BASIC STATISTICAL METHODS

Olaf Dekkers/Sønderborg/2016

Basic statistical methods: overview

- Fixed versus random effect models
- Weighting studies
- Choice of the model

Example

	Aspirin		Placebo		
Study	N_1	Vasc event	N_0	Vasc event	RR
I	832	86	821	120	0.71
II	1620	450	1628	601	0.75
III	521	51	531	76	0.68
Total	2973	587	2980	797	

Example

- Pooled RR by adding the numbers in the two study arms
- RR = (587/2973) / (797/2980) =

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- Pooled RR by adding the numbers in the two study arms
- RR = (587/2973) / (797/2980) = 0.74

Example

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Example

	aspirin		Placebo		
Study	N_1	Vasc event	N_0	Vasc event	RR
I	832	86	821	120	0.71
II	1620	450	**406**	**150**	0.75
III	521	51	531	76	0.68
Total	2973	587	1758	346	

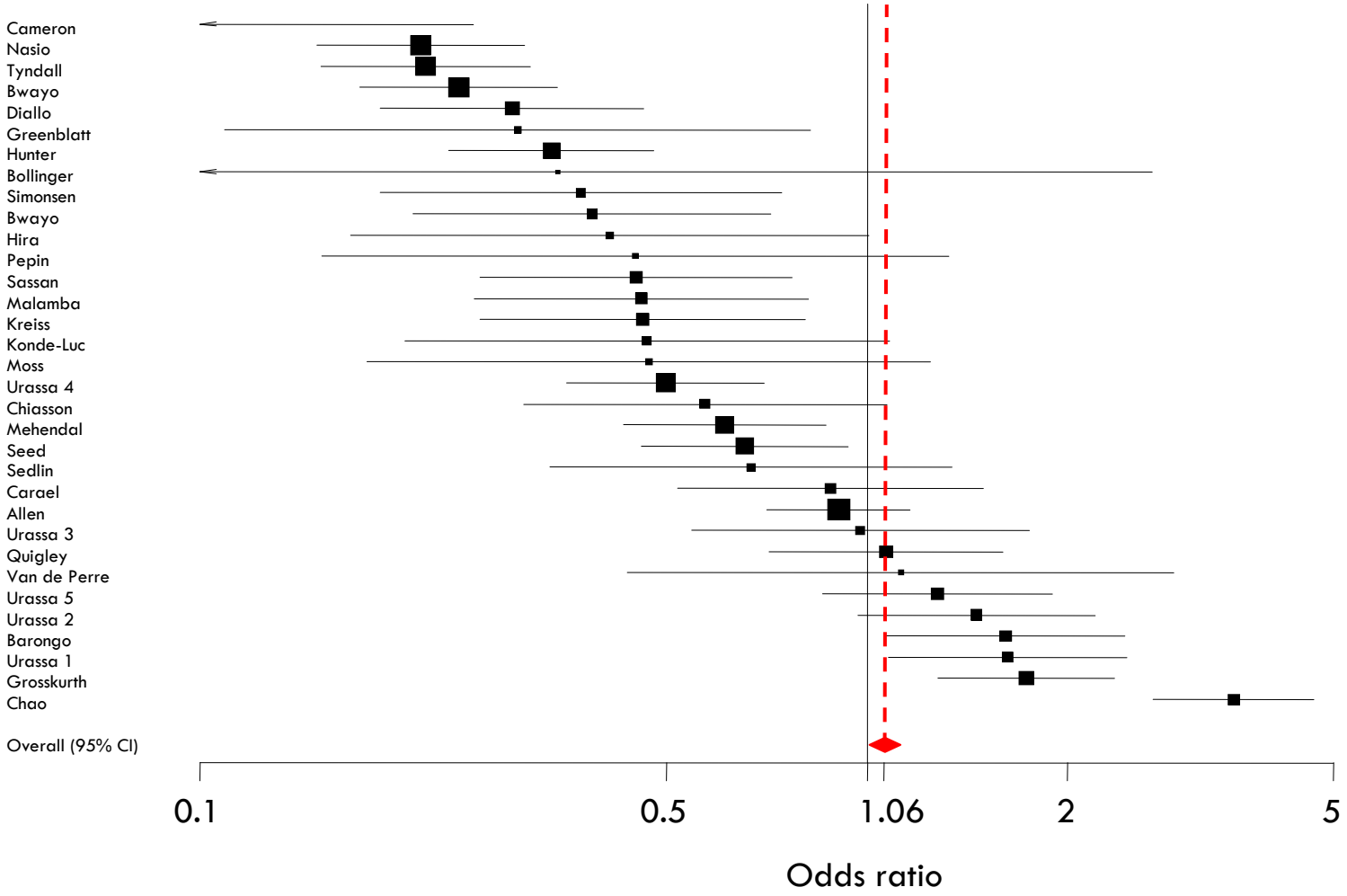
Example

- RR = (587/2973) / (346/1758) =

Example

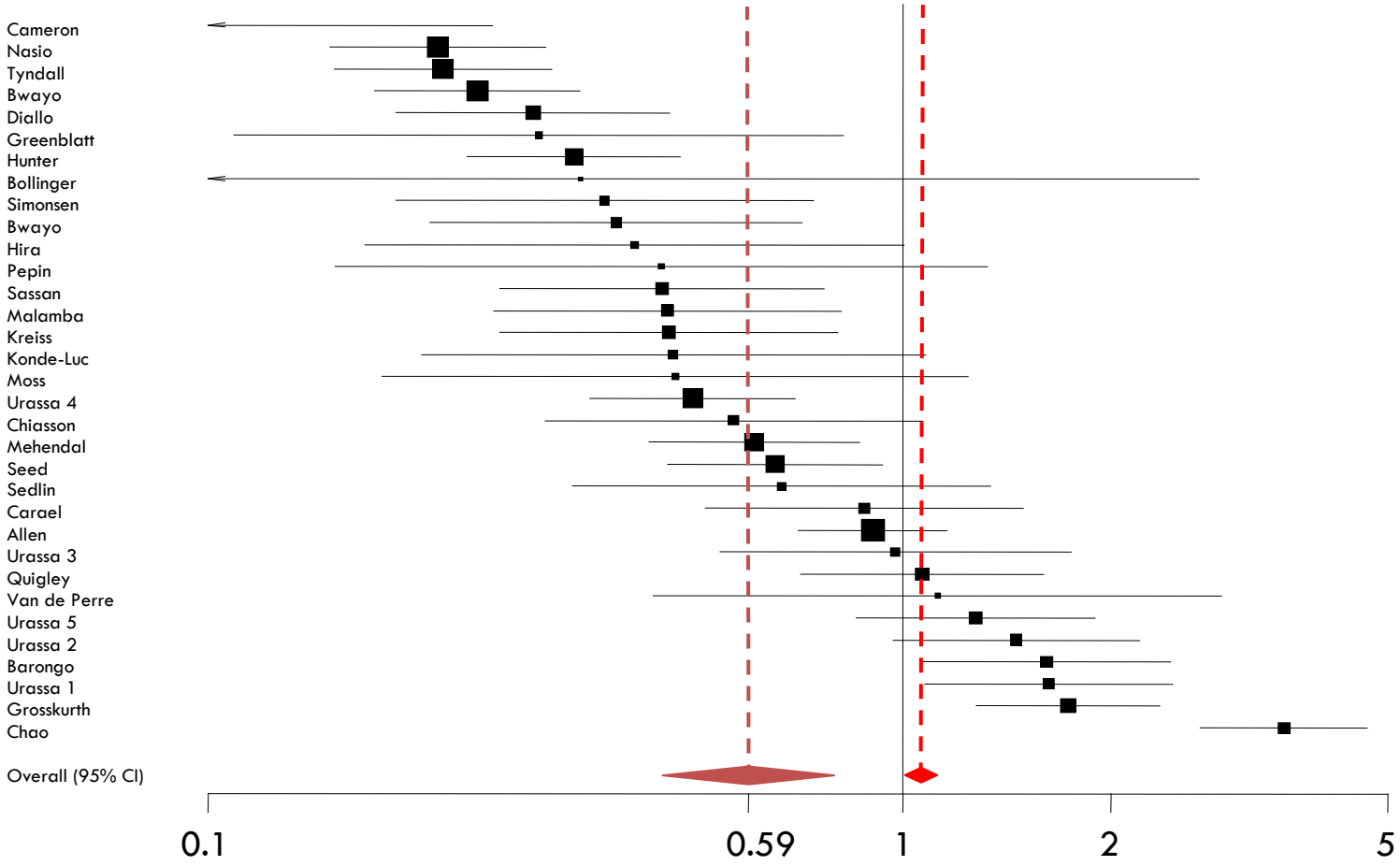
	aspirin		Placebo		
Studie	N_1	Vasc event	N_0	Vasc event	RR
I	832	86	821	120	0.71
II	1620	450	**406**	**150**	0.75
III	521	51	531	76	0.68
Total	2973	587	1758	346	**1.00**

33 observational studies on the association between circumcision and the risk of HIV infection in men



Van Howe et al 1999

Results from 33 observational studies examining the association between circumcision and the risk of HIV infection in men



O'Farrell & Egger 2000

Fixed effect analysis

Fixed effects analysis

Principle

- Basic unit is the effect estimate of individual studies
- Weighted average of studies
- Weighting according to standard error (SE) from every effect estimate (precision) = ***Inverse variance weighting***
- Weights: 1/variance (= 1/SE squared)
  - How larger the SE (less precise estimate), how smaller the weights

Example

	Aspirin		Placebo		
Study	N_1	Vasc event	N_0	Vasc event	RR
I	832	86	821	120	0.71
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Total	2973	587	2980	797	

Weighted average

- For every study i:
  - E_i = effect (**ln**RR)
  - Se_i = se lnRR

- Weight $$Wi = \frac{1}{SE_i^2}$$

- $E_{pooled(ln\ scale)}$ $$E_{pooled} = \frac{\Sigma w_i E_i}{\Sigma w_i}$$

Example

- Study I
  - lnRR -0.34 (= ln 0.71)
  - SE(lnRR) = 0.132

- $w_I = \frac{1}{SE_i^2} = 57.5$

Example

	Aspirine		Placebo			
Studie	N_1	Vasc event	N_0	Vasc event	lnRR	Weight
I	832	86	821	120	-0.34	57.5
II	1620	450	406	150	-0.29	173.3
III	521	51	531	76	-0.38	34.6
Totaal	2973	587	1758	346		

Weighted average

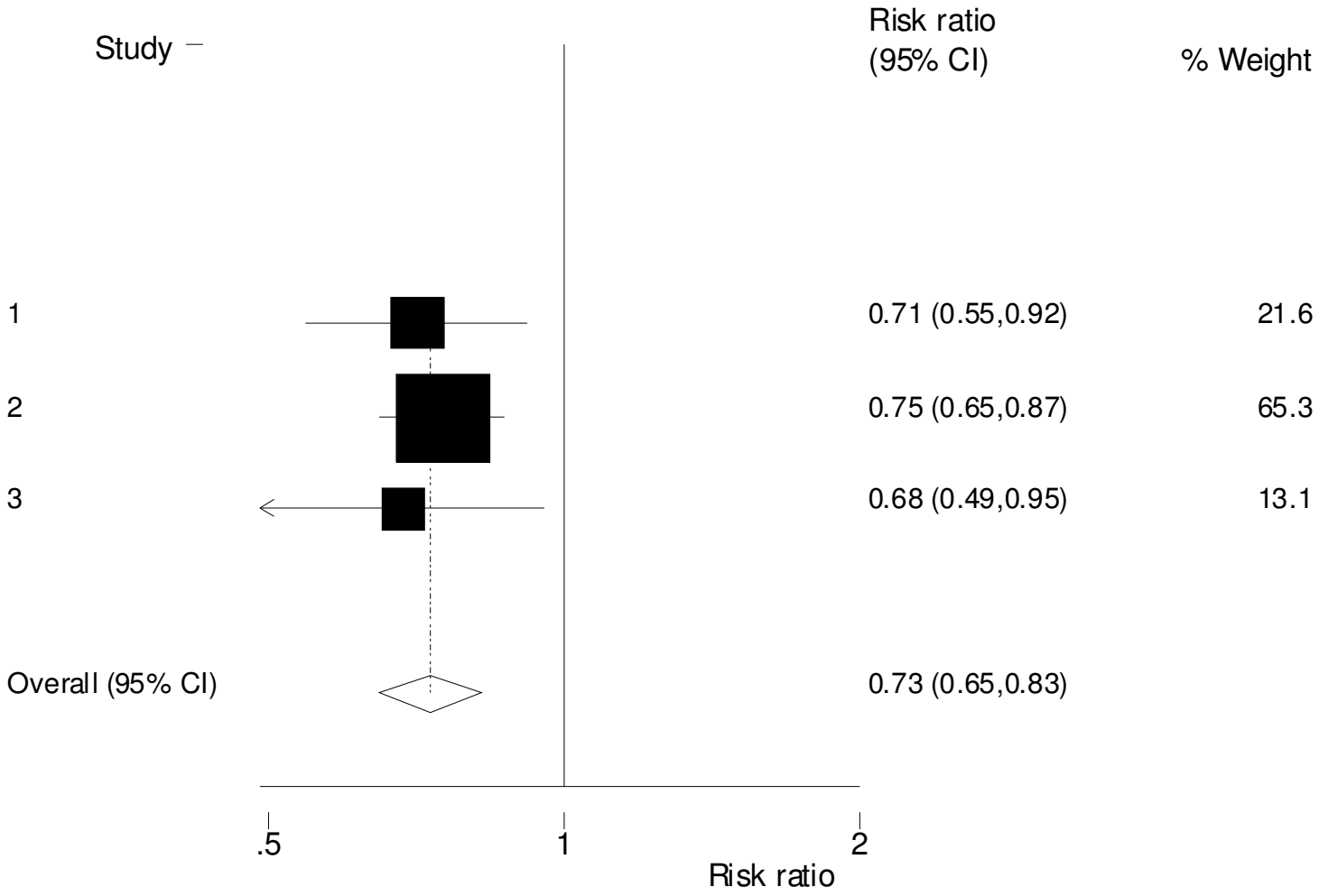
$$E_{pooled} = \frac{\Sigma w_i E_i}{\Sigma w_i}$$

$$\frac{57.5 * -0.34 + 173.3 * -0.29 + 34.6 * -0.39}{57.5 + 173.3 + 34.6} = -0.32$$

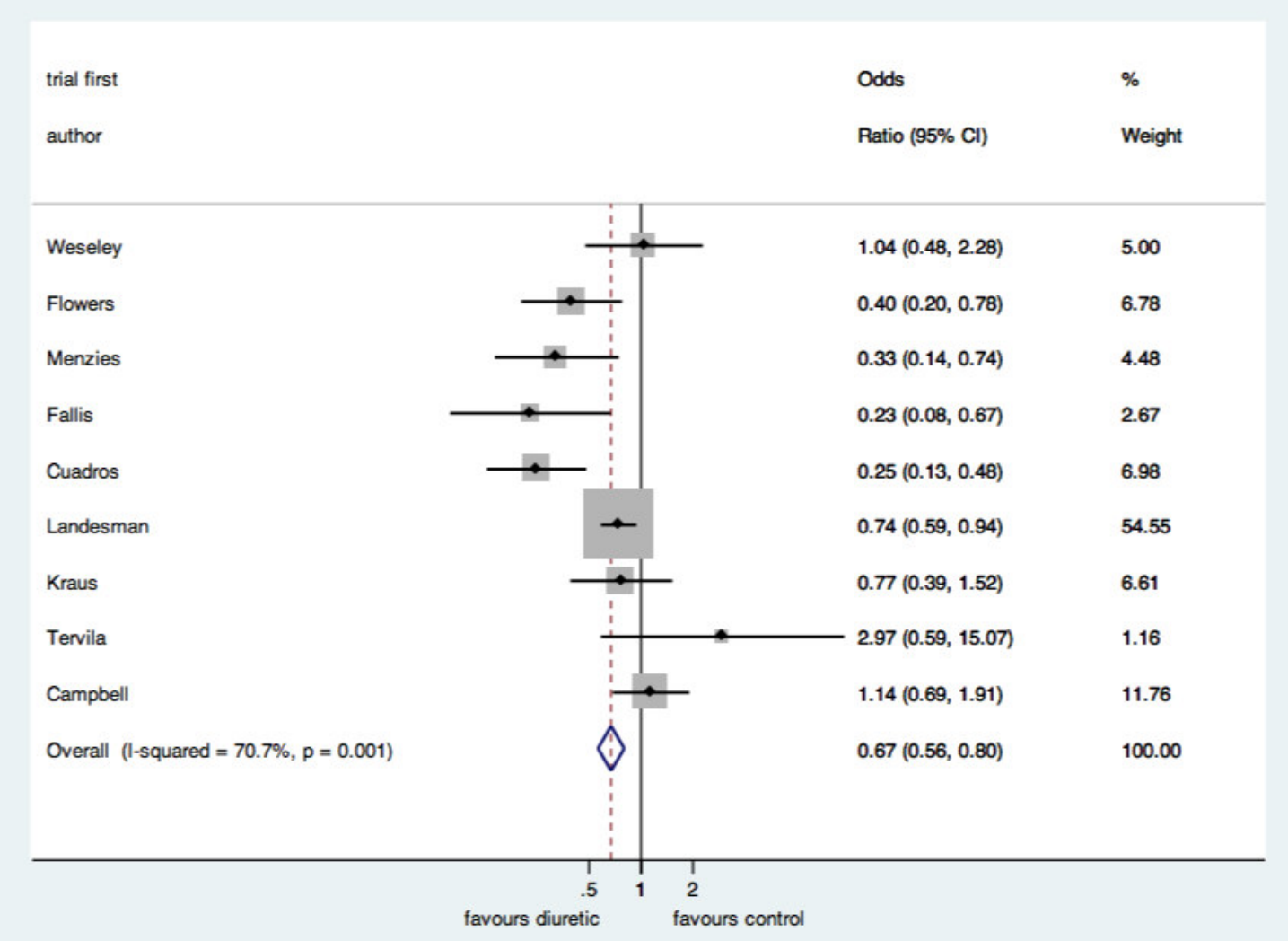
= pooled lnRR

→ Pooled RR = 0.73

Finally…


Study
Risk ratio
(95% CI)
% Weight
1
0.71 (0.55,0.92)
21.6
2
0.75 (0.65,0.87)
65.3
3
0.68 (0.49,0.95)
13.1
Overall (95% CI)
0.73 (0.65,0.83)
.5
1
2
Risk ratio

Fixed effect analysis



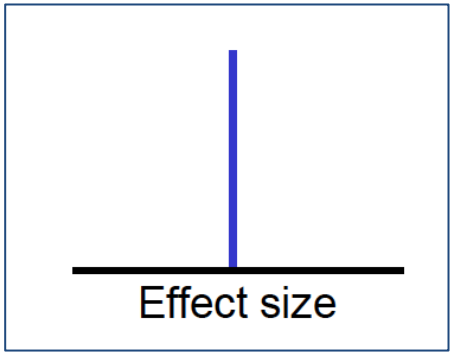
Forest plots

- Individual effect estimates are displayed with 95% CIs
- Box area is proportional to the weight of the study
  - Bigger studies get more weight
- The diamond represents the overall summary estimate with 95% CI represented by its width
- This overall summary estimate can be based on a fixed effect analysis or a random effects analysis

Fixed effects: interpretation

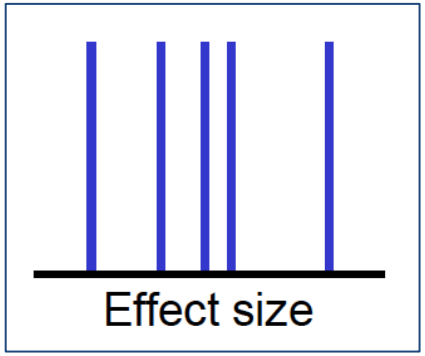
Interpretation 1

- All studies estimate the same underlying true effect
- Estimate this single effect



Interpretation 2

- Studies may have different true effects
- Estimate the average of these effects



Fixed effects: interpretation

- For both interpretations the CI reflects only within study error (standard deviation)
- Variation across studies is ignored

Fixed effect analysis methods

- Inverse variance method
  - Difficulties with zero cells (to add 0.5 to every cell)
- Mantel Haenszel
  - Weighting scheme depends on which effect estimate is used (OR, RR, RD)
  - Better statistical properties than IV in case of few events
- Peto method
  - Mainly usefull in case of few events

Random effects model

Random vs fixed effects

- Fixed effect model assumes that the true effect does not differ between studies (Interpretation 1)

- In a random effects model this assumption is relaxed by taken between study variation into account

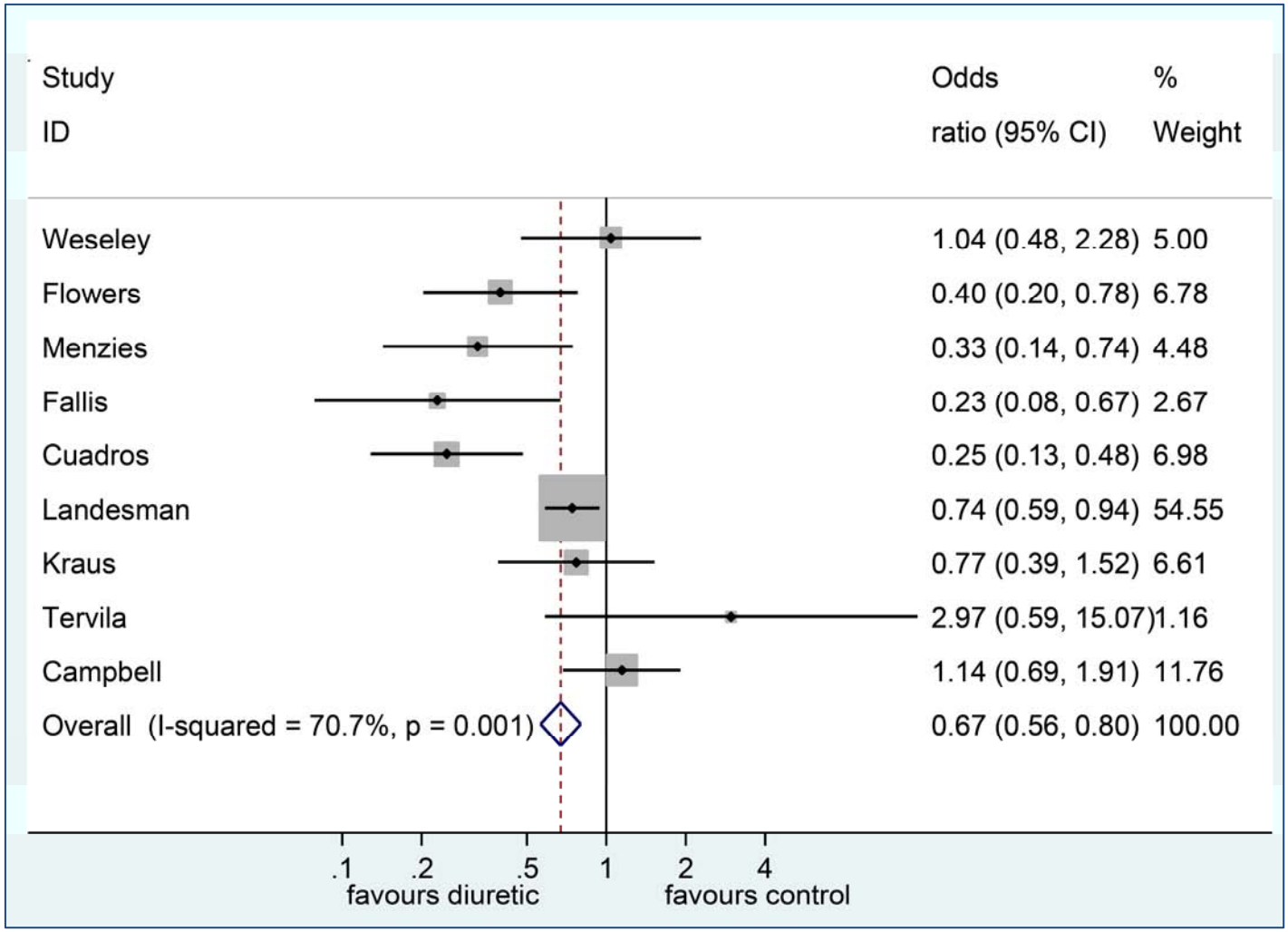
Random effects model

- We assume that the true effect in each study is normally distributed with variance between studies = tau-squared

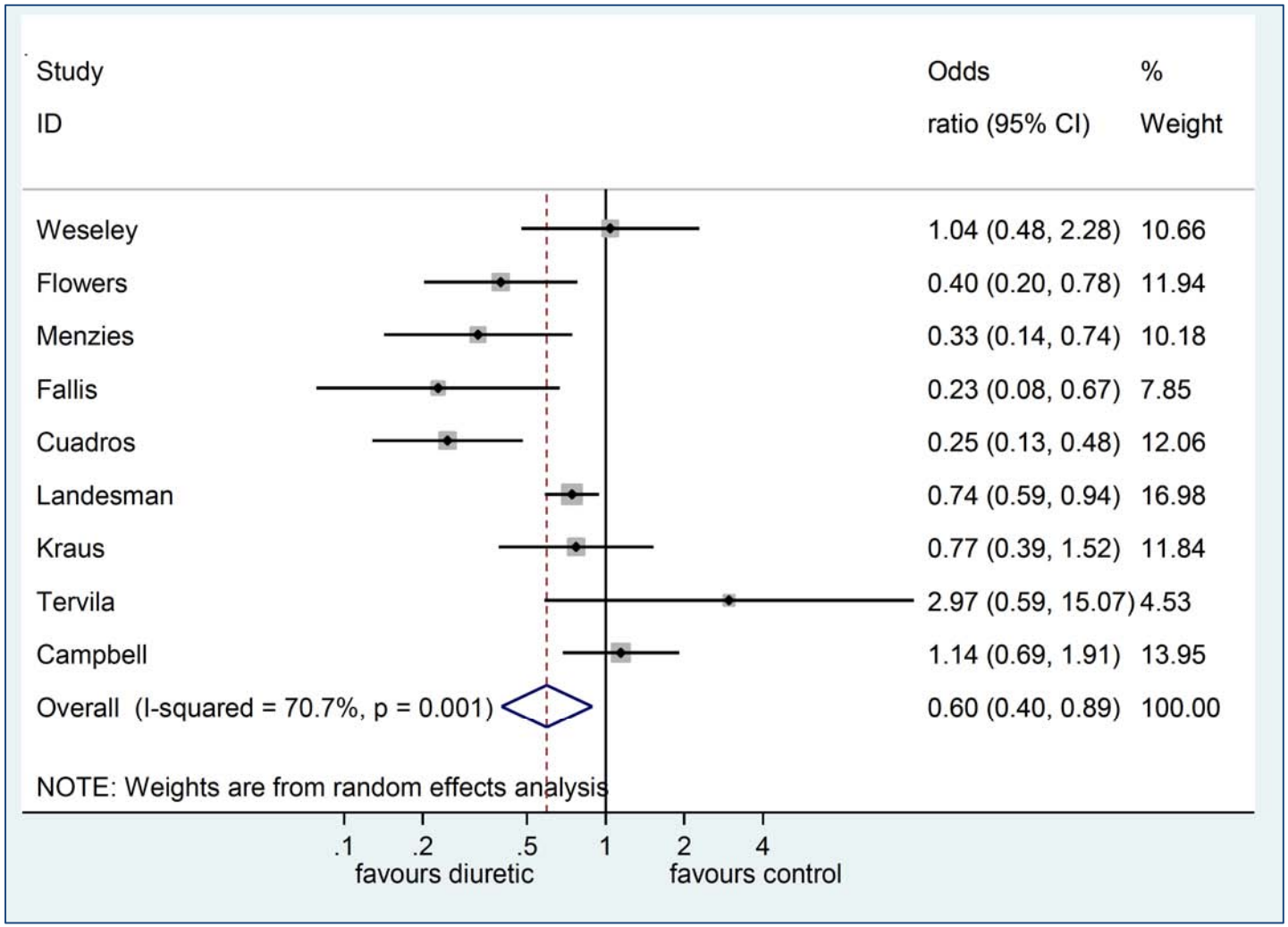
- This tau-squared is used to modify study weights

- Weight is $\frac{1}{SE_i^2 + tau^2}$

Fixed effect analysis



Random effects analysis

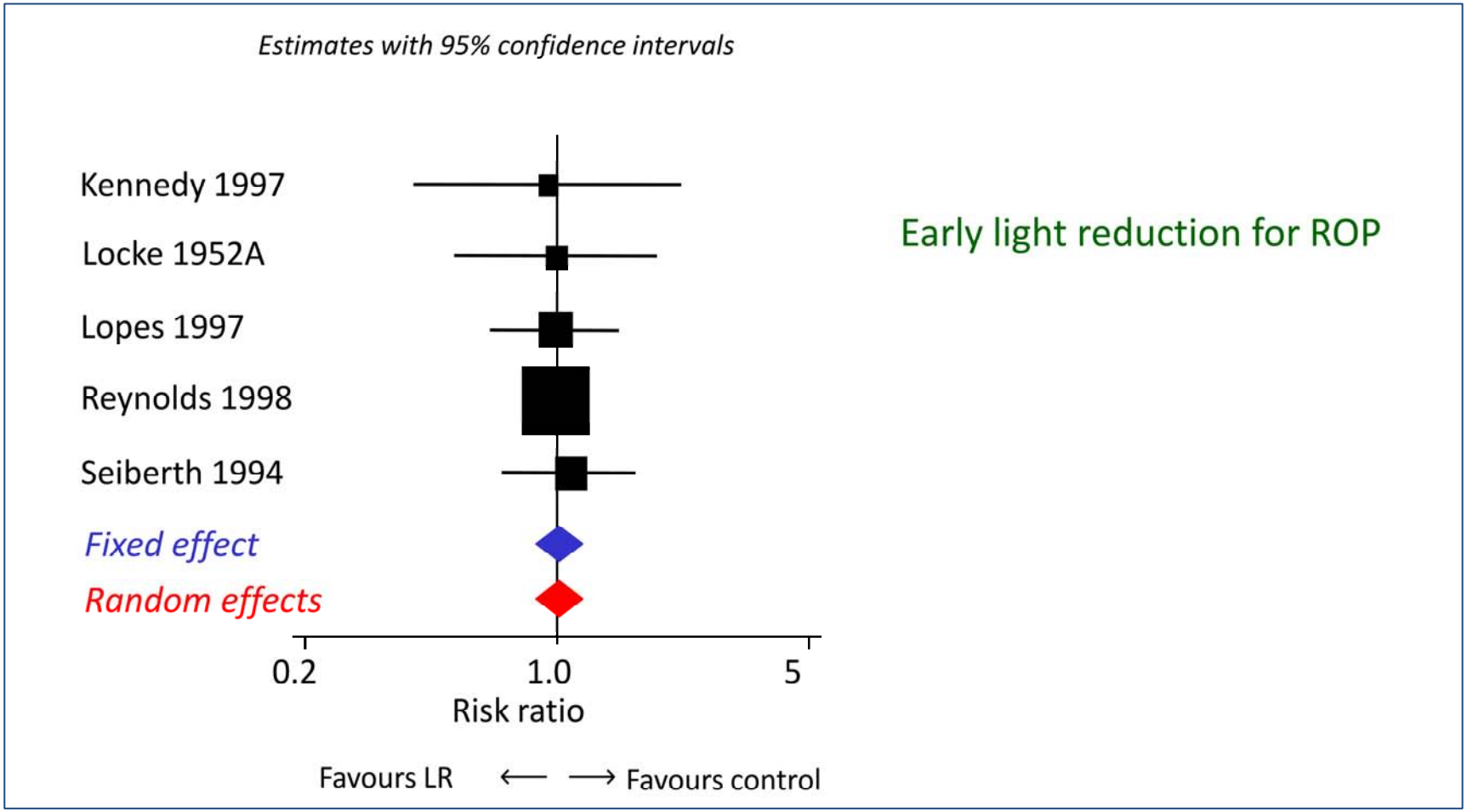


Fixed vs random effects model

- Smaller studies get more weight in a random effect model
- Wider CIs in random effects models because the true effect may vary
- Random effect estimates are more conservative
- If between study variance is zero than random and fixed effect model are identical
- If number of studies is small, tau-sqaured can not be estimated reliably (<5 studies)

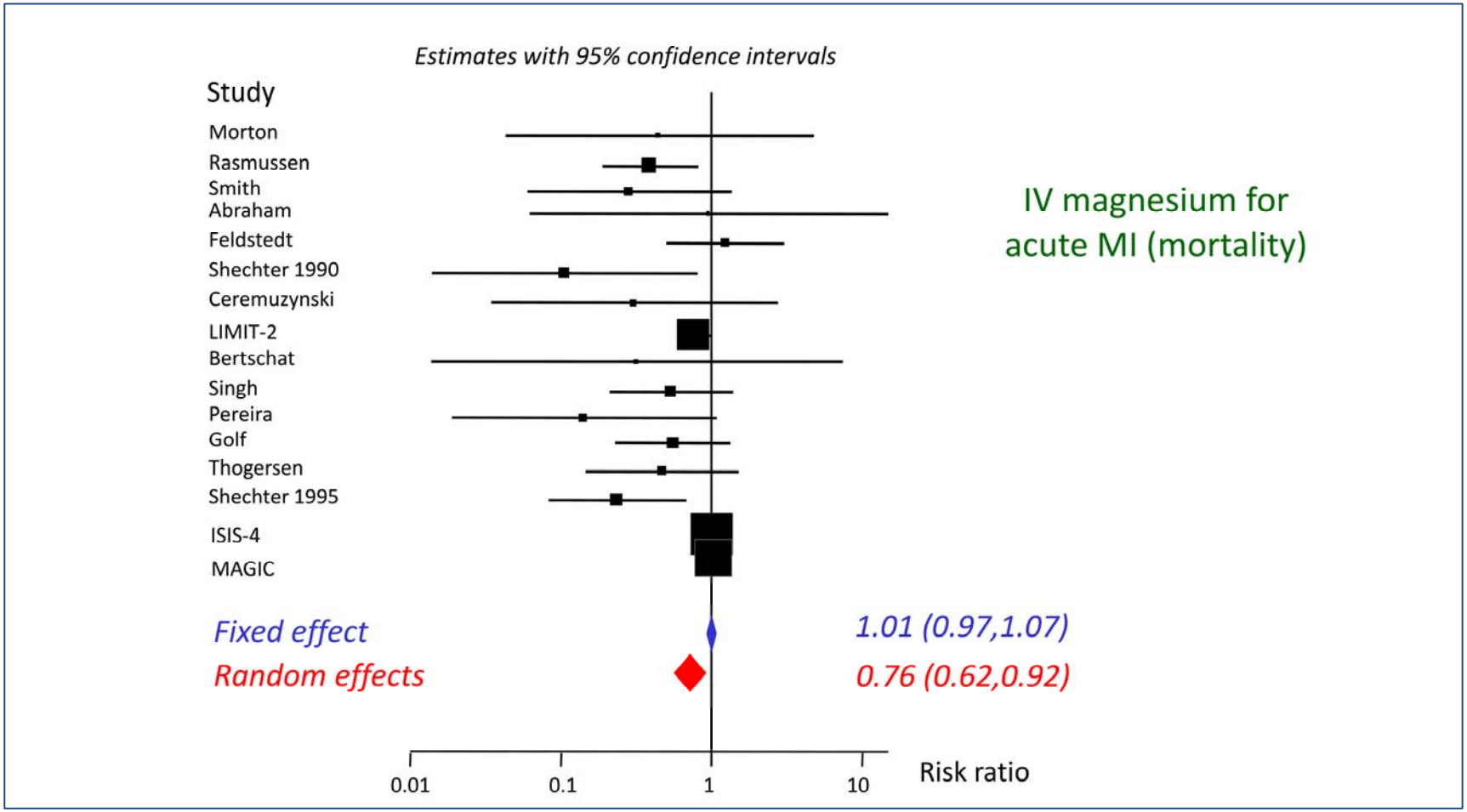
- And: probably the random effect assumption are more realistic

Fixed vs random effect models I



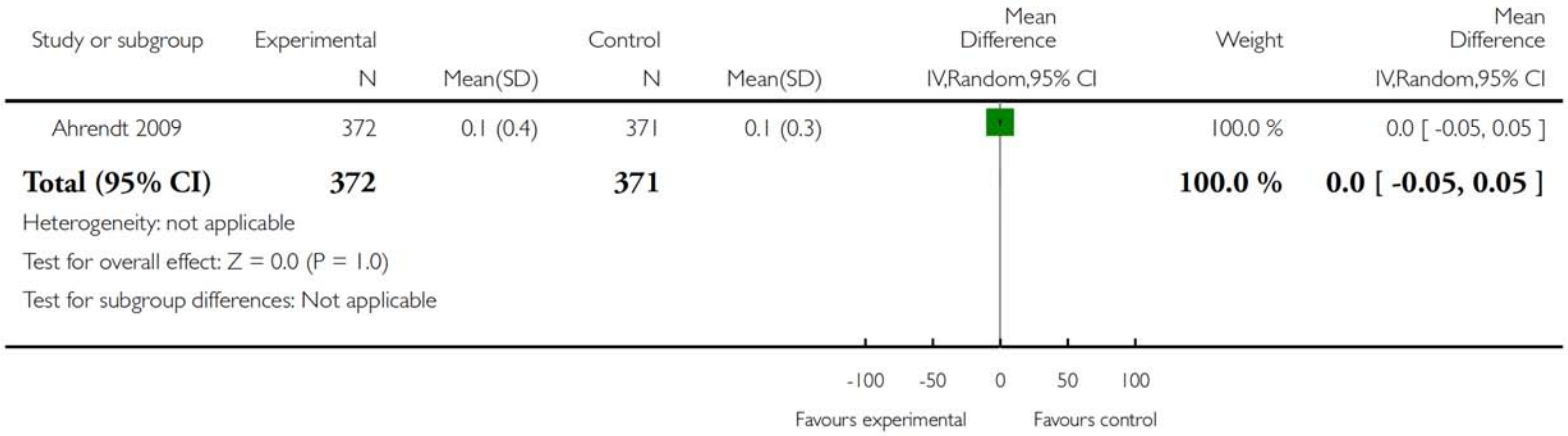
From: Higgins

Fixed vs random effect models II



From: Higgins

What do you think?



Vliet Cochrane 2011

What's the correct model?

Choice of the model

- Main decision: fixed vs random model
- Other choice: depend on data structure

Study	Event T	Total T	Event C	Total C
1				
2				

Allows for complete flexibility
IV, MH, Peto

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- Main decision: fixed vs random model
- Other choice: depend on data structure

Study	Event T	Total T	Event C	Total C
1				
2				

Allows for complete flexibility
IV, MH, Peto

Study	lnRR	selnRR
1		
2		

Only IV and DS&L can be estimated

What's the correct model?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

NEJM 2007;356;24

Meta-analysis *NEJM* 2007

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

NEJM 2007:356;24

What's the correct model?

Table II. Myocardial infarction.

Method	Estimated relative risk	95 per cent CL	p-value two-sided
Random effects	1.51	0.91–2.48	0.11
Fixed effects			
Nissen and Wolski	1.43	1.03–1.98	0.03
Cox analysis	1.43	1.03–1.96	0.033
Logistic regression	1.43	1.03–1.98	0.033
STATXACT	1.43	1.01–1.98	0.037
STATXACT (asymptotic)	1.43	1.03–1.98	0.033

Shuster Stat Med 2007;26

What's the correct model?

Calculation method	Nissen *et al.* (42 studies)	
	Myocardial infarction OR (95% CI)	Cardiovascular death OR (95% CI)
Fixed effects, Peto OR	1.43 (1.03–1.98)	1.64 (0.98–2.74)
Fixed effects, MH (TAC)	1.36 (1.00–1.84)	1.51 (0.94–2.44)
Fixed effects, MH (CC)	1.28 (0.95–1.72)	1.33 (0.83–2.13)
Fixed effects, MH (TACZ)	1.35 (1.00–1.82)	1.39 (0.91–2.13)
Fixed effects, MH (CCZ)	1.26 (0.93–1.69)	1.17 (0.77–1.77)

Dahabreh Clin Trials 2008;5

What's the correct model?

Table 1. **Meta-analytic Odds Ratios for Myocardial Infarction and Cardiovascular Death***

Meta-analytic Method	Myocardial Infarction		Cardiovascular Death	
	k	Odds Ratio (95% CI)	*k*	Odds Ratio (95% CI)
Fixed, Peto	38	1.43 (1.03–1.98)	23	1.64 (0.98–2.74)
Fixed, IV (TAC)†	38	1.34 (0.97–1.84)	23	1.46 (0.88–2.42)
Fixed, IV (CC)†	38	1.29 (0.94–1.76)	23	1.31 (0.80–2.13)
Fixed, MH (TAC)	38	1.36 (1.00–1.84)	23	1.51 (0.94–2.44)
Fixed, MH (CC)	38	1.28 (0.95–1.72)	23	1.33 (0.83–2.13)
Fixed, MH (TAC+)	42	1.35 (1.00–1.82)	42	1.39 (0.91–2.13)
Fixed, MH (CC+)	42	1.26 (0.93–1.69)	42	1.17 (0.77–1.77)

Diamond Ann Int Med 2007;147

Substantial limitations?

" Alternative meta-analytic approaches that use continuity corrections show lower odds ratios that are not statistically significant. We conclude that the risk for myocardial infarction and death from cardiovascular disease for diabetic patients taking rosiglitazone is uncertain: Neither increased nor decreased risk is established."

Diamond Ann Int Med 2007;147

NYT 23-02-2010: Nissen vs GSK

Executives asked Dr. Nissen why he would publish his study if a more detailed look at the data — called a patient-level analysis — would provide a more reliable result.

"But suppose we did this patient-level analysis and it looked very different from what you have?" Dr. Krall asked.

"But there's no way it can," Dr. Nissen soon said. "Come on, guys. You already did your patient-level analysis for 42 trials. You're about to add in two trials that went the wrong way. What do you think's going to happen?"

Dr. Krall said the two sides disagreed on the numbers.

"And, the last thing we want to do is get into a public debate about whose analysis is right" Dr. Krall said.

"No, public debates are just fine," Dr. Nissen interjected. "In fact, the best way I know of to get to the truth is you just get it all out there and you let the chips fall where they may."

One of the executives responded: "And I supposed the science is the issue. And that's why we think this patient-level approach is the right one."

"It is the right approach," Dr. Nissen said. "Now I'm going to be equally blunt: you should have done this a long time ago."