Methods for meta-analysis in medical research

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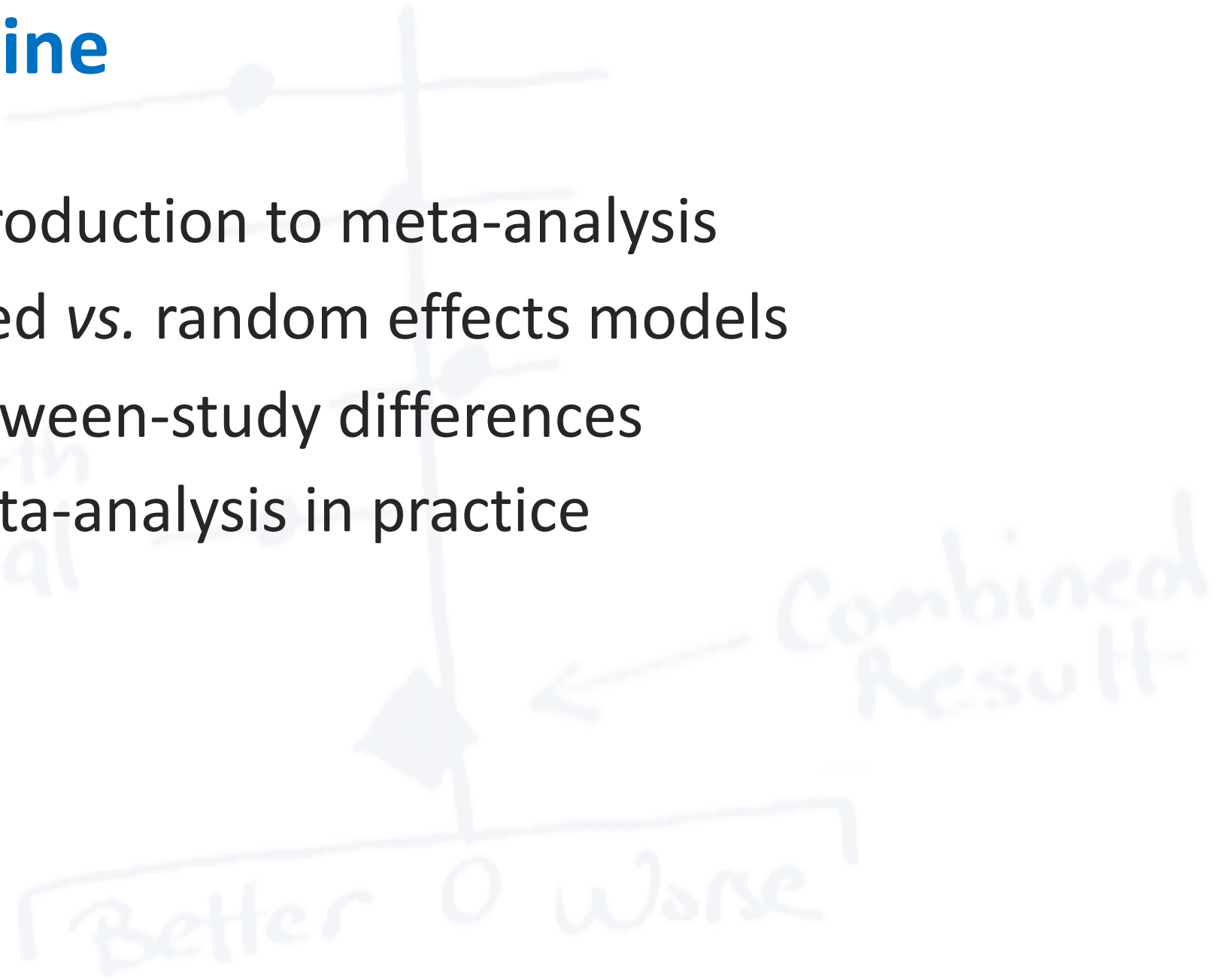
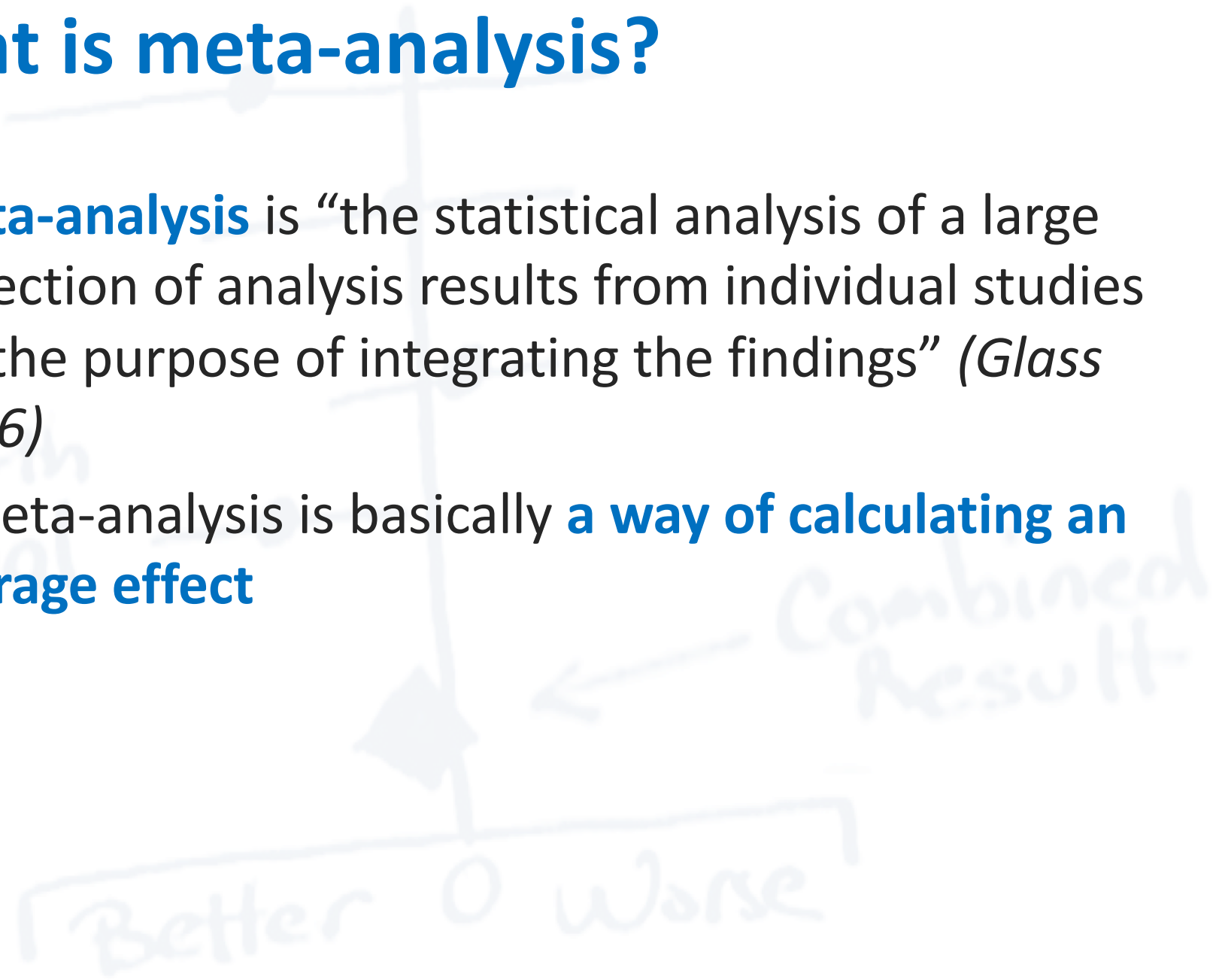
Outline

- Introduction to meta-analysis
- Fixed *vs.* random effects models
- Between-study differences
- Meta-analysis in practice



What is meta-analysis?

- **Meta-analysis** is “the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings” *(Glass 1976)*
- A meta-analysis is basically **a way of calculating an average effect**

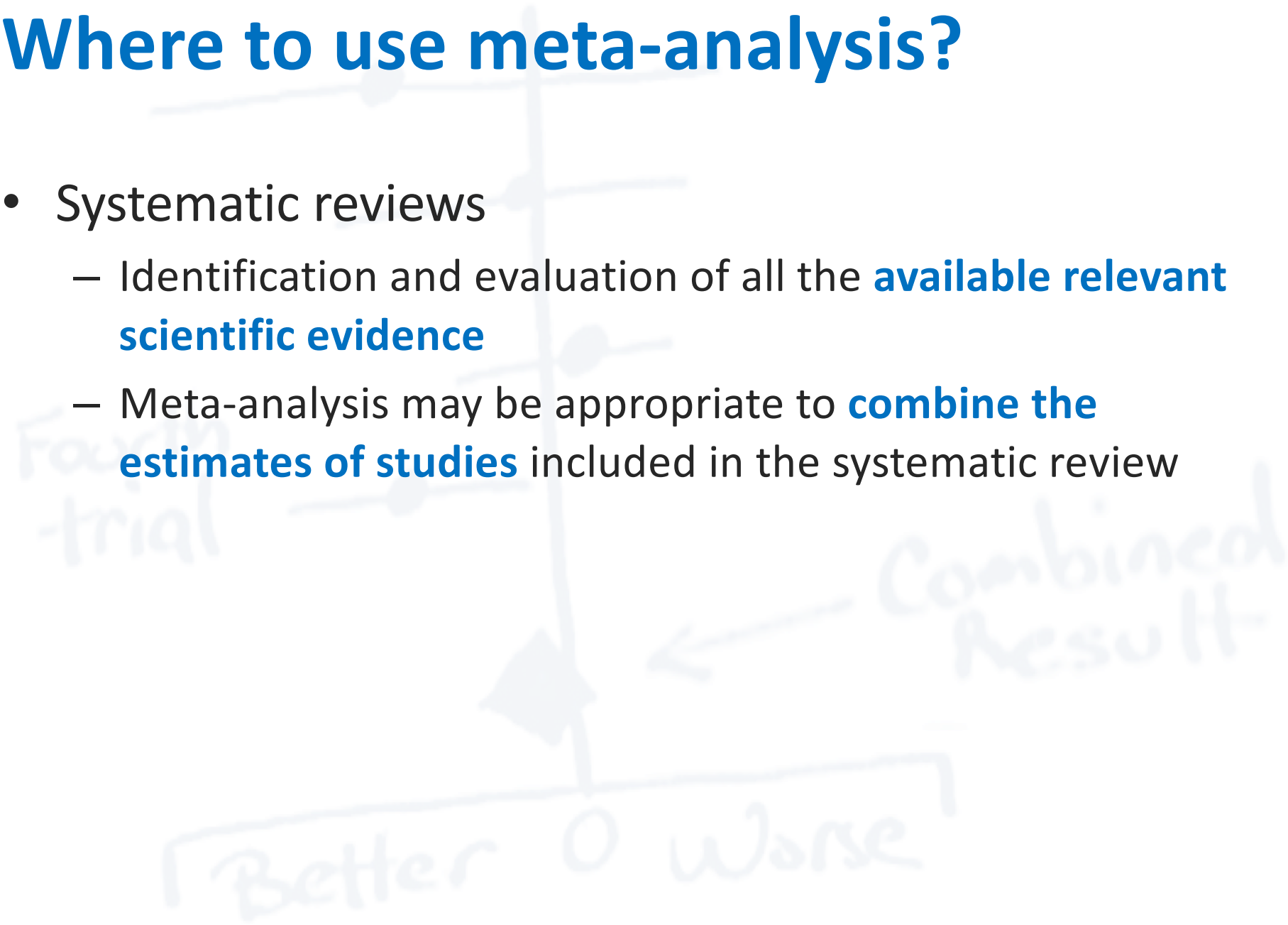


Usual meta-analysis *slang*

Statistical analysis. We estimated a pooled RE with 95% CI based on fixed- and random-effects models depending on the heterogeneity of the analysis. Statistical heterogeneity among studies included in the meta-analysis was assessed using the Q (10) and I^2 statistics (11).

Where to use meta-analysis?

- Systematic reviews
  - Identification and evaluation of all the **available relevant scientific evidence**
  - Meta-analysis may be appropriate to **combine the estimates of studies** included in the systematic review



Where to use meta-analysis?

- Systematic reviews
  - Identification and evaluation of all the **available relevant scientific evidence**
  - Meta-analysis may be appropriate to **combine the estimates of studies** included in the systematic review
- Multi-centre studies
  - Each participating **centre analyses its own individual data** under the same (or not) protocol
  - Meta-analysis may be appropriate to **combine the estimates reported** from each study-centre

Why do a meta-analysis?

- Objectives
  - To **increase statistical power** and precision
  - To **assess consistency** of results
  - To **answer questions** not comprised by the individual studies
- Views
  - **Synthetic** view to summarise study results
  - **Analytic** view to identify differences between study results

Summarized data

- Effect size

i) Binary outcome

  - **Odds Ratio** (OR)
  - **Risk Ratio** (RR)
  - **Risk Difference** (RD)

ii) Continuous outcome

  - **Mean Difference** (D)

- Variability

i) **95% CI** (low, upp)

ii) Standard error (se)

iii) Variance (s^2)

- Converting between scales

  95% CI = effect size $\pm$ 1.96 $\times$ se

  se = (upp – low)/(2 $\times$ 1.96)

  s^2 = se $\times$ se

Row data

- **Binary** outcome

Group	*Outcome*	
	Yes	*No*
Treat.	a	b
Control	c	d

$P_{(yes)}$
a/(a+b)
c/(c+d)

  - Absolute risk (symmetric scale)
    - **DR** = (a/(a+b)) – (c/(c+d))
  - Relative risk (asymmetric scale)
    - **RR** = (a/(a+b)) / (c/(c+d))

Row data

- **Binary** outcome

Group	*Outcome*	
	Yes	*No*
Treat.	a	b
Control	c	d

$Odds_{(yes)}$
a/b
c/d

  - Absolute risk (symmetric scale)
    - **DR** = (a/(a+b)) − (c/(c+d))
  - Relative risk (asymmetric scale)
    - **RR** = (a/(a+b)) / (c/(c+d))
    - **OR** = (a/b) / (c/d)

Row data

- **Binary** outcome

Group	*Outcome*	
	Yes	*No*
Treat.	a	b
Control	c	d

  - Absolute risk (symmetric scale)
    - **DR** with $s^2_{DR} = (ab/(a+b)^3)-(cd/(c+d)^3)$
  - Relative risk (asymmetric scale)
    - **RR** with $s^2_{log(RR)} = (1/a)-(1/(a+b))+(1/c)-(1/(c+d))$
    - **OR** $s^2_{log(OR)} = (1/a)+(1/b)+(1/c)+(1/d)$

Row data

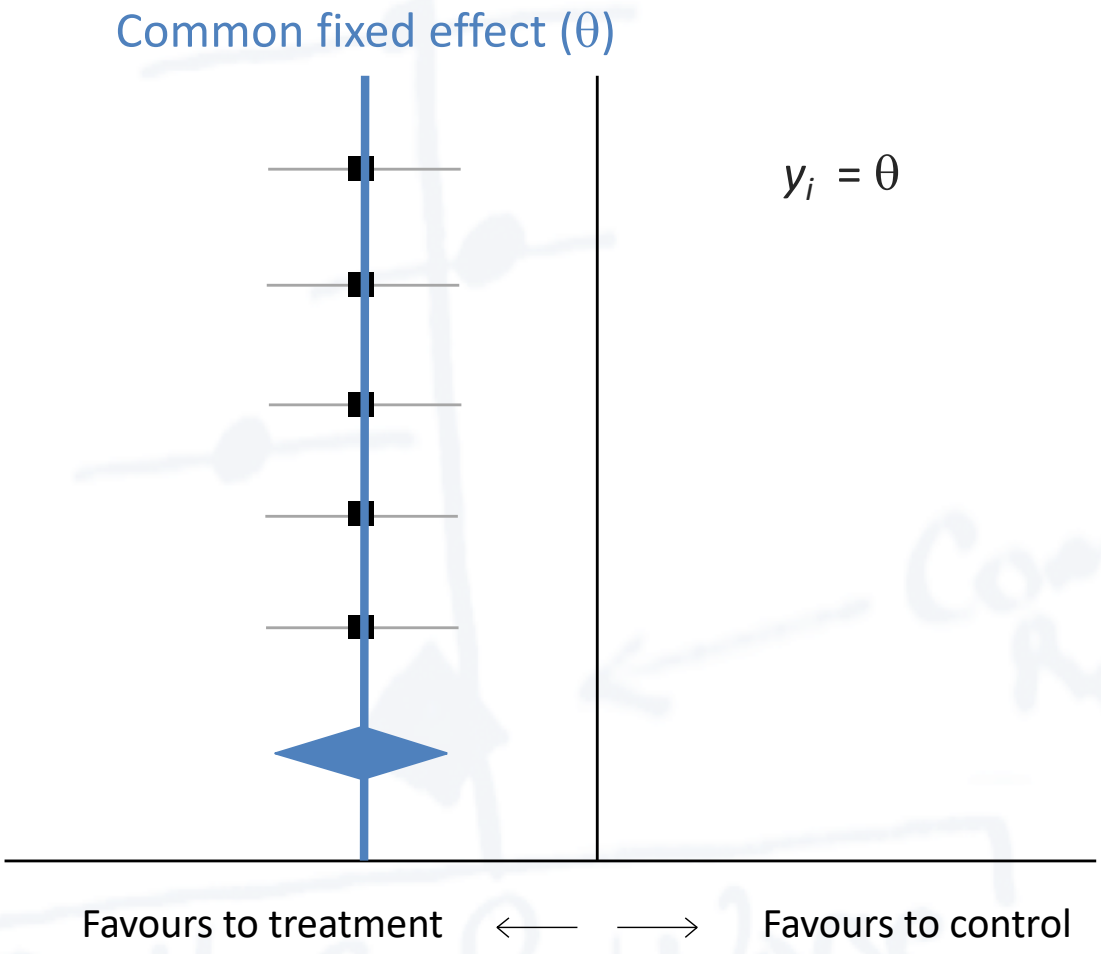
- **Continuous** outcome

	Outcome		
Group	*n*	*mean*	*(sd)*
Treat.	n_1	m_1	(s_1)
Control	n_2	m_2	(s_2)

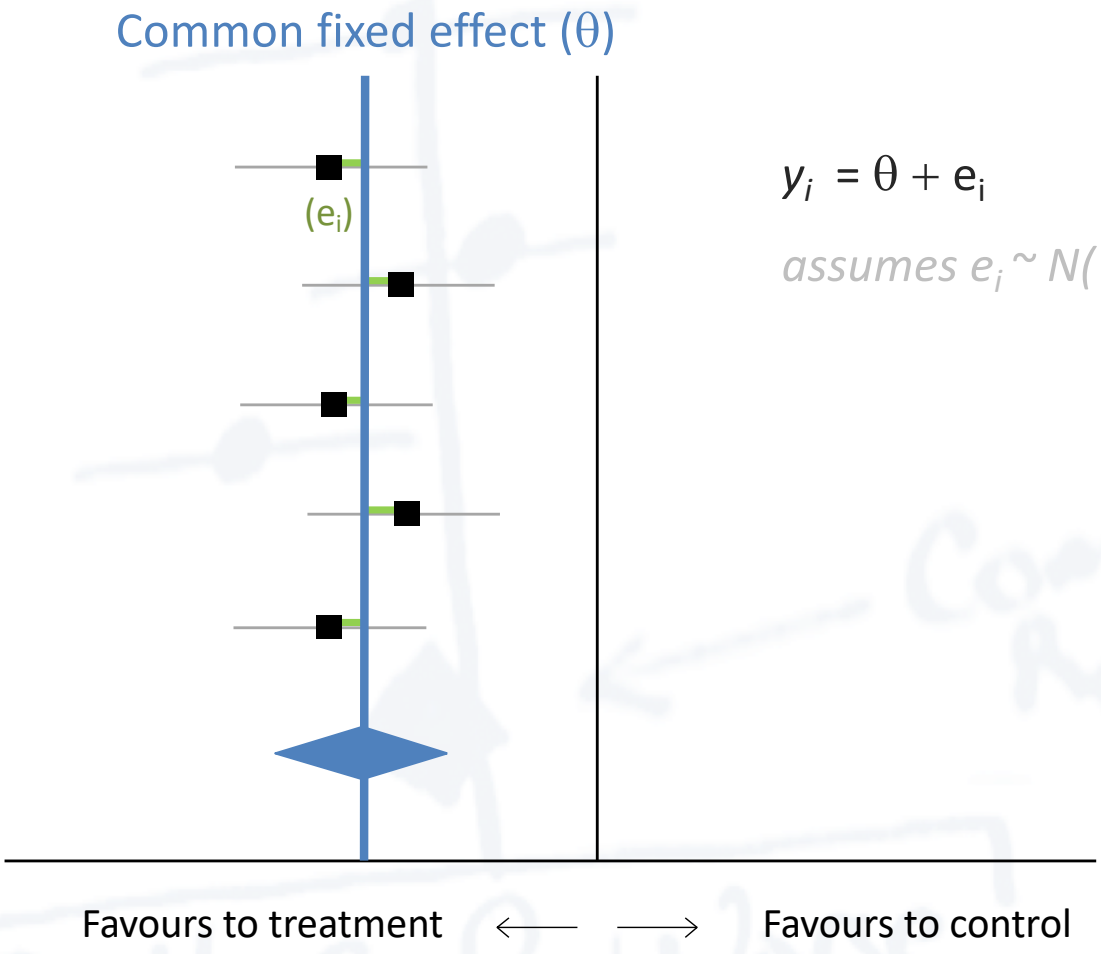
  - Mean difference
    - **D** = $m_1 - m_2$ with $s^2_D = ((n_1-1)s_1^2+(n_2-1)s_2^2)/(n_1+n_2-2)$
  - Standardized mean difference
    - **d** = $(m_1 - m_2)/s$ with $s^2_d = (n_1+n_2)/(n_1n_2)+d^2/2(n_1+n_2-2)$

      and $\sqrt{((n_1-1)s_1^2+(n_2-1)s_2^2)/(n_1+n_2-2)}$

Fixed effects model



Fixed effects model



$y_i = \theta + e_i$

assumes $e_i \sim N(0, s_i^2)$

Fixed effects model

- Assumes **homogeneity of effects**

  $H_0: y_1 = y_2 = \ldots = y_k$

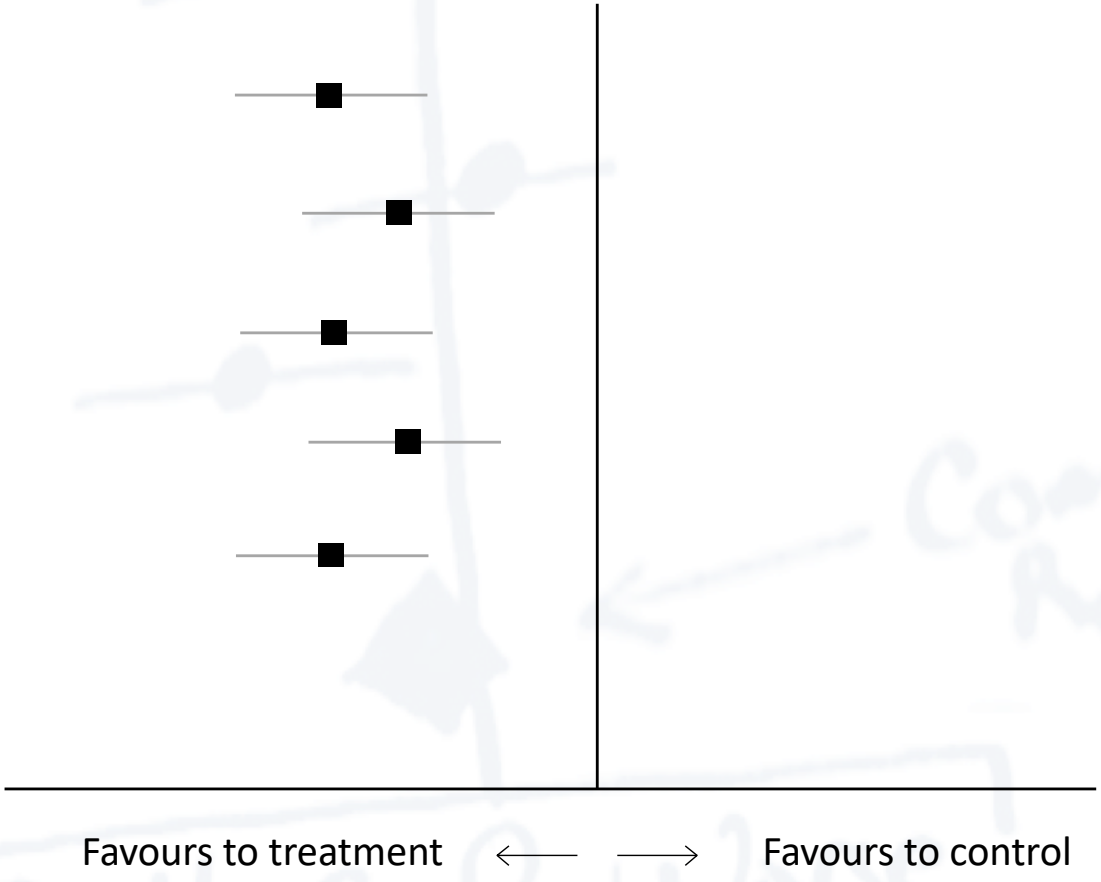
- Meta-analysis **pooled estimate**

$$\hat{\theta} = \sum w_i y_i / \sum w_i \qquad \text{with } s^2_{\hat{\theta}} = 1 / \sum w_i$$

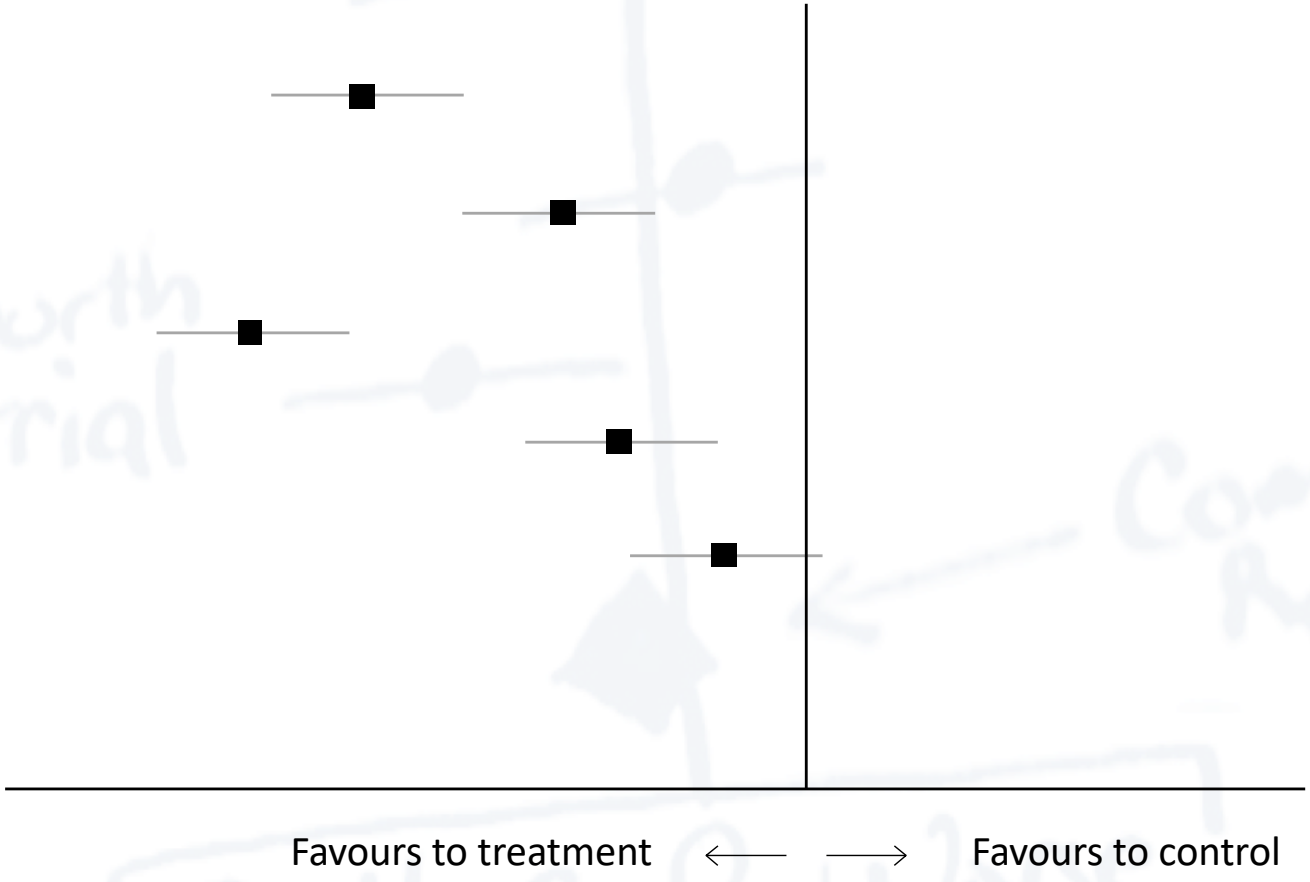
  - With weights as $\mathbf{w_i} = 1/s_i^2$
  - **Inverse variance weight** method (*Cochran 1937*)

Fixed effects model

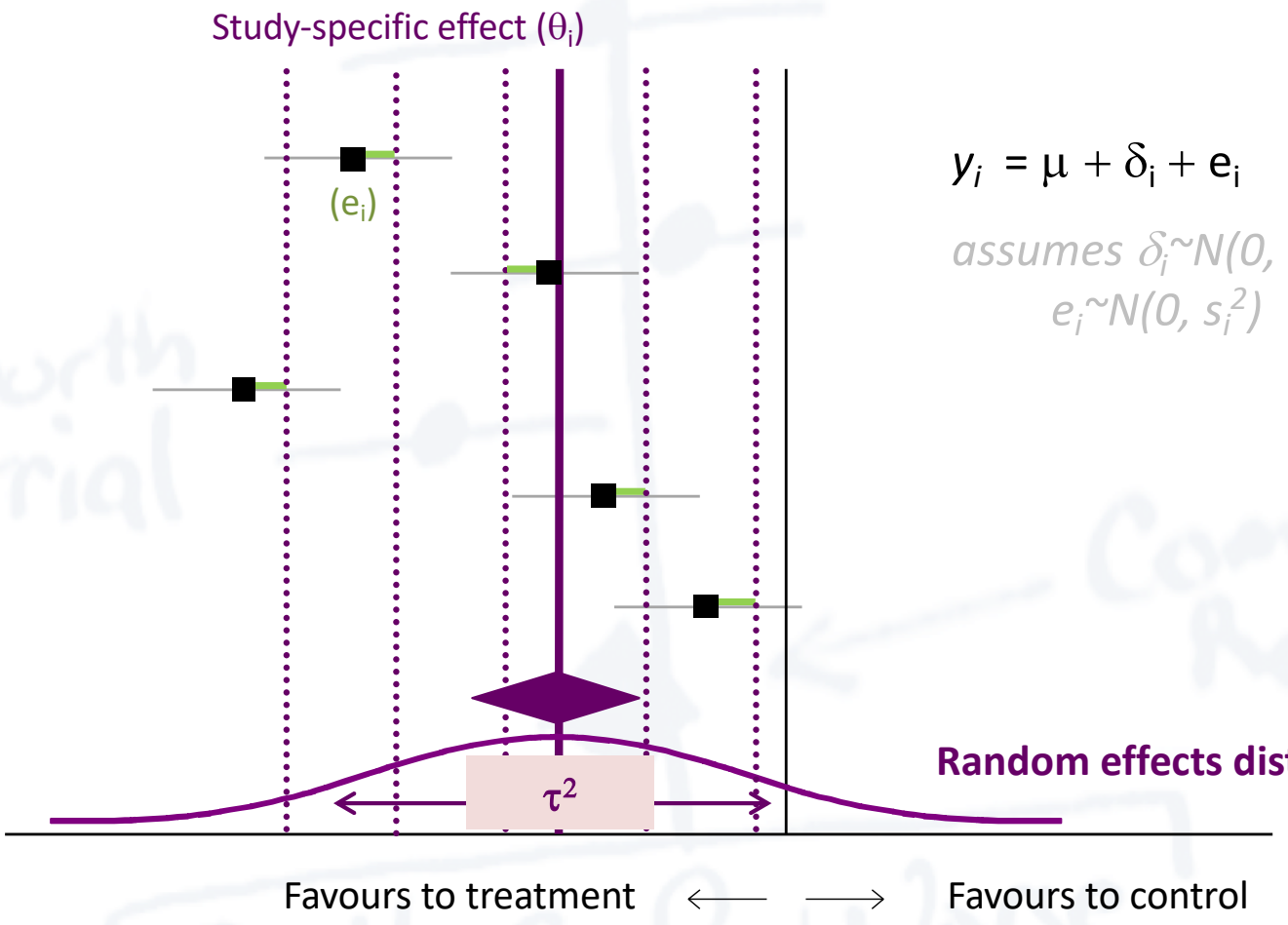
Fixed effects model



Random effects models



Random effects models



$$y_i = \mu + \delta_i + e_i$$

assumes $\delta_i \sim N(0, \tau^2)$

$e_i \sim N(0, s_i^2)$

Random effects model

- Assumes that the **treatment effect in each study is randomly distributed** across studies, with a given mean and variance (τ^2)
- Meta-analysis **pooled estimate**

$$\hat{\mu} = \sum w_i^* y_i / \sum w_i^* \qquad \text{with } s^2_{\hat{\mu}} = 1 / \sum w_i^*$$

  - With weights as $\mathbf{w_i}^* = 1/(s_i^2 + \tau^2)$
  - ***DerSimonian & Laird's*** method (*1986*)

Heterogeneity

- **Testing** for heterogeneity
  - H_0: $y_1 = y_2 = \ldots = y_k$

$$Q = \sum w_i \left(y_i - \hat{\theta} \right)^2 \sim \chi^2_{k-1}$$

  - The test has **low power** when there are few studies, thus, the **p-value is difficult to interpret**

Heterogeneity

- **Testing** for heterogeneity
  - H_0: $y_1 = y_2 = \ldots = y_k$

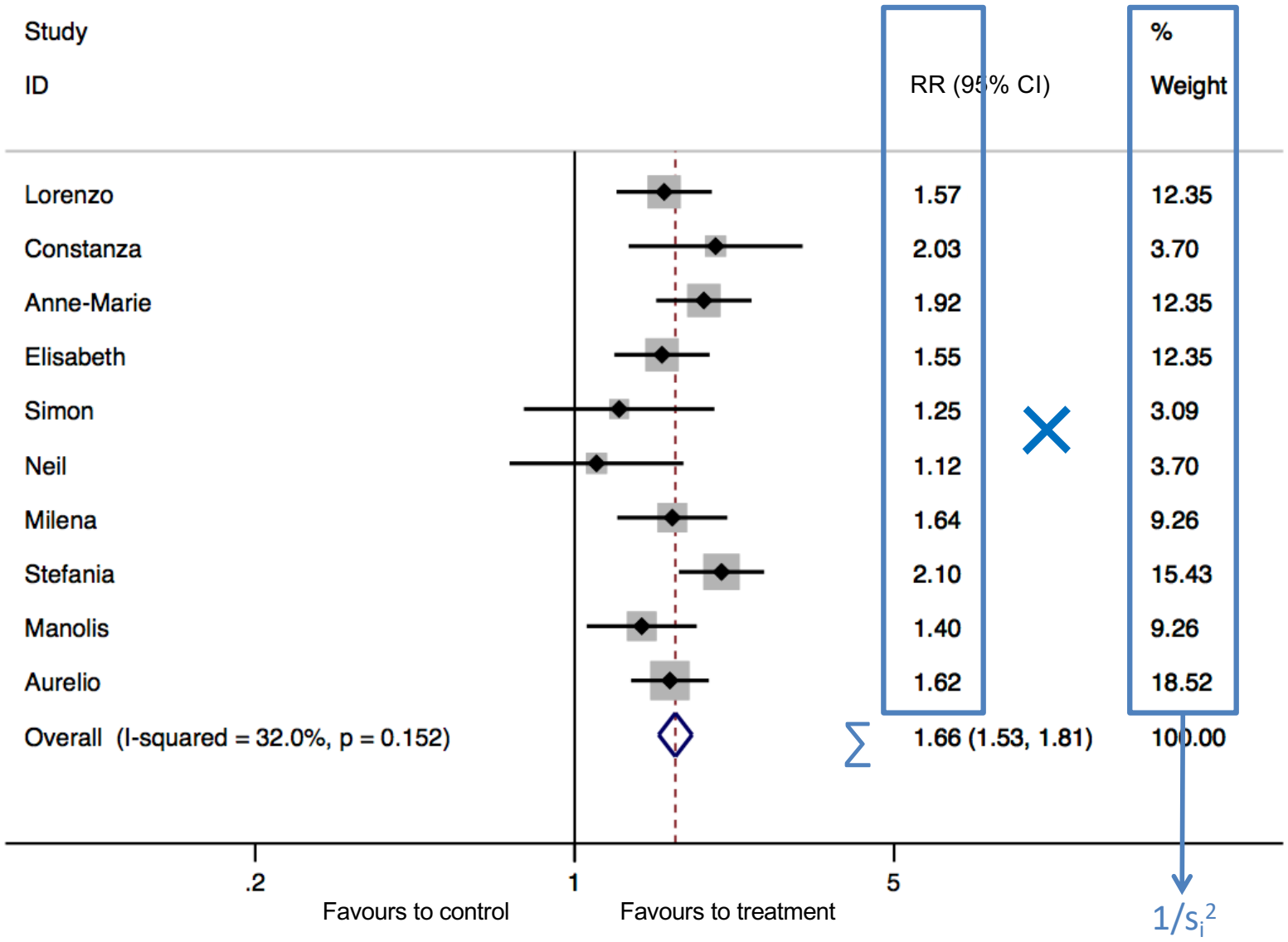
$$Q = \sum w_i \left(y_i - \hat{\theta}\right)^2 \sim \chi^2_{k-1}$$

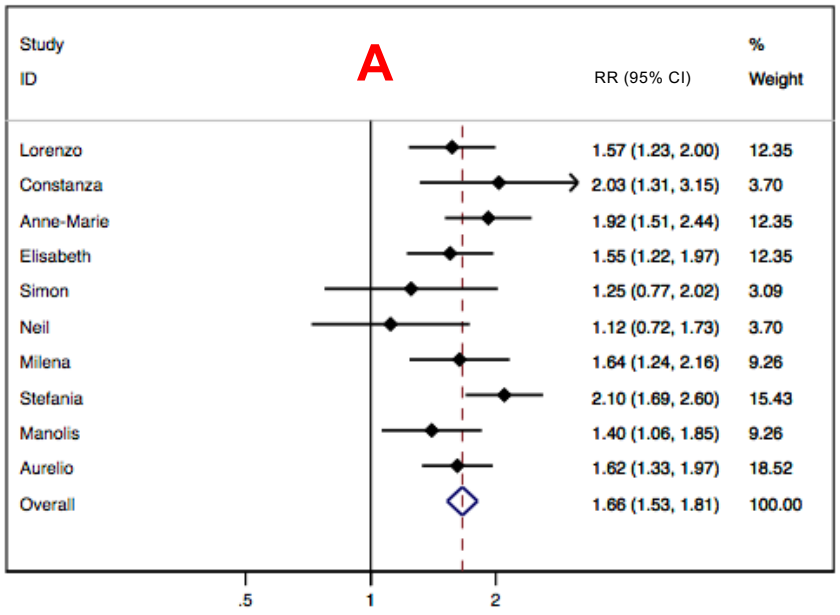
  - The test has low power when there are few studies, but high when there are many, so the **p-value is difficult to interpret**

- **Quantifying** heterogeneity
  - Based on Q s

$$I^2 = \frac{Q - (k-1)}{Q} \times 100\%$$

  - Proportion of total variability explained by heterogeneity
  - Cut-off values of **25%, 50% and 75%** might be considered as **low, moderate, high and very high** heterogeneity, respectively


Study
ID
RR (95% CI)
%
Weight
Lorenzo
1.57
12.35
Constanza
2.03
3.70
Anne-Marie
1.92
12.35
Elisabeth
1.55
12.35
Simon
1.25
3.09
Neil
1.12
3.70
Milena
1.64
9.26
Stefania
2.10
15.43
Manolis
1.40
9.26
Aurelio
1.62
18.52
Overall (I-squared = 32.0%, p = 0.152)
1.66 (1.53, 1.81)
100.00
.2
1
5
Favours to control
Favours to treatment
$1/s_i^2$


A
Study
ID
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Weight
Lorenzo 1.57 (1.23, 2.00) 12.35
Constanza 2.03 (1.31, 3.15) 3.70
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Simon 1.25 (0.77, 2.02) 3.09
Neil 1.12 (0.72, 1.73) 3.70
Milena 1.64 (1.24, 2.16) 9.26
Stefania 2.10 (1.69, 2.60) 15.43
Manolis 1.40 (1.06, 1.85) 9.26
Aurelio 1.62 (1.33, 1.97) 18.52
Overall 1.66 (1.53, 1.81) 100.00
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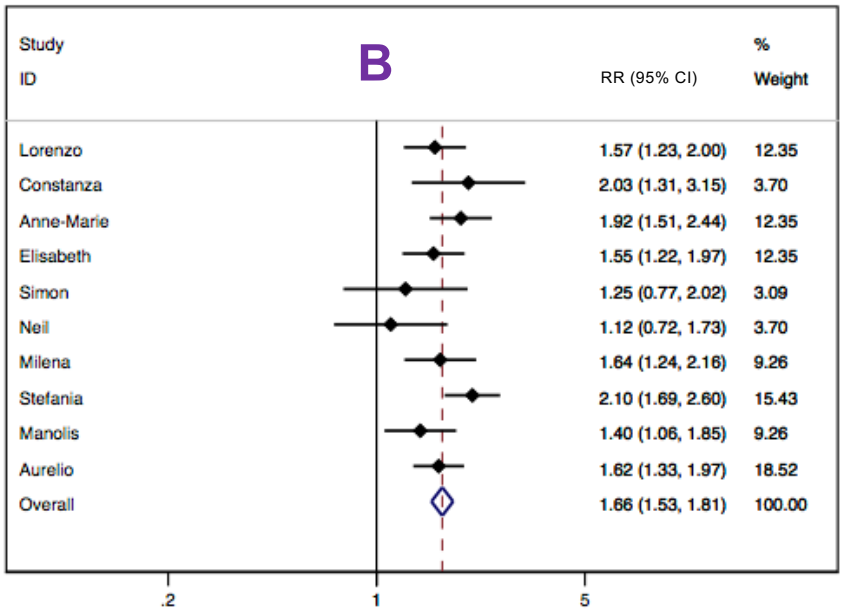
2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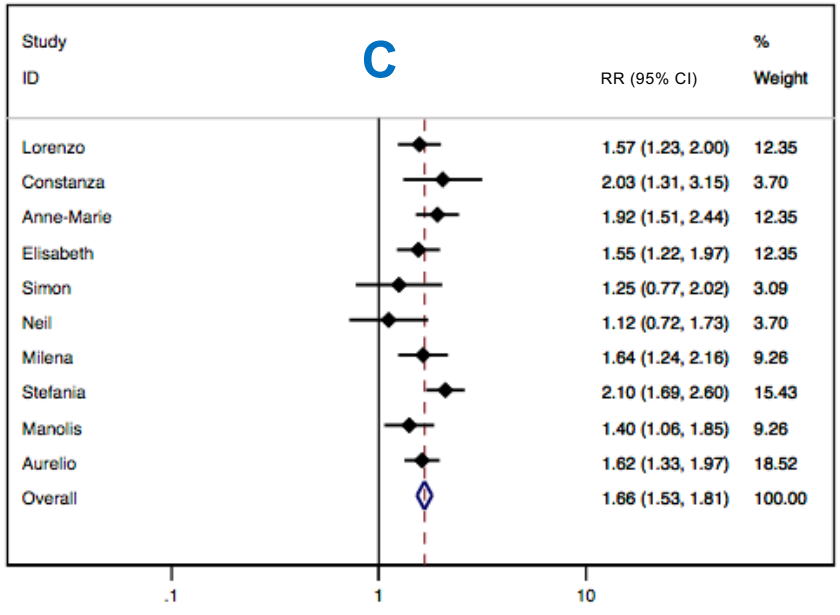
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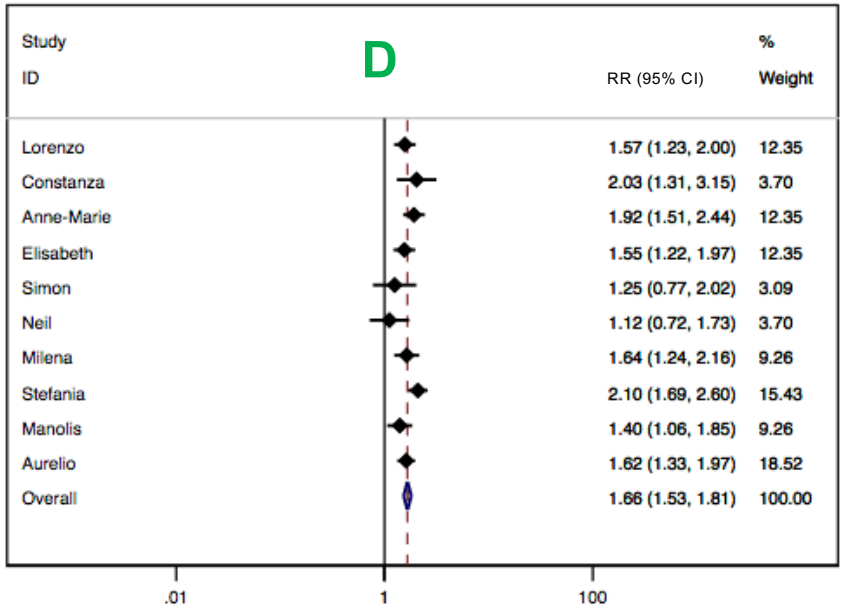
10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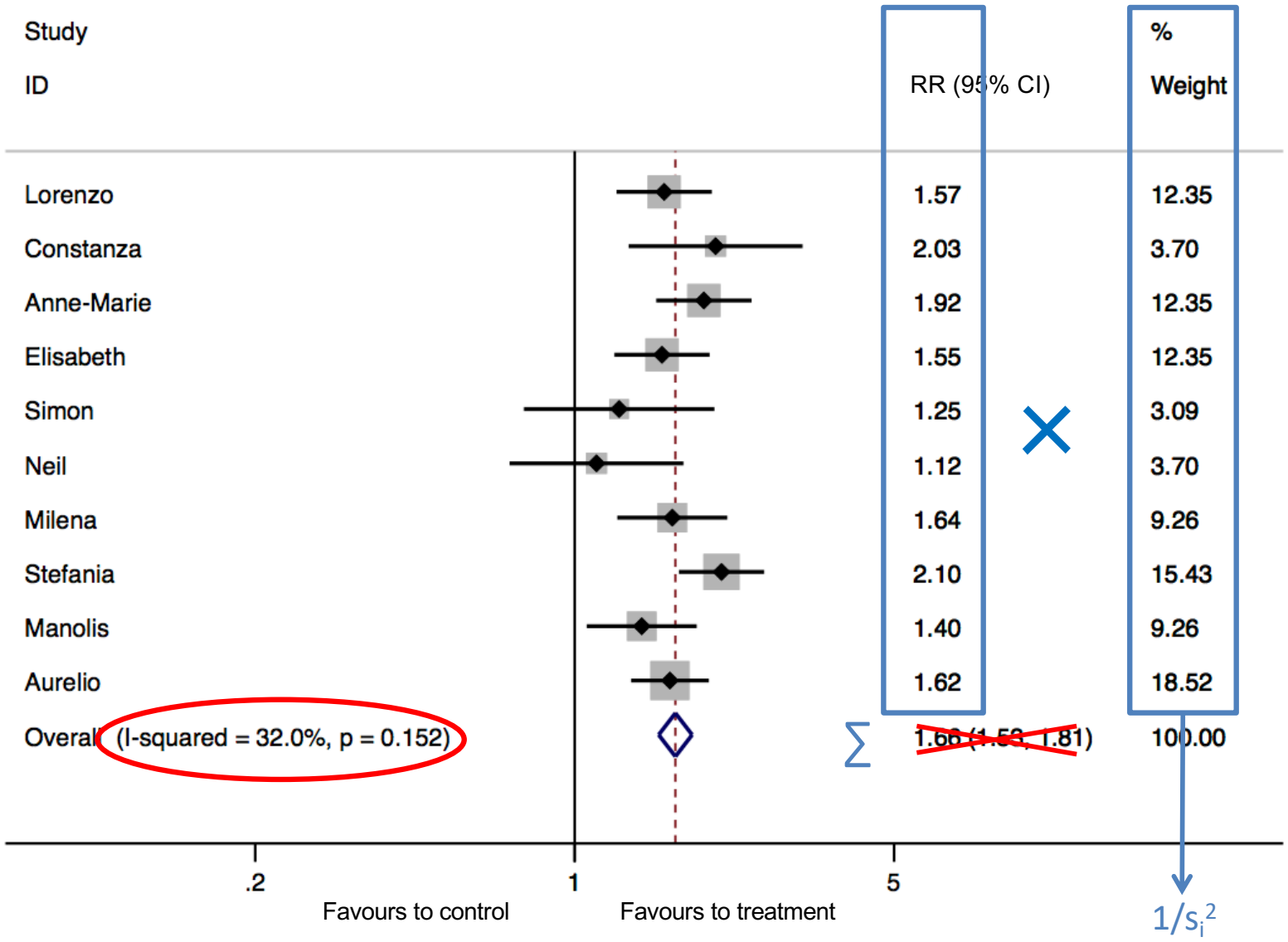
100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100.00
.2
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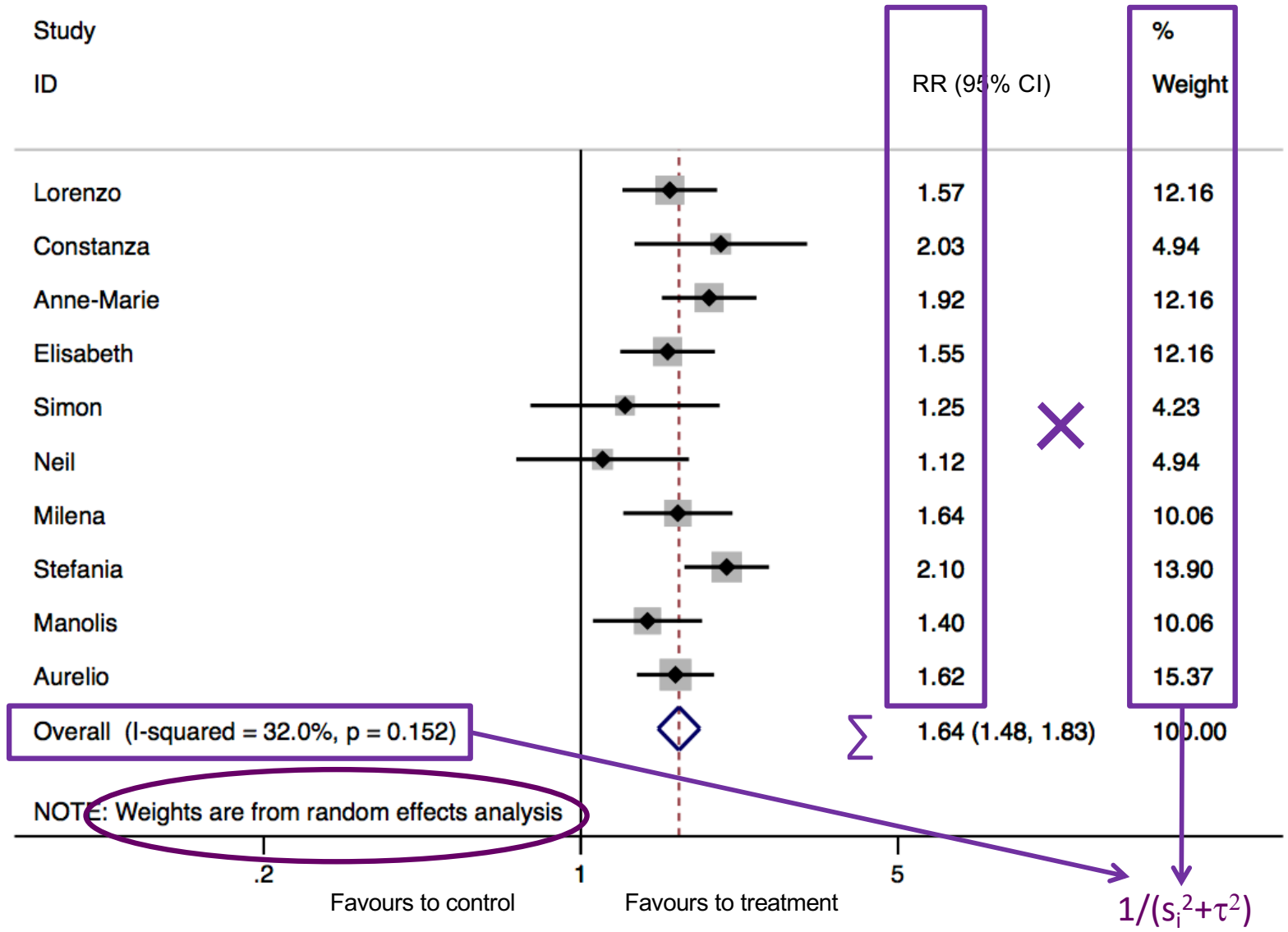
5
Favours to control
Favours to treatment
1/s_i^2


Study
ID
RR (95% CI)
%
Weight
Lorenzo
1.57
12.16
Constanza
2.03
4.94
Anne-Marie
1.92
12.16
Elisabeth
1.55
12.16
Simon
1.25
4.23
Neil
1.12
4.94
Milena
1.64
10.06
Stefania
2.10
13.90
Manolis
1.40
10.06
Aurelio
1.62
15.37
Overall (I-squared = 32.0%, p = 0.152)
1.64 (1.48, 1.83)
100.00
NOTE: Weights are from random effects analysis
.2
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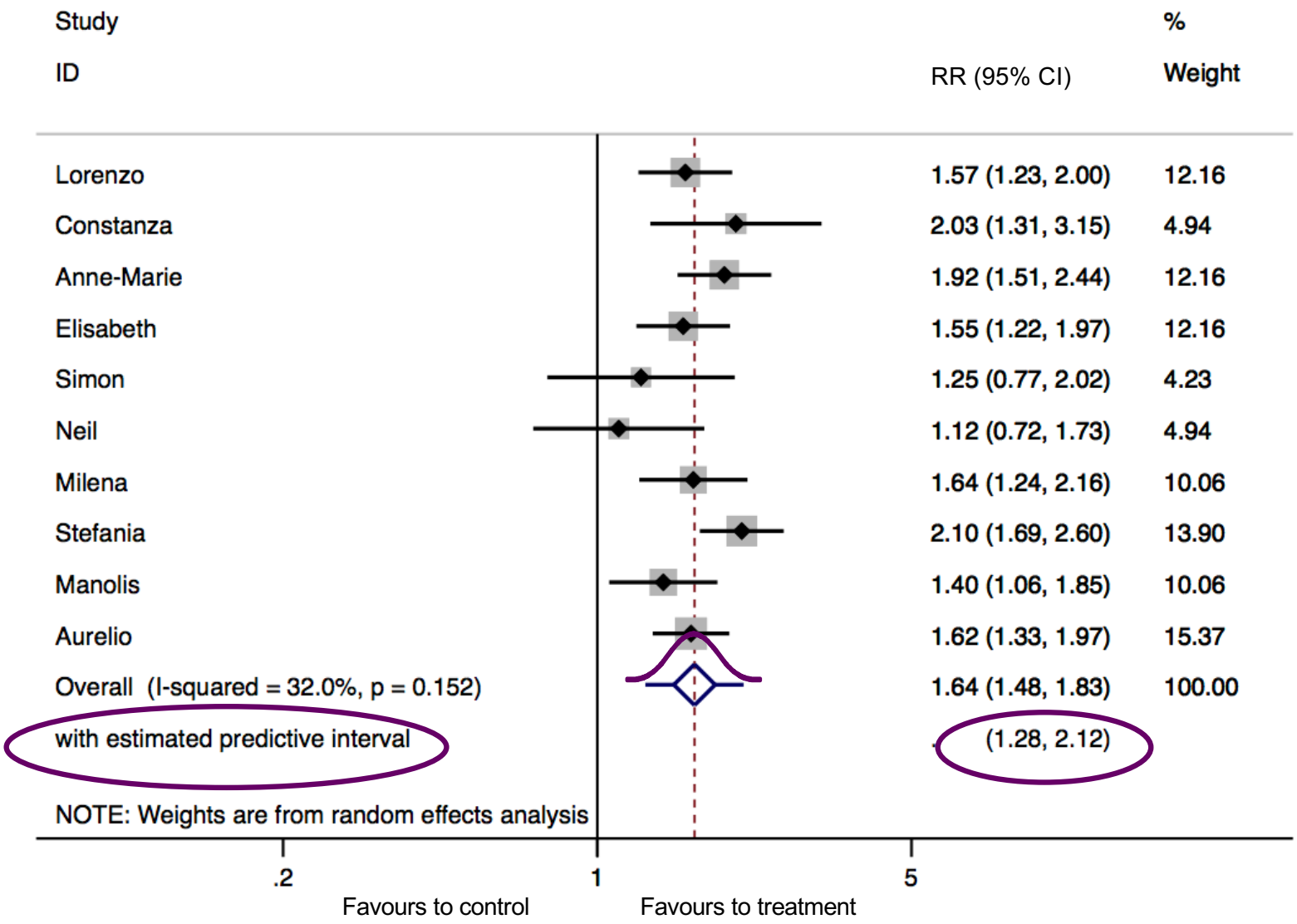
5
Favours to control
Favours to treatment
$1/(s_i^2+\tau^2)$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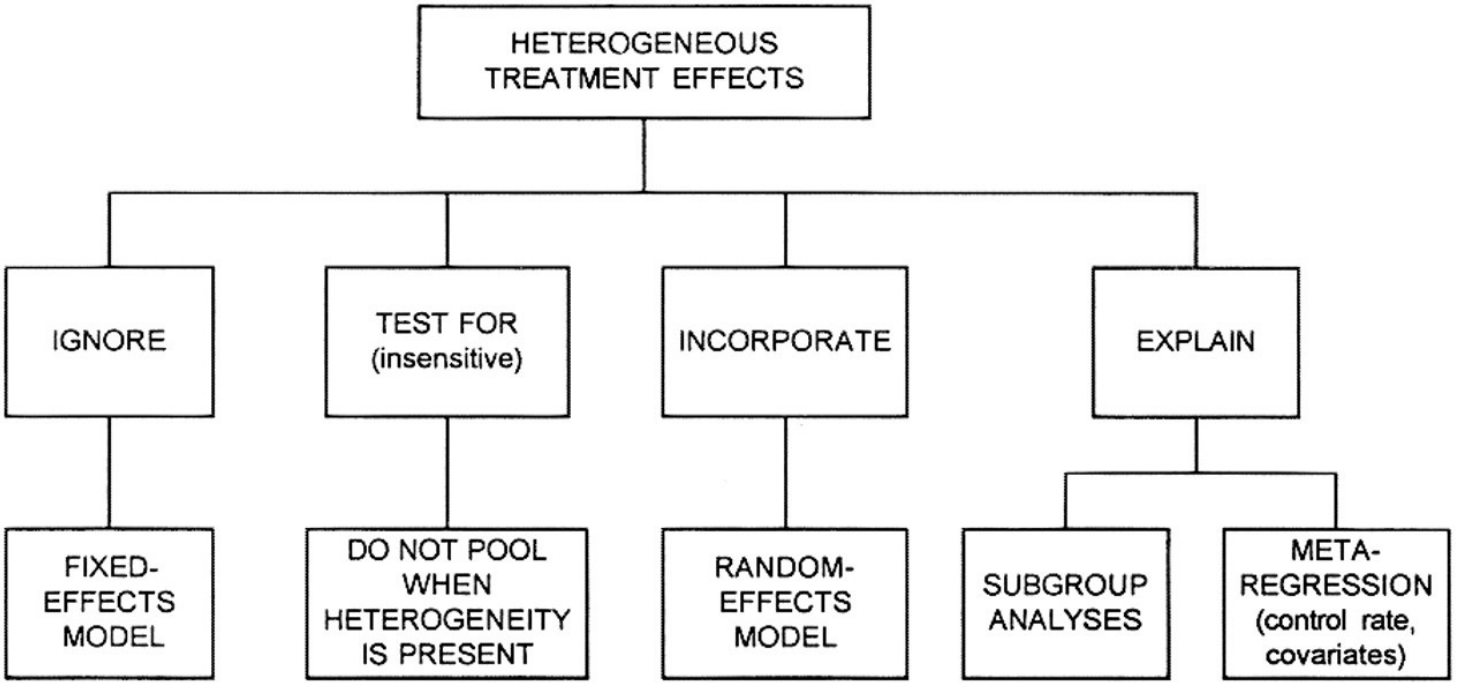
1.12 (0.72, 1.73)
4.94
Milena
1.64 (1.24, 2.16)
10.06
Stefania
2.10 (1.69, 2.60)
13.90
Manolis
1.40 (1.06, 1.85)
10.06
Aurelio
1.62 (1.33, 1.97)
15.37
Overall (I-squared = 32.0%, p = 0.152)
1.64 (1.48, 1.83)
100.00
with estimated predictive interval
(1.28, 2.12)
NOTE: Weights are from random effects analysis
.2
1
5
Favours to control
Favours to treatment

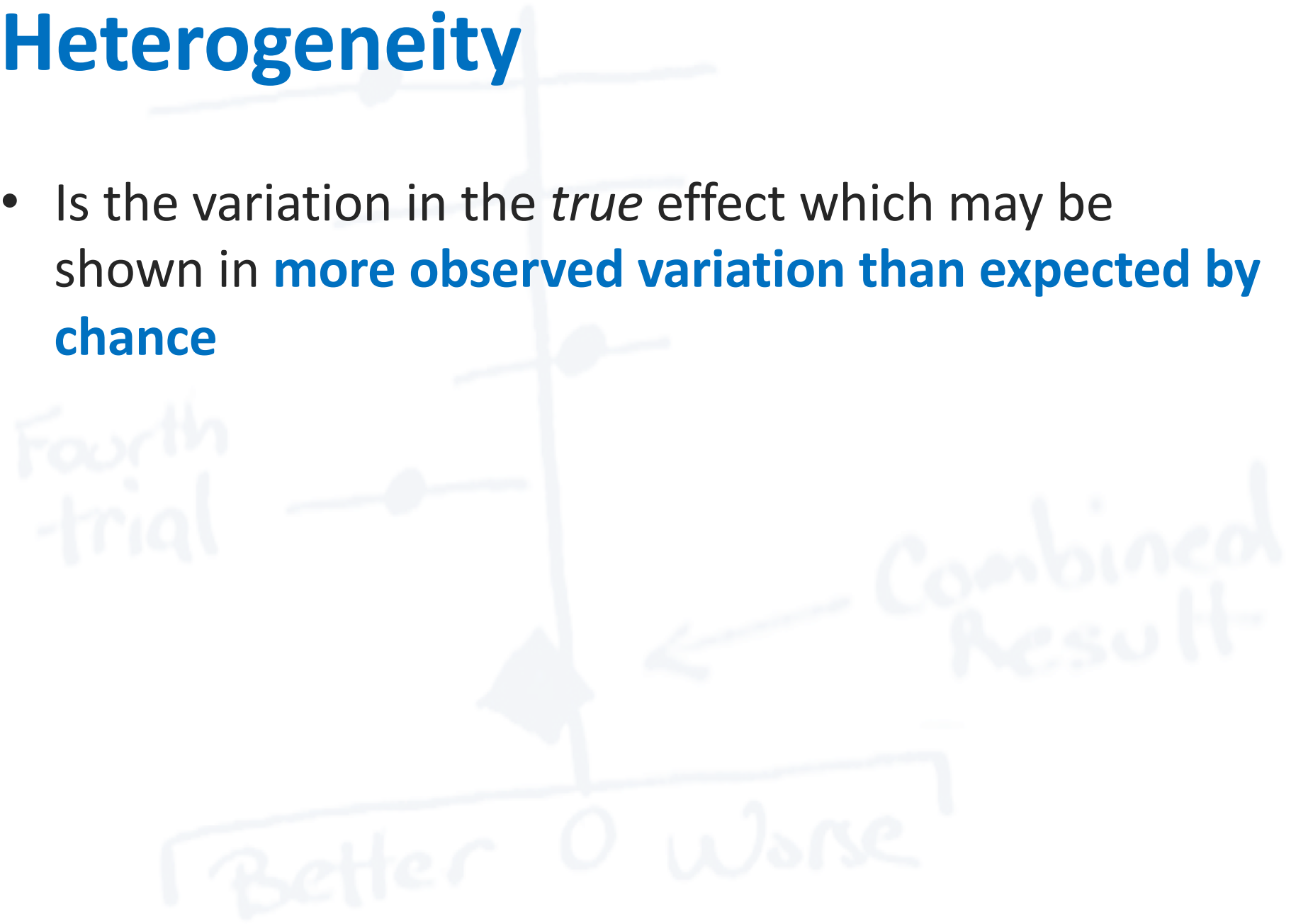
Heterogeneity



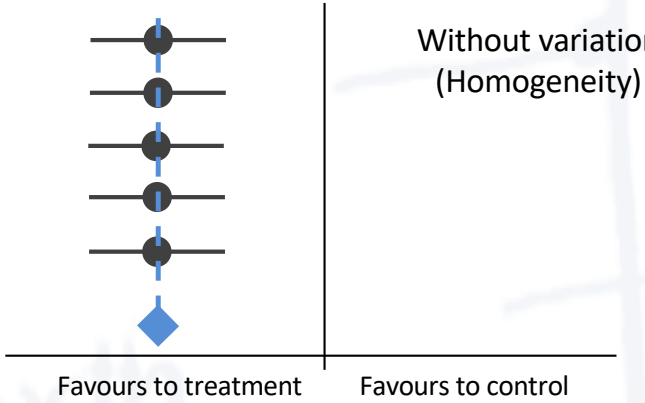
(Lau et al. 1997)

Heterogeneity

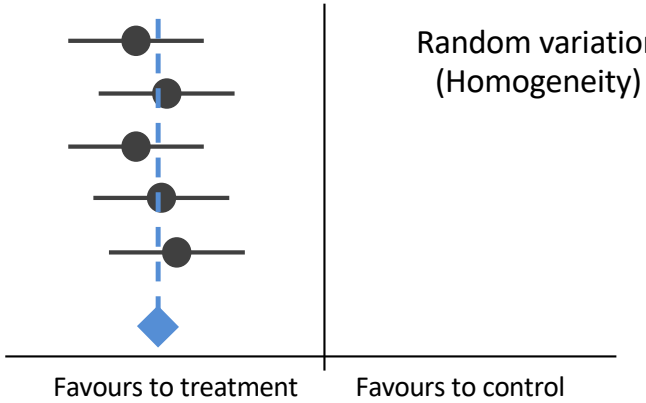
- Is the variation in the *true* effect which may be shown in **more observed variation than expected by chance**



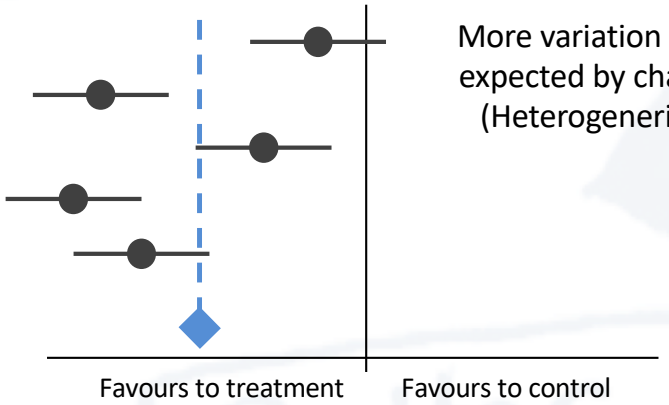
Heterogeneity



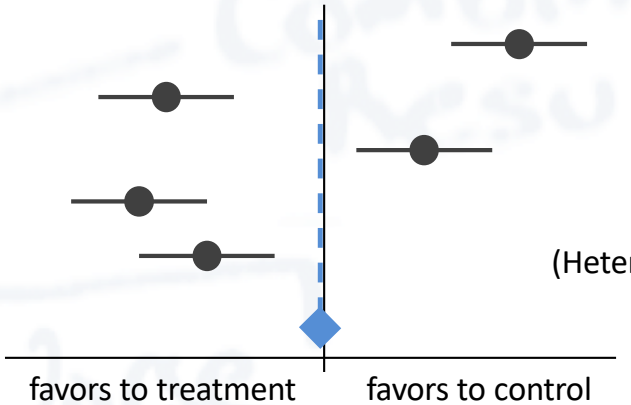
Without variation
(Homogeneity)



Random variation
(Homogeneity)



More variation than
expected by chance
(Heterogenerity)



(Heterogeneity)

Heterogeneity

- Is the variation in the *true* effect which may be shown in **more observed variation than expected by chance**
- Heterogeneity should **not be ignored**, it must be explained
- Studies are conducted in **different places, times and populations**, leading to different between-study estimates

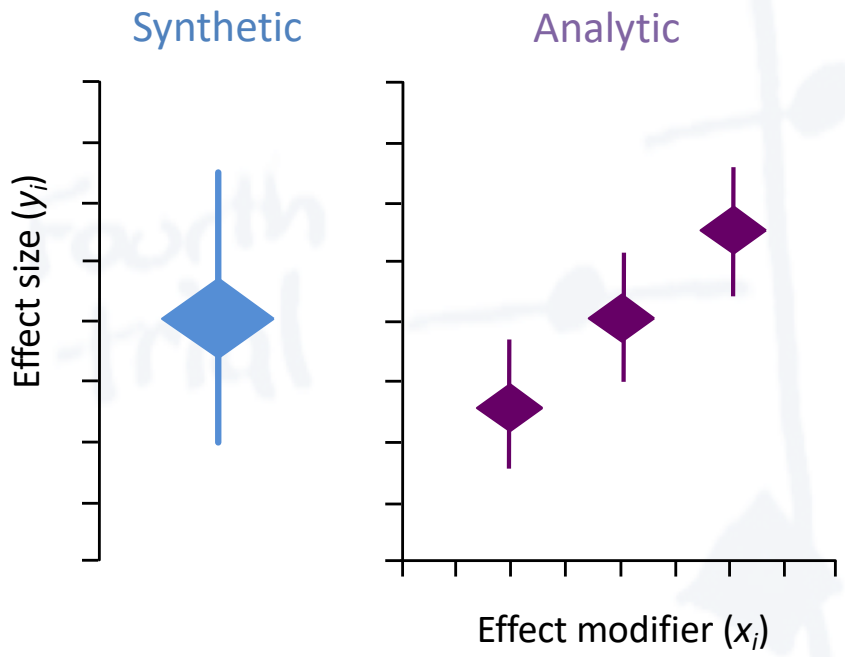
Causes of heterogeneity

1) **Study** characteristics
   - Variations in the study designs
   - Development of studies
   - Attrition
- Methodological (statistical) heterogeneity due to **bias**

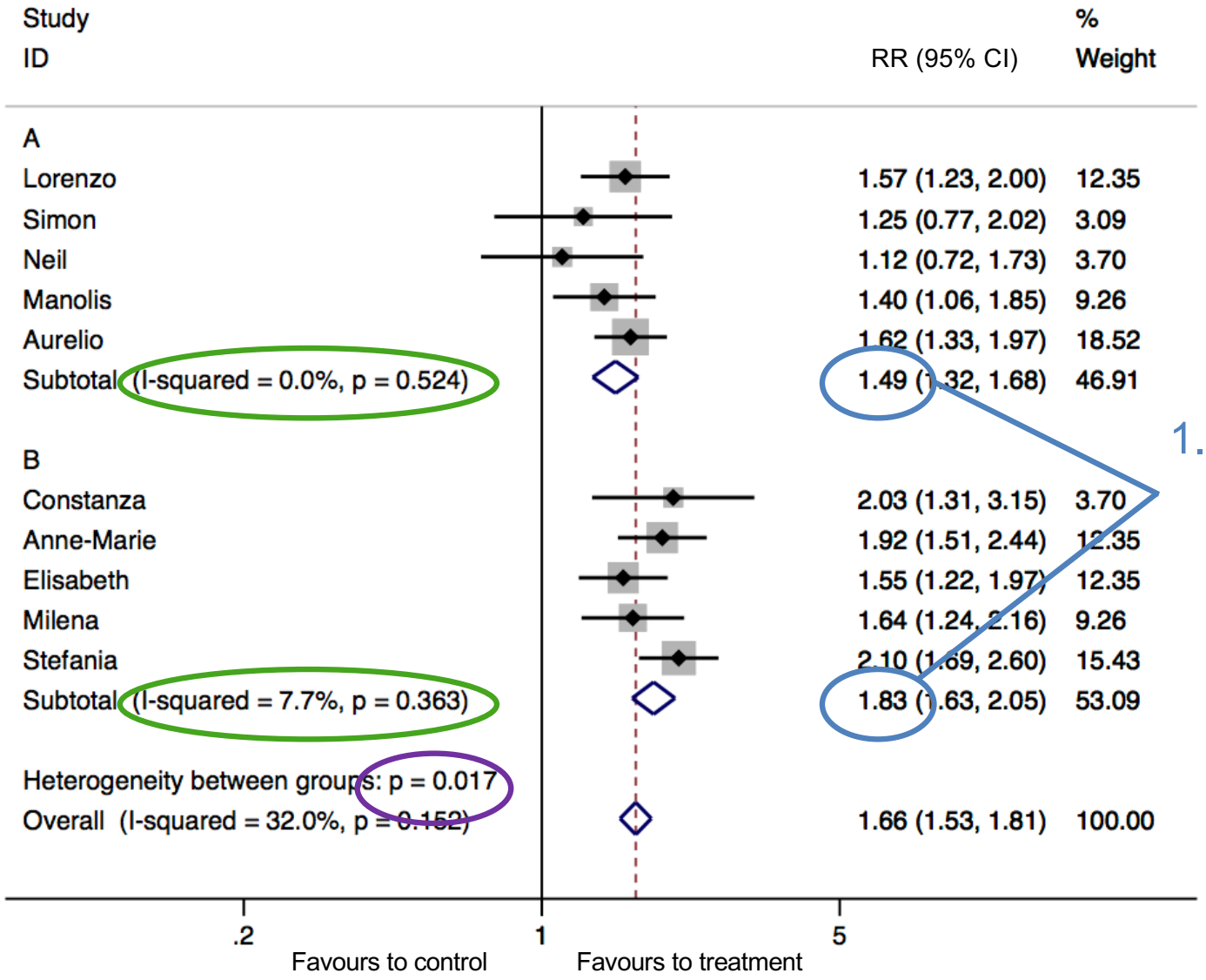
2) **Population** characteristics
   - Type of participants
   - Temporal/geographical settings
   - Treatment (or exposure) and outcome measures
- Clinical heterogeneity due to biological **diversity**

Subgroup meta-analysis

- Synthetic *vs.* analytic views



- **Stratified meta-analysis** by study/population characteristics
- Clear definitions of subgroups is essential
- Identify **homogeneity within** each subgroup, but **heterogeneity between** subgroups


Study
ID
RR (95% CI)
%
Weight
A
Lorenzo
1.57 (1.23, 2.00)
12.35
Simon
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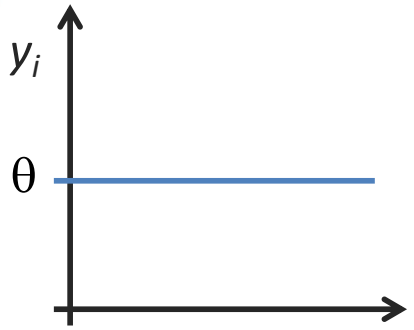
3.09
Neil
1.12 (0.72, 1.73)
3.70
Manolis
1.40 (1.06, 1.85)
9.26
Aurelio
1.62 (1.33, 1.97)
18.52
Subtotal (I-squared = 0.0%, p = 0.524)
1.49 (1.32, 1.68)
46.91
B
Constanza
2.03 (1.31, 3.15)
3.70
Anne-Marie
1.92 (1.51, 2.44)
12.35
Elisabeth
1.55 (1.22, 1.97)
12.35
Milena
1.64 (1.24, 2.16)
9.26
Stefania
2.10 (1.69, 2.60)
15.43
Subtotal (I-squared = 7.7%, p = 0.363)
1.83 (1.63, 2.05)
53.09
Heterogeneity between groups: p = 0.017
Overall (I-squared = 32.0%, p = 0.152)
1.66 (1.53, 1.81)
100.00
.2
1
5
Favours to control
Favours to treatment
1.83/1.49 =
= 1.23

Meta-analysis as a linear model

- Fixed effects

$$y_i = \theta + e_i$$

$$e_i \sim N(0, s_i^2)$$

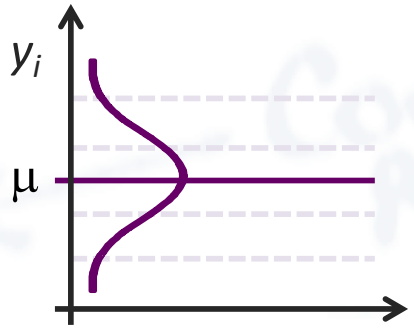


- Random effects

$$y_i = \mu + \delta_i + e_i$$

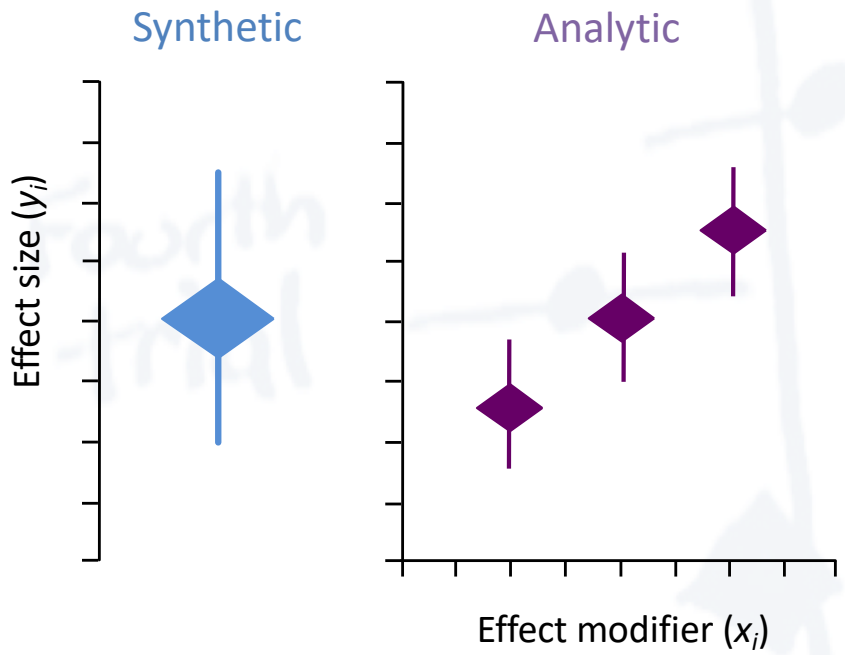
$$\delta_i \sim N(0, \tau^2)$$

$$e_i \sim N(0, s_i^2)$$



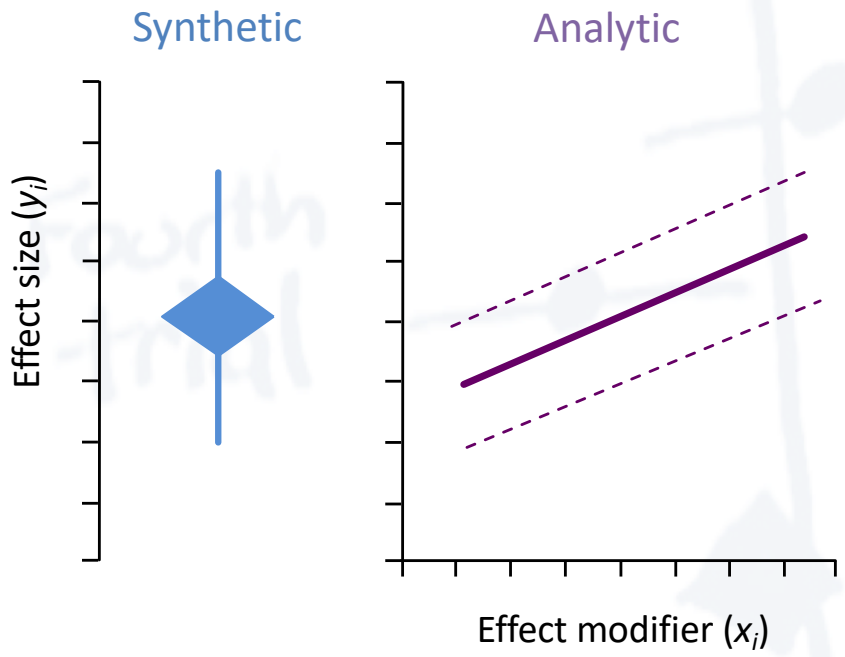
Subgroup meta-analysis

- Synthetic *vs.* analytic views



Meta-regression

- Synthetic *vs.* analytic views



- **Weighted random effects linear regression** model

$$y_i = \mu + \beta x_i + \delta_i + e_i$$

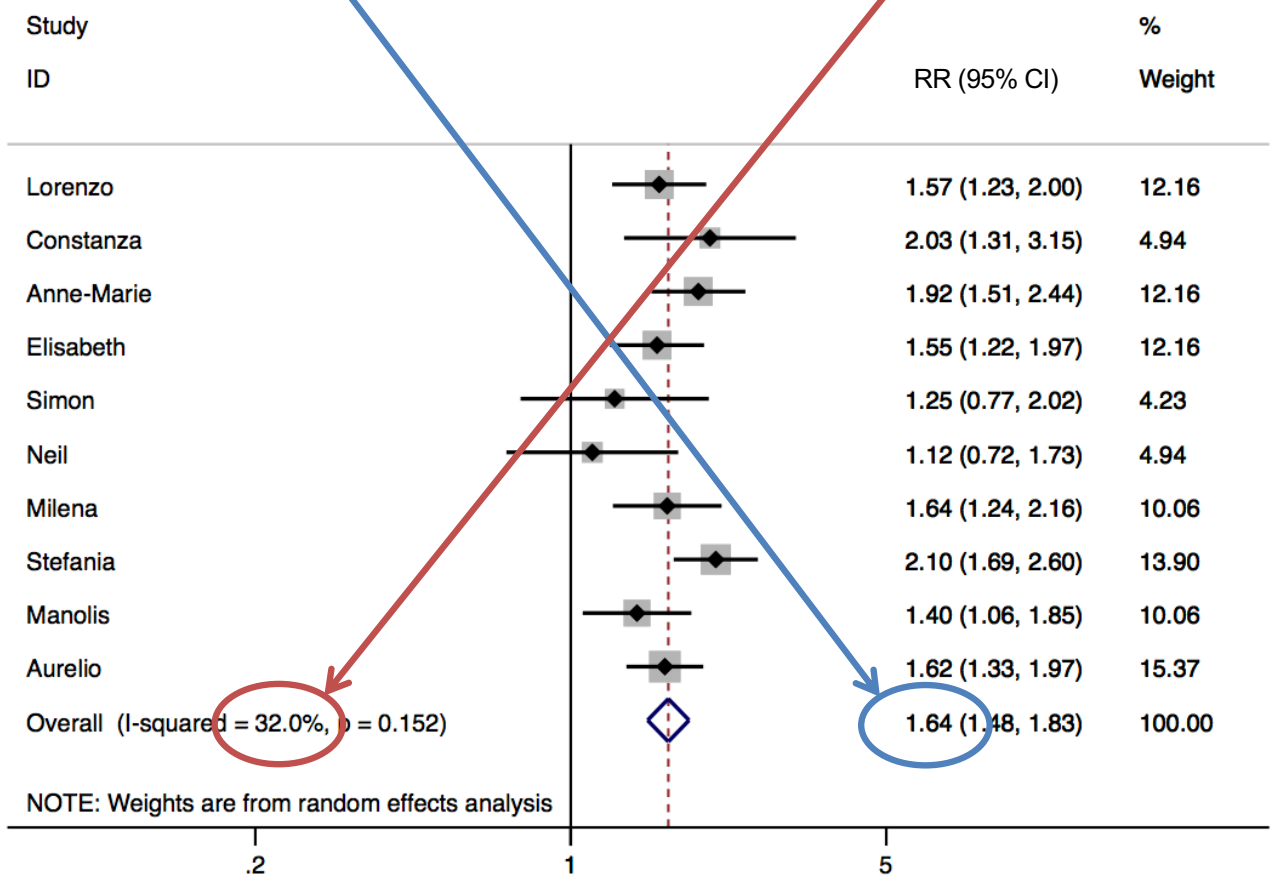
y_i is the *i*-study effect size

x_i is a covariate for a given study/population characteristic

- Explain great part of heterogeneity and the remaining as **residual heterogeneity**

```
                                                    I-squared_res  =    32.01%
------------------------------------------------------------------------------
     log(RR) |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   .4977309   .0539899     9.22   0.000     .3919126    .6035491
------------------------------------------------------------------------------
```

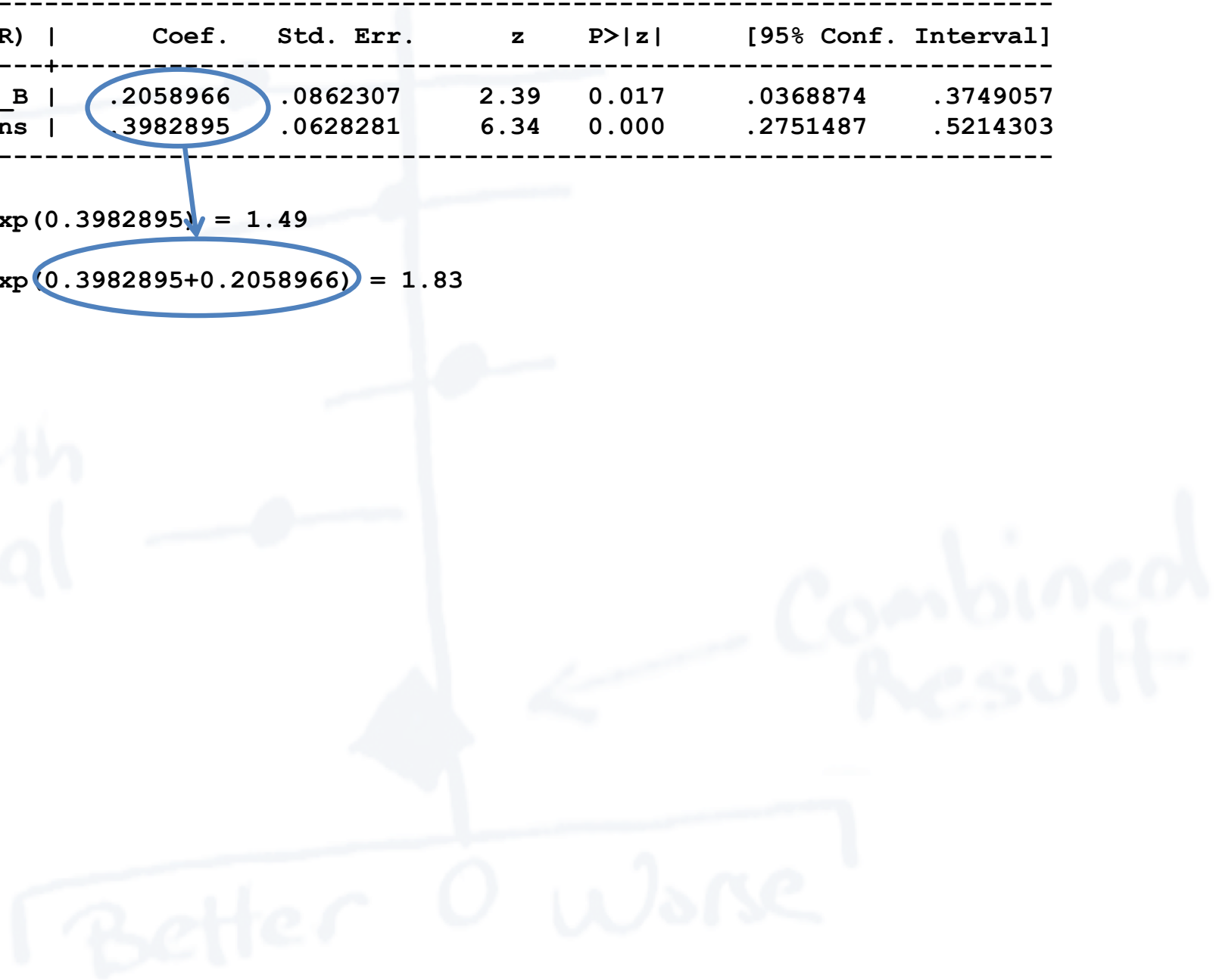
RR = exp(0.4977309) = 1.64



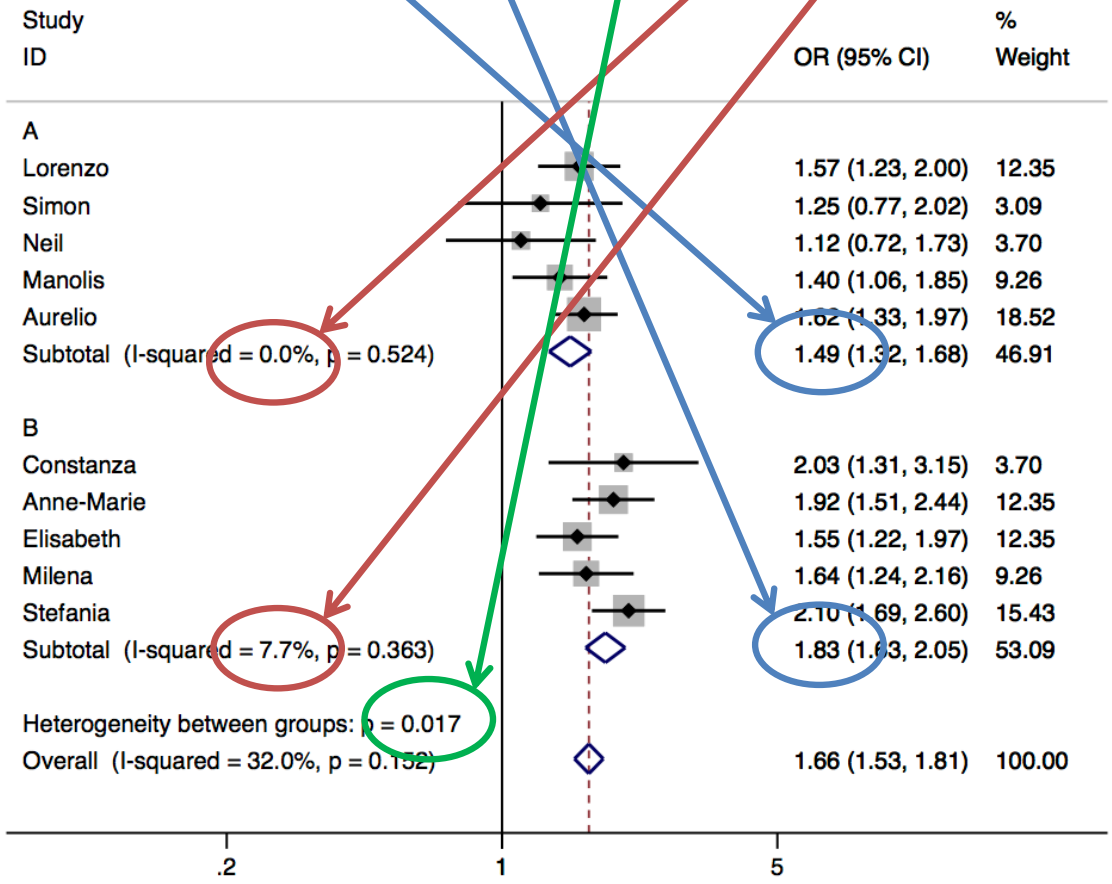
```
                                                    I-squared_res  =   0.00%
------------------------------------------------------------------------------
[y]  log(RR) |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
[x]  group_B |   .2058966   .0862307     2.39   0.017     .0368874    .3749057
       _cons |   .3982895   .0628281     6.34   0.000     .2751487    .5214303
------------------------------------------------------------------------------
```

group_A: exp(0.3982895) = 1.49

```
                                                    I-squared_res  =    0.00%
------------------------------------------------------------------------------
     log(RR) |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     group_B |   .2058966   .0862307     2.39   0.017     .0368874    .3749057
       _cons |   .3982895   .0628281     6.34   0.000     .2751487    .5214303
------------------------------------------------------------------------------

group_A: exp(0.3982895) = 1.49

group_B: exp(0.3982895+0.2058966) = 1.83
```

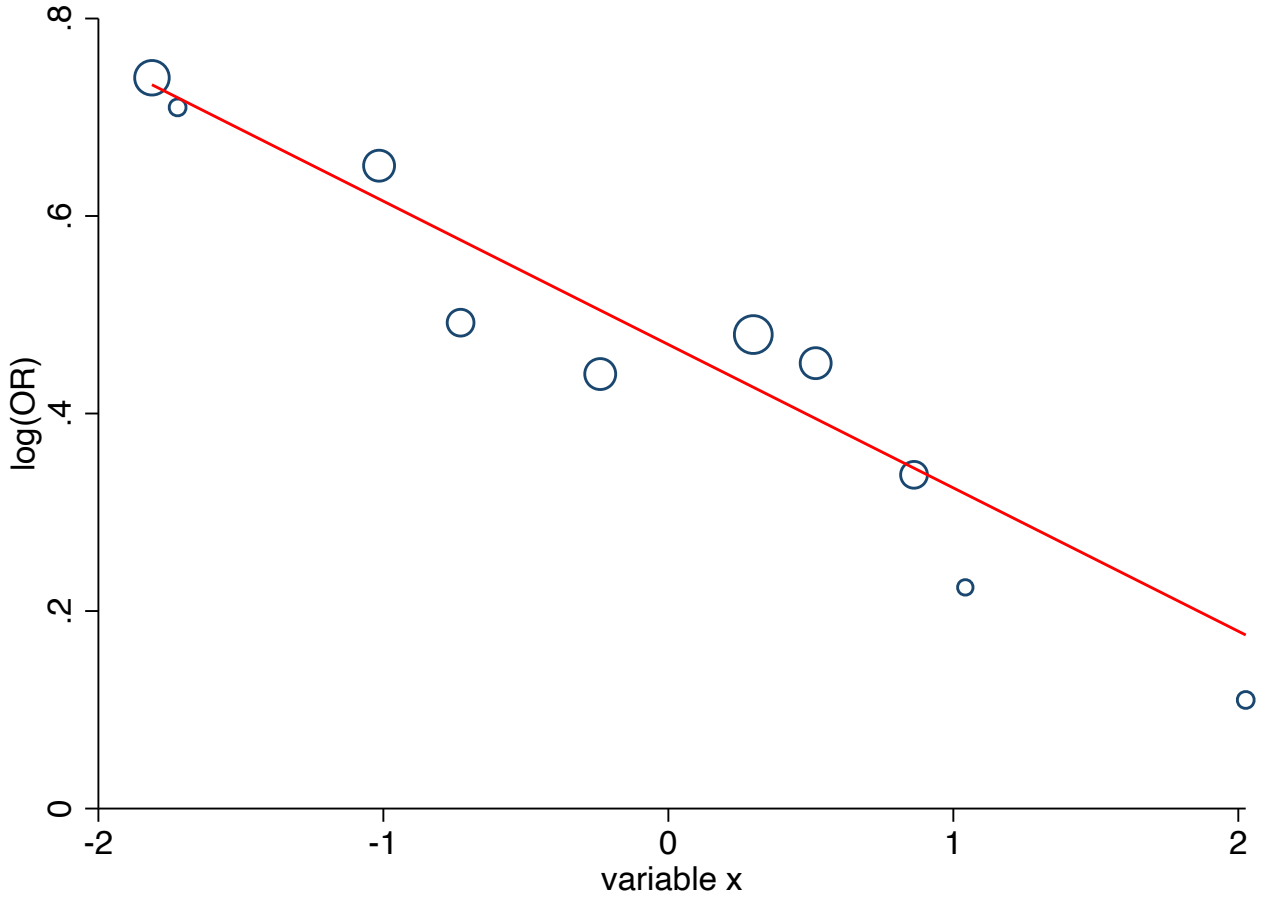


```
                                                    I-squared_res  =    0.00%
------------------------------------------------------------------------------
     log(RR) |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    group_B |   .2058966   .0862307     2.39   0.017     .0368874    .3749057
      _cons |   .3982895   .0628281     6.34   0.000     .2751487    .5214303
------------------------------------------------------------------------------

group_A: exp(0.3982895) =  1.49
group_B: exp(0.3982895+0.2058966) =  1.83
```



```
                                                I-squared_res  =    0.00%
------------------------------------------------------------------------------
     log(RR) |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       xcont |   -.145176   .0422727    -3.43   0.001    -.2280291    -.062323
       _cons |   .4698907   .0444114    10.58   0.000      .382846    .5569354
------------------------------------------------------------------------------
```

OR per 1 unit increase of x = exp(-.145176) = 0.86
When x=0 the OR = exp(0.4698907) = 1.60



Limitations

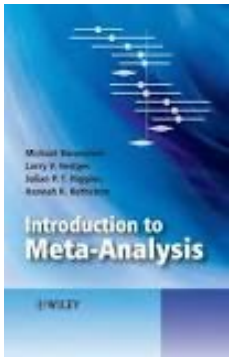
- Small number of studies – **low statistical power**
- Observational relationship *between* studies – **confounding bias**
- Definition of sub-groups and use of aggregated covariates – **information bias**
- Too many sources of methodological and clinical heterogeneity – **interpretation bias**

Summary

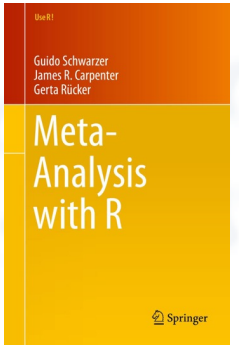
- Simple **statistical basis** for meta-analysis
  - Homogeneity of effects assumption
  - Weighted mean
- In case of **heterogeneity** between studies
  - The fixed effects model is clearly inappropriate … but the random effects models is inappropriate too
  - Heterogeneity should not be ignored, must be explained, but avoid over-interpretation of findings

Further readings

- Borestein M, Hedges LV, Higgins JPT, Rothstein HR. ***Introduction to Meta-analysis*** (mainly Chapters 4, 5, 11, 12, 13, 16, 19 and 20). Wiley, 2009



- Schwarzer G, Carpenter JR, Rücker G. ***Meta-analysis with R*** (mainly Part II). Springer, 2015



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