Explaining heterogeneity

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Outline

1. Revision and remarks on fixed-effect and random-effects meta-analysis methods (and interpretation under heterogeneity)

Explaining heterogeneity:

2. Subgroup analysis
3. Meta-regression
4. Problems

5. Closing remarks

- Example 1: Trials of exercise for treatment of depression

Part 1: Revision and remarks on fixed-effect and random-effects meta-analysis methods

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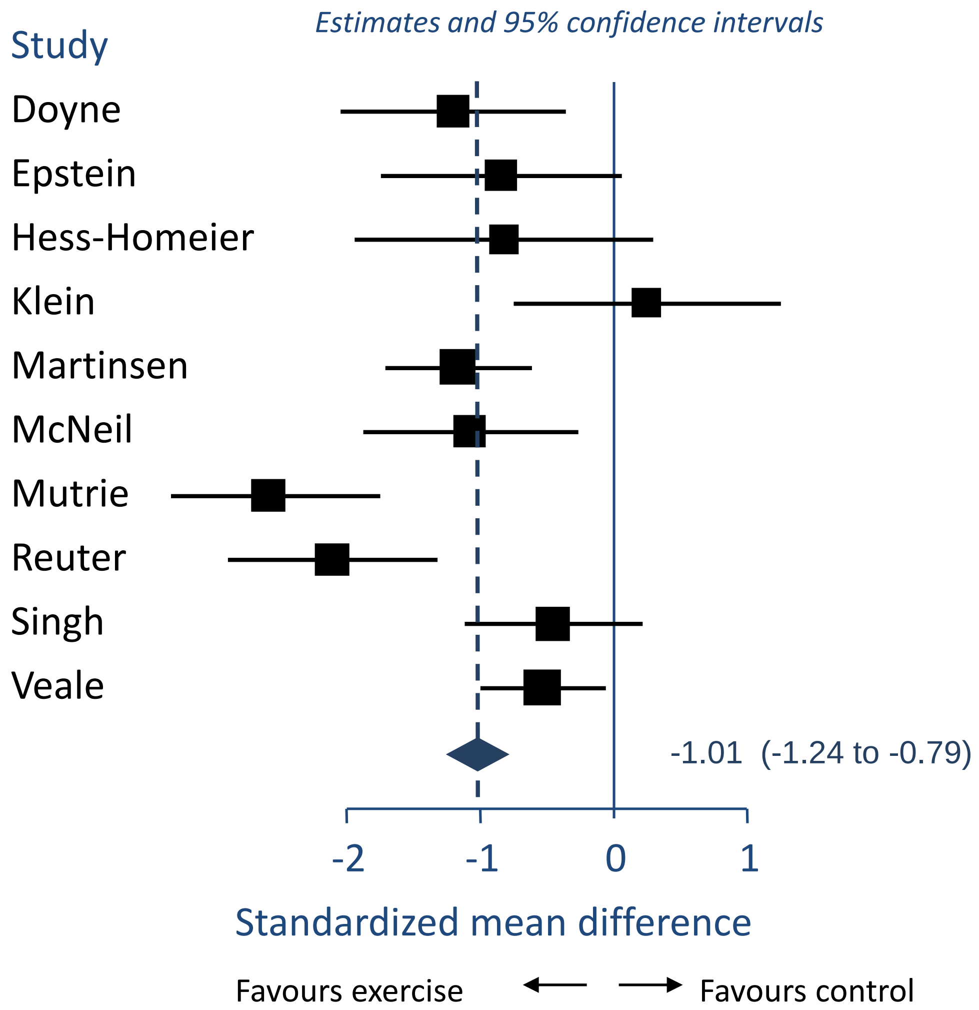
Revision (1)

- Fixed-effect(s) meta-analysis
  - weights $w_i = \frac{1}{v_i}$
  - (minimise variability of the summary estimate)



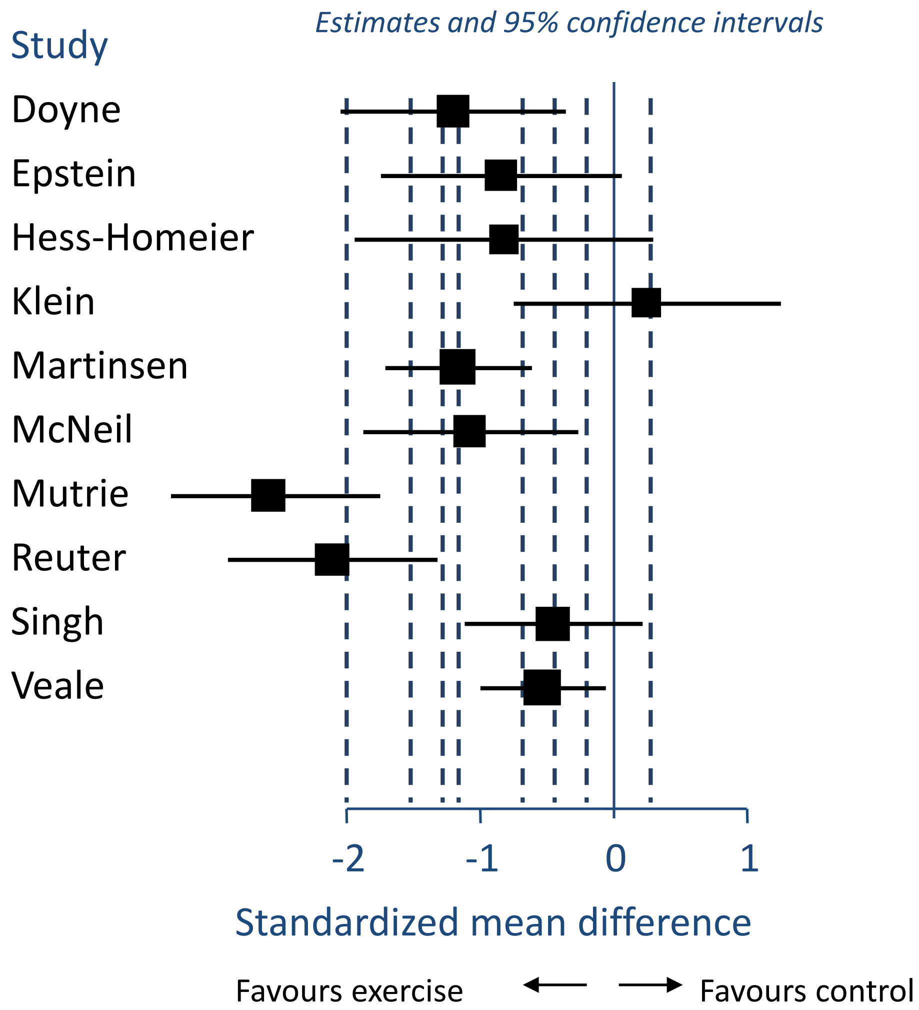
Revision (2)

- examine whether effect vary across studies

$Q = 35.4$ (9 d.f.)
($p = 0.00005$)

$\tau_{DL} = 0.64$ (for example)

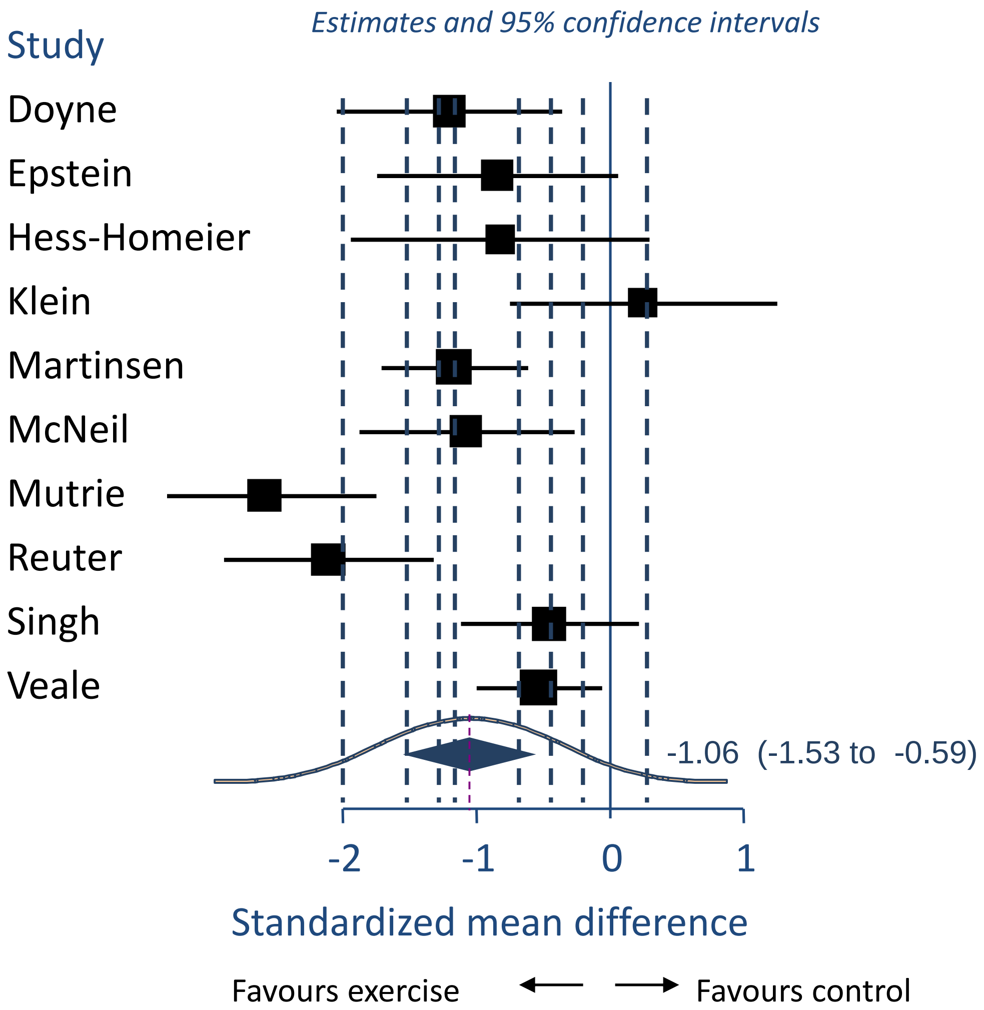
$I^2 = 75\%$



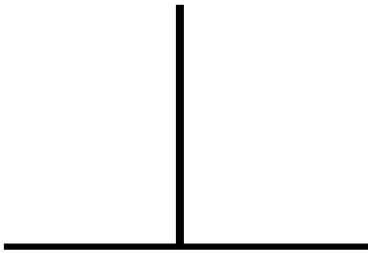
Revision (3)

- Meta-analysis under random-effects assumption
  - effect size varies across studies
  - between-study variance= τ^2
  - weights

$$w_i^* = \frac{1}{v_i + \hat{\tau}^2}$$



Three simple models for relationships of effect size parameters across studies



Effect size

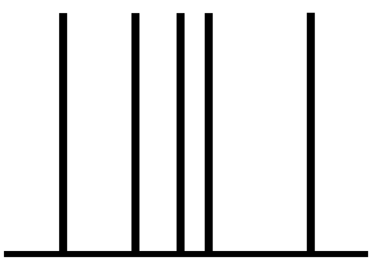
The underlying effect sizes are identical

Common-effect model
(or fixed-effect model)

Effect size

The underlying effect size are different and related through some distribution

Random-effects model

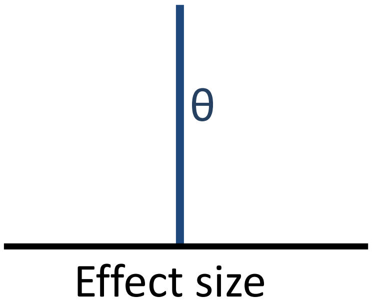


Effect size

The underlying effect sizes are different and unrelated (independent)

Fixed-effects model

Two simple *methods* for combining effect size *estimates* across studies

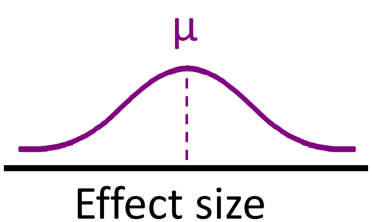


Common-effect model

$$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i}$$

Estimate of: θ

Variance: $\dfrac{1}{\sum w_i}$ $\quad w_i = \dfrac{1}{s_i^2}$

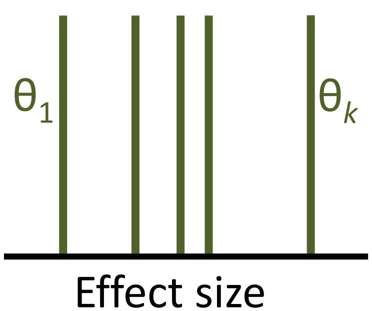


Random-effects model

$$\hat{\mu} = \frac{\sum w_i{}^* y_i}{\sum w_i{}^*}$$

Estimate of: μ

Variance: $\dfrac{1}{\sum w_i{}^*}$ $\quad w_i^* = \dfrac{1}{s_i^2 + \hat{\tau}^2}$



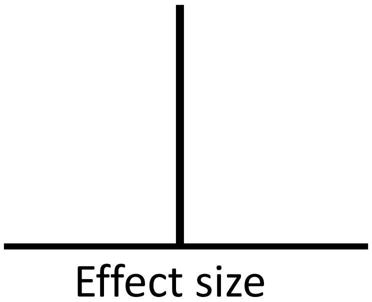
Fixed-effects model

$$\hat{\phi} = \frac{\sum w_i y_i}{\sum w_i}$$

Estimate of: $\dfrac{\sum w_i \theta_i}{\sum w_i}$

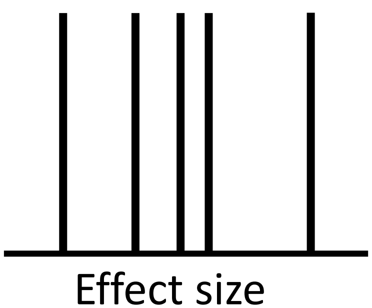
Variance: $\dfrac{1}{\sum w_i}$

Three simple models for relationships of effect size parameters across studies



Common-effect model
(or fixed-effect model)

Complication is that the fixed-effect meta-analysis **method** can be interpreted under either of these **models**



Fixed-effects model

Aside: an interpretation of the weighted average under fixed-effects model

$$\mu = \frac{\sum p_i r_i \theta_i}{\sum p_i r_i}$$

- A weighted average of the study-specific effects seen in the individual study populations, where the weight for study population *i* is proportional to both the number of participants selected (p_i) and to how much information is contributed per subject (r_i)
- No assumption of homogeneity is required
- But heterogeneity is ignored in the analysis so inference on this is required
  - this inference is statistically independent
- The empirical weights are poor estimates of $p_i r_i$ unless the studies are large

Rice, Higgins and Lumley (submitted)

What is heterogeneity?

- Variation beyond that expected by chance alone
  - Observed result = **true effect** + **bias** + **random error**
- True effects vary due to 'clinical diversity'
  - variants in PICO
- Biases vary due to 'methodological diversity'
  - design, conduct, problems

- In practice, true effects and biases inseparable, so group them together
- Variation in true effect + bias measured by the between-study variance τ^2

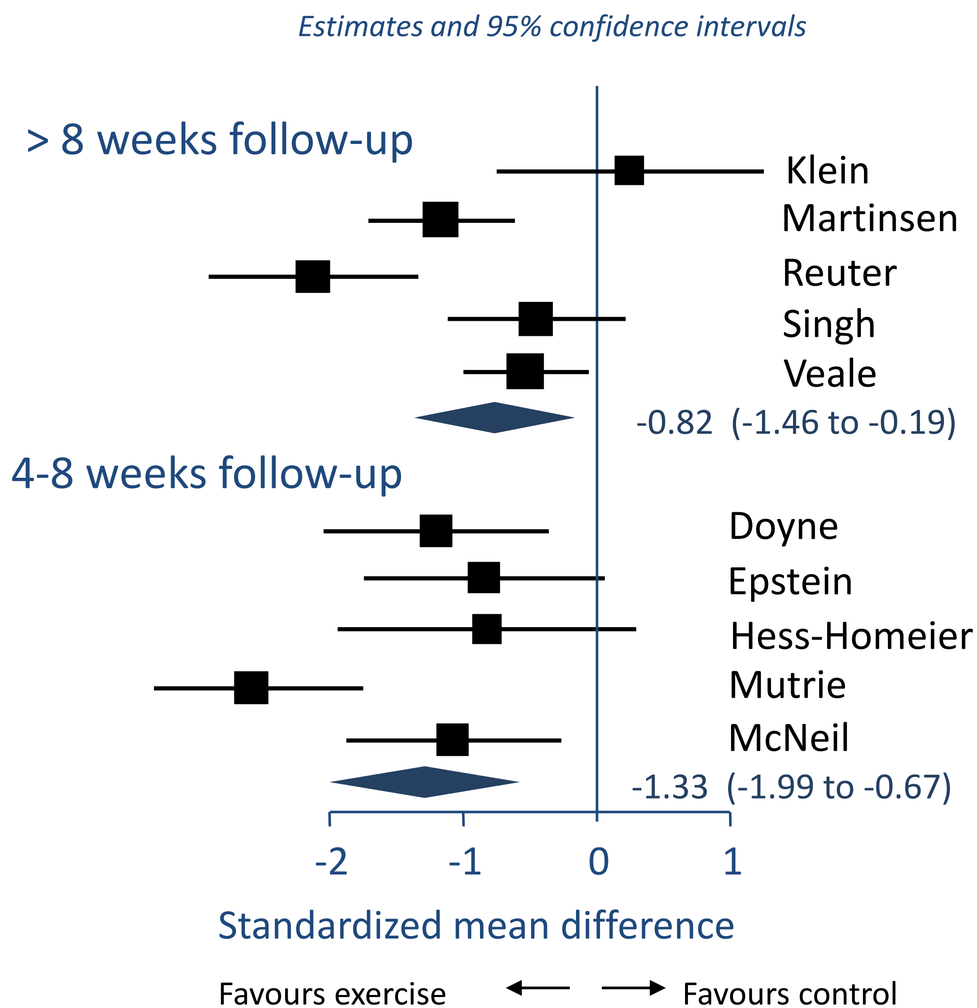
Exploring heterogeneity

In which types of trials does the intervention work best?

- Characteristics of studies may be associated with the size of treatment effect
  - Does the intervention work better if given for longer?
  - Are smaller odds ratios observed in high-risk populations?
  - Is there a relationship between sample size and effect size (e.g. due to publication bias)?
  - Is inadequate allocation concealment associated with a larger effect estimate?
  - Is A better than B, when they've each only been compared with C? For discrete characteristics, can use subgroup analyses
- We can use subgroup analyses or meta-regression to answer questions like these

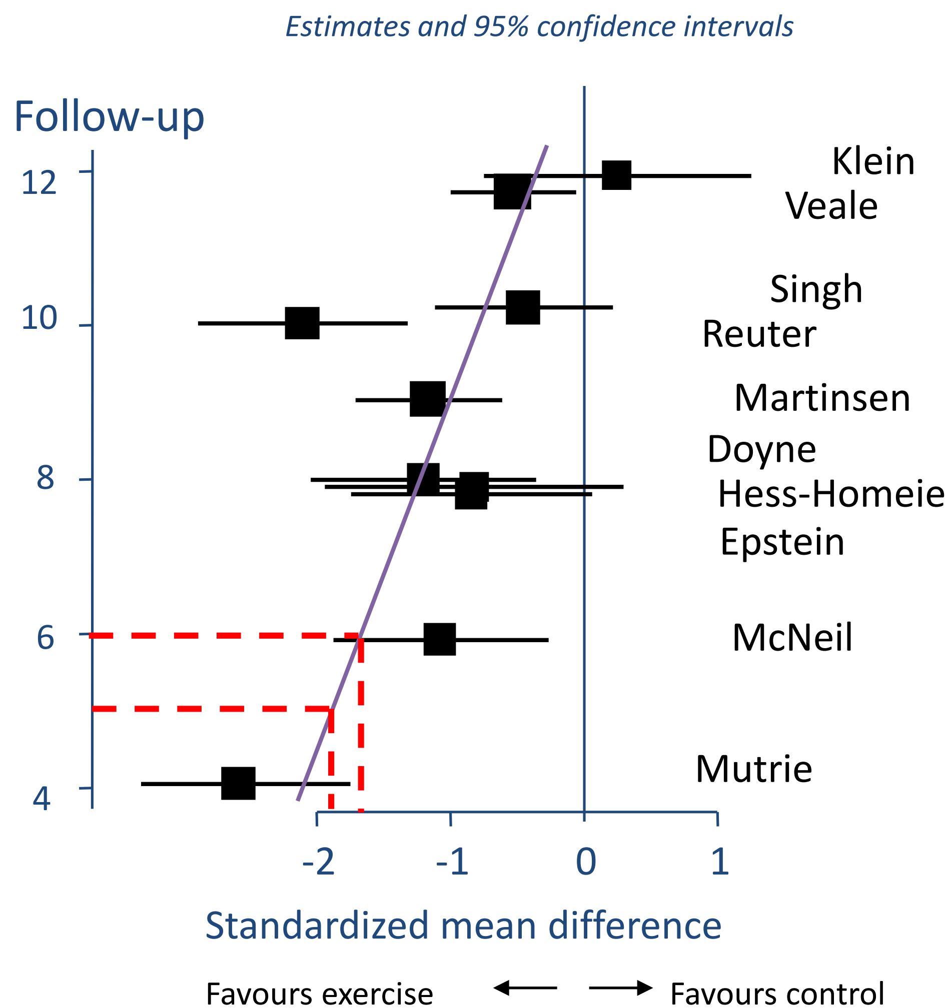
Subgroup analysis

- Divide up the studies
  - e.g. by duration of trial
- Test for subgroup differences:
  - can apply Q test to subgroup results
  - here, $P = 0.28$



Meta-regression

- Examine heterogeneity
- Predict effect according to length of follow-up
- *Difference in SMDs* = 0.18 (95% CI 0.02 to 0.34): i.e. SMD decreases by 0.2 for each extra week of follow up



Part 2: Subgroup analysis

Subgroup analyses

- Split data into subgroups:
  - Subsets of patients
  - Subsets of studies
- Do separate meta-analyses for each

- Subgroup analyses done for three reasons
  - To answer multiple questions (one for each subset of studies)
  - To examine whether the effect is different in different subgroups (comparing subgroups)
  - To assess whether restricting analysis to one subgroup changes the conclusion (sensitivity analysis)

Subgroup analyses

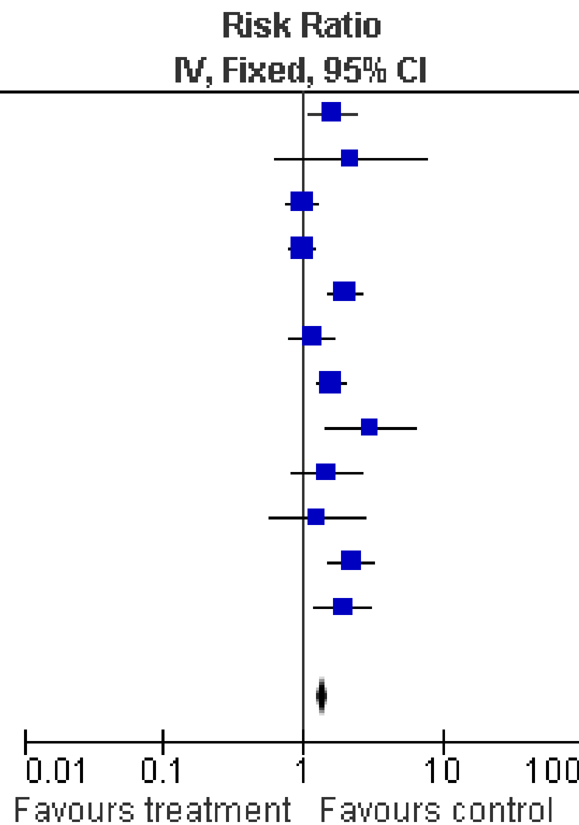
Behavioural interventions for smokeless tobacco use cessation

Abstinence from all tobacco use (where reported) at 6 months or more

	Treatment		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Boyle 2004	44	109	28	112	6.3%	1.61 [1.09, 2.39]
Cigrang 2002	7	31	3	29	0.6%	2.18 [0.62, 7.65]
Cummings 1995	76	316	102	417	14.6%	0.98 [0.76, 1.27]
Gansky 2005	103	285	130	352	23.0%	0.98 [0.80, 1.20]
Seversen 2006	119	393	60	392	12.8%	1.98 [1.50, 2.61]
Seversen 2007a	60	535	52	534	7.9%	1.15 [0.81, 1.64]
Seversen 2007b	159	1260	100	1263	17.3%	1.59 [1.26, 2.02]
Severson 1998	40	394	8	239	1.8%	3.03 [1.44, 6.37]
Stevens 1995	25	245	19	273	3.0%	1.47 [0.83, 2.60]
Stotts 2003	19	198	8	105	1.6%	1.26 [0.57, 2.78]
Walsh 1999	60	171	30	189	6.6%	2.21 [1.50, 3.25]
Walsh 2003	38	141	23	166	4.5%	1.95 [1.22, 3.10]
Total (95% CI)	**750**	**4078**	**563**	**4071**	**100.0%**	**1.38 [1.25, 1.53]**

Heterogeneity: $\text{Chi}^2 = 39.56$, $df = 11$ ($P < 0.0001$); $I^2 = 72\%$

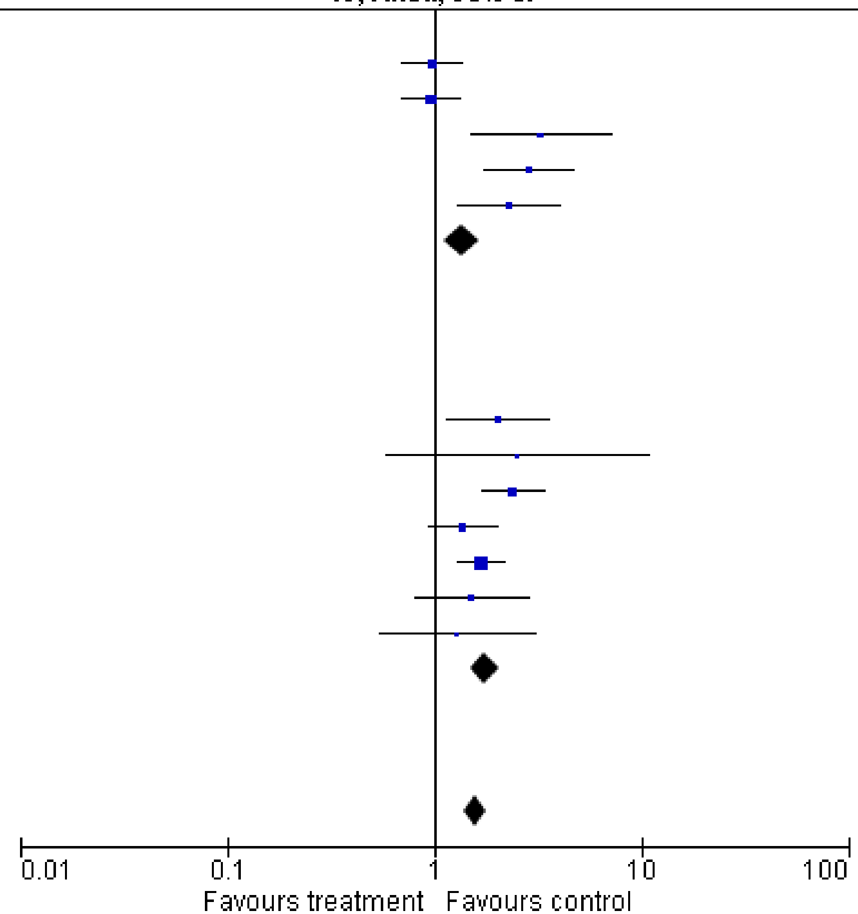
Test for overall effect: $Z = 6.41$ ($P < 0.00001$)



Subgroup analyses

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.1.1 Randomisation by organisation						
Cummings 1995	76	316	102	417	13.5%	0.98 [0.70, 1.38]
Gansky 2005	103	285	130	352	14.9%	0.97 [0.70, 1.34]
Severson 1998	40	394	8	239	2.6%	3.26 [1.50, 7.10]
Walsh 1999	60	171	30	189	6.3%	2.86 [1.74, 4.73]
Walsh 2003	38	141	23	166	4.7%	2.29 [1.29, 4.08]
Subtotal (95% CI)		**1307**		**1363**	**42.0%**	**1.36 [1.12, 1.64]**
Total events	317		293			
Heterogeneity: Chi² = 24.38, df = 4 (P < 0.0001); I² = 84%						
Test for overall effect: Z = 3.08 (P = 0.002)						
1.1.2 Individual randomisation						
Boyle 2004	44	109	28	112	4.8%	2.03 [1.14, 3.60]
Cigrang 2002	7	31	3	29	0.7%	2.53 [0.59, 10.90]
Seversen 2006	119	393	60	392	12.9%	2.40 [1.69, 3.41]
Seversen 2007a	69	535	52	534	10.8%	1.37 [0.94, 2.01]
Seversen 2007b	159	1260	100	1263	22.6%	1.68 [1.29, 2.19]
Stevens 1995	25	245	19	273	4.0%	1.52 [0.81, 2.83]
Stotts 2003	19	198	8	105	2.1%	1.29 [0.54, 3.05]
Subtotal (95% CI)	**442**	**2771**	**270**	**2708**	**58.0%**	**1.76 [1.49, 2.07]**
Heterogeneity: Chi² = 6.00, df = 6 (P = 0.42); I² = 0%						
Test for overall effect: Z = 6.72 (P < 0.00001)						
Total (95% CI)	**759**	**4078**	**563**	**4071**	**100.0%**	**1.58 [1.39, 1.79]**
Heterogeneity: Chi² = 34.42, df = 11 (P = 0.0003); I² = 68%						
Test for overall effect: Z = 7.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.04, df = 1 (P = 0.04), I² = 75.3%						

Odds Ratio
IV, Fixed, 95% CI



Comparing two subgroups

- Simple statistics: take the difference in point estimates and add their variances
  - all on the log scale for ratio measures

Subgroup	**OR**	**OR_CI_low**	**OR_CI_upp**	**lnOR**	**lnOR_CI_low**	**lnOR_CI_upp**	**lnOR_var**
Randomisation by organisation	1.36	1.12	1.64	0.307	0.113	0.495	0.009
Individual randomisation	1.76	1.49	2.07	0.565	0.399	0.728	0.007
	RATIO			DIFF			SUM
Comparison of subgroups	0.773	0.601	0.994	-0.258	-0.510	-0.006	0.016

Fixed-effects test for subgroup differences

- Simple method

Q_{all} : chi-squared statistic for all the studies

$Q_1, \ldots, Q_m$: chi-squared statistic for *m* different subgroups

- Heterogeneity explained by differences between subgroups (Q_{bet}):

$$Q_{bet} = Q_{all} - (Q_1 + \ldots + Q_m)$$

- Has degrees of freedom

$$df = m - 1$$

Fixed-effects test for subgroup differences

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Severson 1998	40	394	8	[illegible]	[illegible]2.6%	3.26 [1.50, 7.10]
Walsh 1999	60	171	30	[illegible]	[illegible]6.3%	2.86 [1.74, 4.73]
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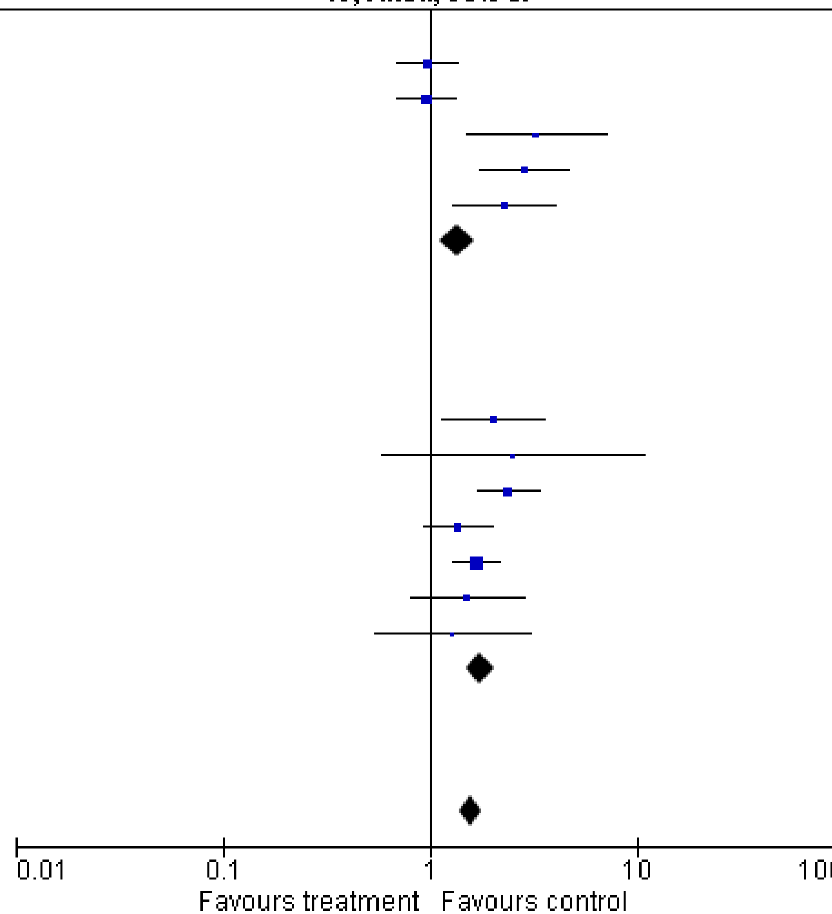
Q_1

Q_2

Q_{all}

Odds Ratio
IV, Fixed, 95% CI



Fixed-effects test for subgroup differences

$$Q_{bet} = 34.42 - (24.38 + 6.00)$$
$$= 4.04$$

- Two subgroups, so 2 – 1 = 1 degree of freedom
- Chi-squared value of 4.04 with 1 degree of freedom:
  P = 0.044

Test for subgroup differences

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1.1.1 Randomisation by organisation						
Cummings 1995	76	316	102	417	13.5%	0.98 [0.70, 1.38]
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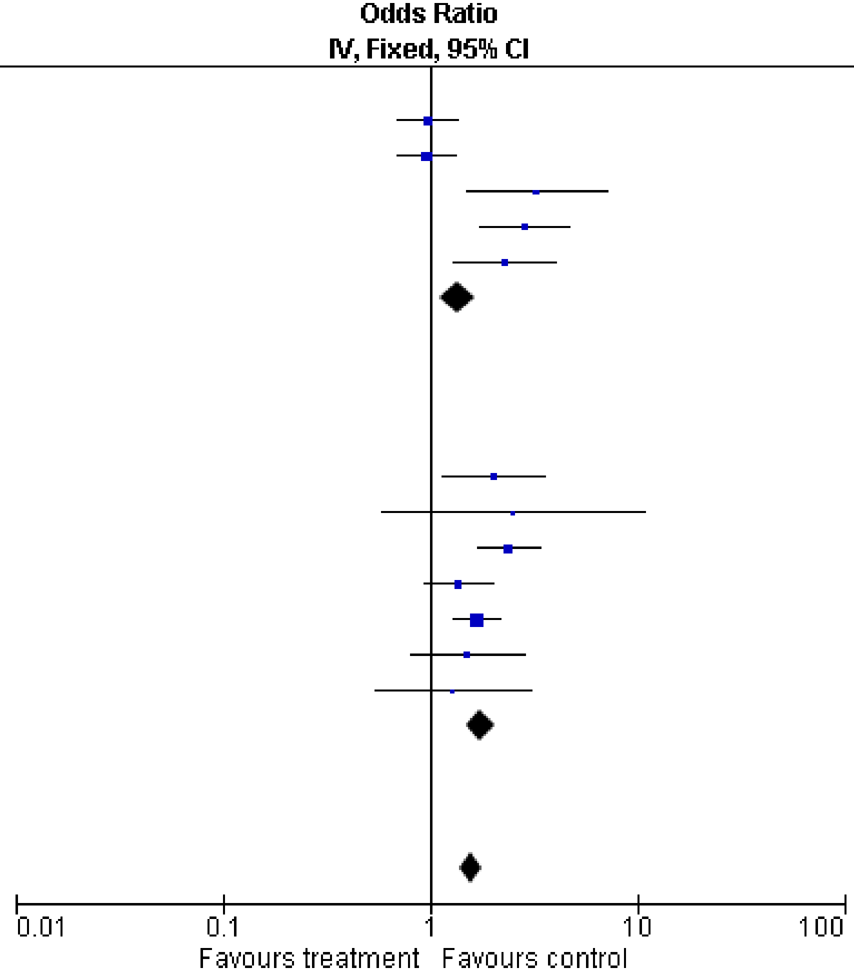

General test for subgroup differences

- Just do a test for heterogeneity across the results of all the subgroups
- Fine for any number of subgroups, and any type of analysis within the subgroups

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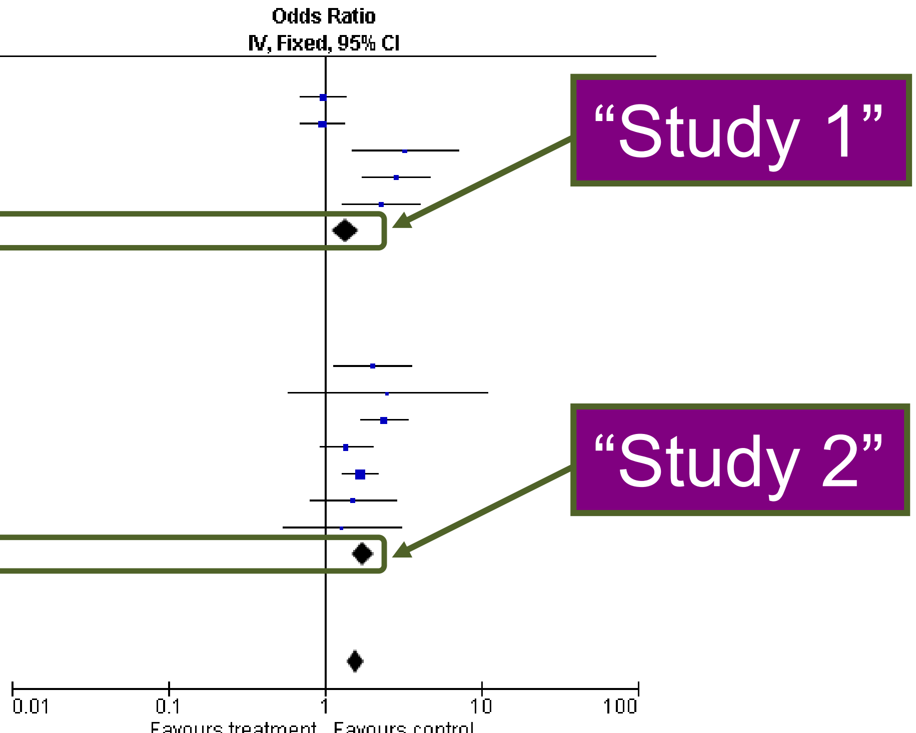


Part 3: Meta-regression

Meta-regression

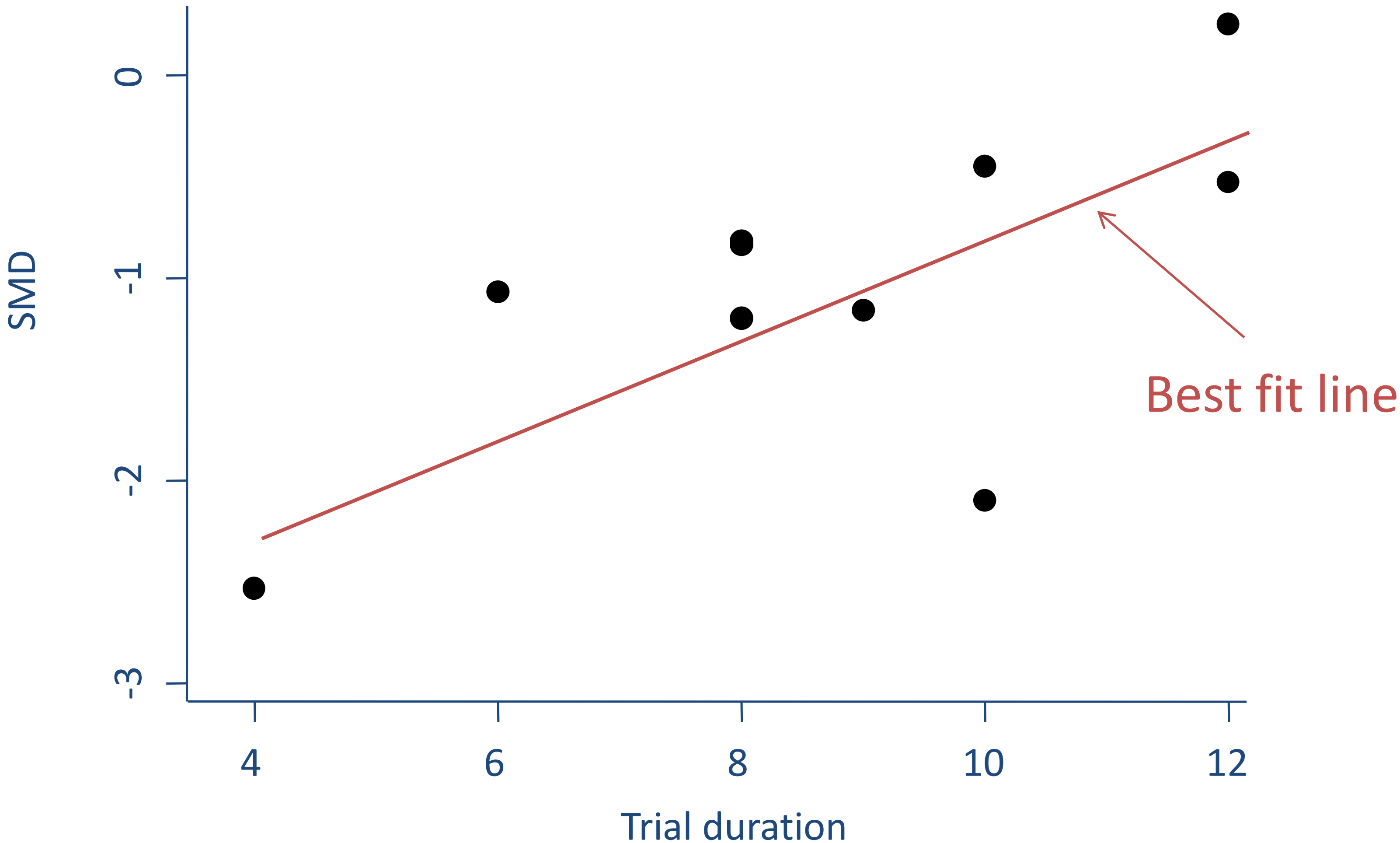
- A general framework for looking at possible explanations for differences in effect sizes across studies

- A test for subgroup differences can be done using meta-regression

- But meta-regression also good for continuous characteristics

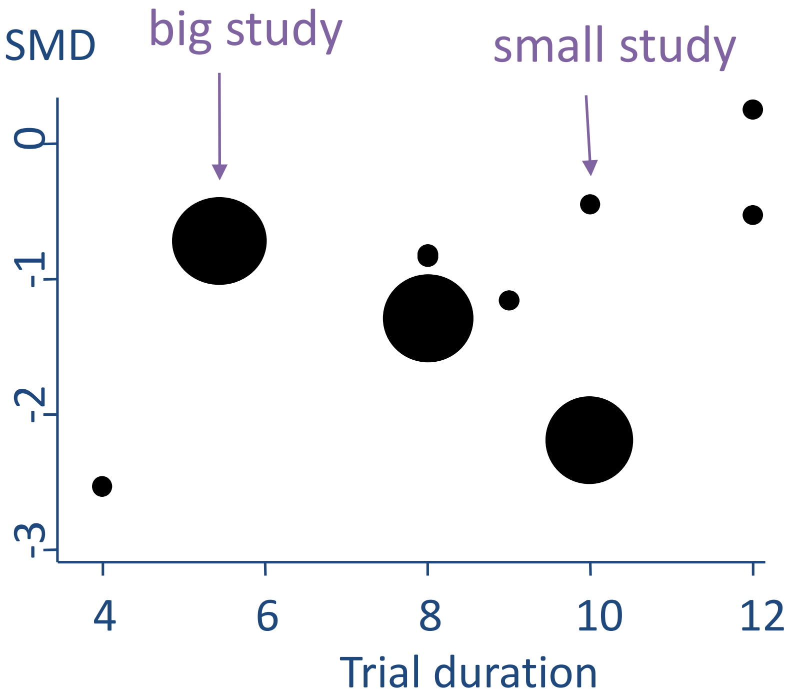
- Linear regression
  - outcome variable = effect size (e.g. SMD or logRR)
  - explanatory variable = summary description of study (e.g. duration or location)

Simple linear regression

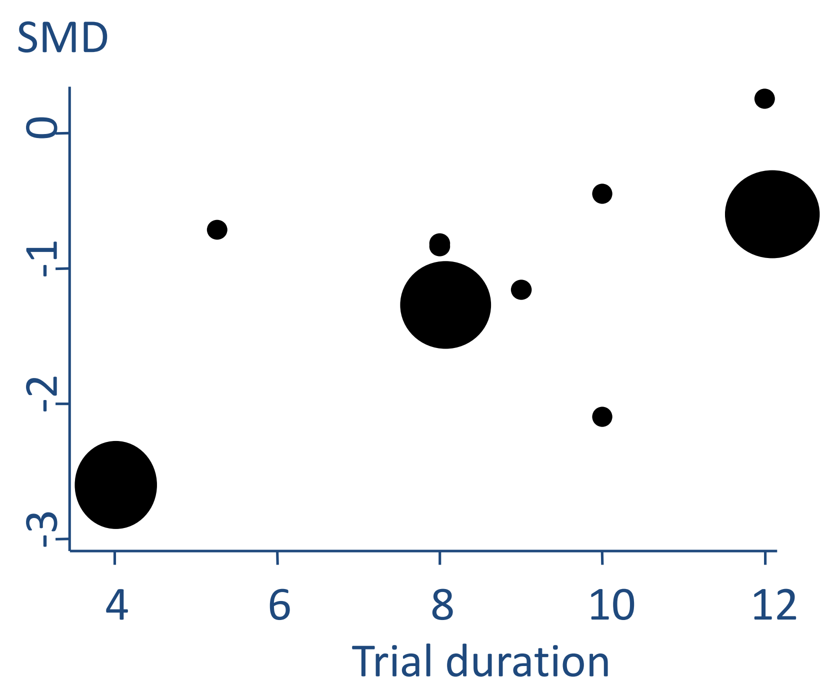


Why we don't use simple linear regression

- Just as in meta-analysis, the studies are different sizes, and should have different influences on the analysis
- There's a difference between

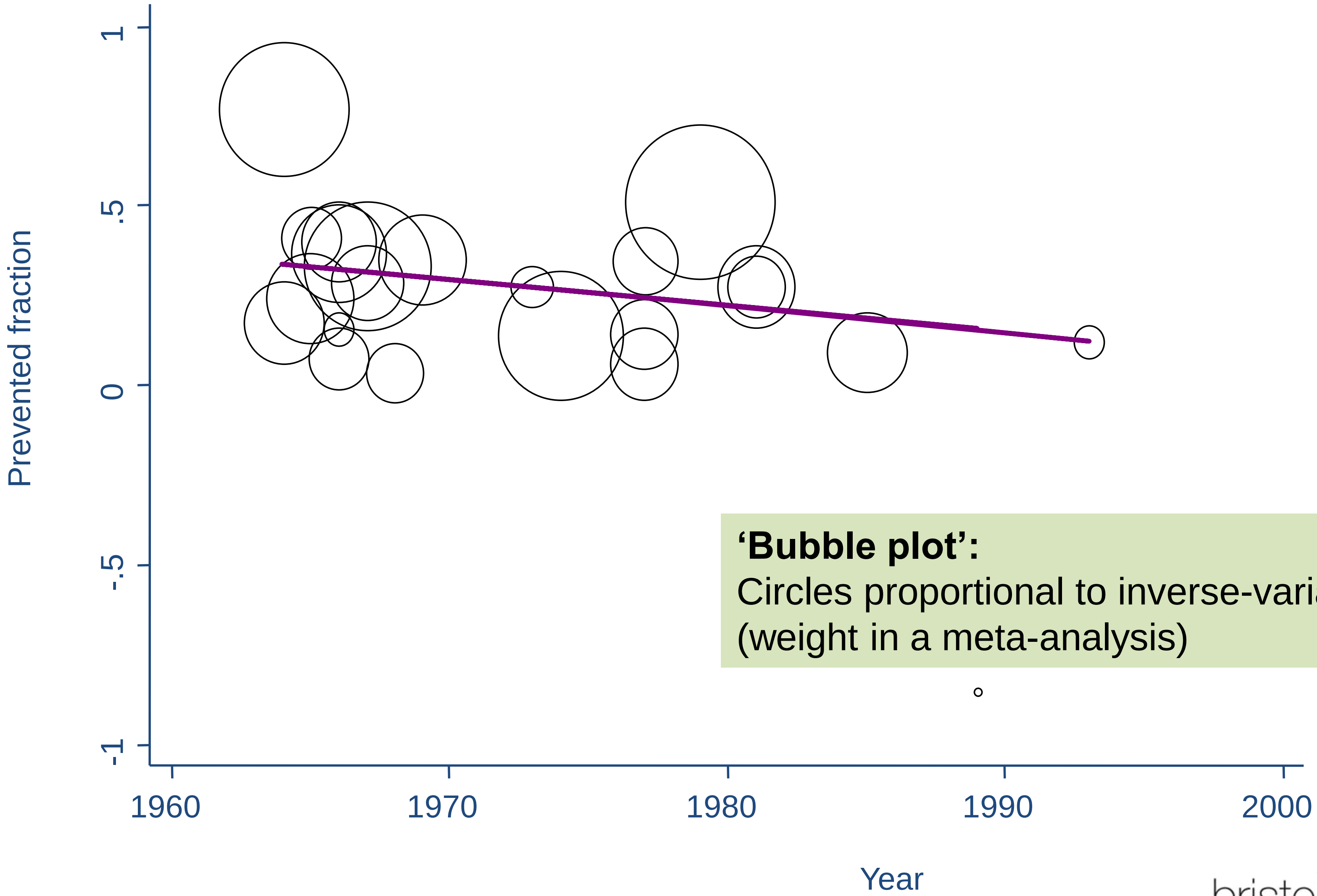


and



Has effectiveness of fluoride gels changed over time?

Marinho et al (2004)



‘Bubble plot’:
Circles proportional to inverse-variance (weight in a meta-analysis)

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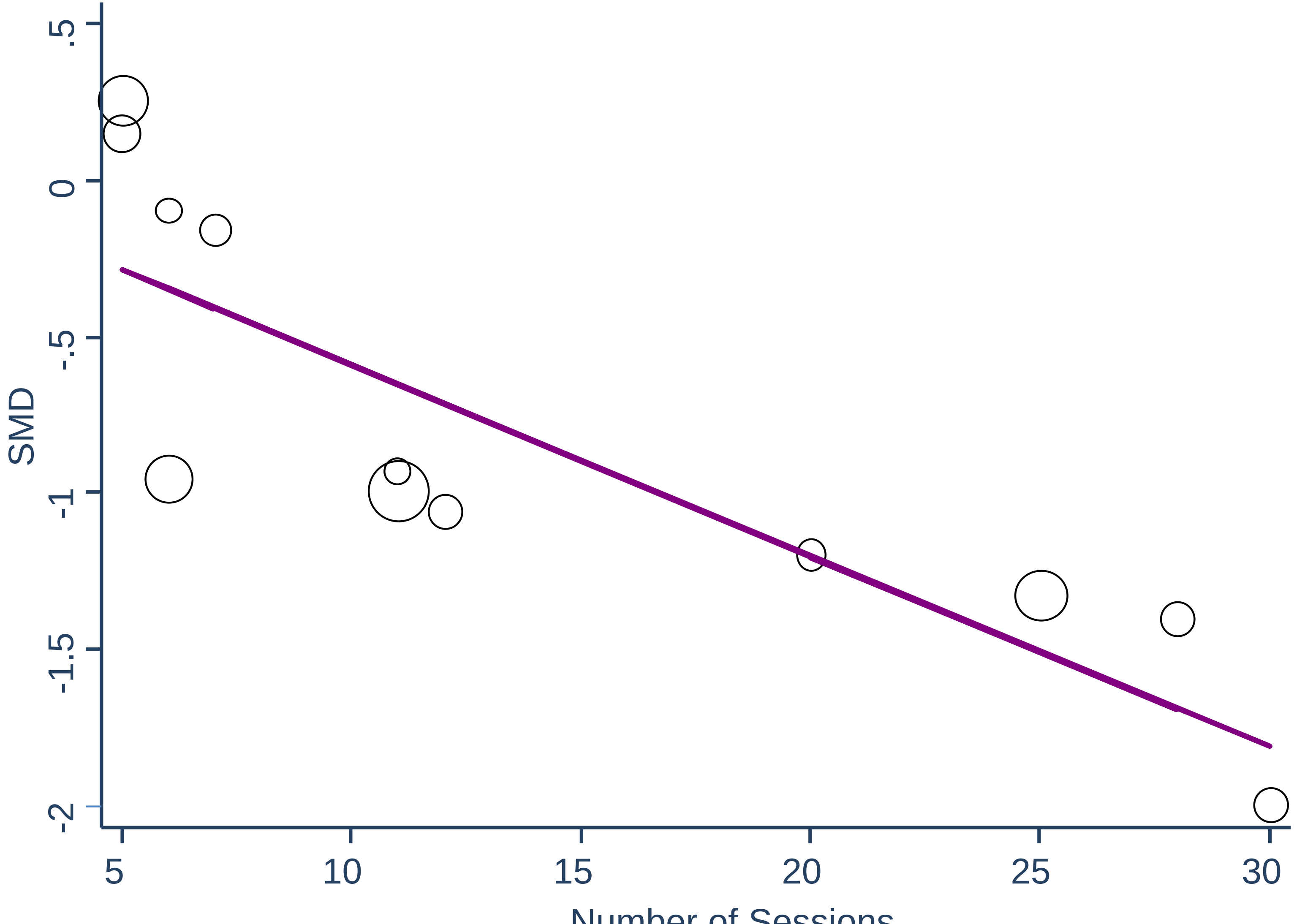
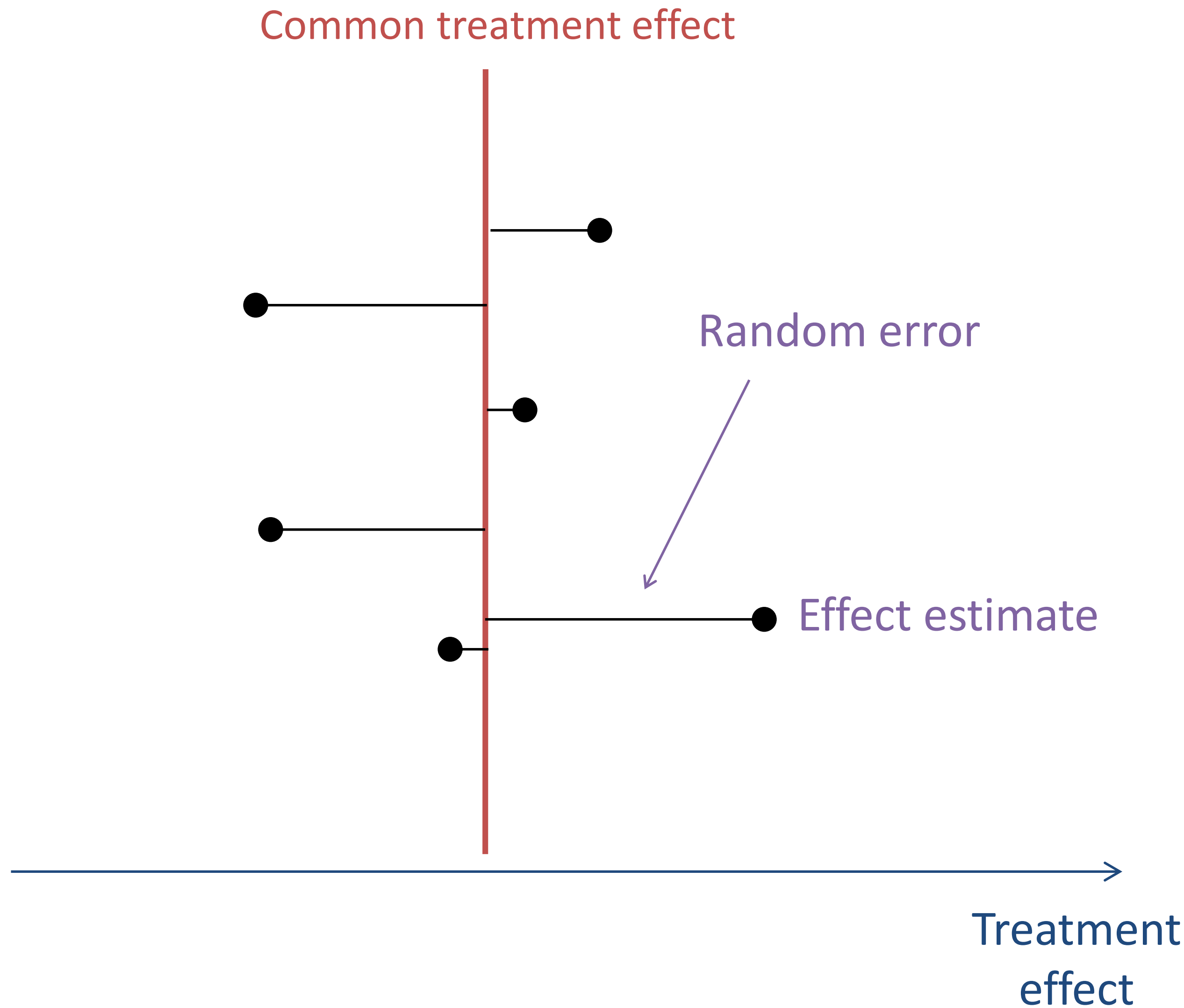
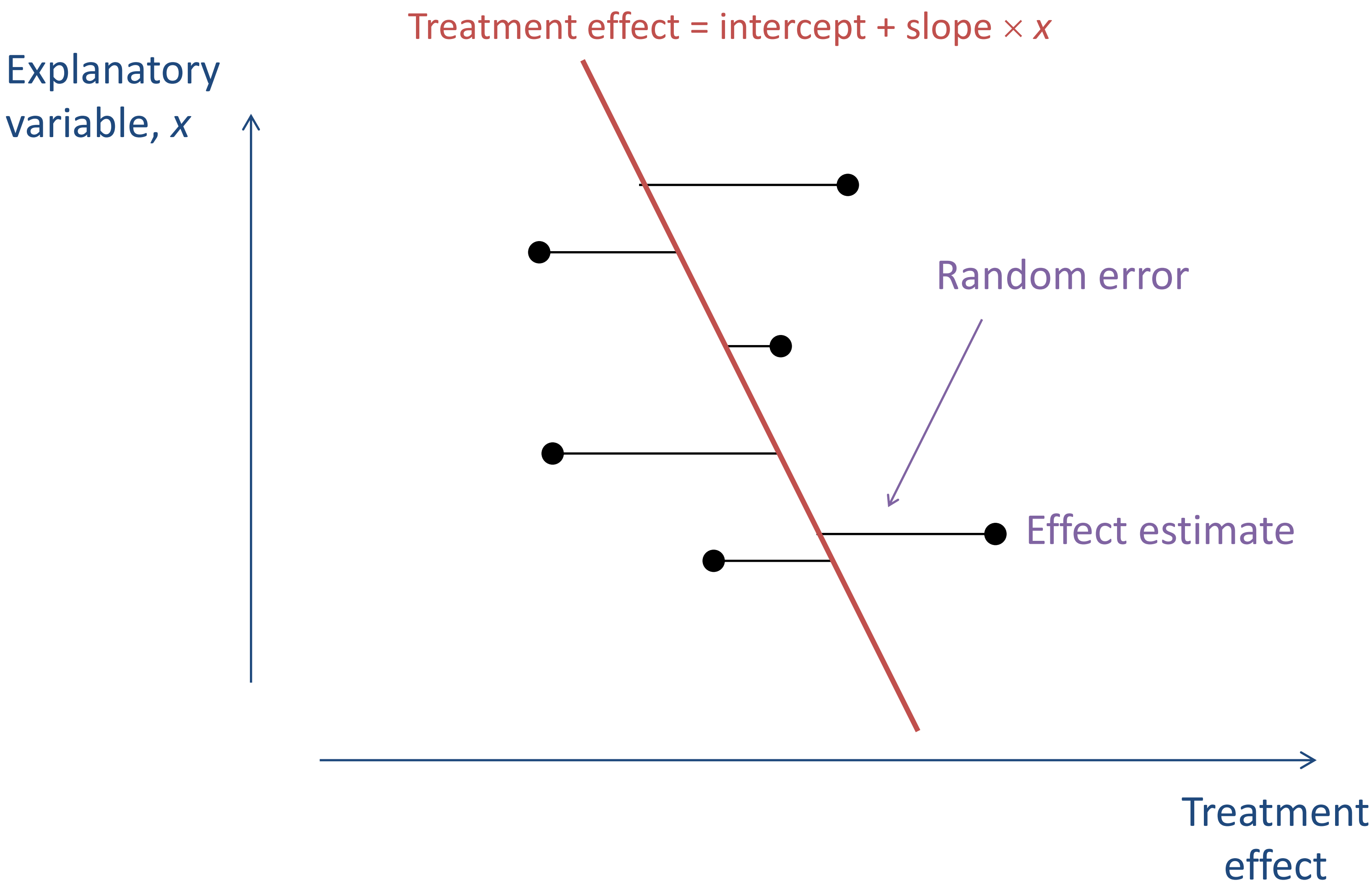
Number of sessions of CBT



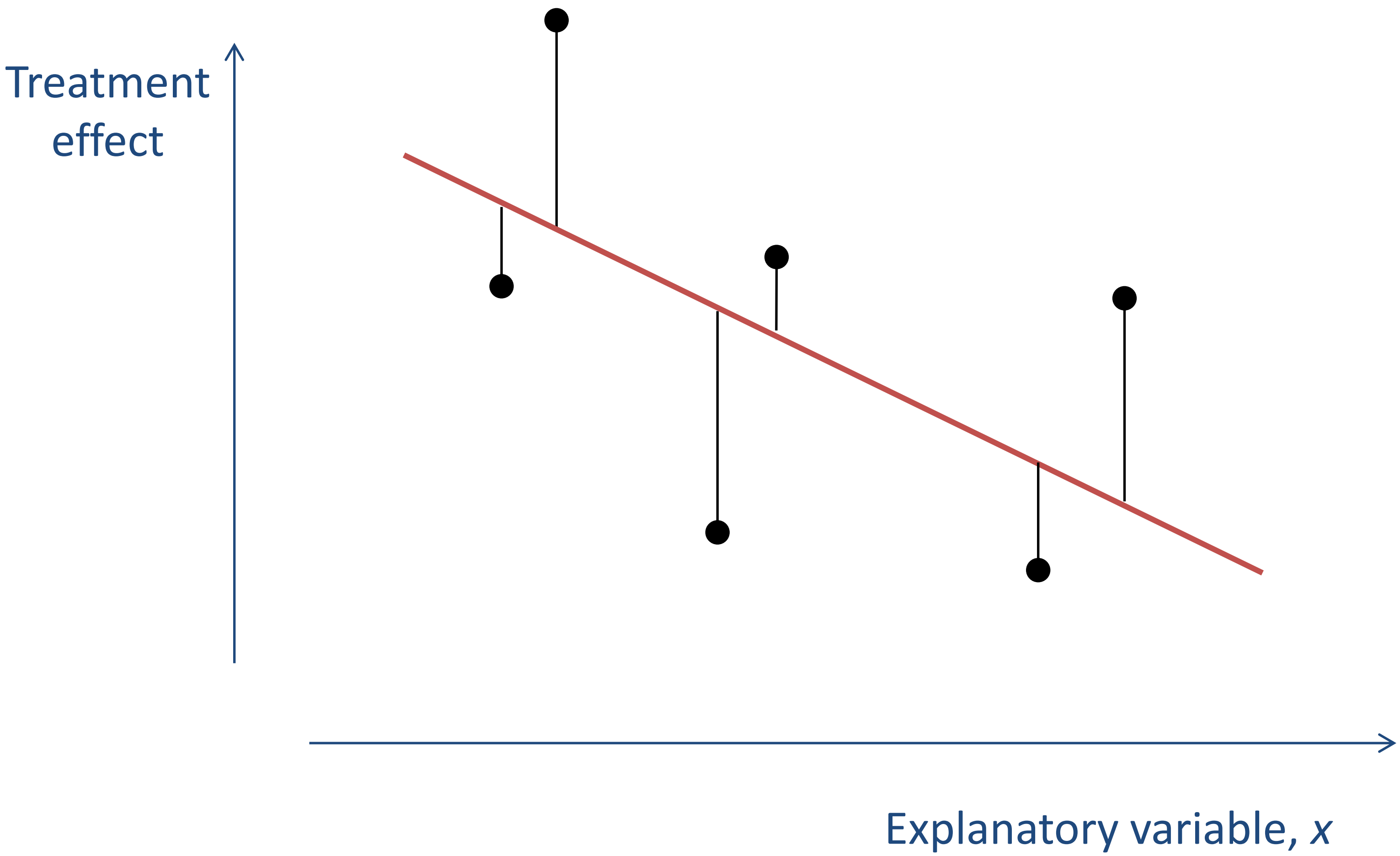
Fixed-effect meta-analysis



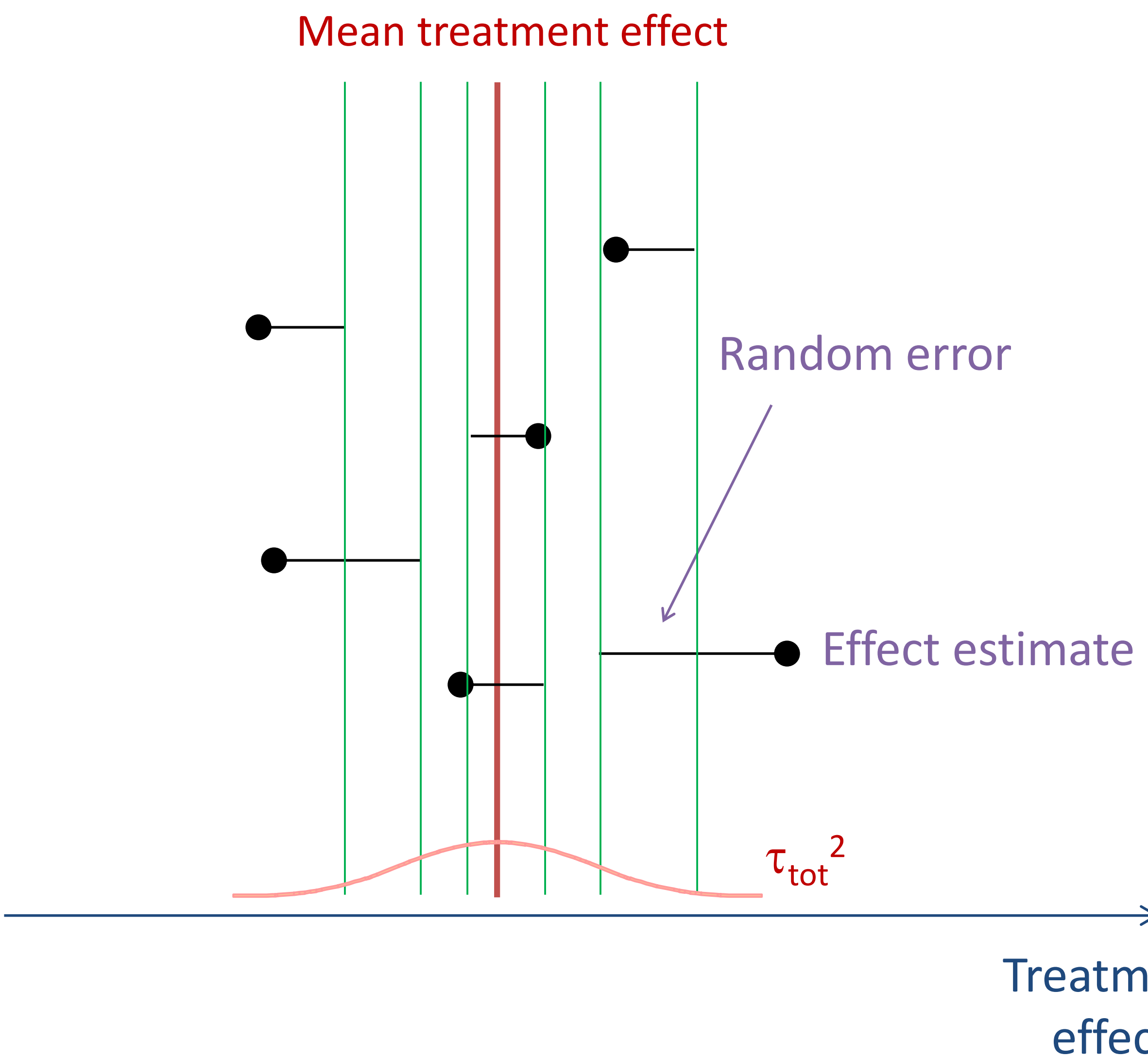
Fixed-effect meta-regression



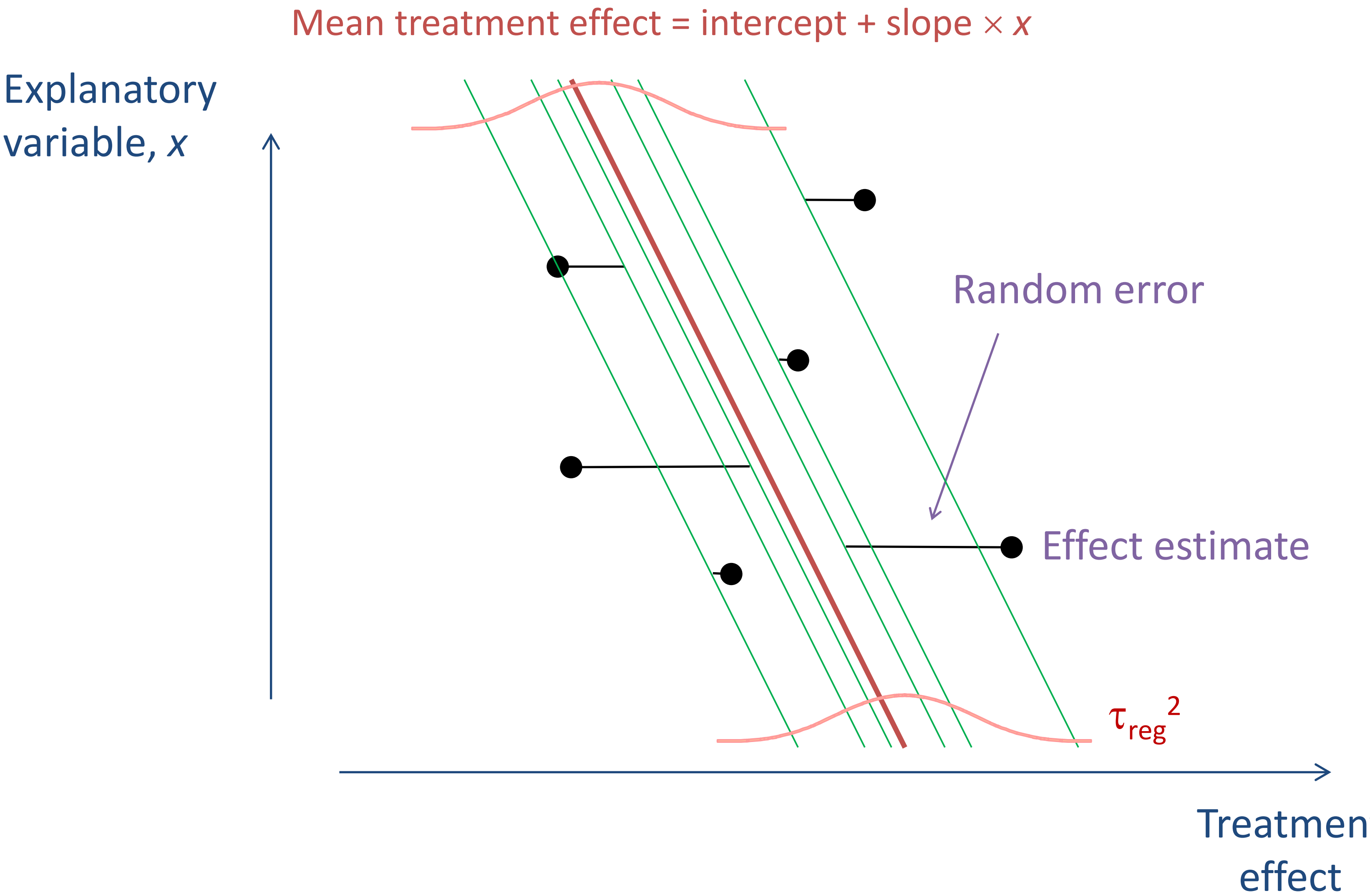
The other way round
(the convention for plotting)



Random-effects meta-analysis



Random-effects meta-regression



Proportion of heterogeneity explained

- Compare

heterogeneity variance from random-effects meta-analysis (τ^2_{tot})

with

heterogeneity variance from random-effects meta-regression (τ^2_{reg})

- % variance explained = $100\% \times \dfrac{\tau^2_{tot} - \tau^2_{reg}}{\tau^2_{tot}}$

- A useful measure of the explanatory ability of a (set of) covariate(s)

Example - BCG vaccination

It has been recognised for many years that the protection given by BCG against tuberculosis varied between trials

Risk ratios:

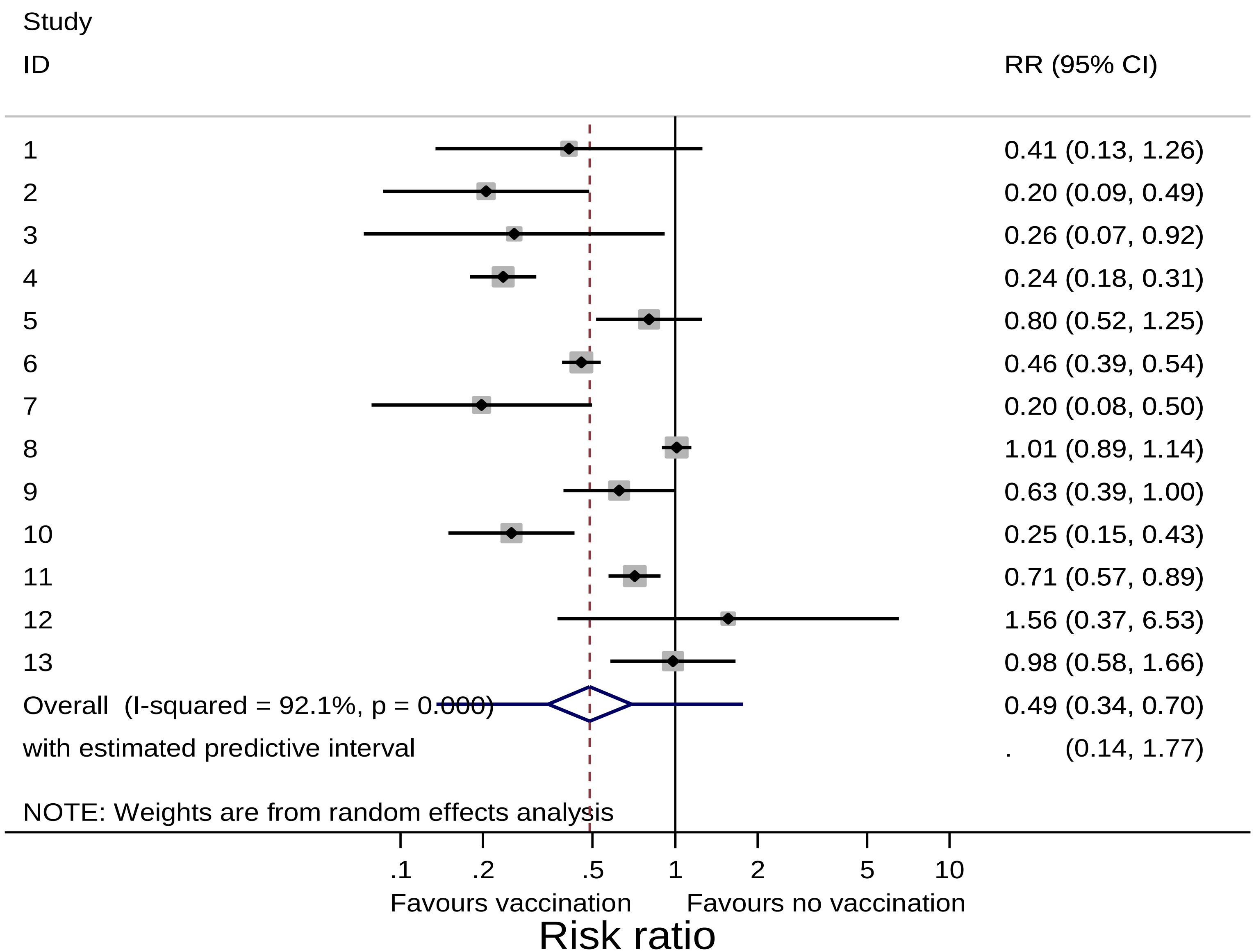
MRC trial (UK)	**0.24 (95% CI 0.18 to 0.31)**
Madras, (South India)	**1.01 (95% CI 0.89 to 1.14)**

Random-effects meta-analysis (Colditz et al. 1994)

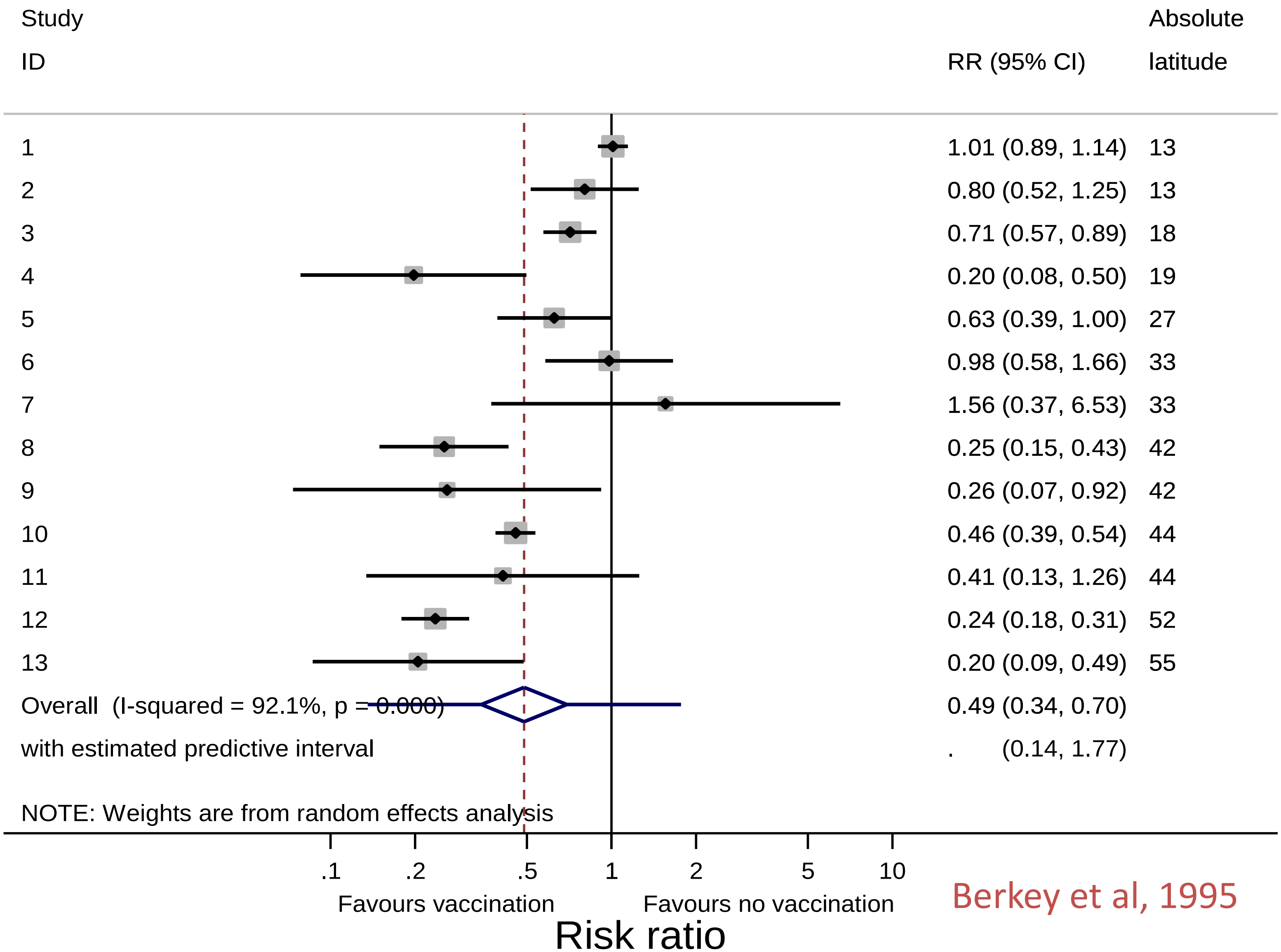
Summary (random effects) RR: 0.49 (95% CI 0.34 to 0.70)

“the results of this meta-analysis lend added weight and confidence to arguments favouring the use of BCG vaccine”

BCG vaccination to prevent tuberculosis

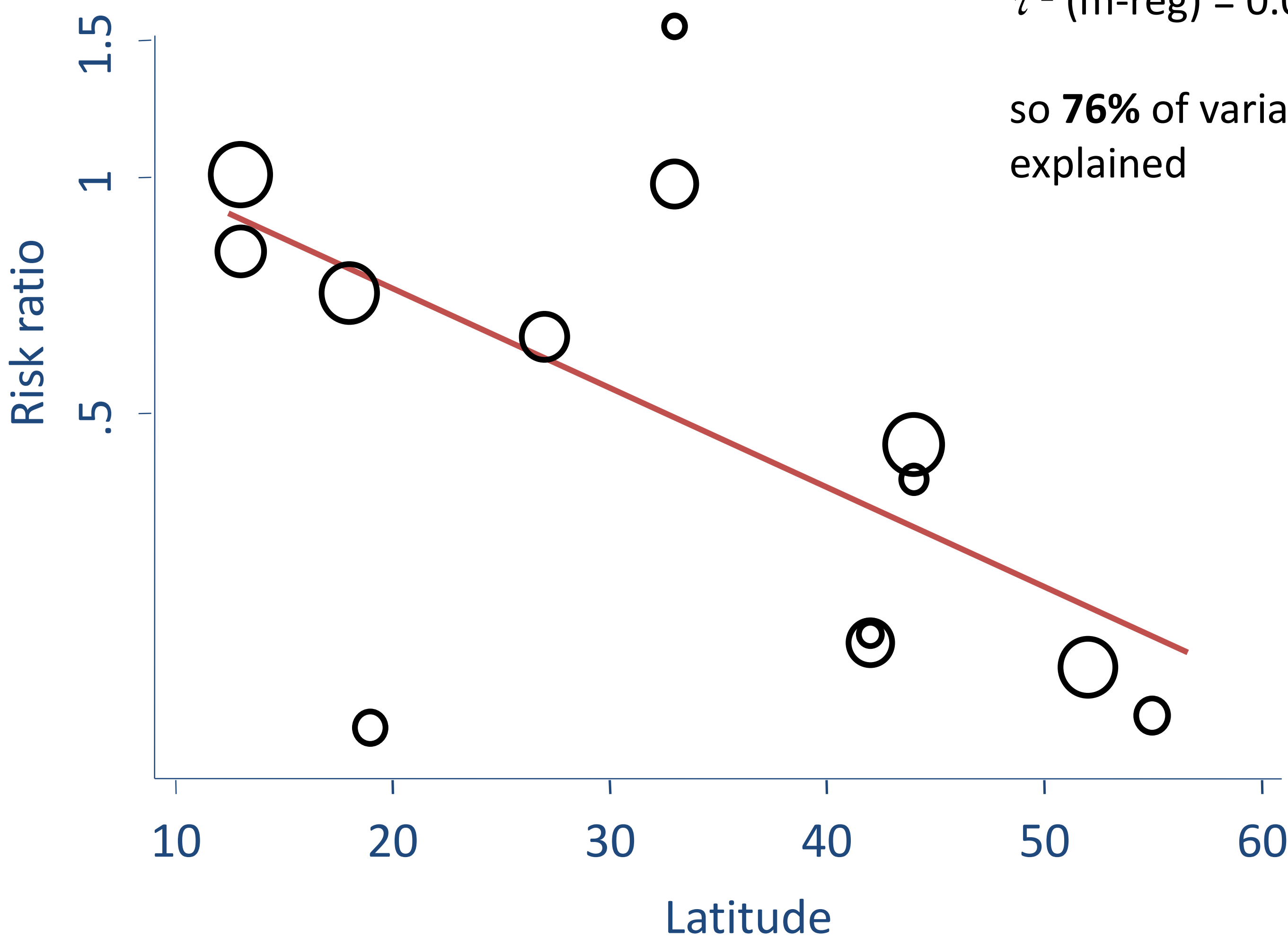


BCG vaccination to prevent tuberculosis



Berkey et al, 1995

Meta-regression: Dependence of BCG vaccine efficacy on study latitude



τ^2 (m-a) = 0.313
τ^2 (m-reg) = 0.076

so **76%** of variance is explained

Hartung-Knapp

- Simulation study:

"Of the different methods evaluated, only the Knapp and Hartung method and the permutation test provide adequate control of the Type I error rate across all conditions. Due to its computational simplicity, the Knapp and Hartung method is recommended as a suitable option for most meta-analyses."

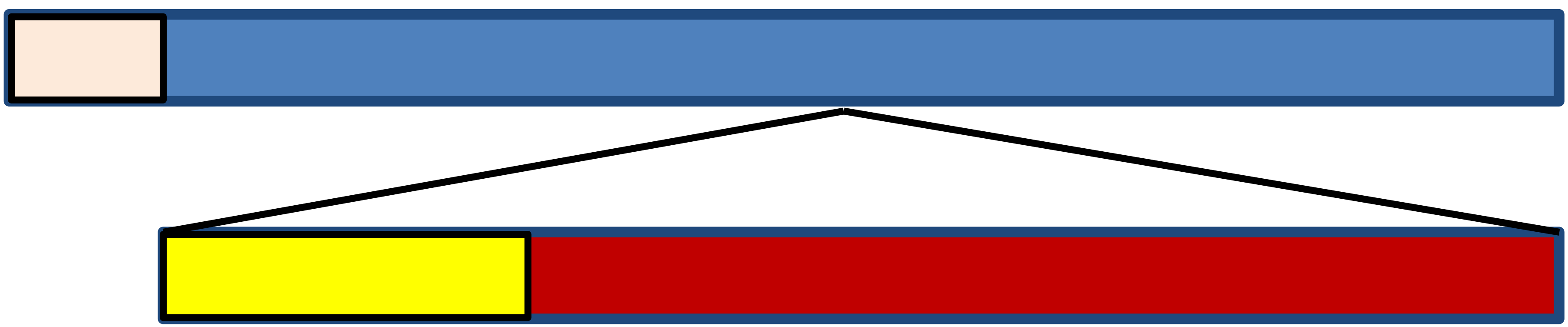
Viechtbauer et al 2015

- More on permutation tests later

Variance explained

Within studies:
8%

Between studies (I^2):
92%



Unexplained:
24%

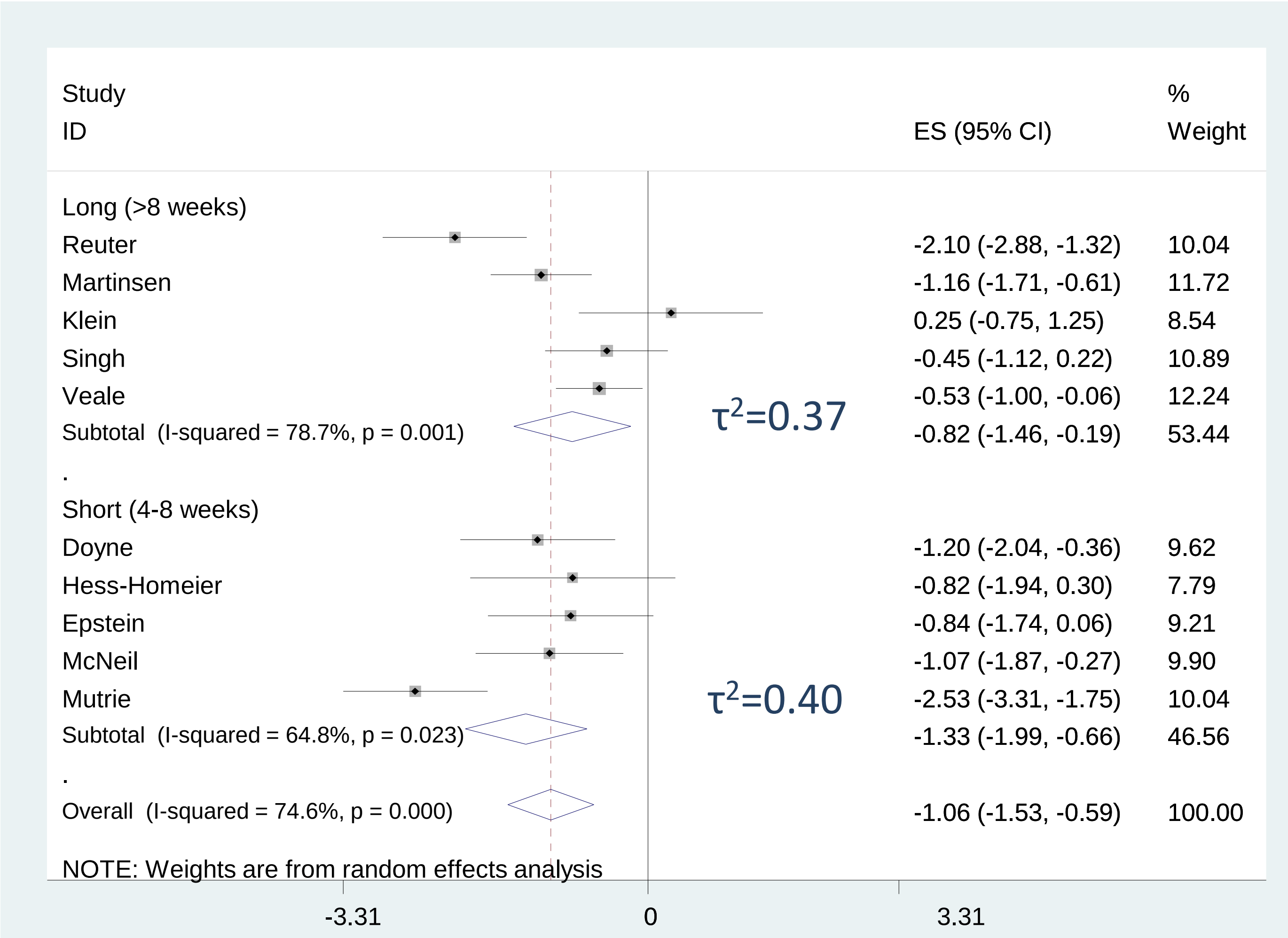
Explained by latitude (R^2):
76%

Subgroup analysis vs meta-regression

- The key difference is the assumption made about heterogeneity in random-effects analyses
  - estimated separately for each subgroup in subgroup analyses
    - (as usually implemented)
  - assumed equal across subgroups in meta-regression
    - (as usually implemented)

- Of course, there is flexibility to do things in different ways
  - some software assumes equal heterogeneity when performing subgroup analyses

```
. metan smd sesmd, random by(duration) label(namevar=study)
```



Tests for subgroup differences

1. Q test from subgroup results: P = 0.28 (RevMan/metan)

2. Meta-regression: P = 0.34 (metareg)

```
. metareg smd duration, wsse(sesmd) mm
Meta-regression                          Number of studies = 10
Method of moments estimate of between-study variance: tau2 =.3893
 smd       |  Coef.     Std. Err.  t     P>|t|  [95% Conf. Interval]
duration |-.5026523 .4990484 -1.01  0.343  -1.65346     .6481553
```

Interpretation of meta-regression coefficients

	Continuous outcome (MD/SMD)	**Dichotomous outcome (OR/RR)**
Continuous explanatory variable	Difference in mean differences or in SMDs *associated with 1 point increase in covariate*	Ratio of ORs or of RRs *associated with 1 point increase in covariate*
Dichotomous explanatory variable	Difference in mean differences or in SMDs *between 2 groups*	Ratio of ORs or of RRs *between 2 groups*

Meta-regression with dichotomous variable gives formal comparison between subgroups

Part 4: Problems

Problems with exploration of heterogeneity

- Observational relationships
  - Confounding (correlation between characteristics)

Treatment effect ↑ Year of randomization

Quality

Confounder

(associated with treatment effect and year)

  - Aggregation bias
- Low power with few studies: false-negative findings
- Multiple characteristics: false-positive findings

Thompson & Higgins (2002)

Aggregation bias

- Beware study characteristics that summarize participants within a study, e.g.
  - average age
  - % females
  - average duration of follow-up
  - % drop out

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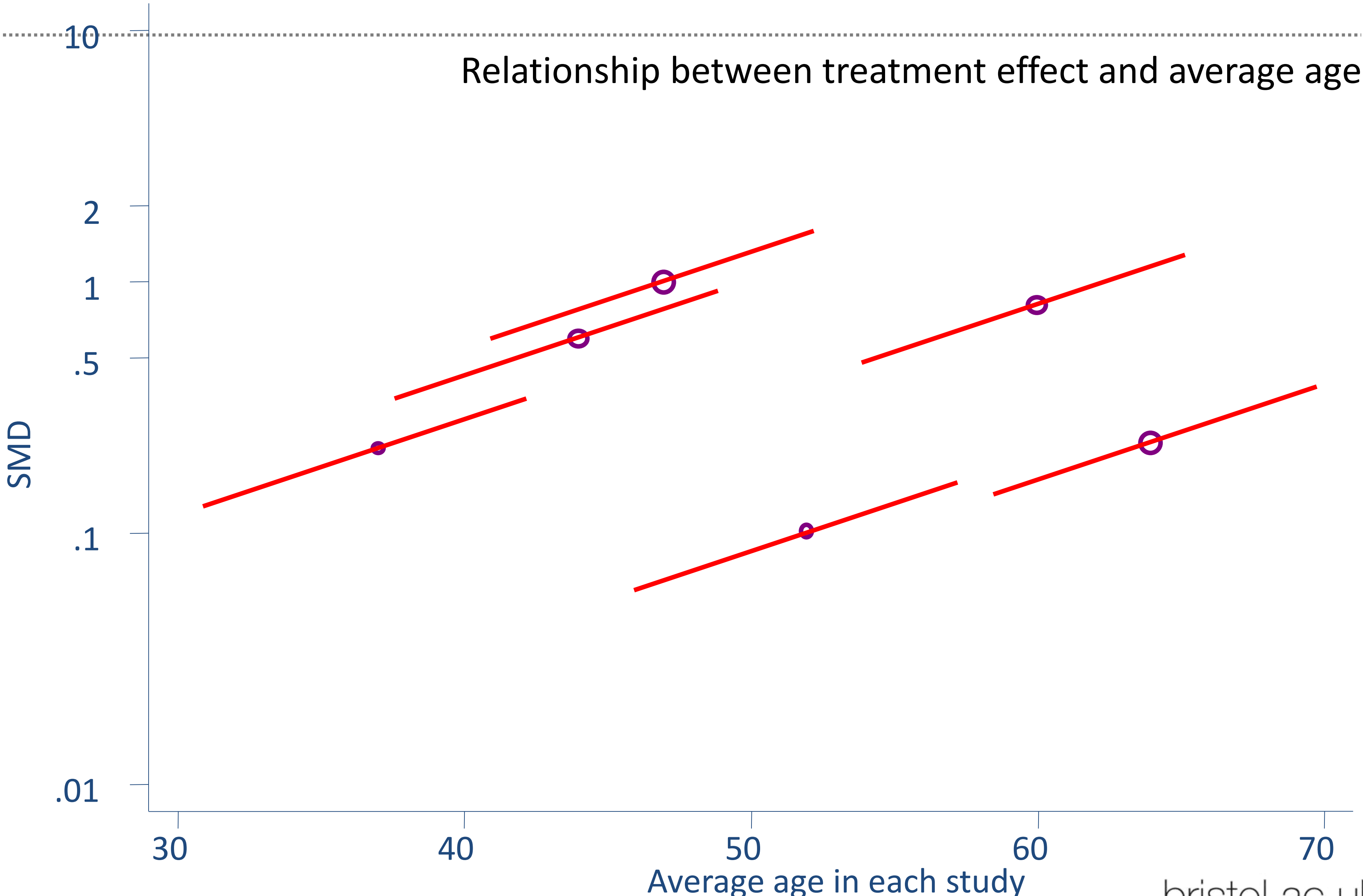

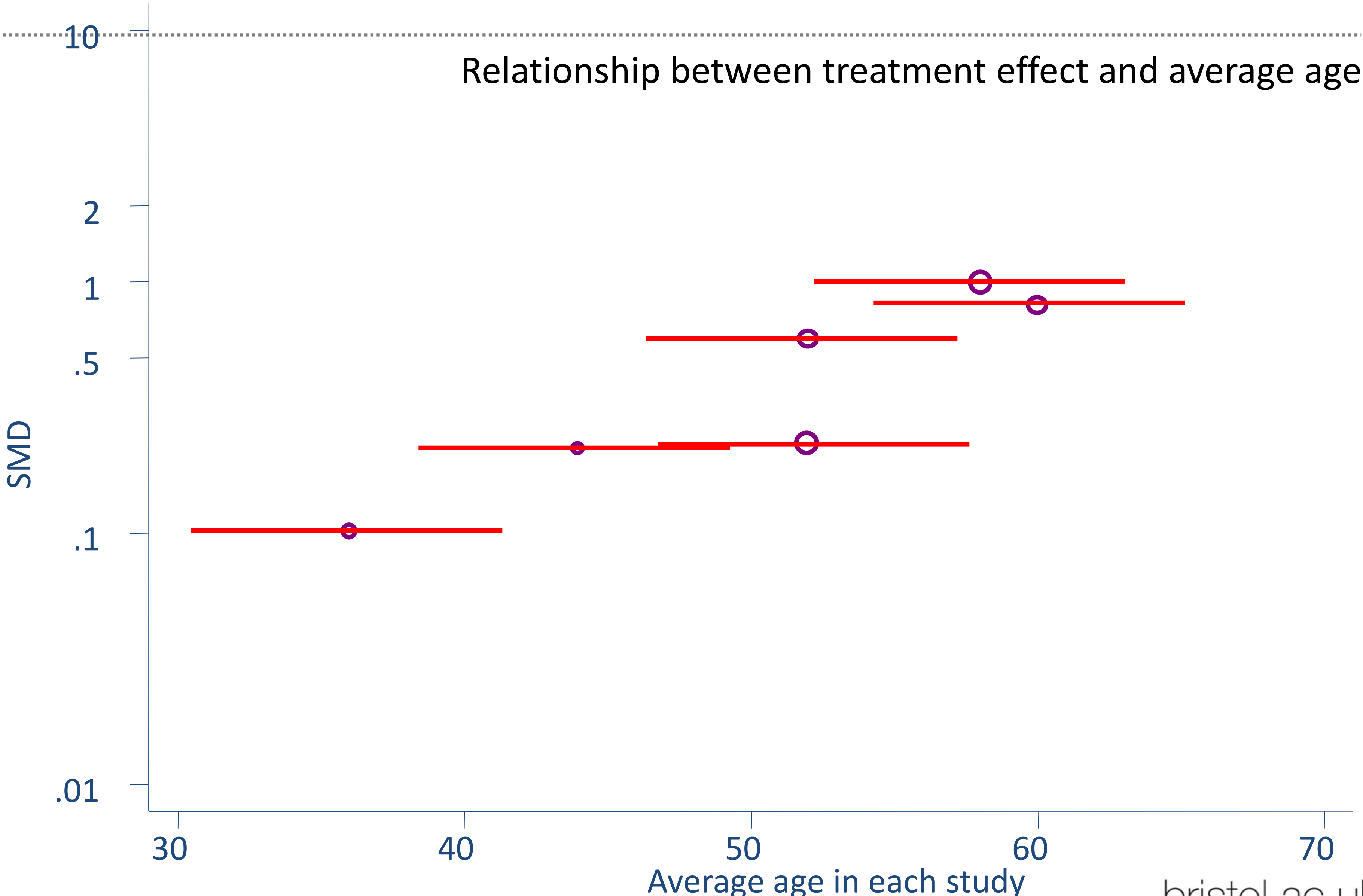
Relationship between treatment effect and average age
SMD
10
2
1
.5
.1
.01
30
40
50
60
70
Average age in each study

Aggregation bias

- Beware study characteristics that summarize participants within a study, e.g.
  - average age
  - % females
  - average duration of follow-up
  - % drop out

- Relationships **across** studies may not reflect relationships **within** studies

- The relationship between treatment effect and age, sex, etc is best measured within a study
  - Needs individual participant data

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Lack of power

- Unfortunately most meta-analyses in Cochrane reviews do not have many studies

- Meta-regression typically has low power to detect relationships

- Model diagnostics / adequacy difficult to assess

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Selecting explanatory variables

- There are typically many, many explanatory variables to choose from
  - Heterogeneity can always be explained if you look at enough of them
  - Great risk of spurious findings

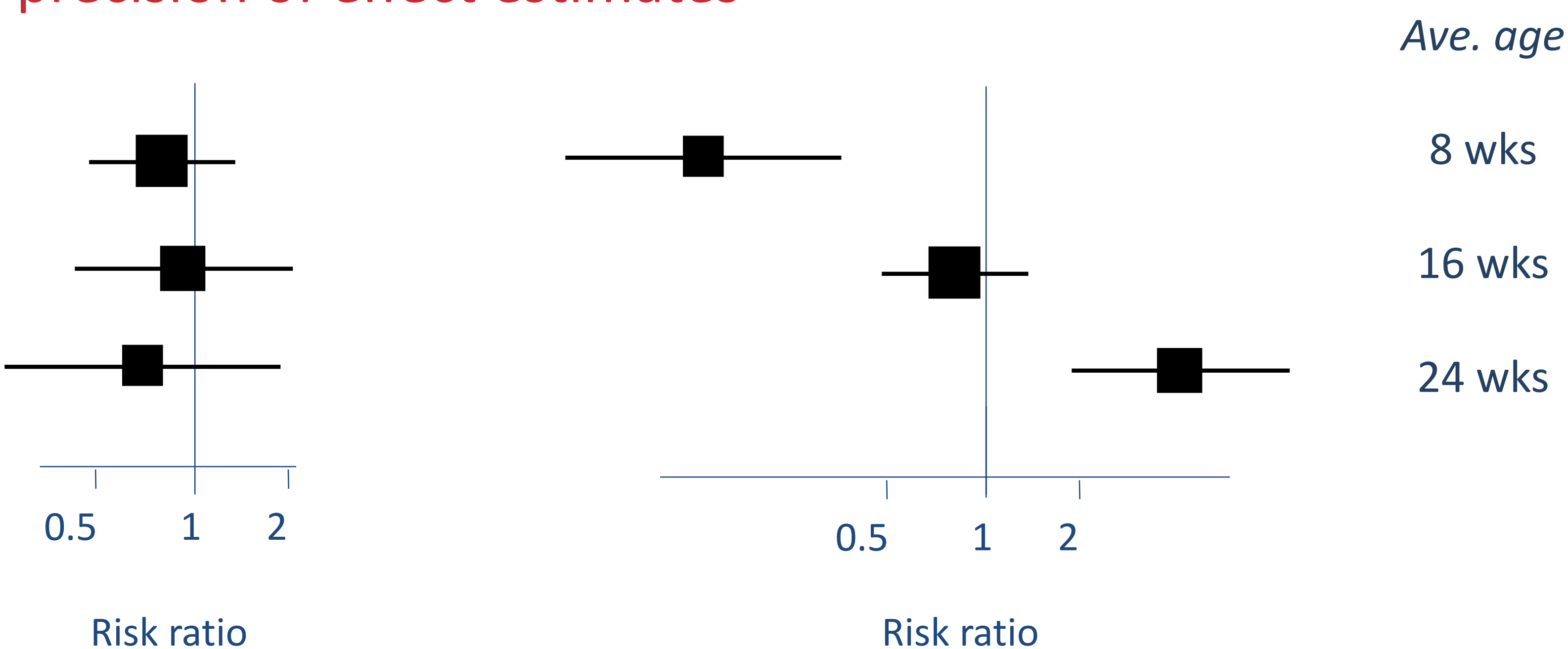
False-positive findings

- To guard against false-positives, meta-analysts are advised to
  - Pre-specify characteristics in a protocol
  - Limit to a small number
  - Have a scientific rationale

  - Beware ‘prognostic factors’
    - Variables that predict clinical outcome don’t necessarily affect treatment effects
    - e.g. age may be strongly prognostic, but risk ratios may well be the same irrespective of age

Risk of false-positive findings

- Depends on
  - number of studies
  - extent of heterogeneity
  - precision of effect estimates



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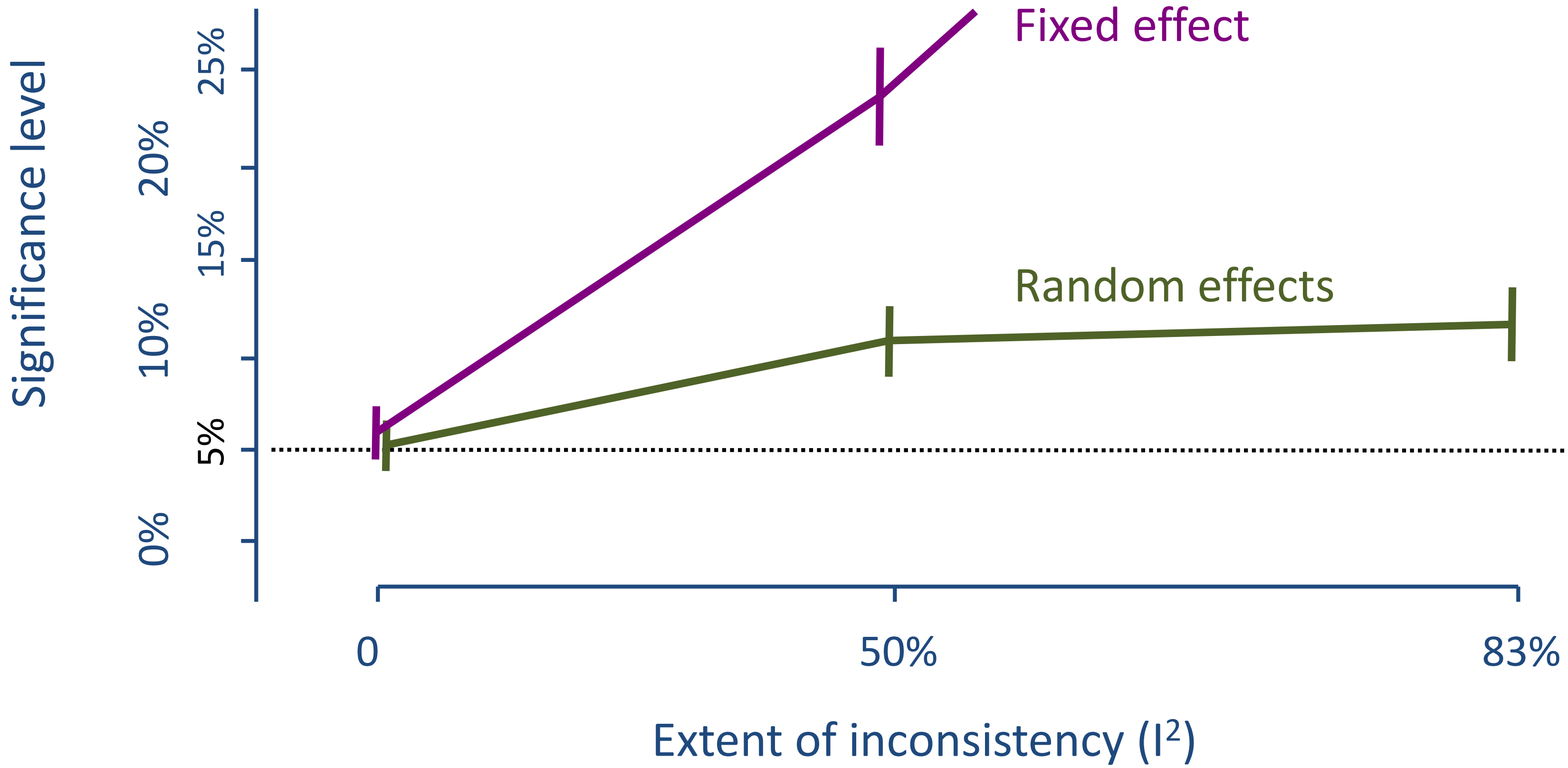
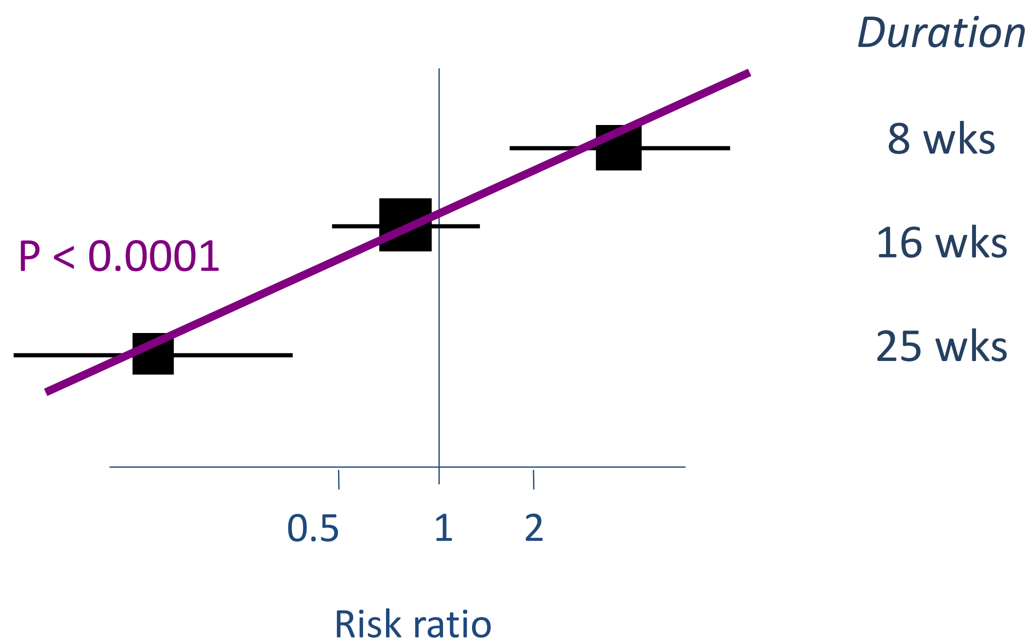
Simulation study of false-positive rates

Example results: 10 studies, typical study weights, 1 covariate



Solution? A permutation test



- But 1/3 of possible permutations give a relationship *at least as strong* as this
- So ‘real’ p = 0.33

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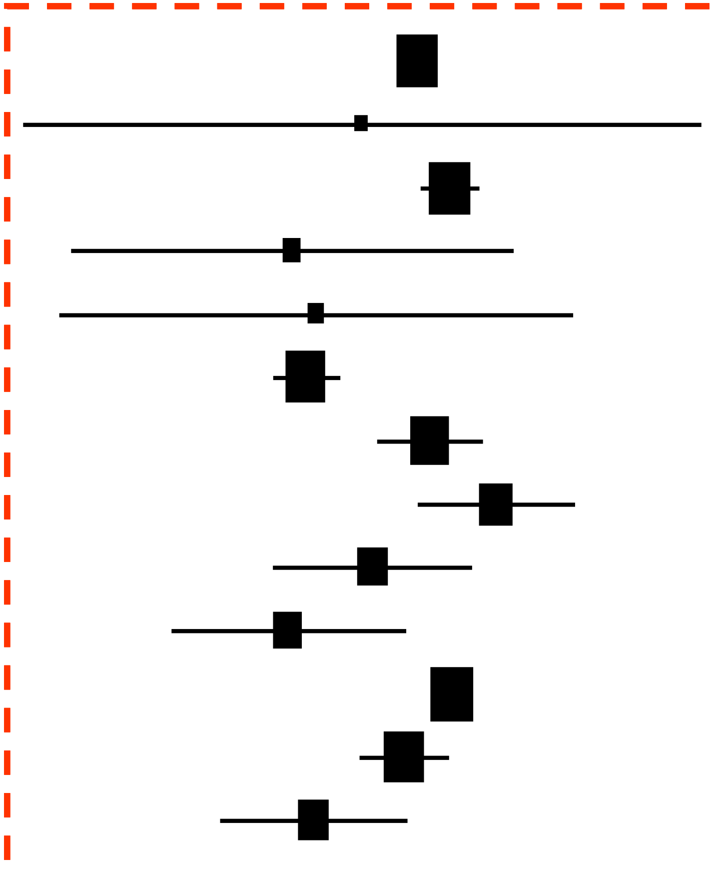
Illustration



Study	Absolute latitude	Shuffle 1		Shuffle 1000
1	18	55		33
2	44	44		27
3	33	42		52
4	55	13		42
5	42	33		44
6	52	52	*1000 times…*	18
7	13	42		19
8	33	18		13
9	44	44		33
10	19	19		44
11	13	13		55
12	27	33		42
13	42	27		13
Meta-regression test statistic	T^{obs}	$T^{(1)}$		$T^{(1000)}$

Permutation test *p*-value

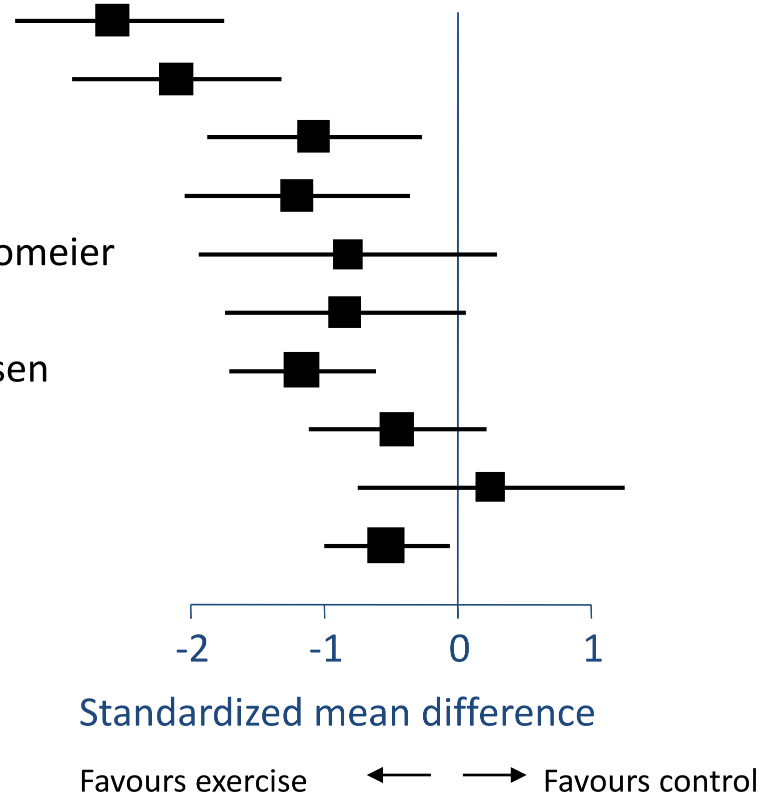
- Compare $\boxed{T^{obs}}$ with the values $\boxed{T^{(1)}}$ … , $\boxed{T^{(1000)}}$
- Count the number of $\boxed{T}$'s that exceed $\boxed{T^{obs}}$

- e.g. for BCG example $\boxed{T^{obs}}$ $= 2.44$ (= slope/SE);
- 54/1000 $\boxed{T}$'s exceed $\boxed{T^{obs}}$: $p = 0.054$

- c.f.
  - FE: $p < 10^{-10}$
  - RE (standard normal): $p = 0.012$

Multiple testing example: Exercise for depression

Study	abstract	duration	ITT	allocation	PhD
Mutrie	1	4	0	0	0
Reuter	1	10	0	0	0
McNeil	0	6	0	0	0
Doyne	0	8	0	0	0
Hess-Homeier	0	8	0	0	1
Epstein	0	8	0	0	1
Martinsen	0	9	0	1	0
Singh	0	10	1	1	0
Klein	0	12	0	0	0
Veale	0	12	0	1	0



	abstract	duration	ITT	allocation	PhD
RE meta-regression (STATA)	p=0.0006	p=0.01	p=0.24	p=0.25	p=0.98
Perm. test for "n^{th}" most significant	p=0.11	p=0.09	p=0.25	p=0.10	p=0.88

Part 5: Closing remarks

Selecting explanatory variables

Meta-regression in Cochrane reviews

Extensions

Summary

Selecting explanatory variables

- Specify a **small number** of characteristics **in advance**
- Ensure there is scientific rationale for investigating each characteristic
  - effect modifier or prognostic factor?
- Make sure the effect of a characteristic can be identified
  - does it differentiate studies?
  - aggregation bias
- Think about whether the characteristic is closely related to another characteristic
  - confounding

How many studies / characteristics?

- Typical guidance is to have 10 studies for each characteristic examined
- Some say 5 studies is enough

Including meta-regression in a Cochrane review

- Authors are encouraged to use meta-regression if appropriate
- ‘Bubble’ plots may be included as an ‘Other figure’
- Results should be presented in an ‘Additional table’
- Consider presenting something like:

Explanatory variable	Slope or Exp(slope)	95% confidence interval	Proportion of variation explained	Interpretation
Duration	OR = 1.3	0.9 to 1.8	14%	Odds ratio increases with duration (not statistically significant)

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Extensions

- Baseline risk of the studied population (as measured in the control group) might be considered as an explanatory variable
  - Beware! It is inherently correlated with treatment effects
  - Special methods are needed (see Thompson et al 1997)

- Precision of the estimate (e.g. its standard error) might be considered as an explanatory variable to look at small study effects (may be suggestive of publication bias)
  - Beware! It is often inherently correlated with treatment effects
  - Special methods are needed (see Sterne et al 2011)

Key messages

- Subgroup analysis and meta-regression examine the relationship between treatment effects and one or more study-level characteristics

- Meta-regression is like usual linear regression, but
  - study weights incorporated
  - variation not explained by the characteristics should be accounted for
  - random effects meta-regression does this;
    fixed effect meta-regression does not

Key messages

- Subgroup analyses are meta-regression are great in theory, and easy to perform in STATA or R (and other software)

- They are fraught with dangers and should be undertaken and interpreted with caution
  - observational relationships
  - too few studies
  - too many sources of diversity and bias
  - confounding and aggregation bias

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