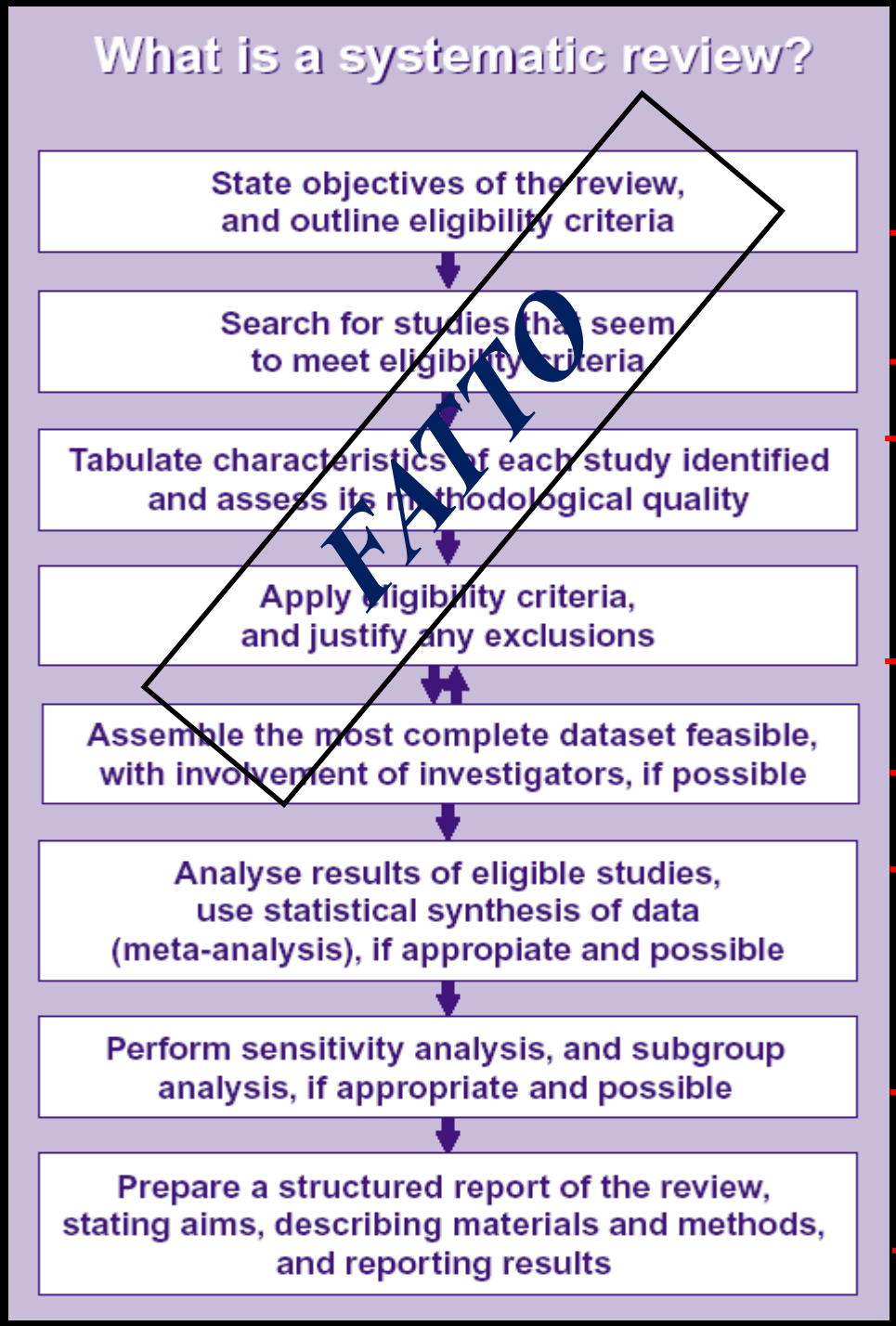
Eterogeneità

Negrar, 6 aprile 2019



I passi di una RS

Definizione del quesito

Ricerca sistematica delle fonti

Valutazione dei criteri di inclusione ed esclusione e della qualità degli studi eleggibili

Ricerca della migliore sintesi qualitativa delle informazioni

Sintesi quantitativa dei risultati (Metanalisi) se fattibile ad appropriata

Scrittura del paper finale

Principi di una meta-analisi

Una **meta-analisi** può:

•Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;

•Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

When can/should you do a meta-analysis?

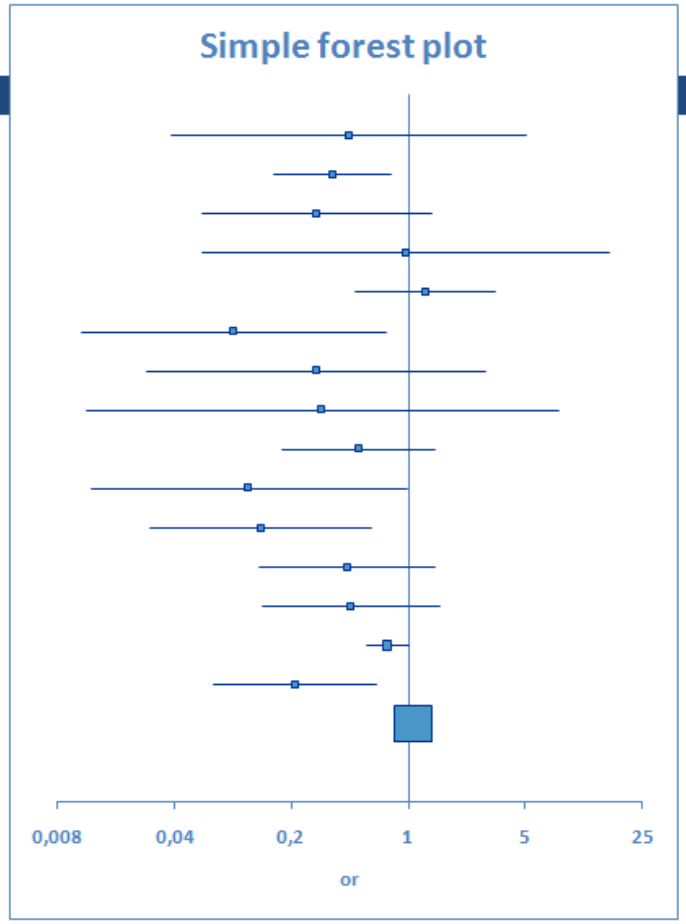
- When more than one study has estimated an effect
- When there are no differences in the study characteristics that are likely to substantially affect outcome
- When the outcome has been measured in similar ways
- When the data are available (take care with interpretation when only some data are available)

E' efficace?

Author(s)		Reference					
Teo et al.		Effects of intravenous magnesium in suspected acute myocardial infarction. BMJ 1991;303:1499–501					
Outcome object	Unit	Intervention (e)		Control (c)			
Mortality	Event	Intravenous magnesium		Control			
Study ID	Ref #	n[e]	n[e](E=1)	n[c]	n[c](E=1)	Study date	-
Morton	1	40	1	36	2	1984	
Rasmussen	2	135	9	135	23	1986	
Smith	3	200	2	200	7	1986	
Abraham	4	48	1	46	1	1987	
Feldstedt	5	150	10	148	8	1988	
Schechter	6	59	1	56	9	1989	
Ceremuzynski	7	25	1	23	3	1989	
Bertschat	8	22	0	21	1	1989	
Singh	9	76	6	75	11	1990	
Pereira	10	27	1	27	7	1990	
Schechter 1	11	89	2	80	12	1991	
Golf	12	23	5	33	13	1991	
Thogersen	13	130	4	122	8	1991	
LIMIT-2	14	1159	90	1157	118	1992	
Schechter 2	15	107	4	108	17	1995	
ISIS-4	16	29011	2216	29039	2103	1995	

Forest plot (meta-graph) analitico

author	year	n[I]	N[I]	n[C]	N[C]	Weight	or	ci-	ci+	p
Morton	1984	1	40	2	36	0,06%	0,44	0,04	5,02	0,51
Rasmussen	1986	9	135	23	135	0,54%	0,35	0,15	0,78	0,01
Smith	1986	2	200	7	200	0,14%	0,28	0,06	1,36	0,11
Abraham	1987	1	48	1	46	0,05%	0,96	0,06	15,77	0,98
Feldstedt	1988	10	150	8	148	0,39%	1,25	0,48	3,26	0,65
Schechter	1989	1	59	9	56	0,08%	0,09	0,01	0,74	0,02
Ceremuzynsk	1989	1	25	3	23	0,07%	0,28	0,03	2,88	0,28
Bertschat	1989	0	22	1	21	0,03%	0,30	0,01	7,88	0,47
Singh	1990	6	76	11	75	0,32%	0,50	0,17	1,43	0,19
Pereira	1990	1	27	7	27	0,08%	0,11	0,01	0,97	0,05
Schechter 1	1991	2	89	12	80	0,15%	0,13	0,03	0,60	0,01
Golf	1991	5	23	13	33	0,24%	0,43	0,13	1,44	0,17
Thogersen	1991	4	130	8	122	0,24%	0,45	0,13	1,54	0,21
LIMIT-2	1992	90	1159	118	1157	4,33%	0,74	0,56	0,99	0,04
Schechter 2	1995	4	107	17	108	0,28%	0,21	0,07	0,64	0,01
ISIS-4	1995	2216	29011	2103	29039	92,99%	1,06	1,00	1,13	0,07



META-ANALYSIS

General

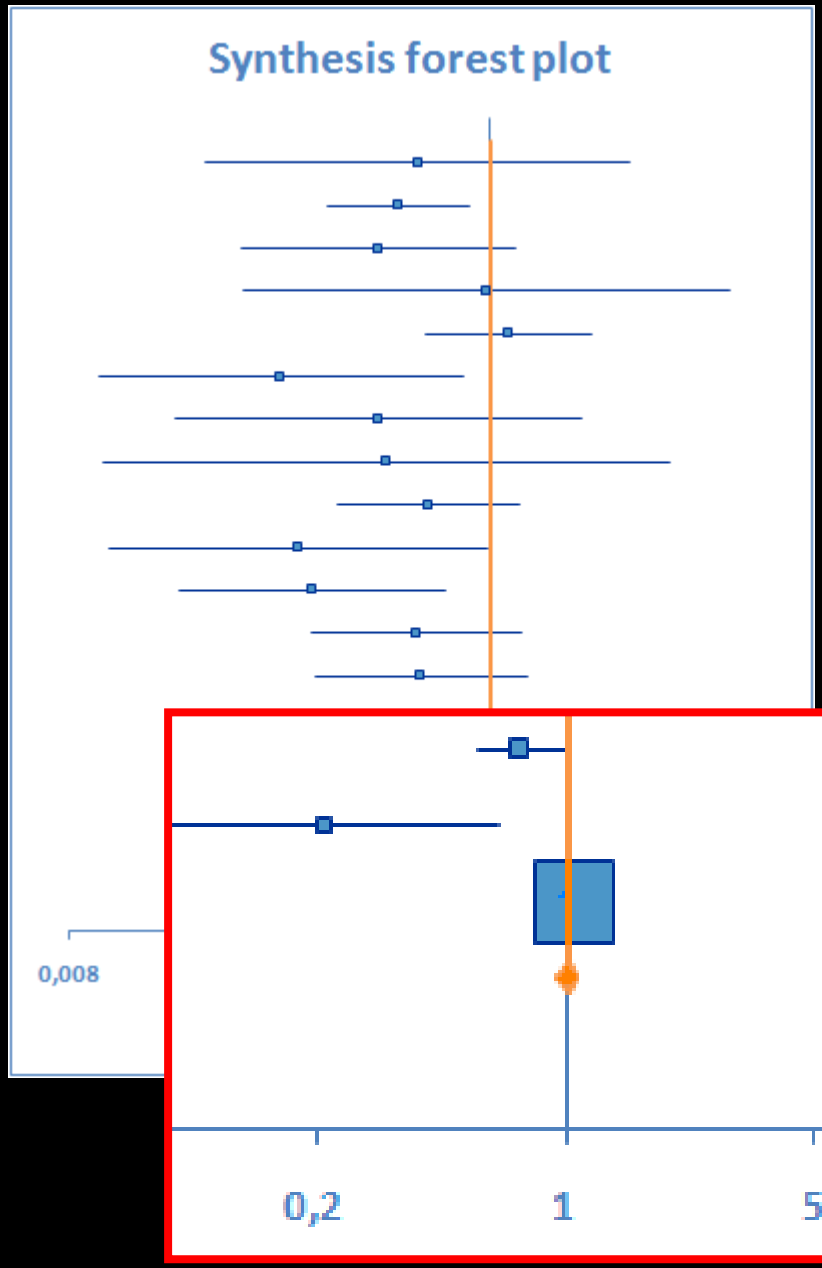
Number of studies	16
Number of participants	62607 (62607)

OR (MH) - Fixed effect model

Meta-analysis outcome	1,0063
95% CI lower limit	0,9482
95% CI upper limit	1,068
z	0,2073
p-value (two-tailed)	0,8358

Heterogeneity

Q	47,1363
p-value (two-tailed)	< 0,0001
I^2	68,18%
95% CI lower limit	46,53%
95% CI upper limit	81,06%



Could we just add the data from all the trials together?

- One approach to combining trials would be to add all the treatment groups together, add all the control groups together, and compare the totals
- This is wrong for several reasons, and it can give the wrong answer

MetaView 3.1 - [Death at end of follow up period (Corticosteroids for acute traumatic brain injury)]

File Display Sort Statistic Window Next Outcome Prev Outcome

Comparison: **Any steroid administered in any dose against no steroid**
Outcome: **Death at end of follow up period**

Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Alexander 1972	16 / 55	22 / 55		6.6	0.73 [0.43,1.23]
Braakman 1983	44 / 81	47 / 80		14.2	0.92 [0.70,1.21]
Chacon 1987	1 / 5	0 / 5		0.2	3.00 [0.15,59.89]
Cooper 1979	26 / 49	13 / 27		5.0	1.10 [0.69,1.77]
Dearden 1986	33 / 68	21 / 62		6.6	1.43 [0.94,2.19]
Faupel 1976	16 / 67	16 / 28		6.8	0.42 [0.24,0.71]
Gaab 1994	19 / 133	21 / 136		6.2	0.93 [0.52,1.64]
Giannotta 1984	34 / 72	7 / 16		3.4	1.08 [0.59,1.98]
Grumme 1995	38 / 175	49 / 195		13.9	0.86 [0.60,1.25]
Hernesniemi 1979	35 / 81	36 / 83		10.7	1.00 [0.70,1.41]
Pitts 1980	114 / 201	38 / 74		16.7	1.10 [0.86,1.42]
Ransohoff 1972	9 / 17	13 / 18		3.8	0.73 [0.43,1.25]
Saul 1981	8 / 50	9 / 50		2.7	0.89 [0.37,2.12]
Stubbs 1989	13 / 98	5 / 54		1.9	1.43 [0.54,3.80]
Zagara 1987	4 / 12	4 / 12		1.2	1.00 [0.32,3.10]
xZarate 1995	0 / 30	0 / 30		0.0	Not Estimable
Total (95%CI)	410 / 1194	301 / 925		100.0	0.96 [0.85,1.08]

Chi-square 18.11 (df=14) Z=0.68

.1 .2 1 5 10

Steroid better Steroid worse

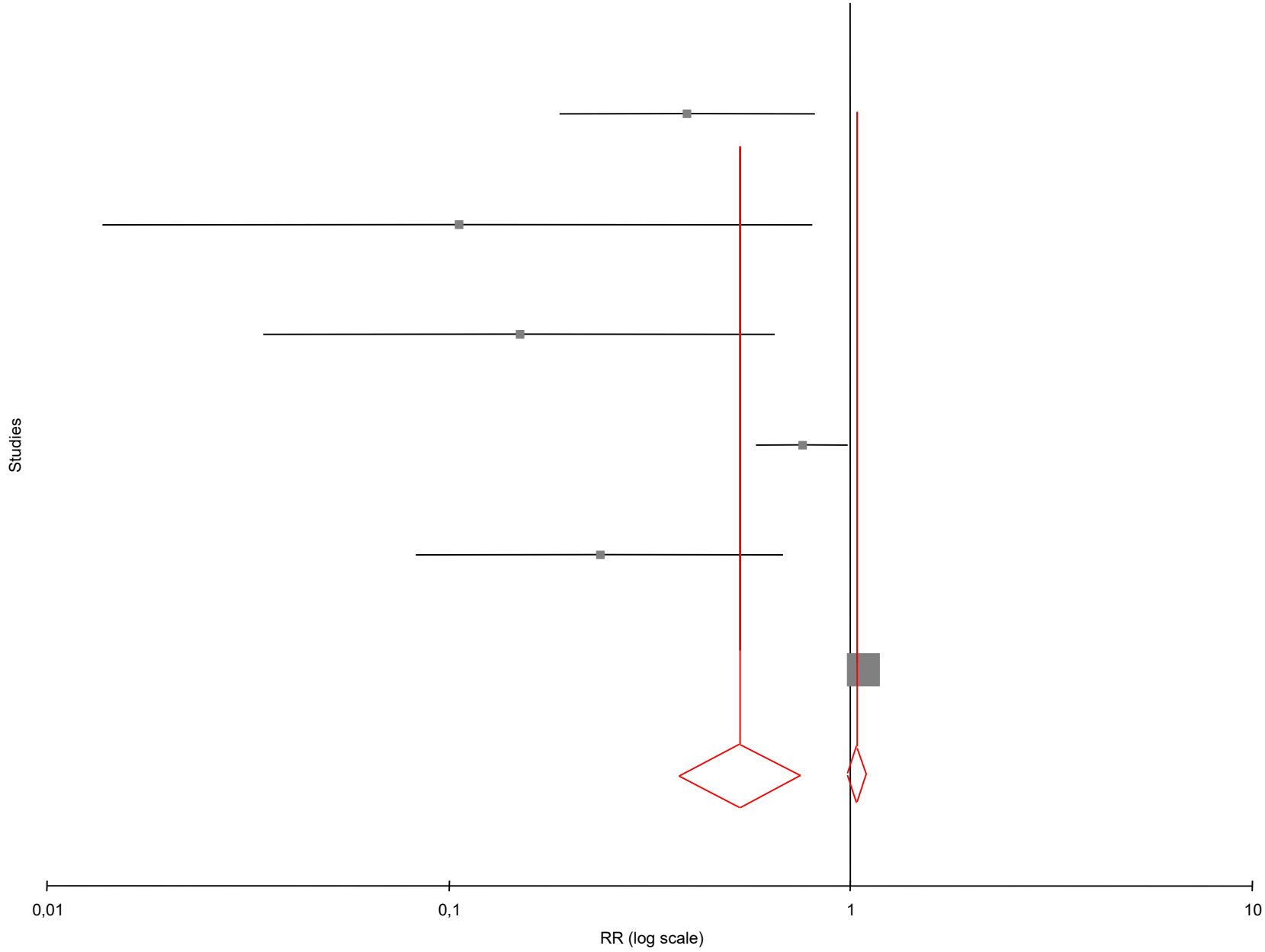
If we add up the columns we get 34.3% vs 32.5% , a RR of 1.06, a higher chance of death in the steroids group

From a meta-analysis, we get RR=0.96 , a lower chance of death in the steroids group

L'intervento funziona?

Valore neutro ("nullo")	Esito sfavorevole (es. morte)	Esito favorevole (es. smettere di fumare)	Effetto avverso (es. vomito)
L'intervento non ha effetto	L'intervento funziona	L'intervento funziona	L'intervento funziona
RD = 0	RD < 0	RD > 0	RD < 0
RR = 1	RR < 1	RR > 1	RR < 1
OR = 1	OR < 1	OR > 1	OR < 1

RD: Risk Difference **RR: Relative Risk** **OR: Odds Ratio**


Studies
0,01
0,1
1
10
RR (log scale)

Come si decide quanto pesa uno studio?

- Il peso è proporzionale al contributo informativo dello studio alla capacità di effettuare una stima
- Studi di ampie dimensione e/o con molti eventi potrebbero contribuire di più
- In gergo sono quelli più precisi

- Ma tutto è relativo … tutti gli studi stanno misurando lo stesso effetto?

Mettere insieme … studi diversi… che testano quesiti diversi… considerando popolazione diverse… usando interventi lievemente diversi…
ma partendo da protocolli profondamente diversi… e dando risultati …

Eterogeneità

What is heterogeneity?

- Heterogeneity is variation between the studies' results

What is heterogeneity?

Differences between studies with respect to:

Clinical heterogeneity (clinical diversity)

- *Participants*
  - e.g. conditions under investigation, eligibility criteria for trials, geographical variation
- *Interventions*
  - e.g. intensity / dose / duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/none/standard care)
- *Outcomes*
  - e.g. definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

What is heterogeneity?

Differences between studies with respect to:

Methodological heterogeneity (methodological diversity)

- *Design*
  - e.g. randomised vs non-randomised, crossover vs parallel group vs cluster randomised, pre-test and long follow up
- *Conduct*
  - e.g. allocation concealment, blinding etc, approach to analysis, imputation methods for missing data

What is heterogeneity?

What do we do if there ***is*** statistical heterogeneity?

- Variation in the *true effects* underlying the studies
- ...which may manifest itself in more observed variation than expected by chance alone

- May be due to clinical diversity (different treatment effects) or methodological diversity (different biases)

Come si misura questa eterogeneità?

- Confidence interval overlapping Eyeball test

- Cochran's Q: to assess whether observed differences in results are compatible with change alone

χ^2 distribution; low power (small number of studies, small sample size)

p=<0.10 (heterogeneity)

- I^2 quantifing heterogeneity (describes the percentage of variation across studies that is due to heterogeneity rather than chance)

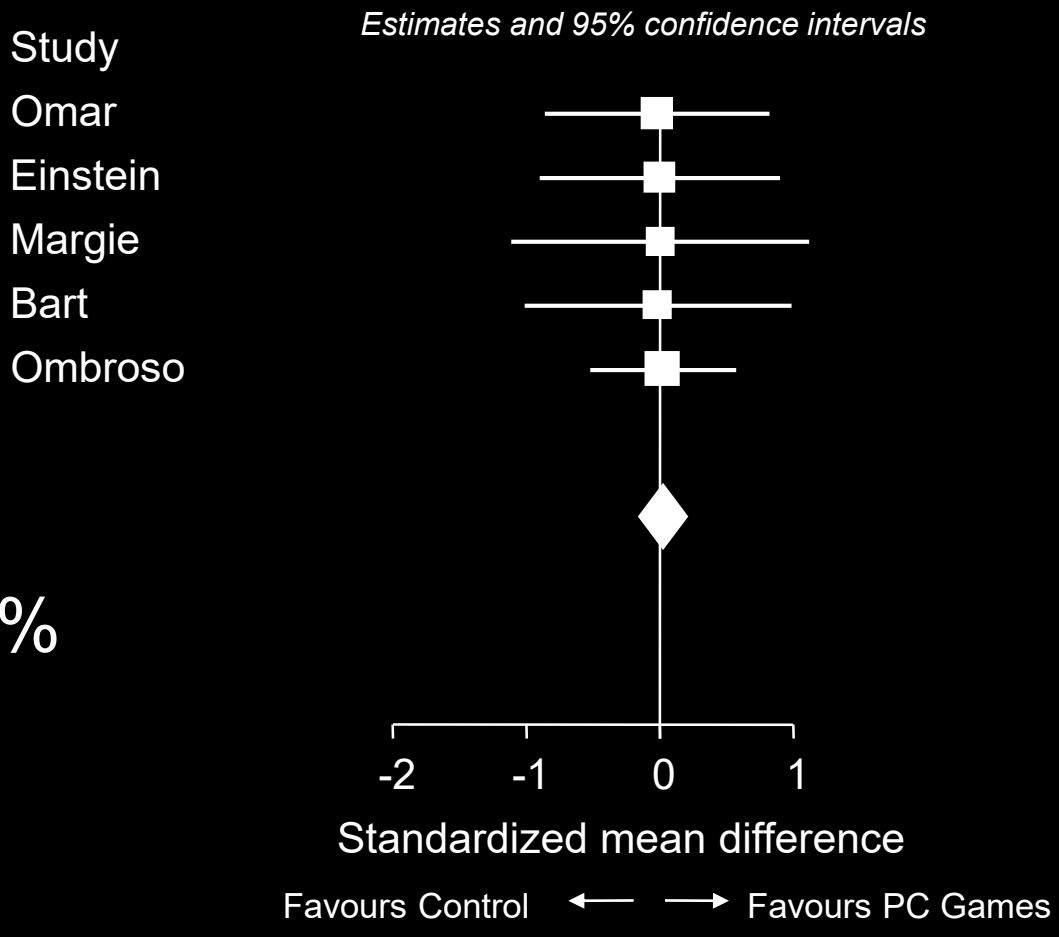
0-40% might not be important
30-60% may represent moderate heterogeneity
50-90% may represent substantial heterogeneity
75-100% considerable heterogeneity

- Tau….

How to deal with heterogeneity

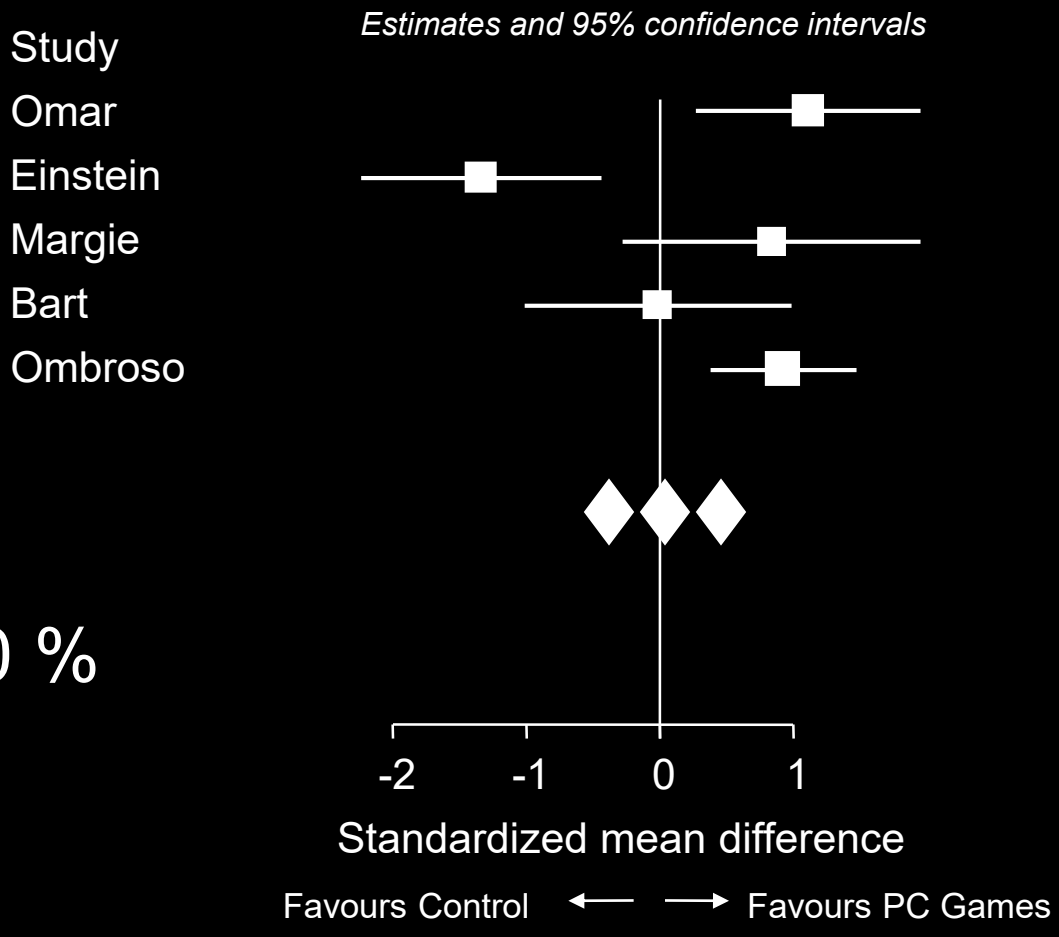
1. Do not pool at all
2. Ignore heterogeneity: use ***fixed effect model***
3. Allow for heterogeneity: use ***random effects model***
4. Explore heterogeneity: subgroups analysis or meta-regression (tricky)

Example: PC Games for intelligence



$I^2 = 0\ \%$

Example: PC Games for intelligence



I^2= 80 %

Fixed and random effects

Fixed effect

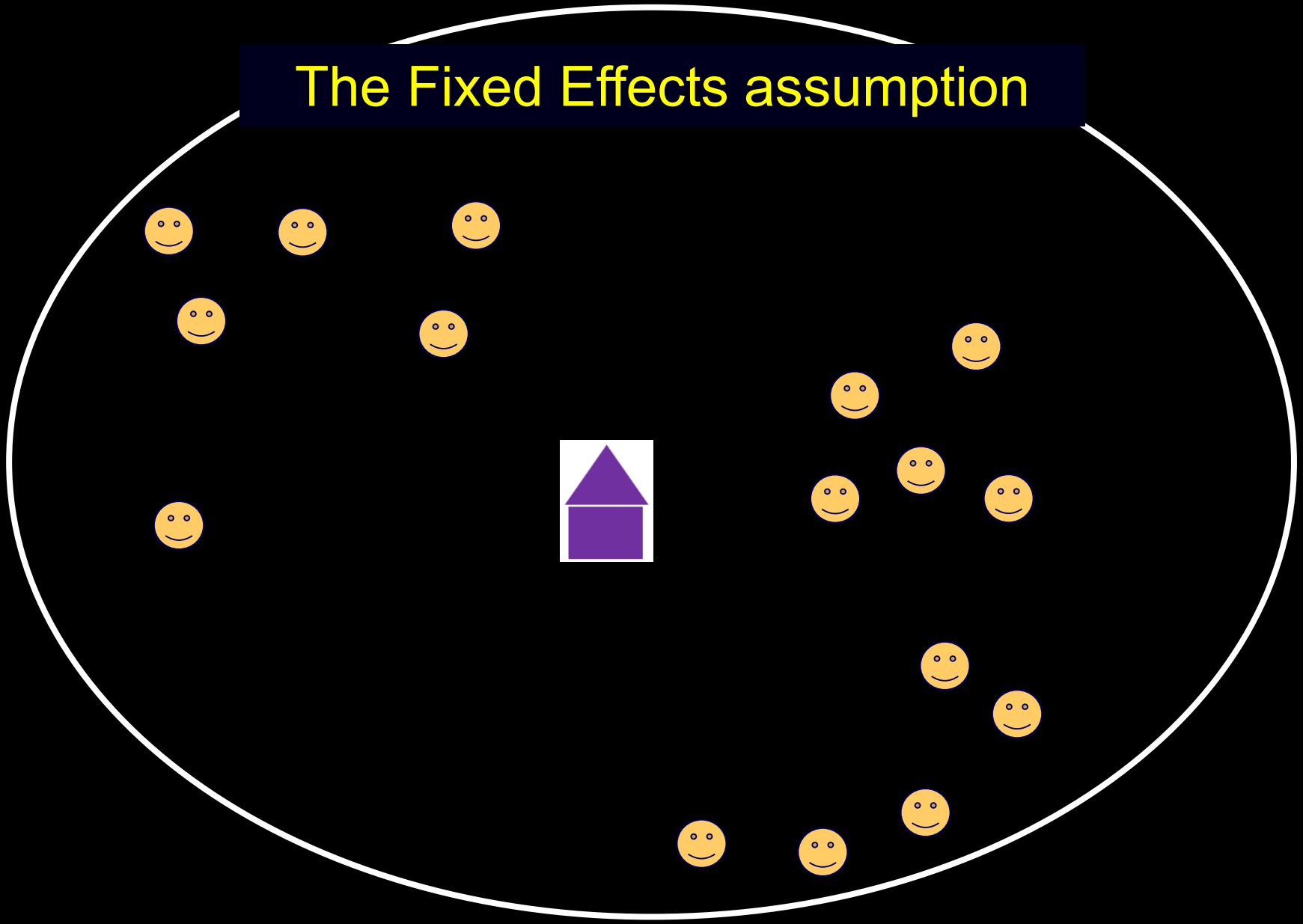
Philosophy behind ***fixed effect model***

- there is one real value for the treatment effect
- all trials estimate this one value

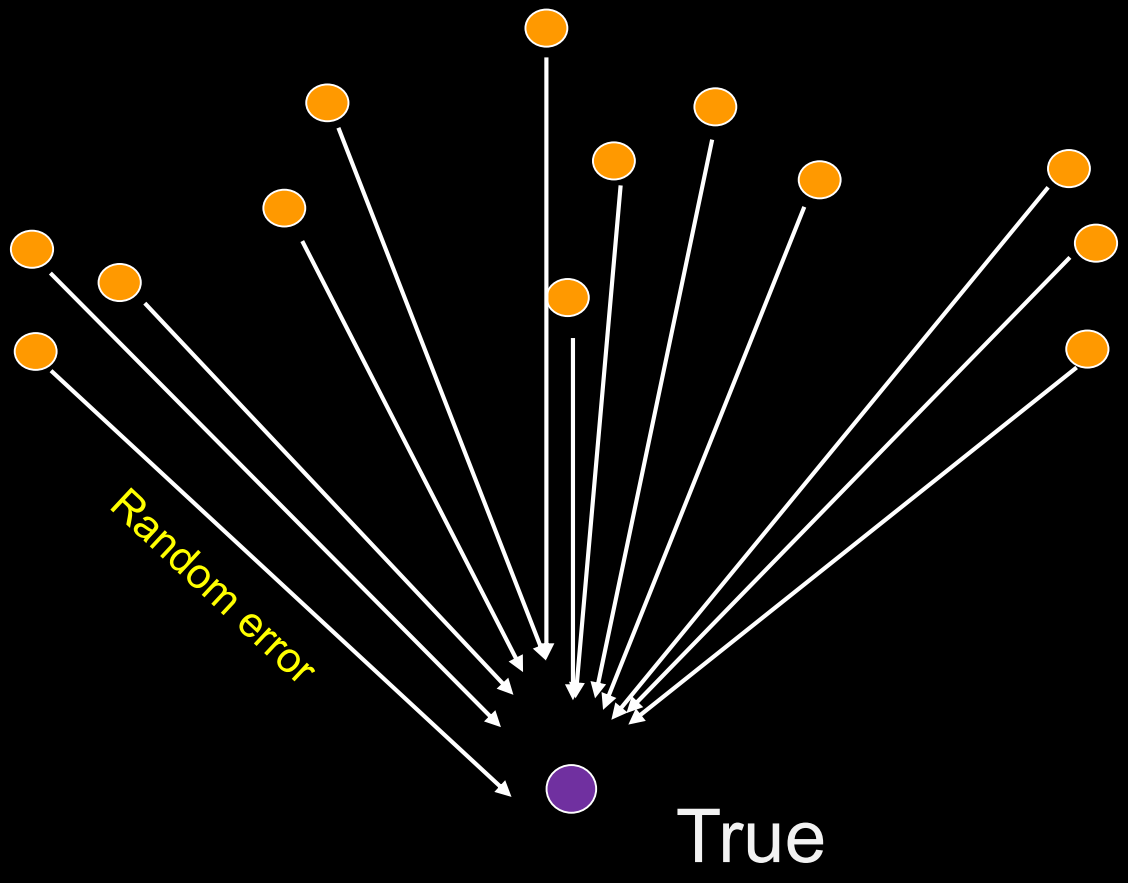
Problems with ignoring heterogeneity:

- confidence intervals too narrow

The Fixed Effects assumption



The Fixed Effects assumption

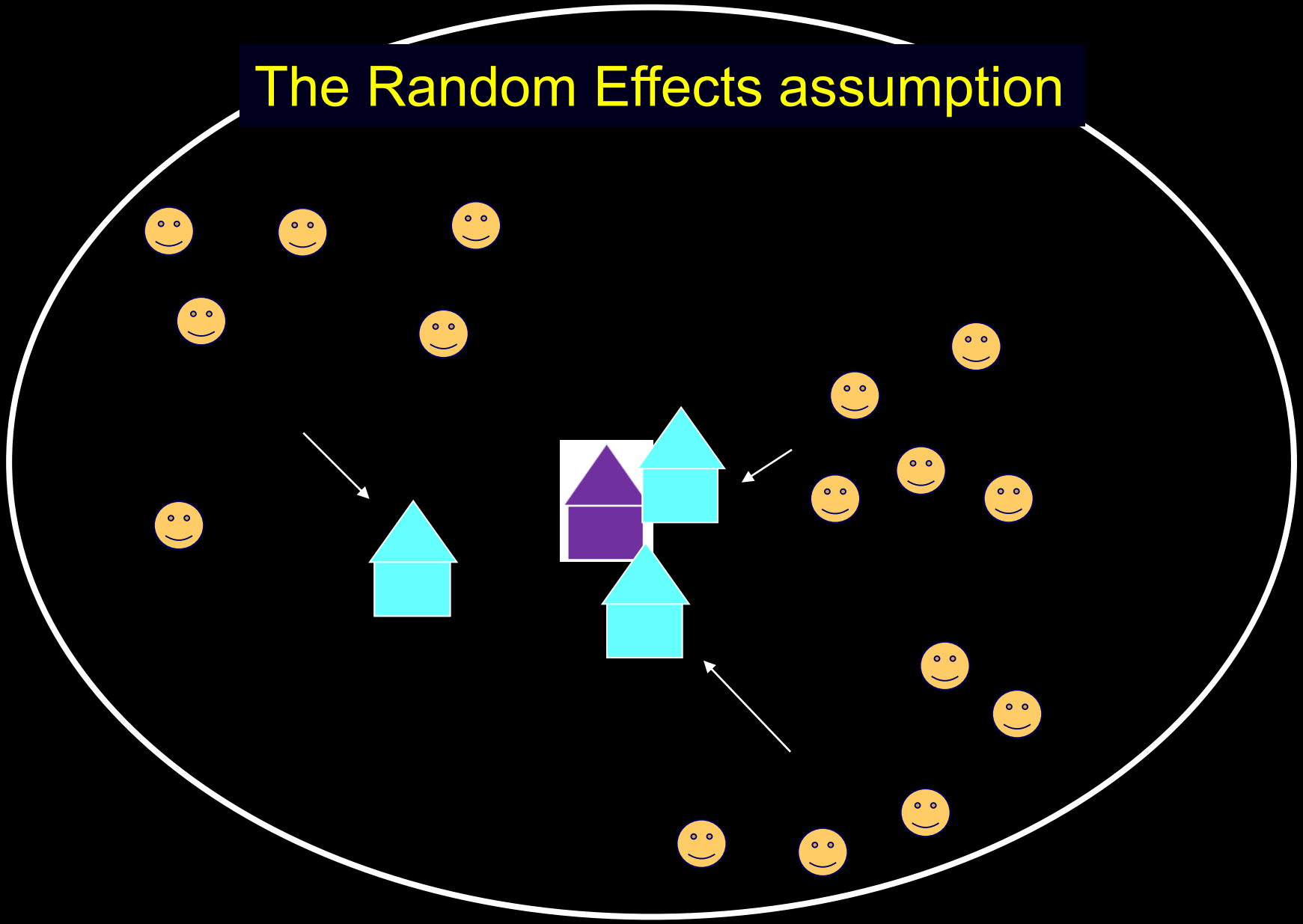


Random effects

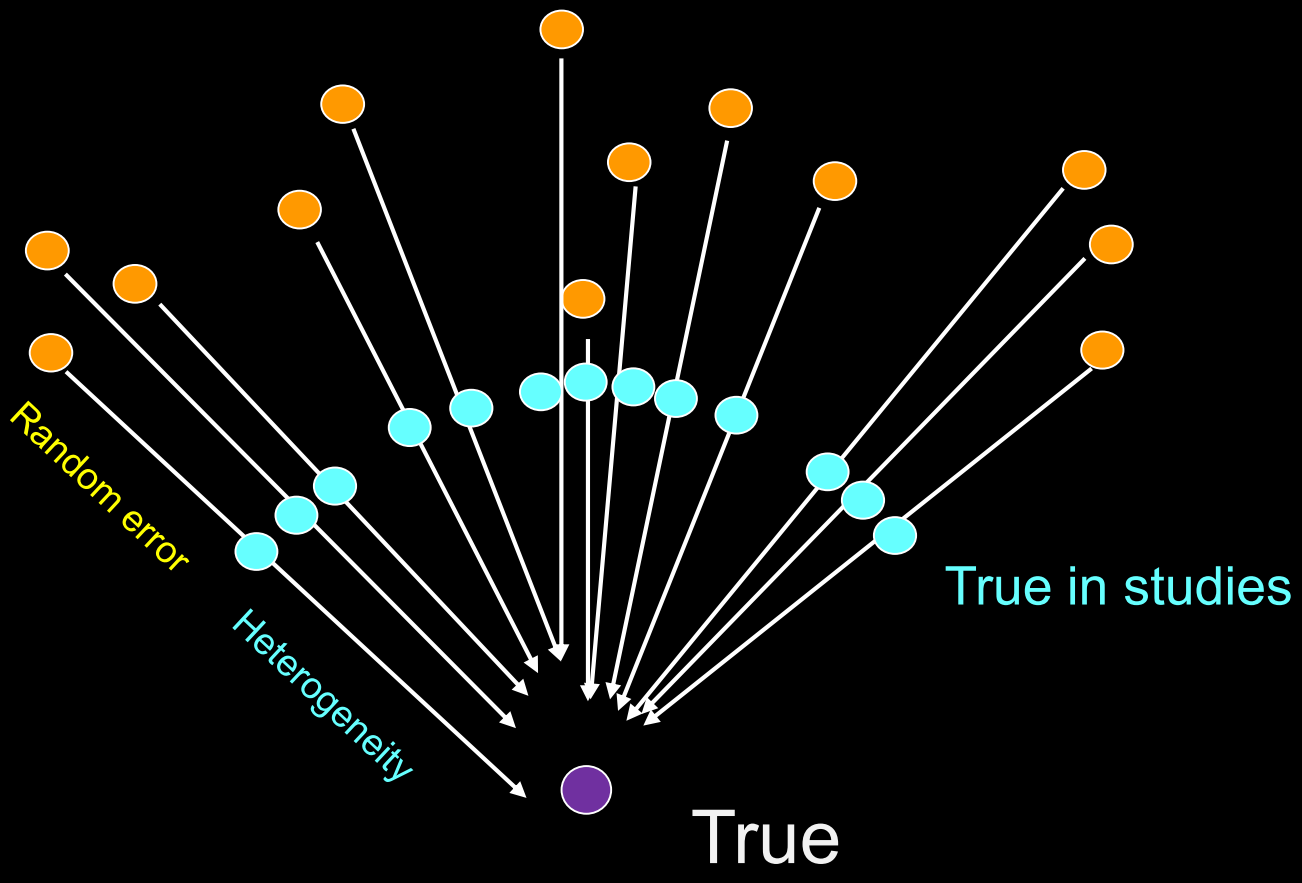
Philosophy behind ***random effects model***

- there are many possible real values for the treatment effect (depending on dose, duration, etc etc).
- each trial estimates its own real value

The Random Effects assumption

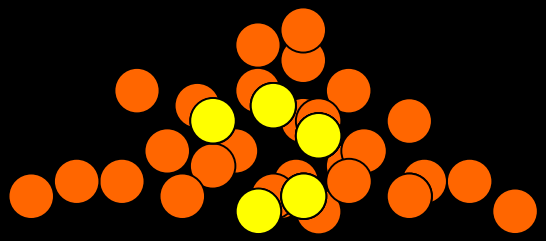


The Random Effects assumption

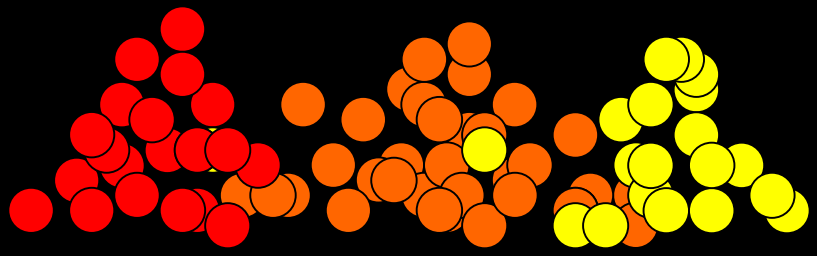


Quale modello?

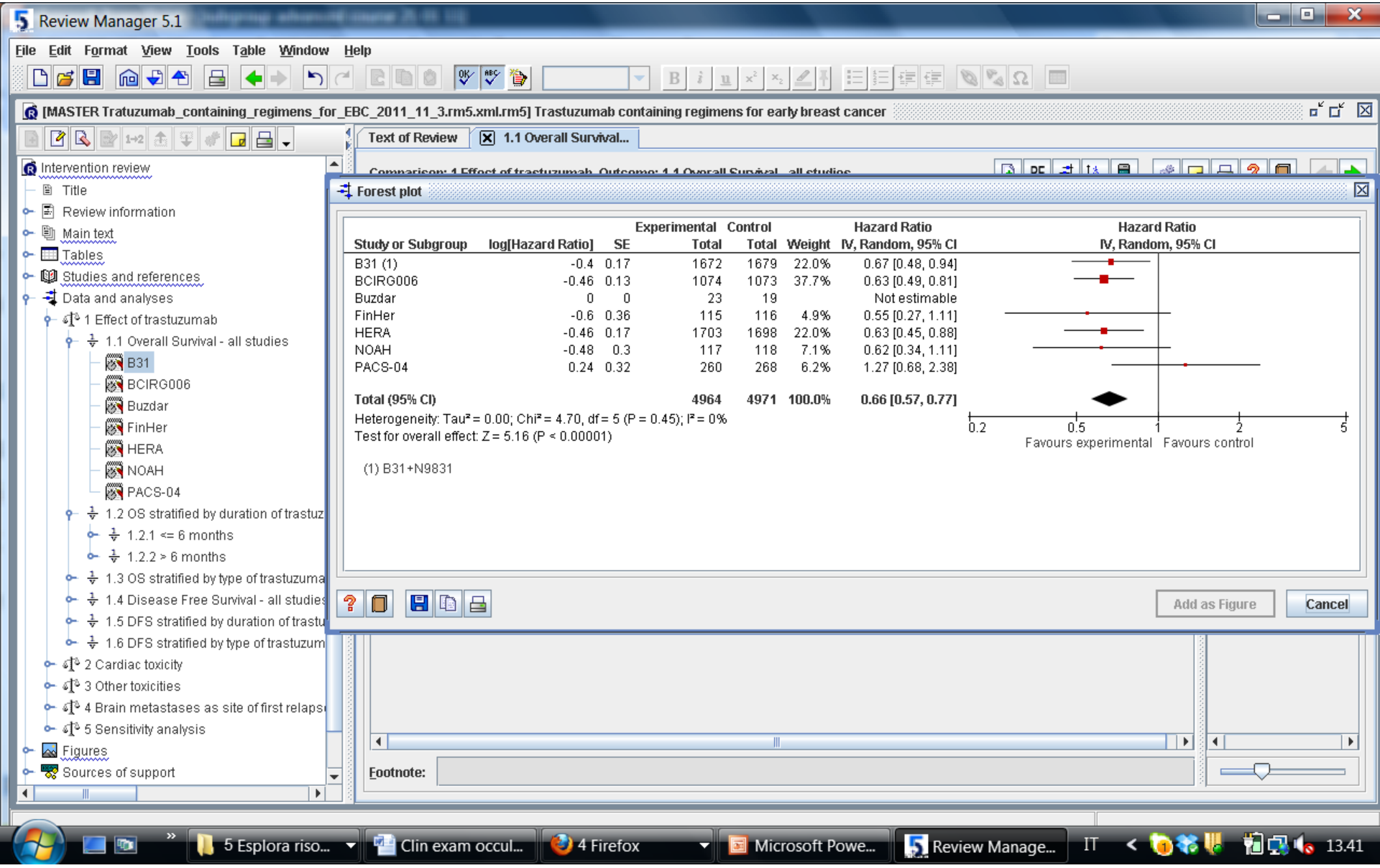
Fixed effect



Random effect



SOTTOGRUPPI


Review Manager 5.1
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[MASTER Tratuzumab_containing_regimens_for_EBC_2011_11_3.rm5.xml.rm5] Trastuzumab containing regimens for early breast cancer
Text of Review
1.1 Overall Survival...
Intervention review
Title
Review information
Main text
Tables
Studies and references
Data and analyses
1 Effect of trastuzumab
1.1 Overall Survival - all studies
B31
BCIRG006
Buzdar
FinHer
HERA
NOAH
PACS-04
1.2 OS stratified by duration of trastuz
1.2.1 <= 6 months
1.2.2 > 6 months
1.3 OS stratified by type of trastuzuma
1.4 Disease Free Survival - all studies
1.5 DFS stratified by duration of trastu
1.6 DFS stratified by type of trastuzum
2 Cardiac toxicity
3 Other toxicities
4 Brain metastases as site of first relaps
5 Sensitivity analysis
Figures
Sources of support
Forest plot
Experimental
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Random, 95% CI
IV, Random, 95% CI
B31 (1) -0.4 0.17 1672 1679 22.0% 0.67 [0.48, 0.94]
BCIRG006 -0.46 0.13 1074 1073 37.7% 0.63 [0.49, 0.81]
Buzdar 0 0 23 19 Not estimable
FinHer -0.6 0.36 115 116 4.9% 0.55 [0.27, 1.11]
HERA -0.46 0.17 1703 1698 22.0% 0.63 [0.45, 0.88]
NOAH -0.48 0.3 117 118 7.1% 0.62 [0.34, 1.11]
PACS-04 0.24 0.32 260 268 6.2% 1.27 [0.68, 2.38]
Total (95% CI) 4964 4971 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
(1) B31+N9831
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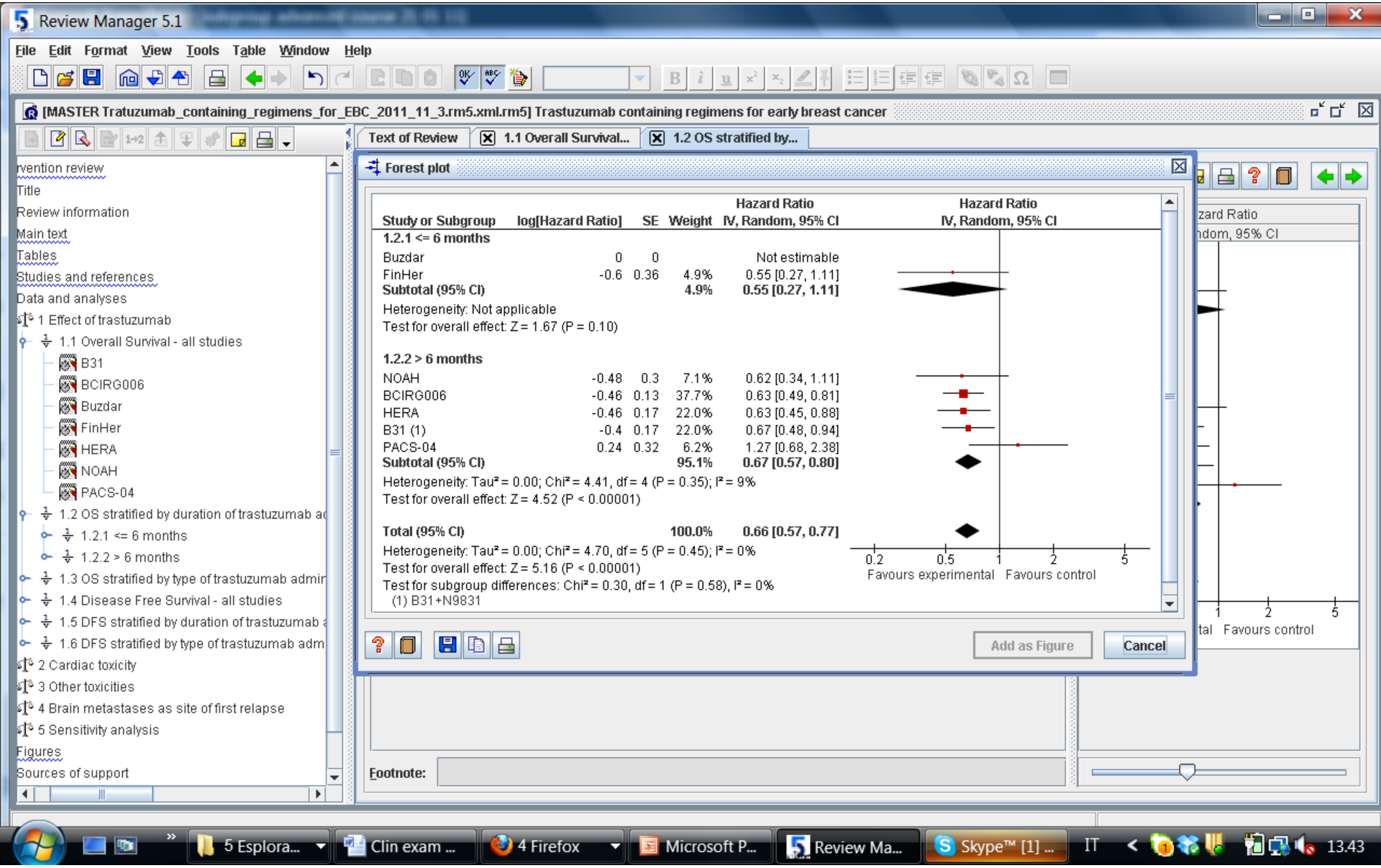
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1.2 OS stratified by...
Forest plot
Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
Hazard Ratio IV, Random, 95% CI
1.2.1 <= 6 months
Buzdar 0 0 Not estimable
FinHer -0.6 0.36 4.9% 0.55 [0.27, 1.11]
Subtotal (95% CI) 4.9% 0.55 [0.27, 1.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.10)
1.2.2 > 6 months
NOAH -0.48 0.3 7.1% 0.62 [0.34, 1.11]
BCIRG006 -0.46 0.13 37.7% 0.63 [0.49, 0.81]
HERA -0.46 0.17 22.0% 0.63 [0.45, 0.88]
B31 (1) -0.4 0.17 22.0% 0.67 [0.48, 0.94]
PACS-04 0.24 0.32 6.2% 1.27 [0.68, 2.38]
Subtotal (95% CI) 95.1% 0.67 [0.57, 0.80]
Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 4.52 (P < 0.00001)
Total (95% CI) 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%
(1) B31+N9831
0.2 0.5 1 2 5
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Add as Figure
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Footnote:
Review Manager 5.1
File Edit Format View Tools Table Window Help
[MASTER Tratuzumab_containing_regimens_for_EBC_2011_11_3.rm5.xml.rm5] Trastuzumab containing regimens for early breast cancer
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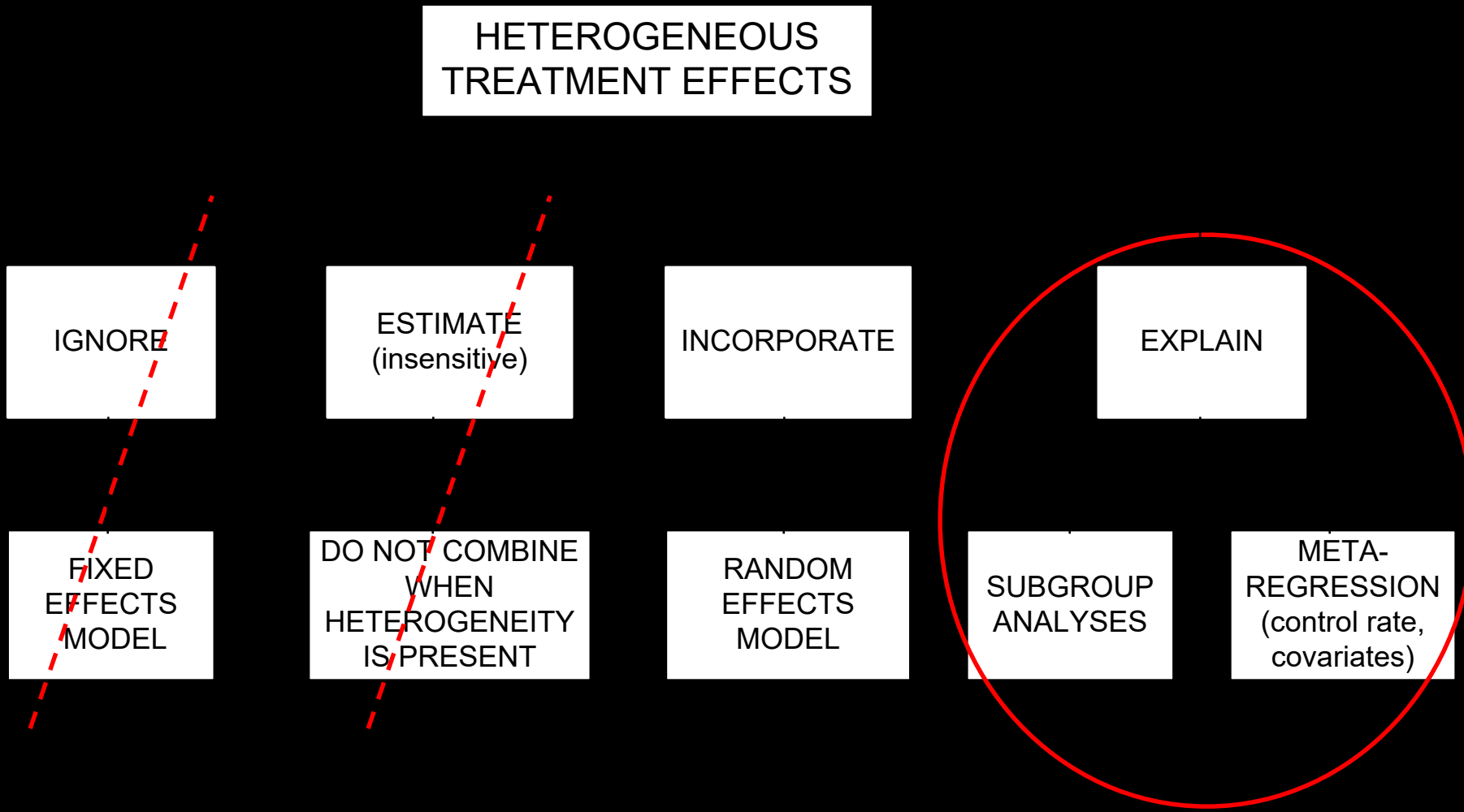
What are subgroup / sensitivity analyses?

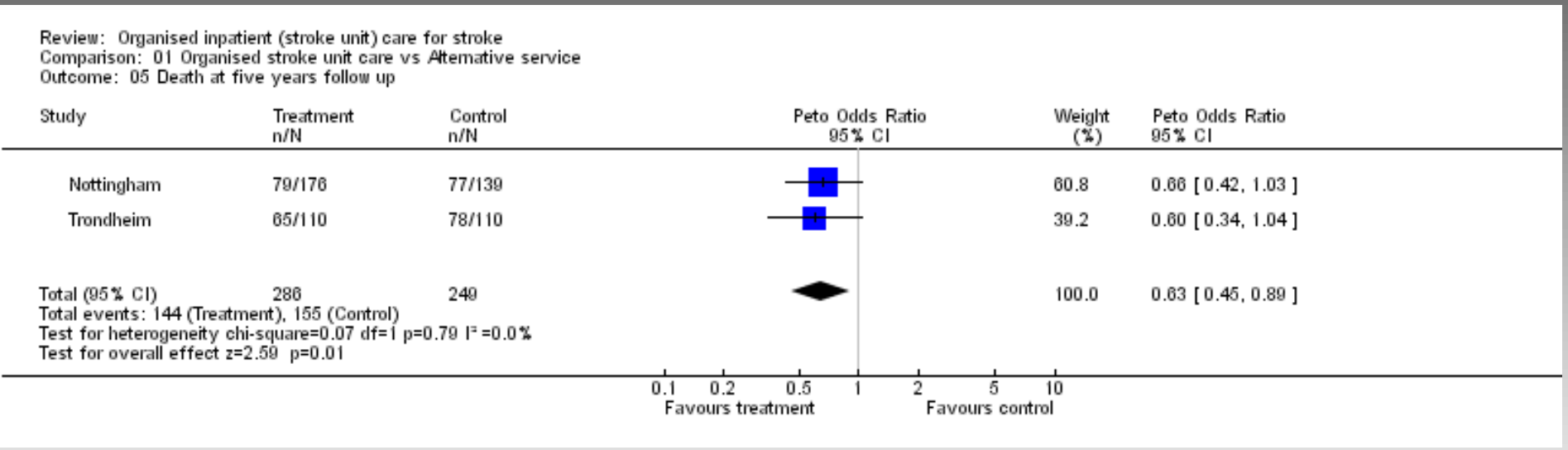
- An analysis of treatment effects within subgroups of patients enrolled on a clinical trial who might be expected to respond to treatment differently
- "Should all patients be given XYZ? Can/should treatment be limited to a selected group?"
- Methods for investigating possible causes of heterogeneity in a meta-analysis

•*Only one thing is worse than doing subgroup analyses---believing the results* R. Peto


HETEROGENEOUS TREATMENT EFFECTS
IGNORE
ESTIMATE (insensitive)
INCORPORATE
EXPLAIN
FIXED EFFECTS MODEL
DO NOT COMBINE WHEN HETEROGENEITY IS PRESENT
RANDOM EFFECTS MODEL
SUBGROUP ANALYSES
META-REGRESSION (control rate, covariates)

I trucchi del mestiere

Esempio di Metaview



Inconsistency (heterogeneity) between studies results

- All statistical approaches have limitations, and their results should be seen in the context of a subjective examination of the variability in point estimates and the overlap in Cis.
- Inconsistency is important only when it reduces confidence in results in relation to a particular decision.
- Non procedere in automatico, ma ragionare avendo in mente il contesto clinico di cui ci si sta occupando

Unexplained heterogeneity

Differenza fra effetto grande e piccolo.

Non importante se anche l'effetto piccolo è clinicamente significativo.

Rilevante se ci sono differenze clinicamente rilevanti (impatto sul paziente) fra effetto piccolo e effetto grande

Problema: dipende

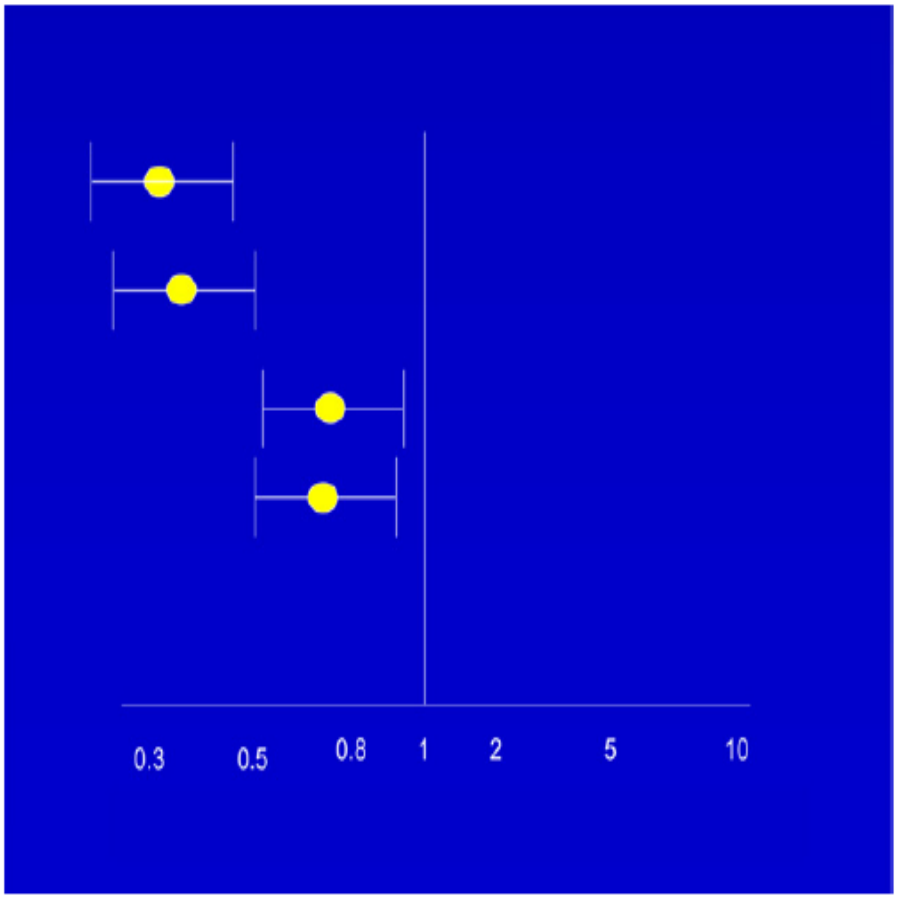


Fig. 2. Substantial heterogeneity, but of questionable importance.

Unexplained heterogeneity

La grandezza della variabilità è la stessa ma in questo caso due studi vanno in una direzione e due in un'altra.

Inconsistency importante

Pooled estimate di non effetto ma con grande eterogeneità

problema: sì

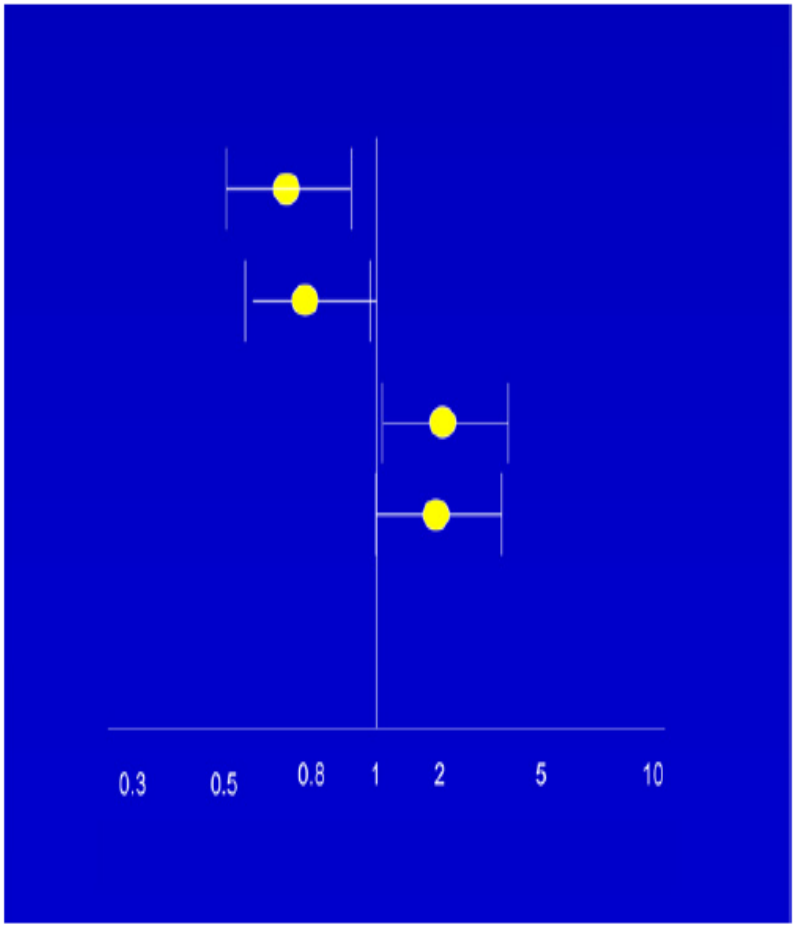


Fig. 3. Substantial heterogeneity, of unequivocal importance.

Unexplained heterogeneity

Pooled estimate di non effetto, come prima, ma in questo caso le differenze fra gli studi sono piccole , tutti concludono per differenze piccole e non significative

problema: no

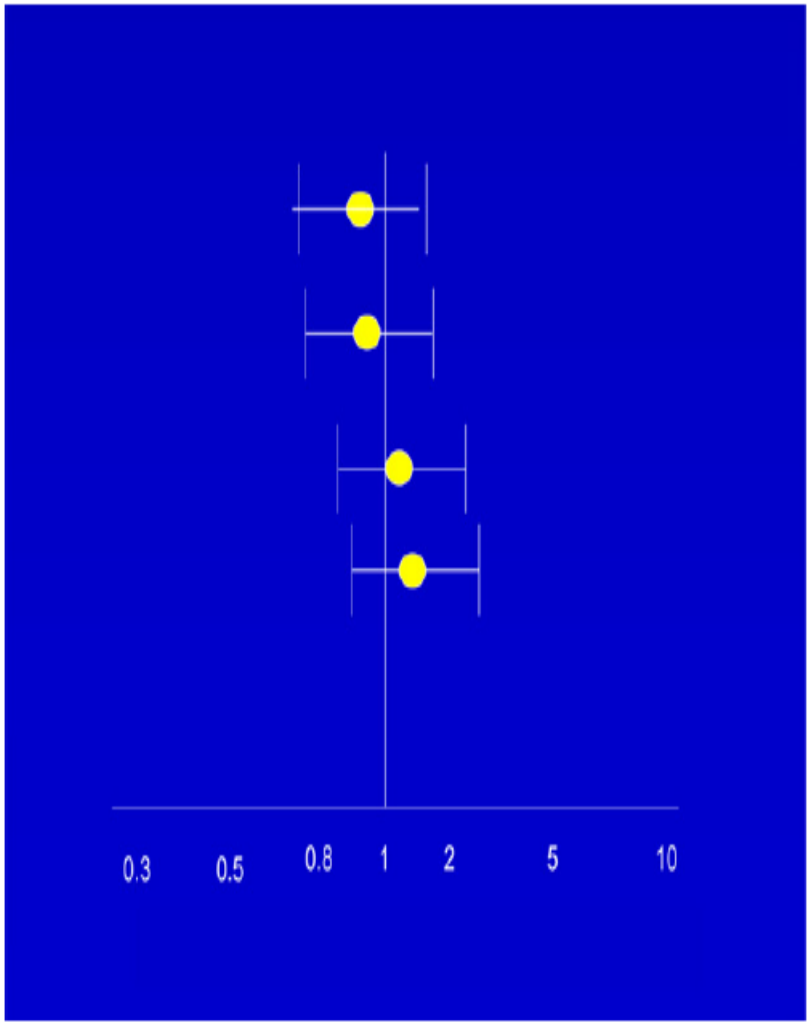


Fig. 1. Differences in direction, but minimal heterogeneity.

Unexplained heterogeneity

Cocaine dependence; outcome: craving

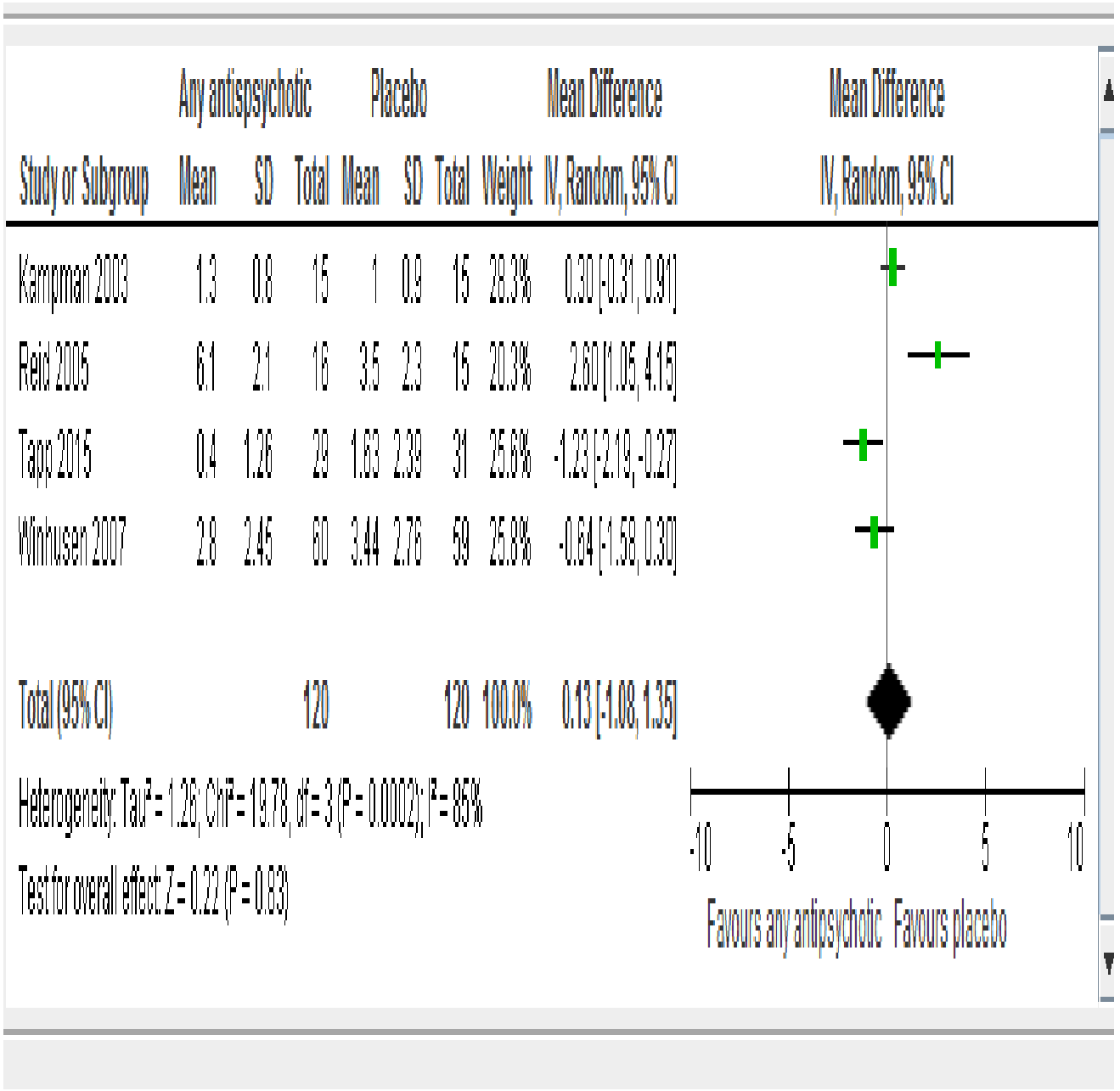
P: 0,0002

I2: 85%

Due studi a favore di trattamento, uno di placebo, uno non differenze.

Non overlapping CI

problema: si



Unexplained heterogeneity

Terapia emorroidi; outcome: failure to improve

P<00001

I2: 65%

tutti gli studi tranne 2 a favore del trattamento

problema: no