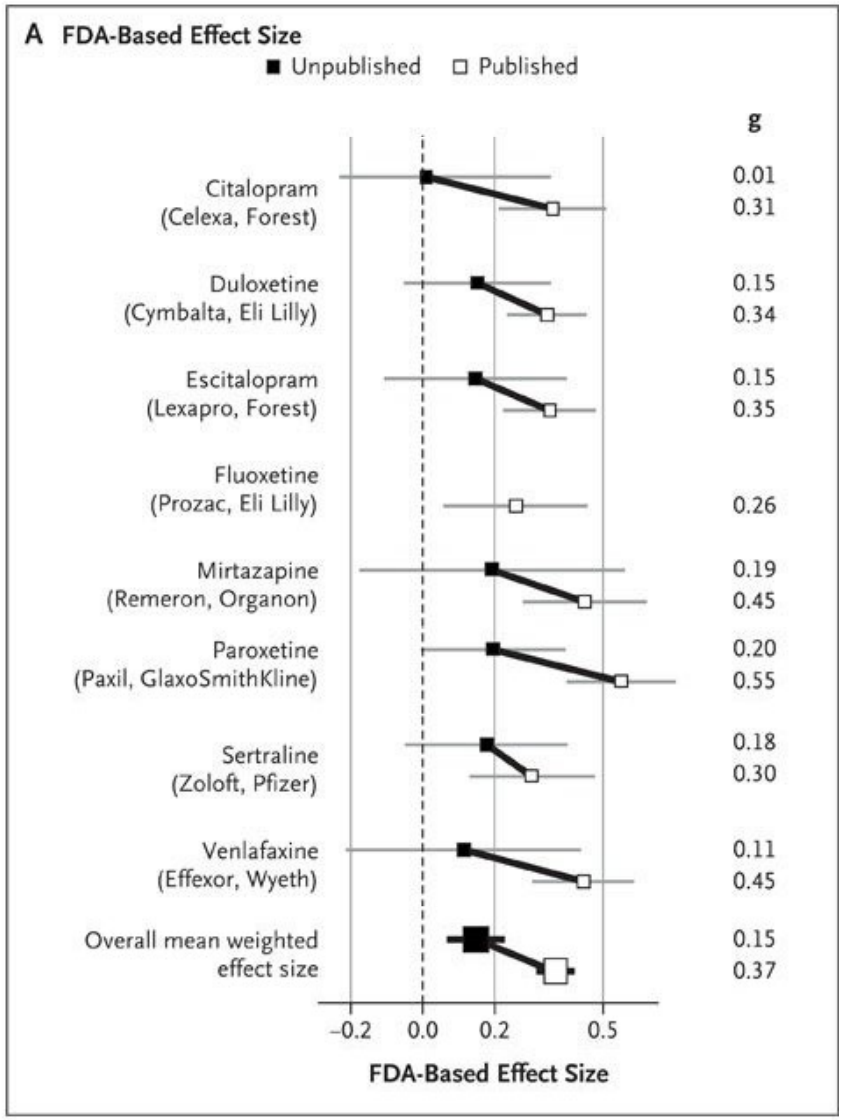
- Positive studies are more likely to be published
- Larger studies are more likely to be published
- Lower quality studies may show larger effects
- Smaller studies tend to show larger effects

→ Bias due to association between study size and treatment effects

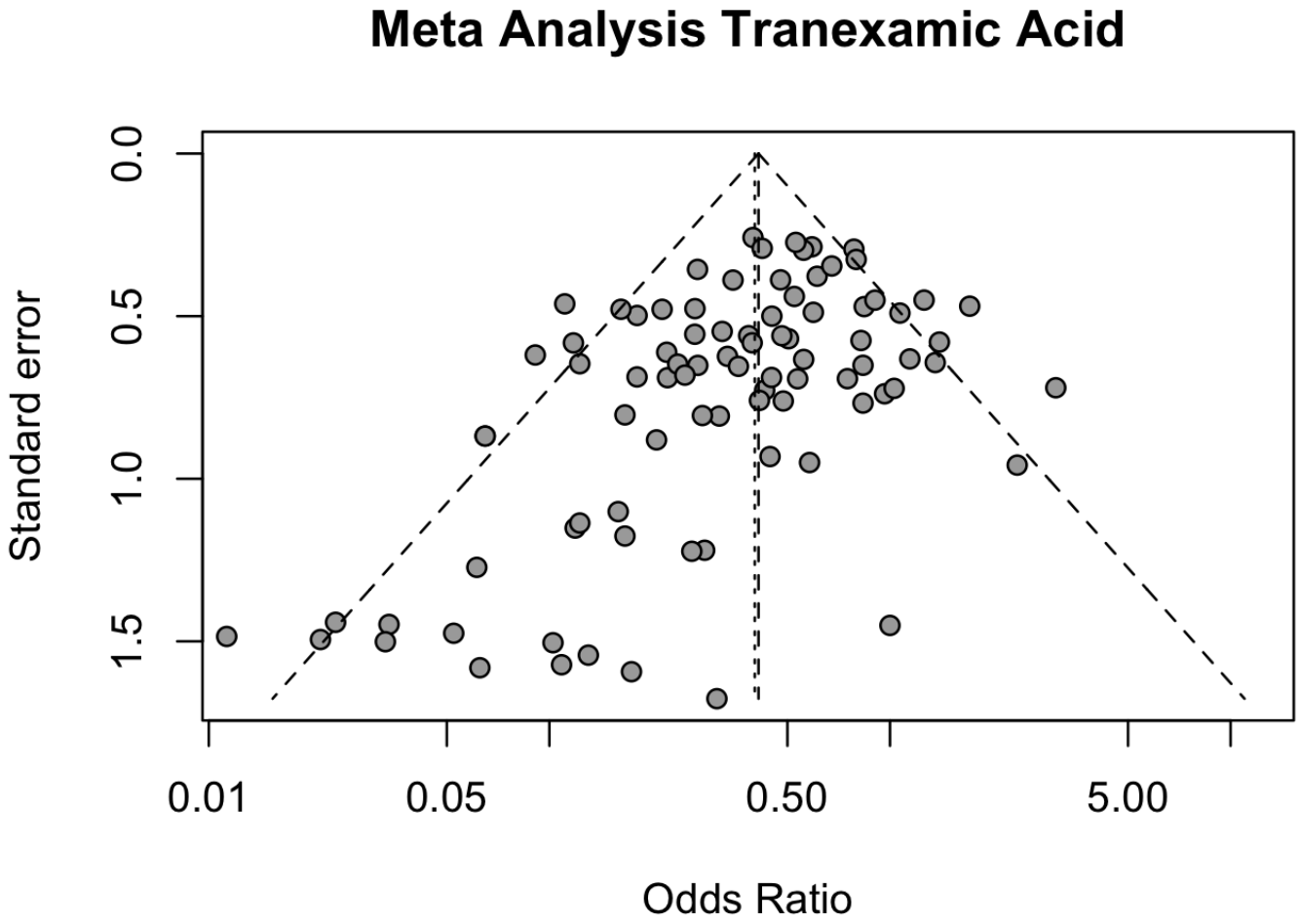
Publication bias



Turner 2008 NEJM



Funnel plot



CAVE

Asymmetry ≠ publication bias

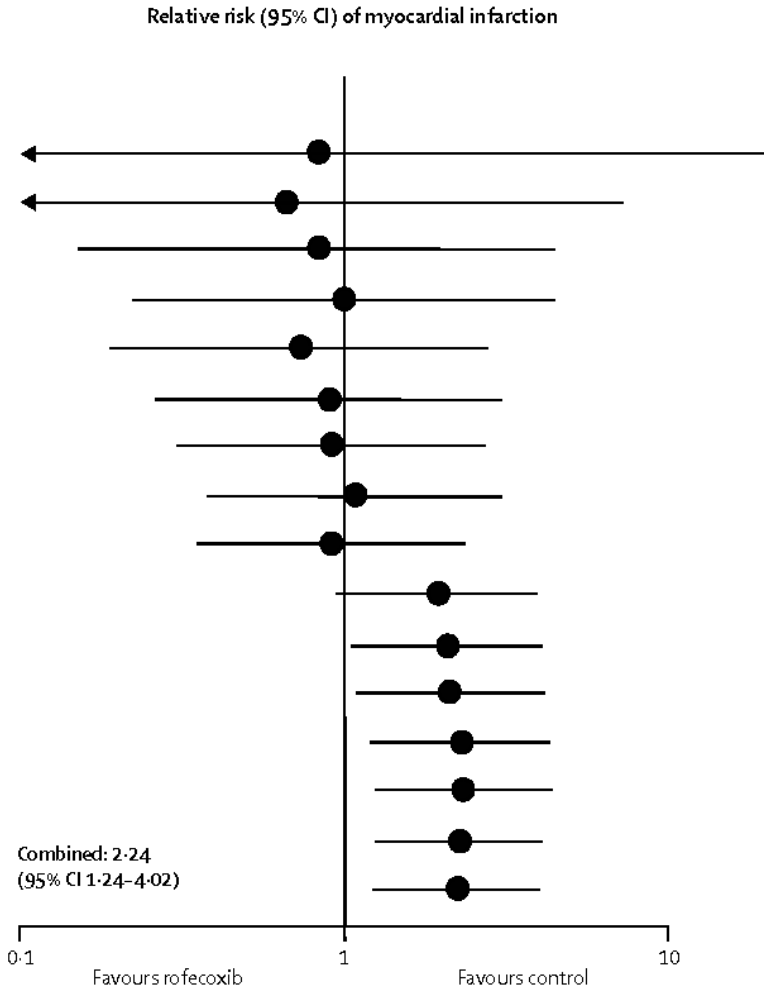
Other reasons:

- Effect differs according to study size
- Smaller studies with poor design, inadequate analysis
- Selective reporting
- Chance

Cool, countcool.com; Ker 2012 BMJ; Sterne 2011 BMJ

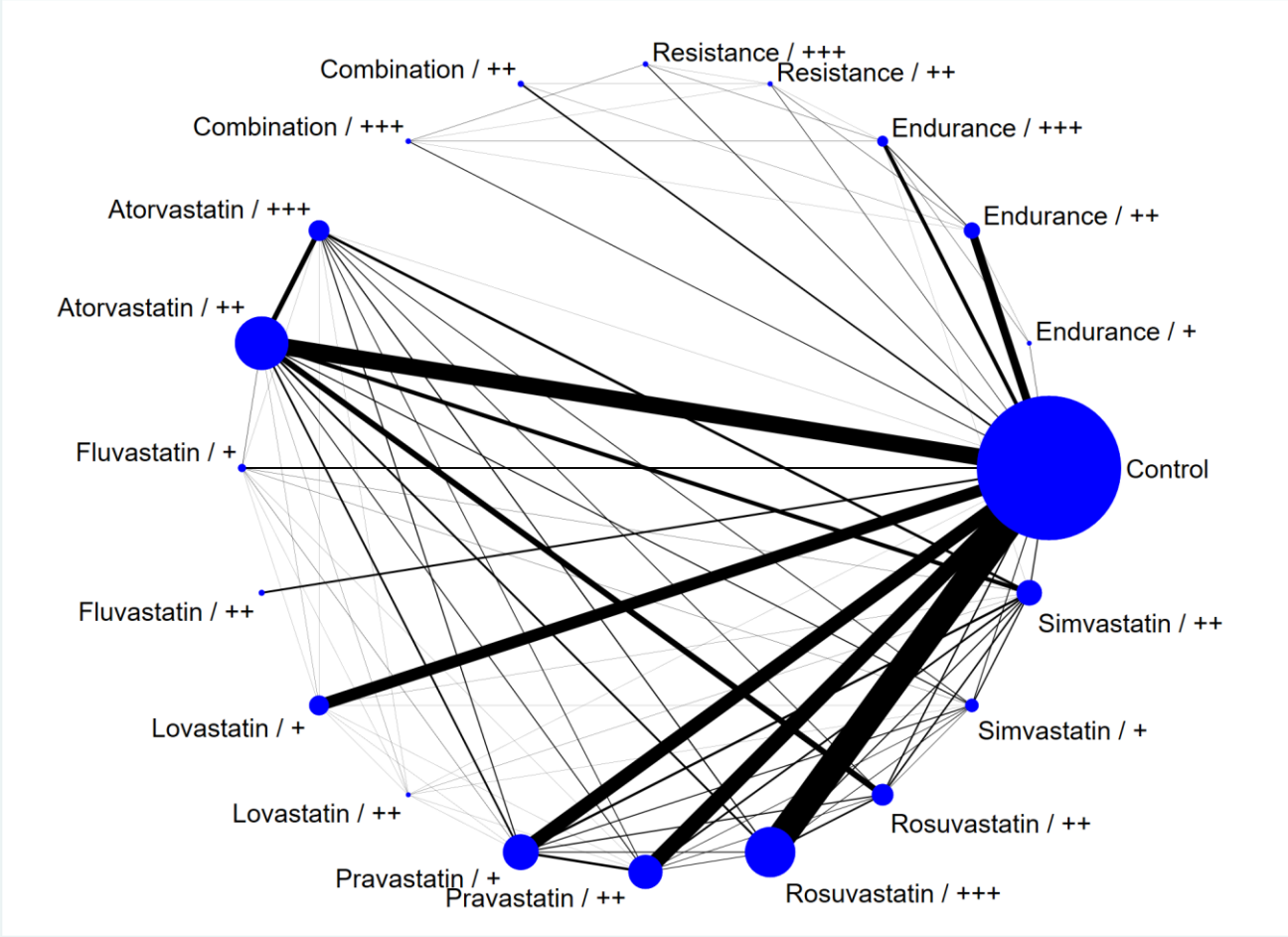
Cumulative meta-analysis

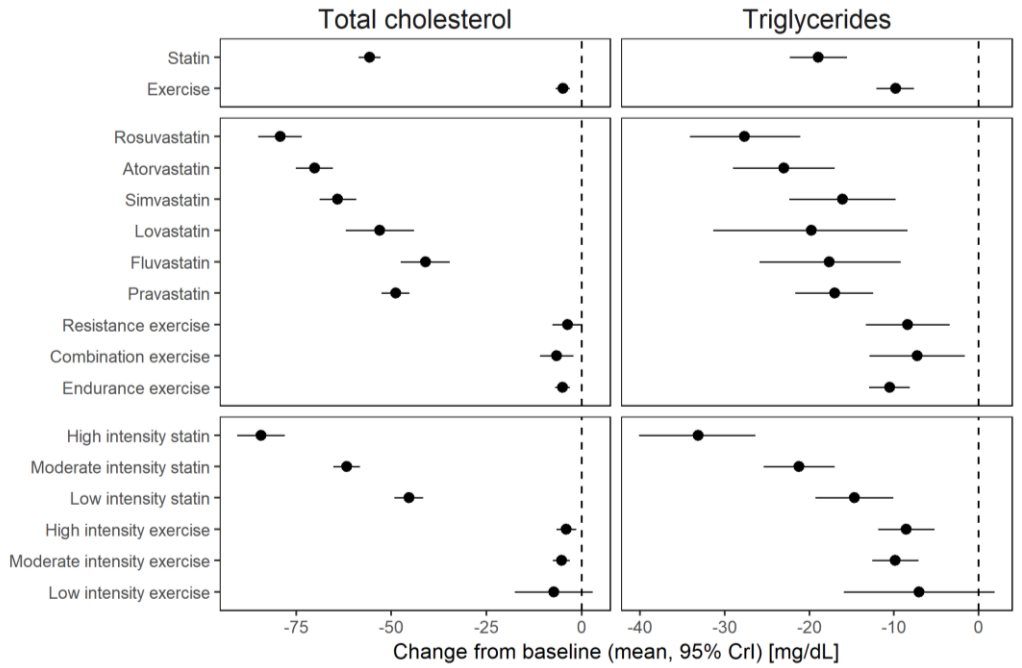
Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007



Jüni 2004 Lancet

Network meta-analysis





Take Home Message

- Meta-analysis is a powerful method to integrate results from several studies into a combined result
- Meta-analysis should be based on a systematic review of the available evidence in regard to a well-formulated research question
- Heterogeneity across studies should be examined, and an attempt to explain it should be done
- Assess for publication bias, ecological fallacy and other sources of metabias (e.g. quality, …)
- Always stay critical!