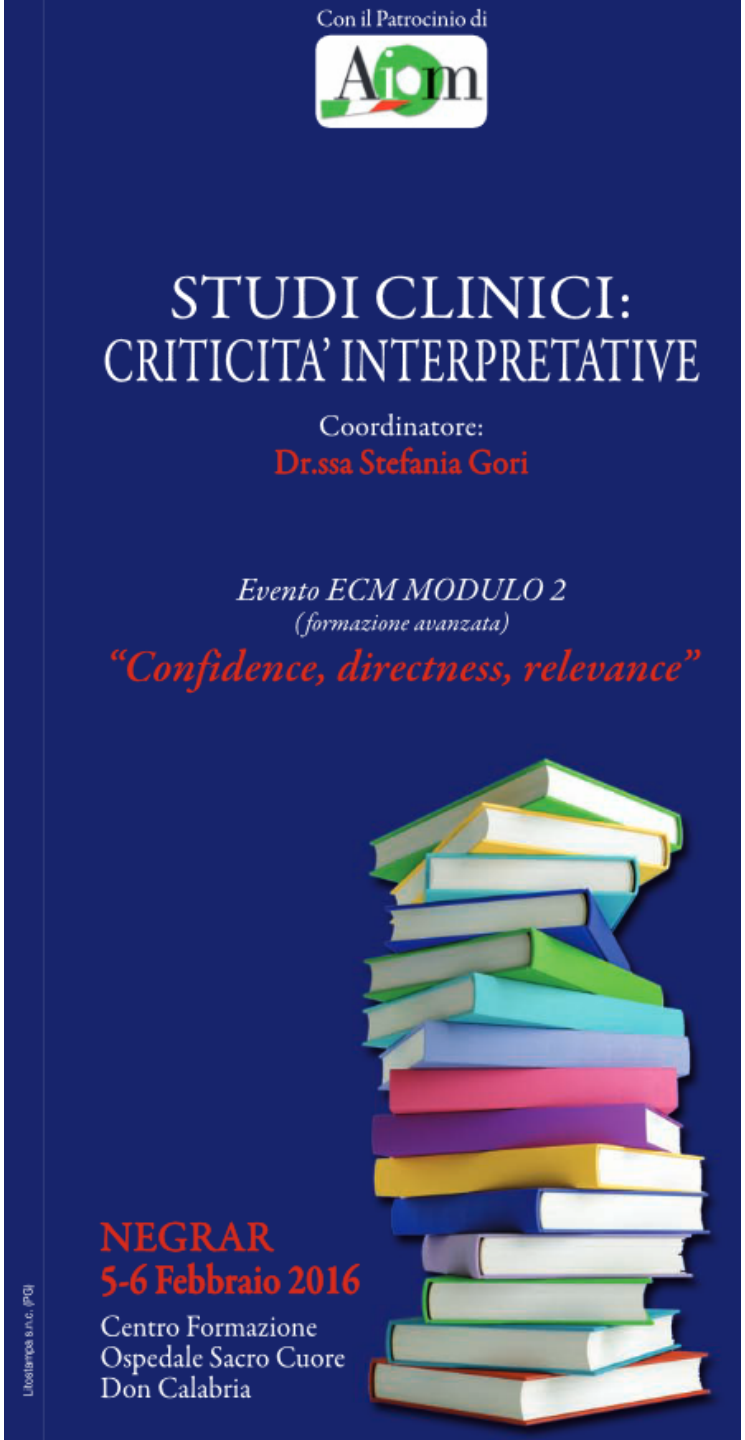


Eterogeneità delle evidenze

Ivan Moschetti

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)

Basic assessments of inconsistency

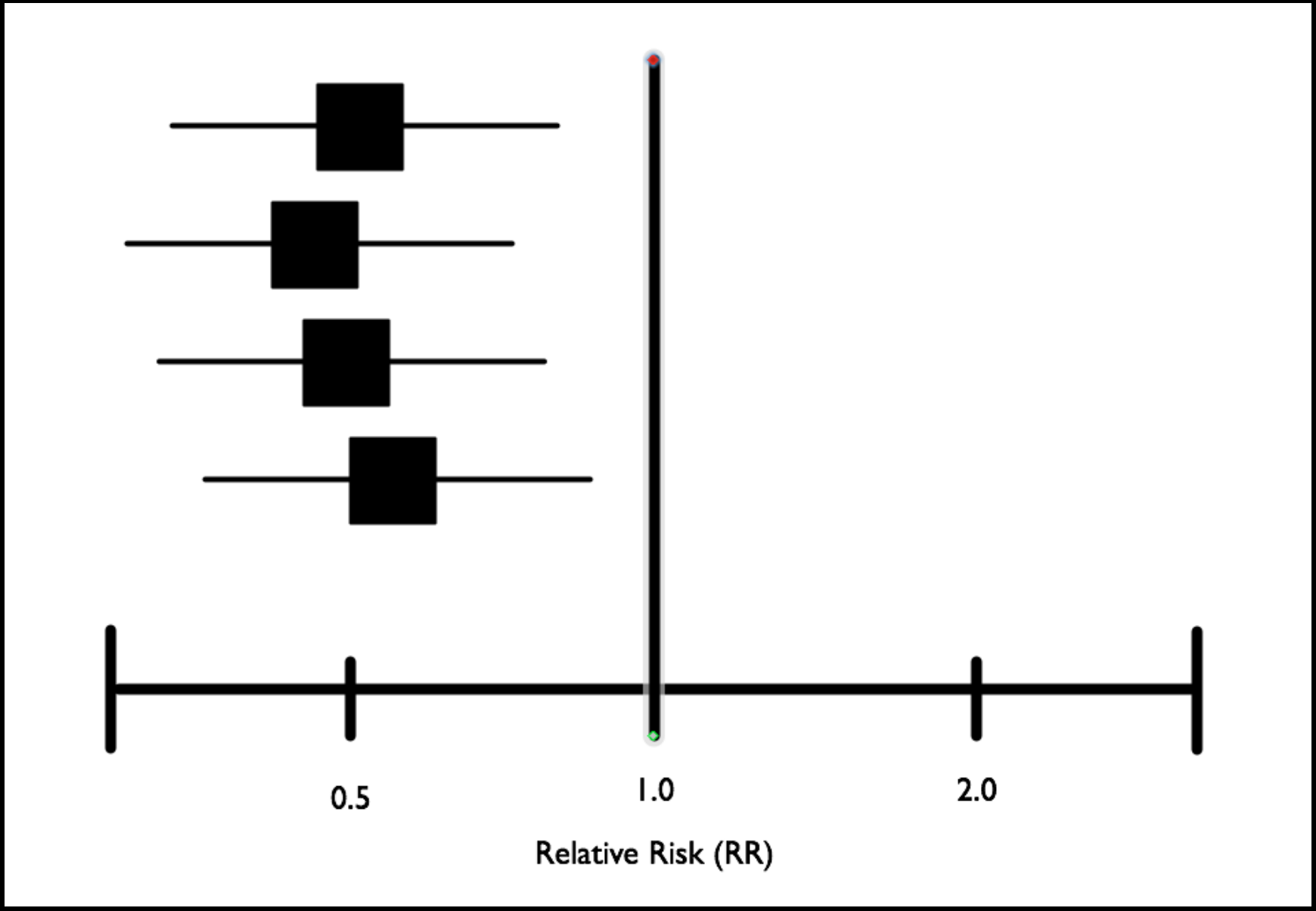
- Point estimates vary widely

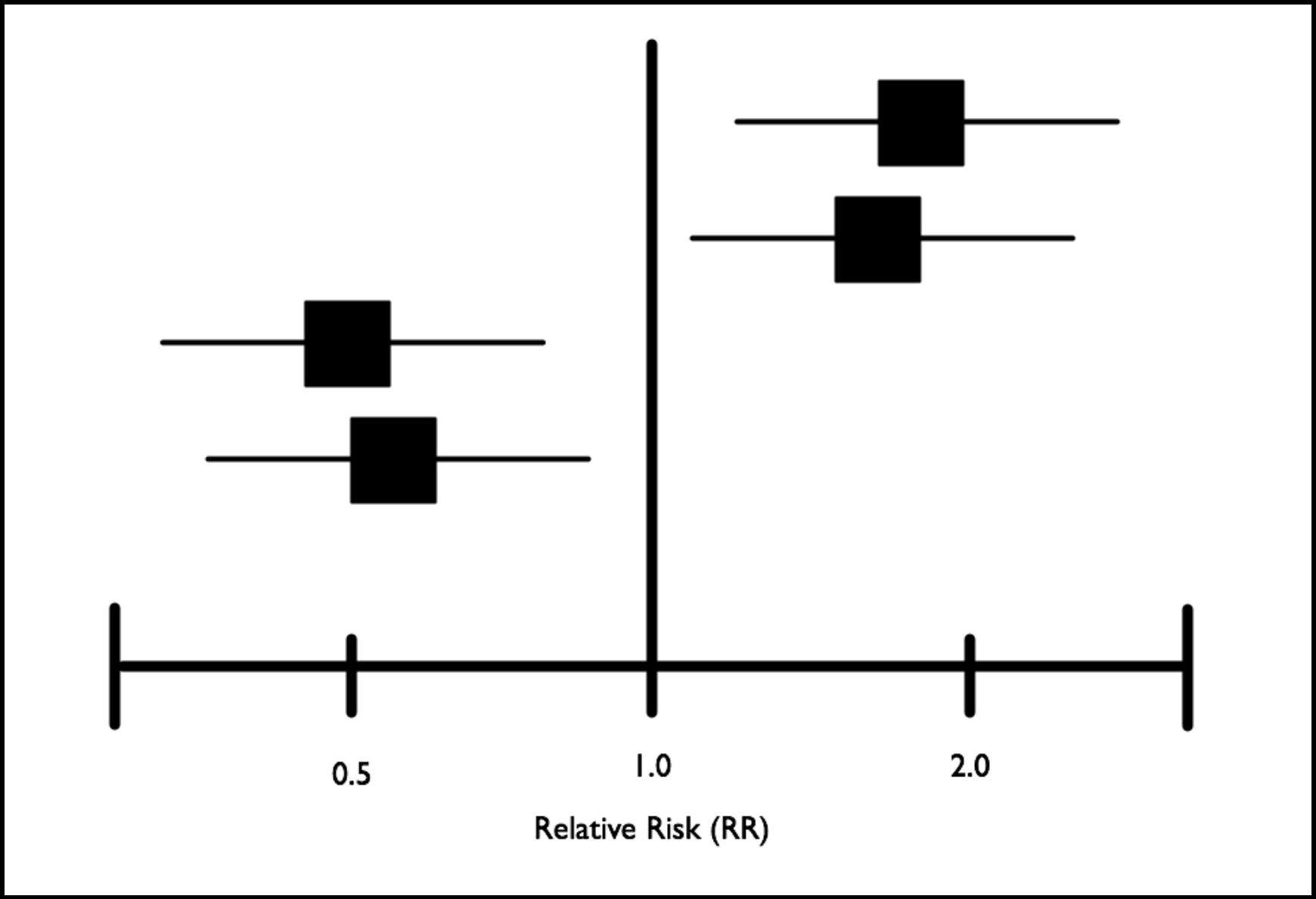
- Little or no CI overlap

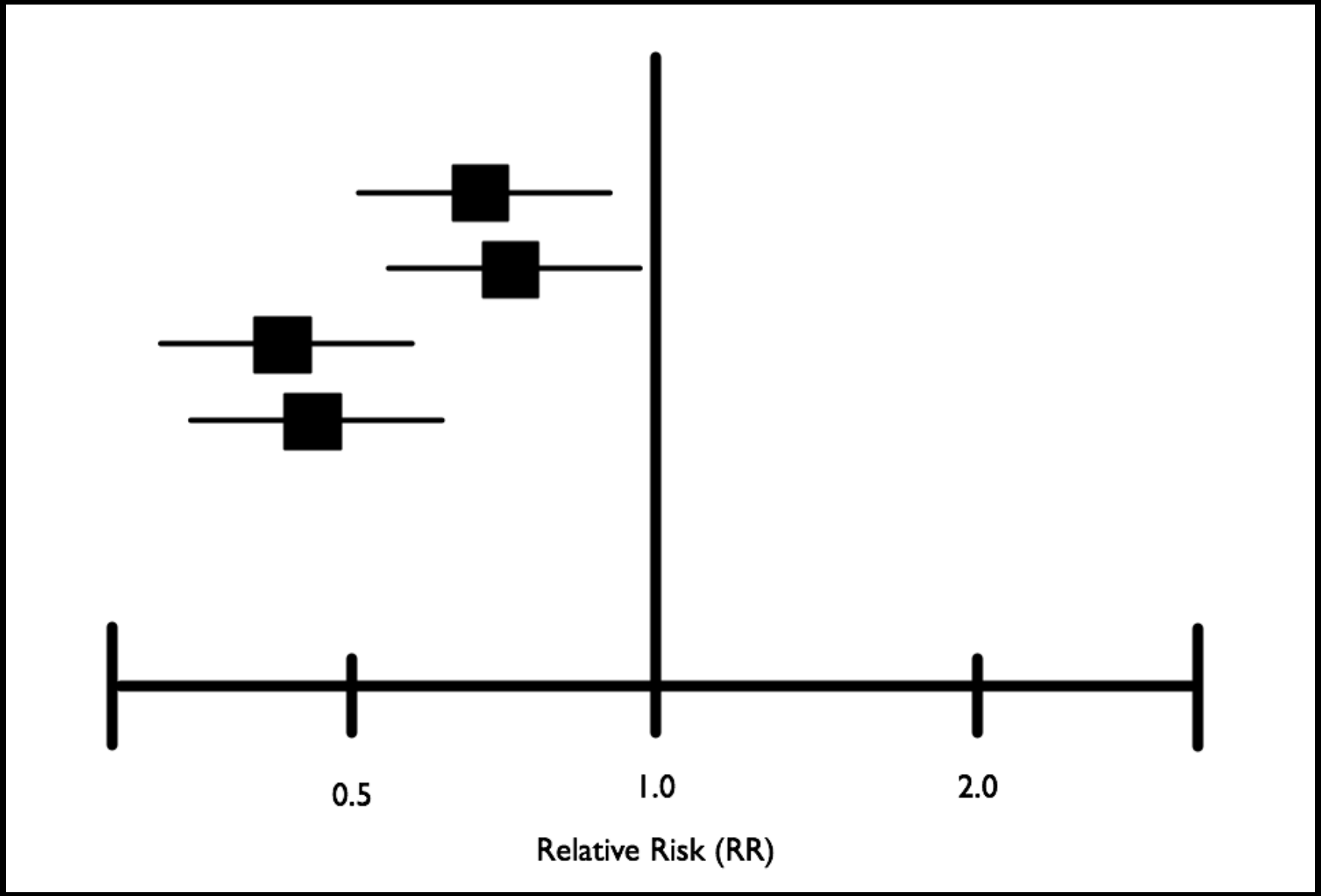
- Test of heterogeneity shows a low p value
  - χ^2
- I^2 is large:

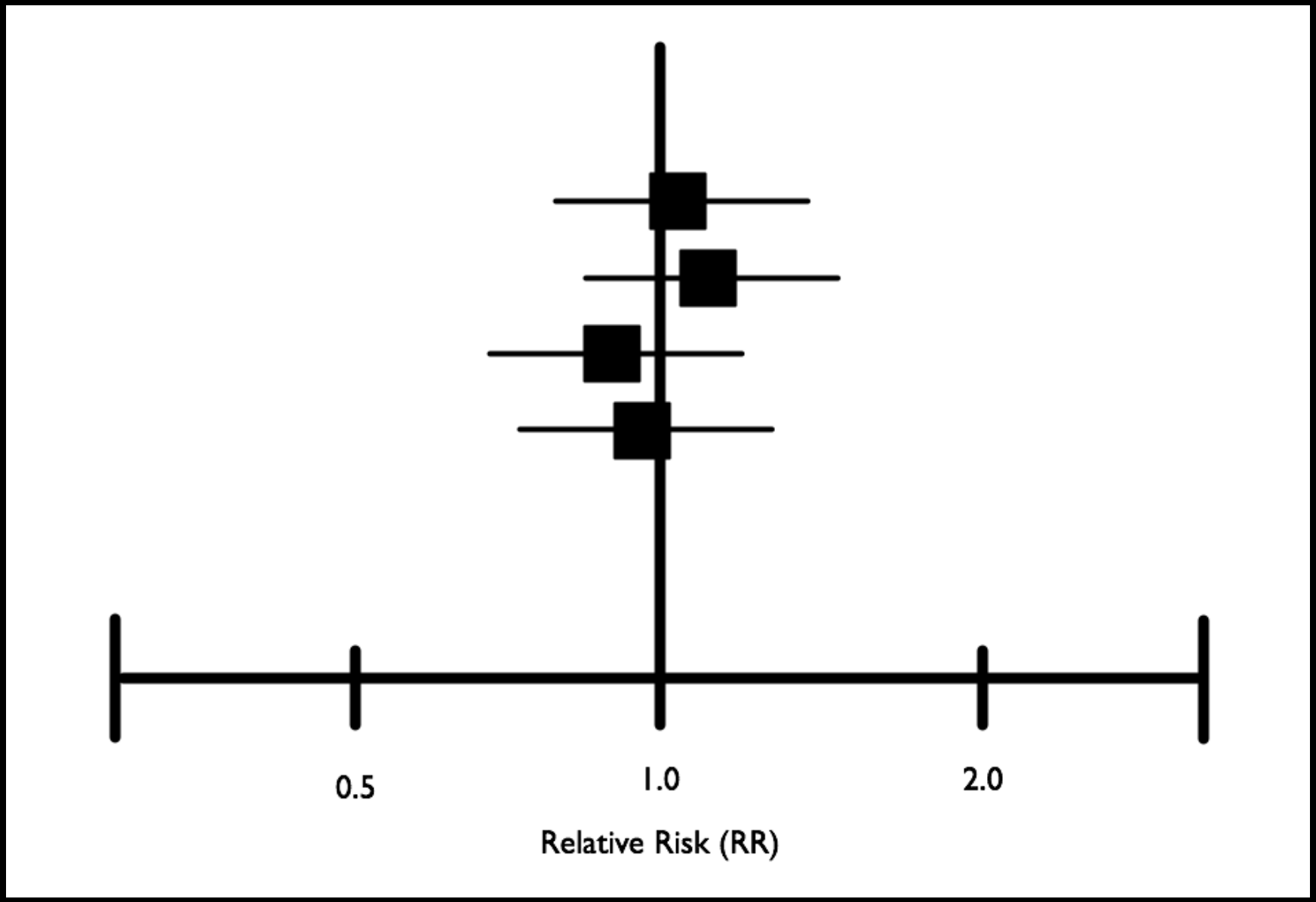
(P ≤ 0.10 may be sufficient)

-<40%: low
-30-60%: moderate
-50-90%: substantial
-75-100%: considerable


0.5
1.0
2.0
Relative Risk (RR)

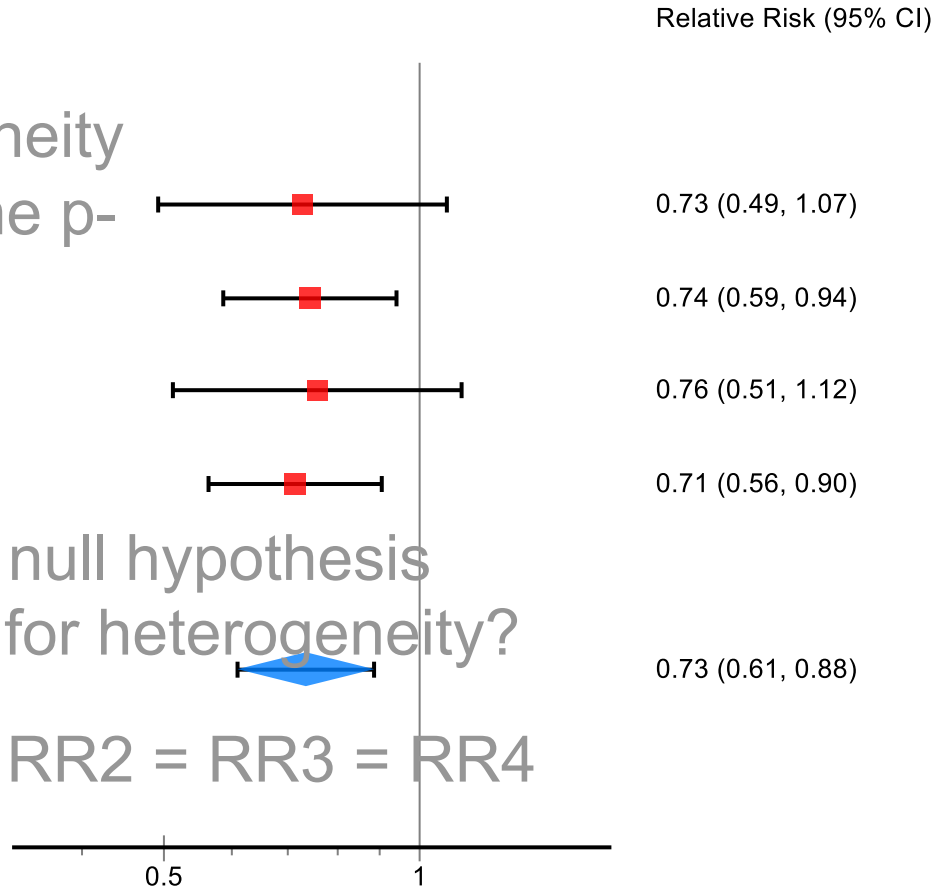

0.5
1.0
2.0
Relative Risk (RR)


0.5
1.0
2.0
Relative Risk (RR)


0.5
1.0
2.0
Relative Risk (RR)

Homogenous

test for heterogeneity what is the p-value?



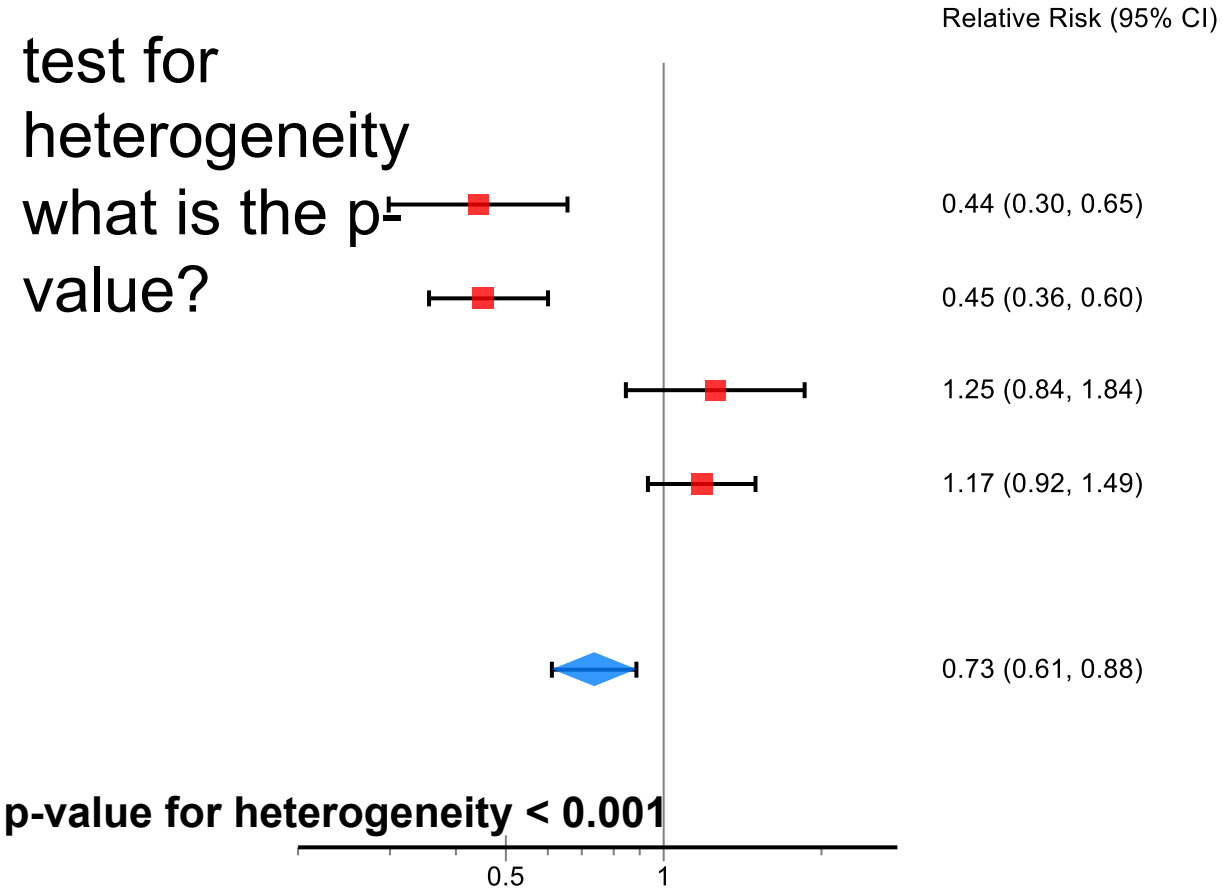
what is the null hypothesis for the test for heterogeneity?

Ho: RR1 = RR2 = RR3 = RR4

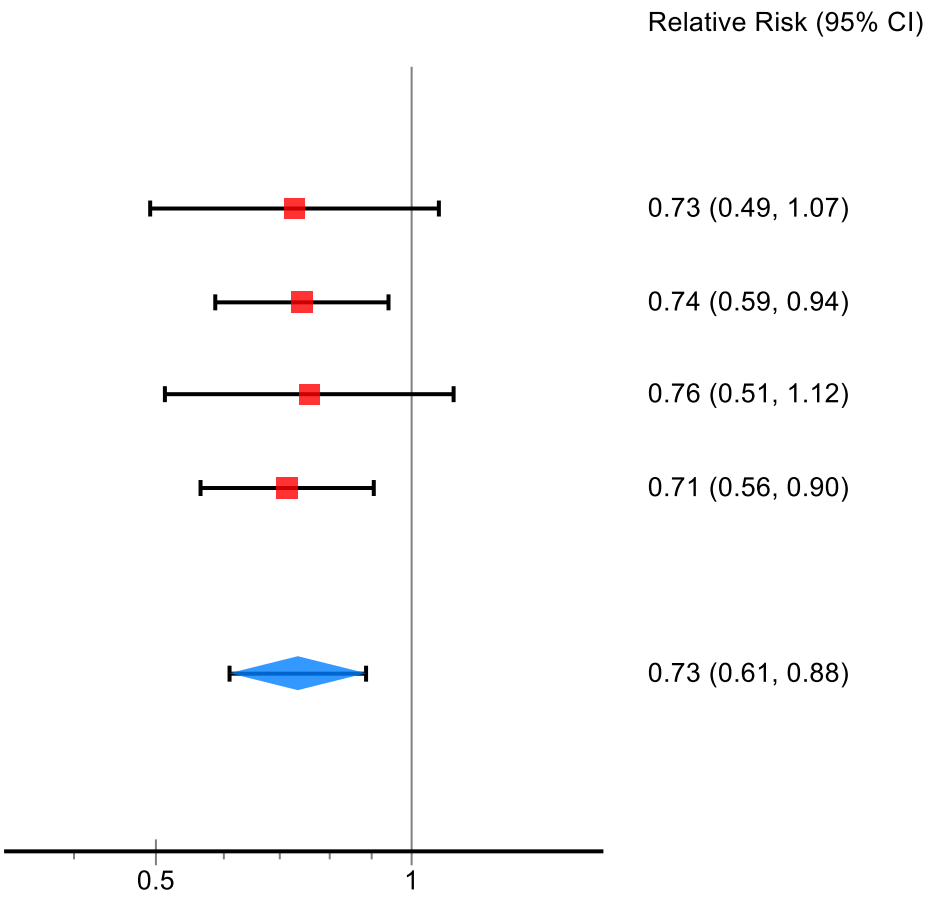
p=0.99 for heterogeneity

Heterogeneous

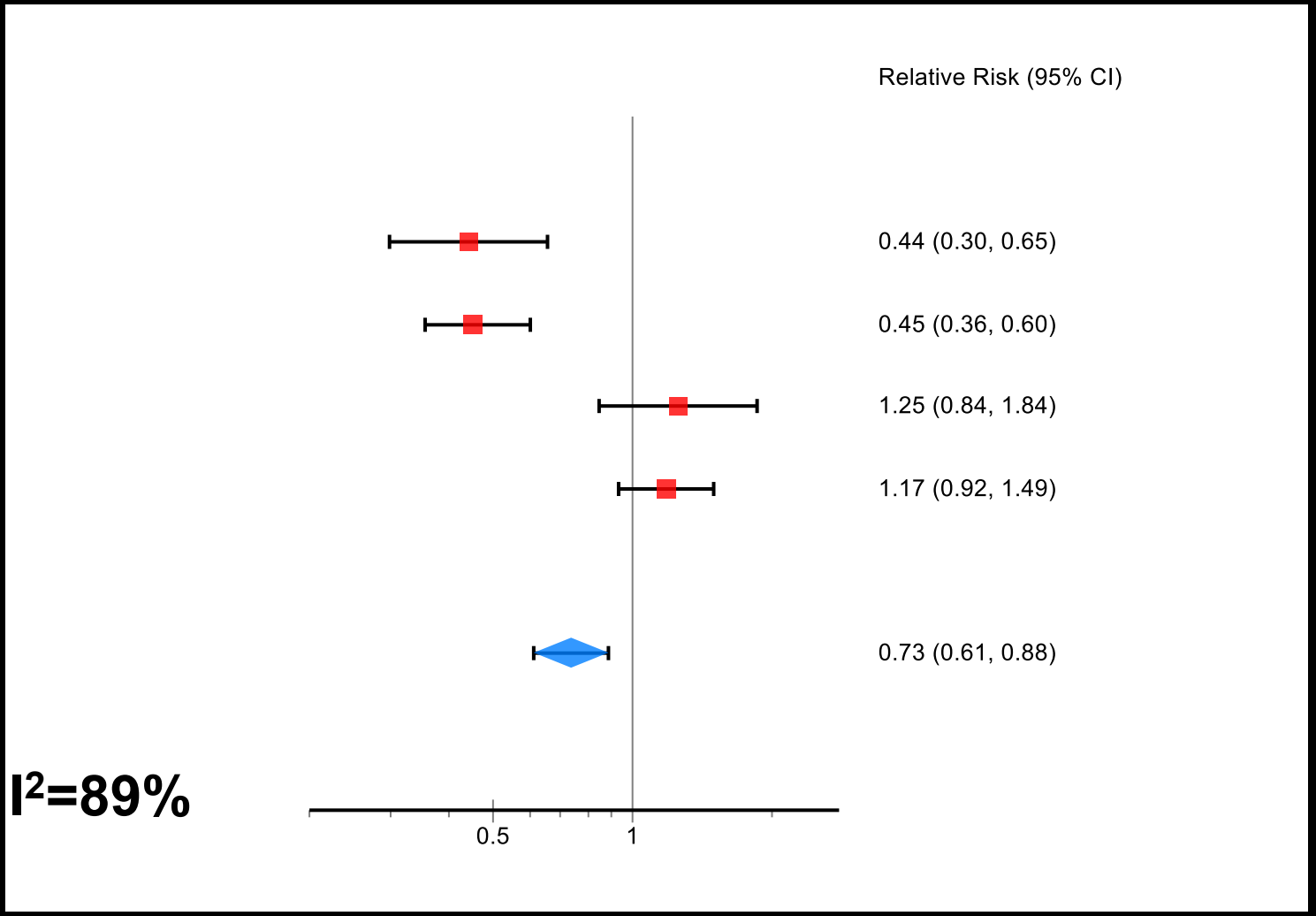
test for heterogeneity what is the p-value?



Homogenous

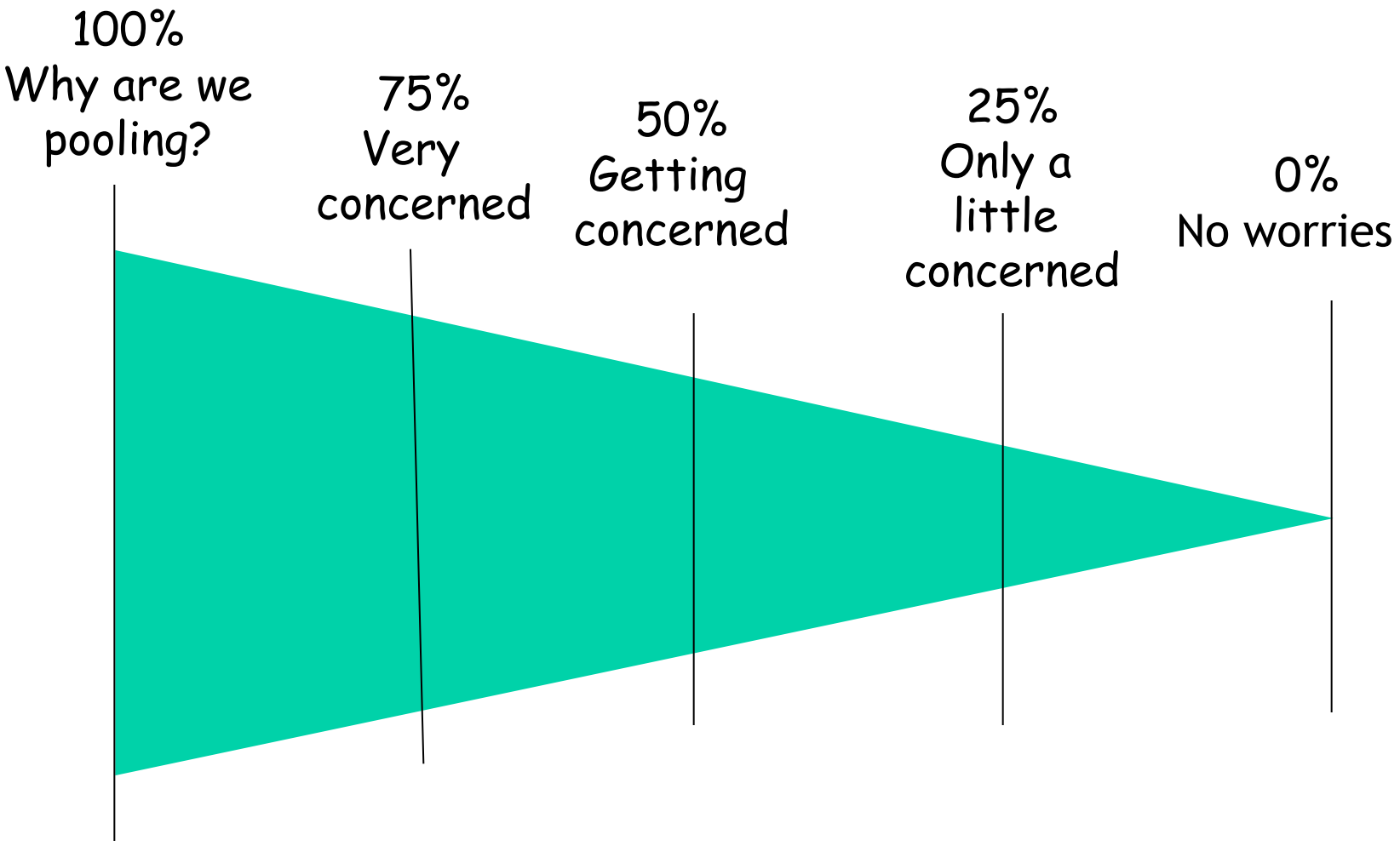

Relative Risk (95% CI)
0.73 (0.49, 1.07)
0.74 (0.59, 0.94)
0.76 (0.51, 1.12)
0.71 (0.56, 0.90)
0.73 (0.61, 0.88)
0.5
1

Heterogeneous

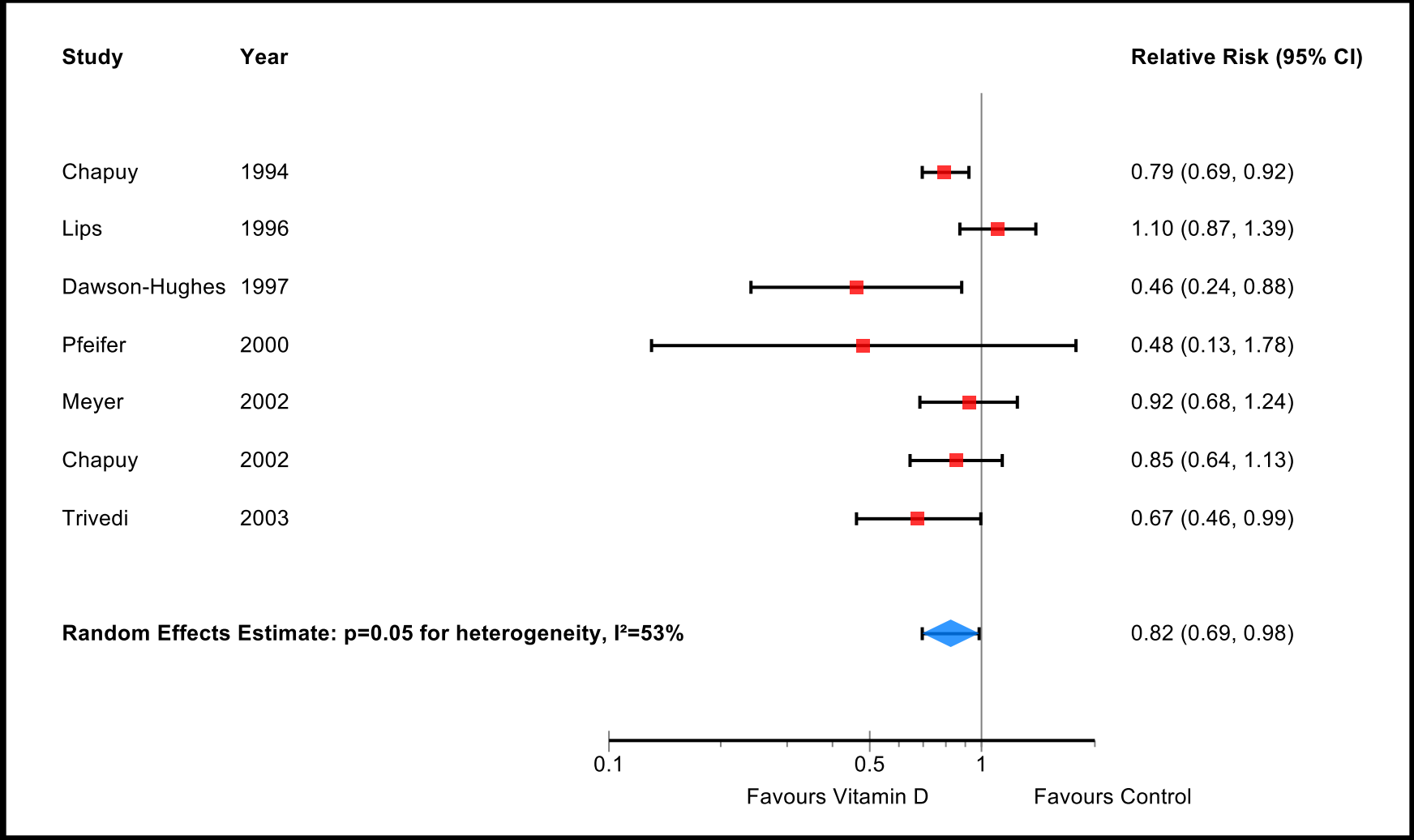


I^2=89%

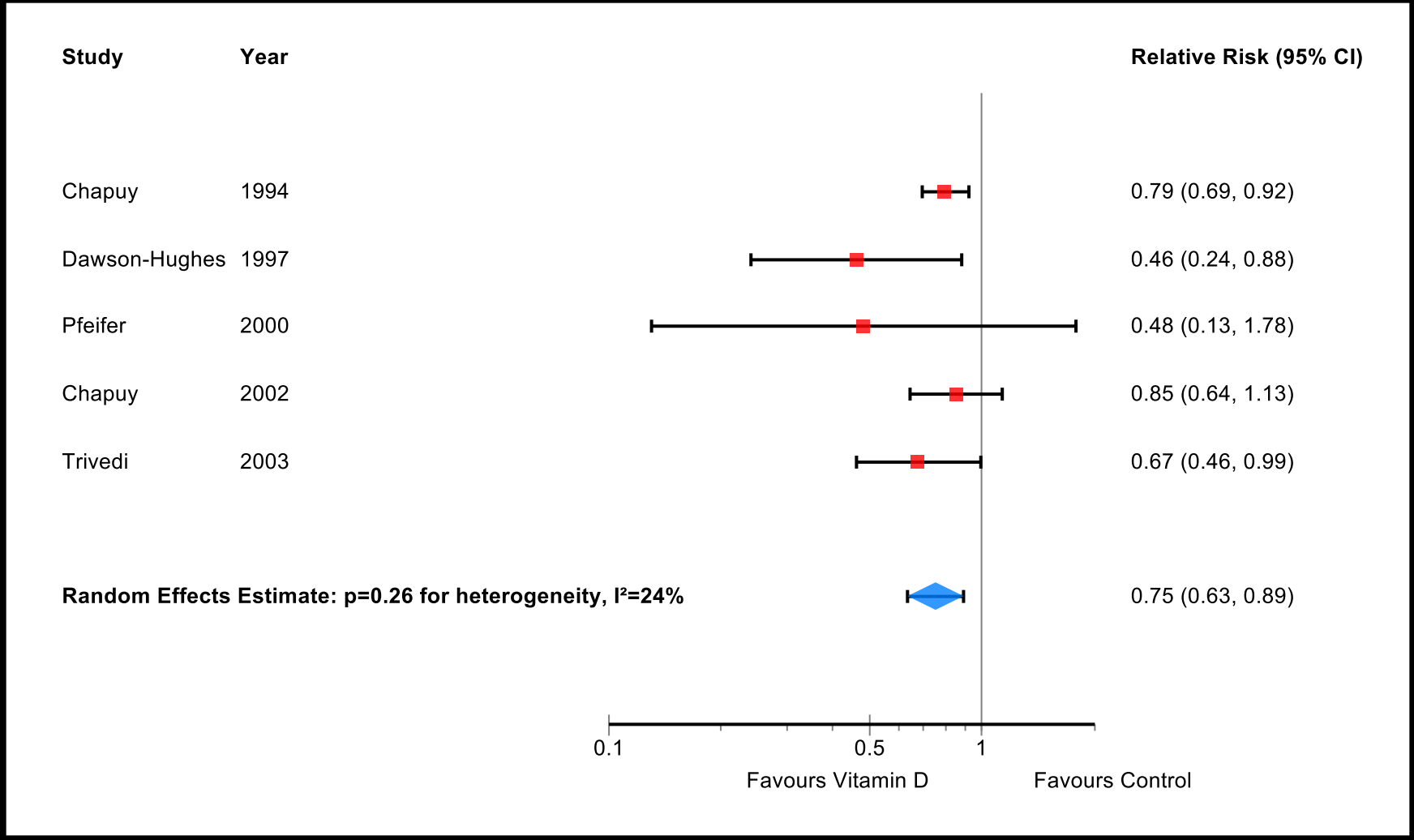
I^2 Interpretation



Relative Risk with 95% CI for Vitamin D Non-vertebral Fractures



Relative Risk with 95% CI for Vitamin D (Non-Vertebral Fractures, Dose >400)



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)

Fixed and random effects

Fixed effect

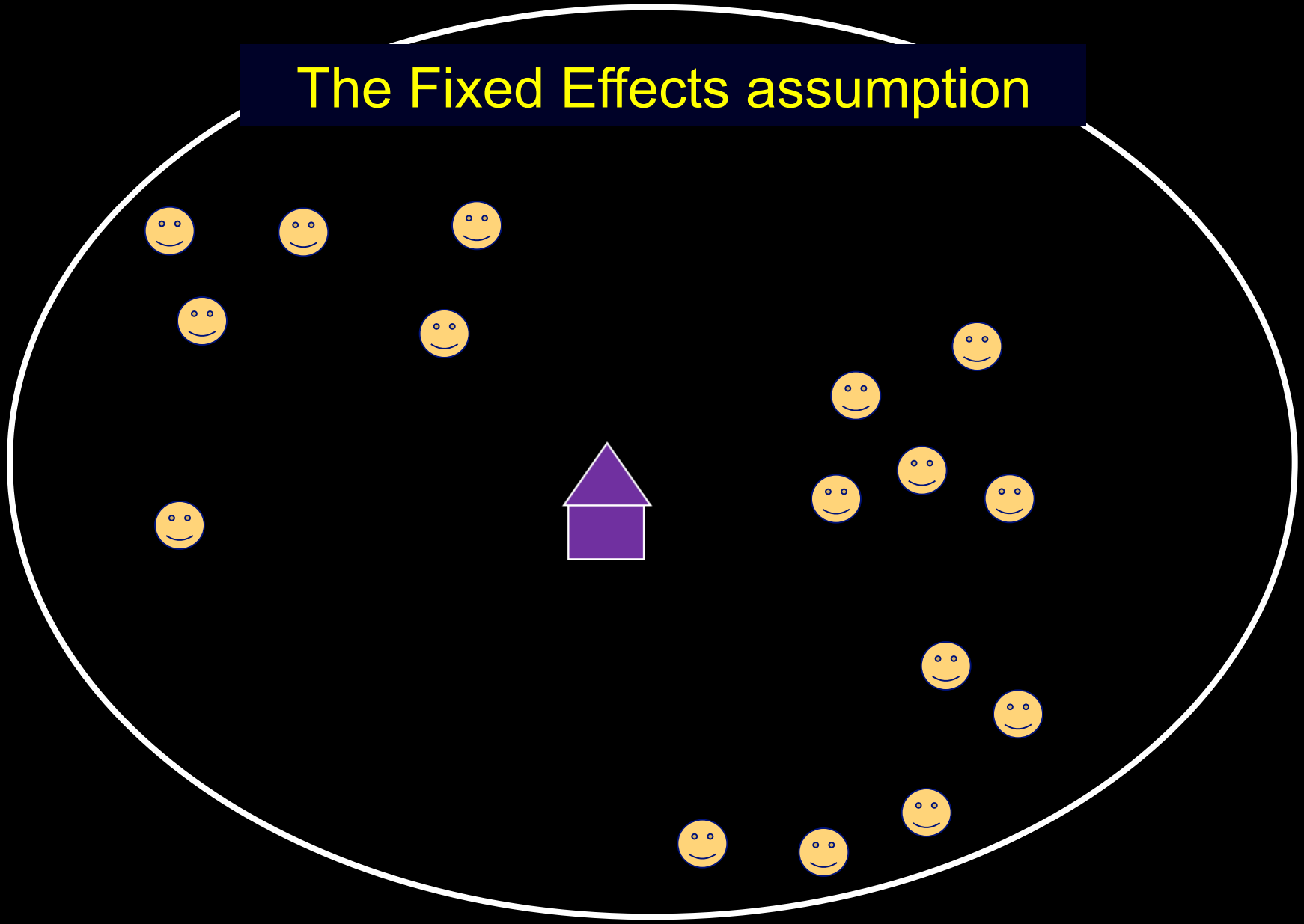
Philosophy behind ***fixed effect model***

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

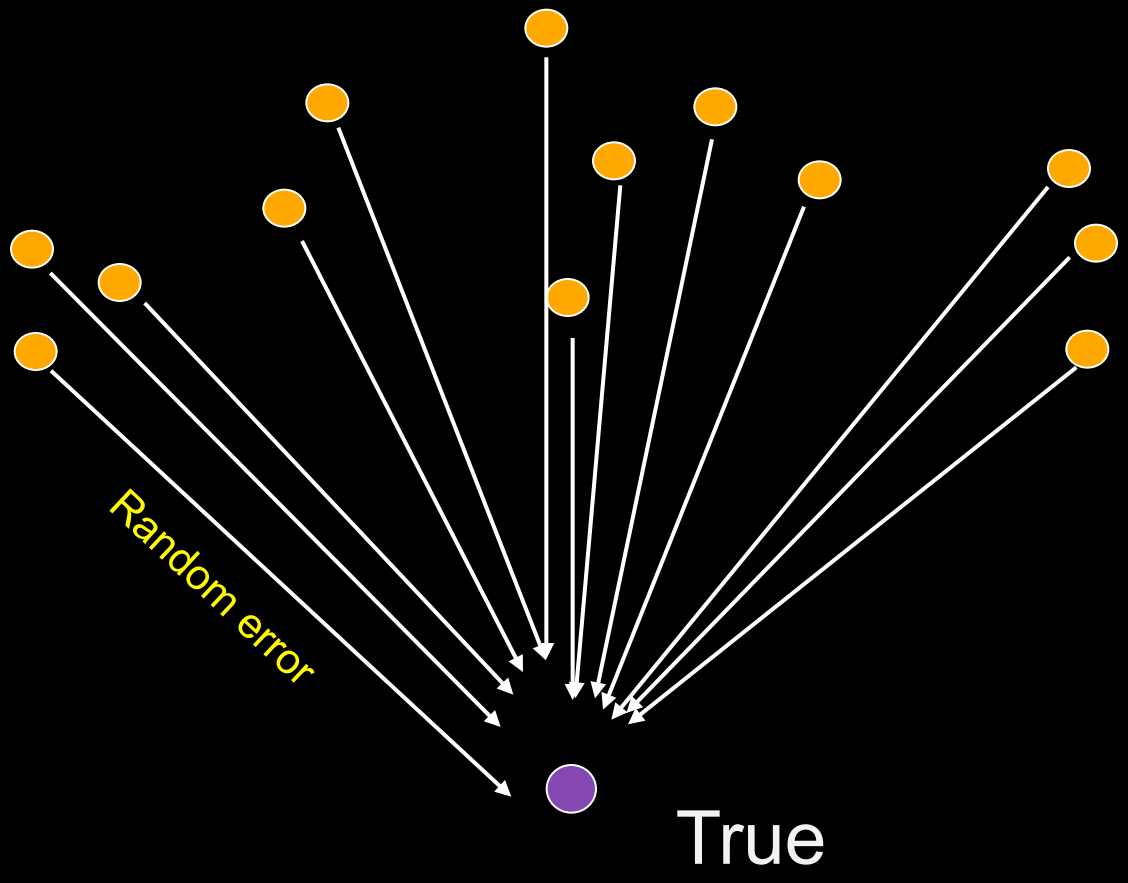
Problems with ignoring heterogeneity:

- confidence intervals too narrow

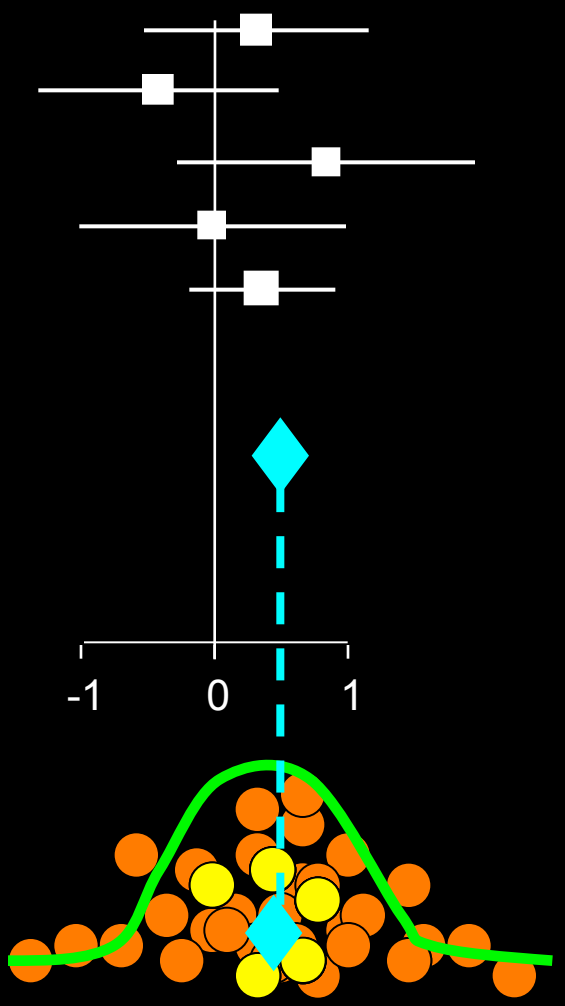
The Fixed Effects assumption



The Fixed Effects assumption



Fixed effects model



In un modello a effetti fissi si assume che tutti gli studi provengano dalla stessa popolazione di studi

Si assume che ci sia un parametro (es.media) unico, fisso

Il peso degli studi è funzione della variabilità intra-studio

Gli intervalli di confidenza del parametro sono ridotti

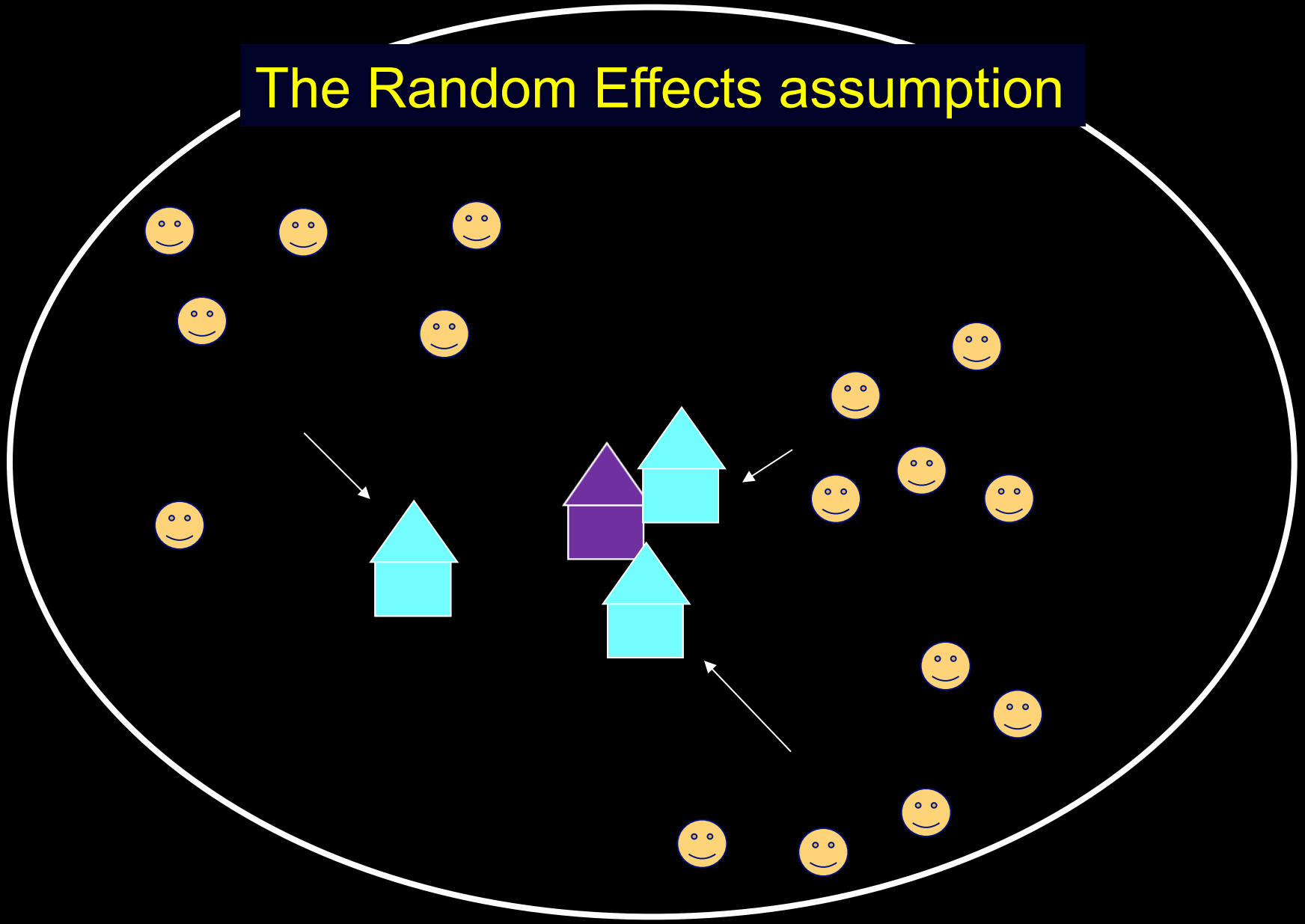
Popolazione di riferimento unica, omogenea

Random effects

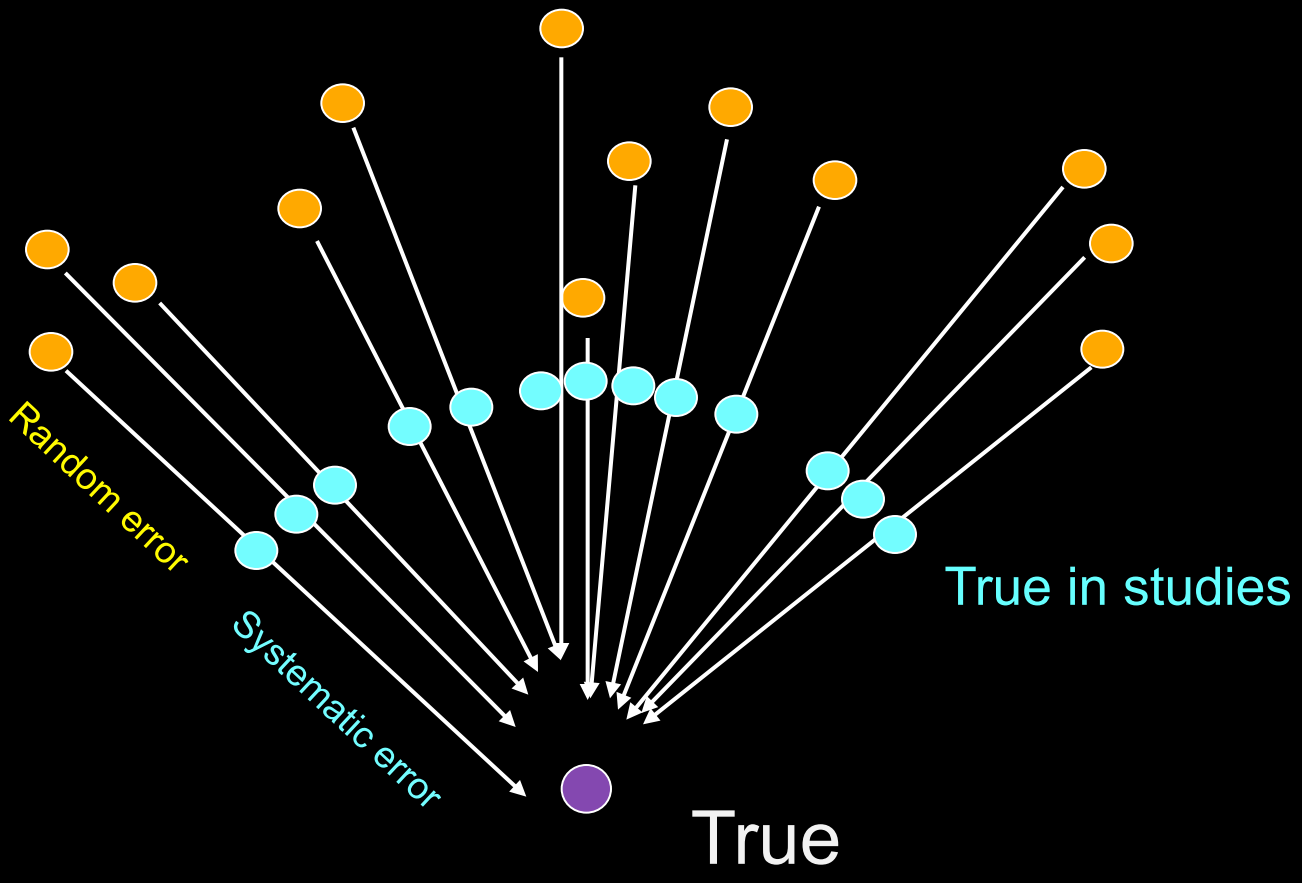
Philosophy behind ***random effects model***

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

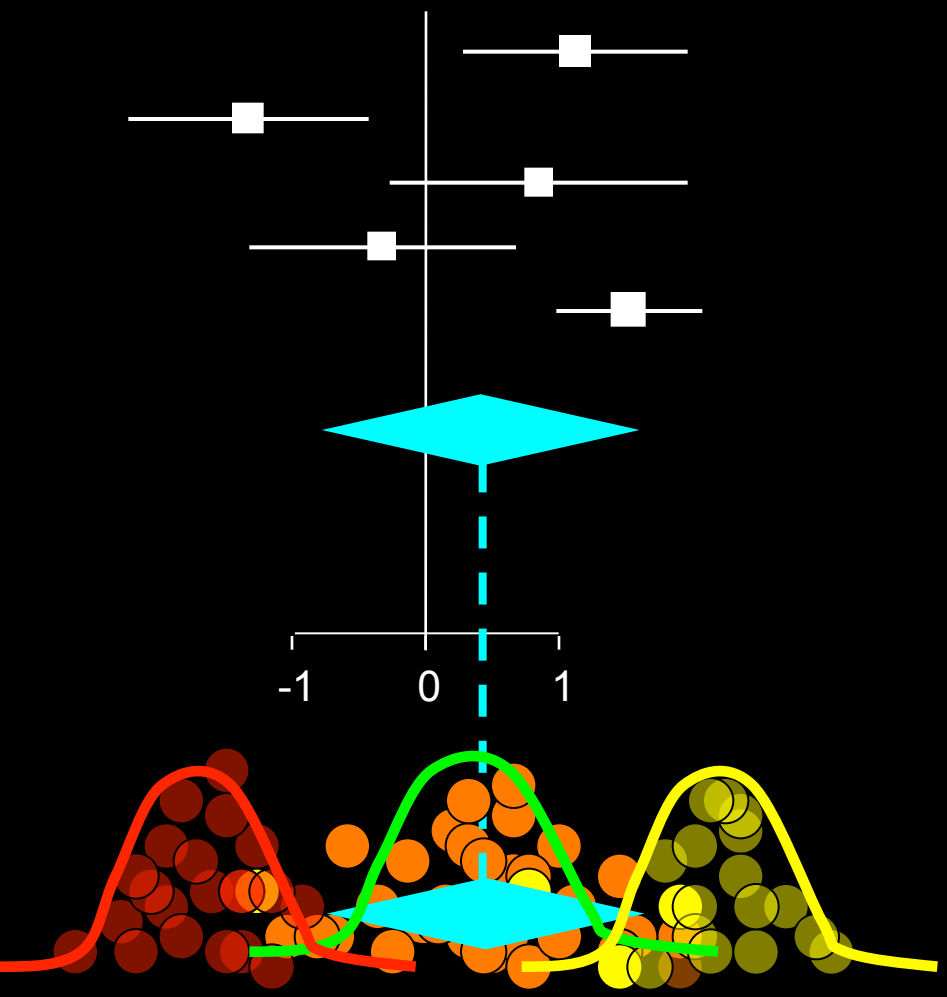
The Random Effects assumption



The Random Effects assumption



Random effects model



In un modello a effetti random gli studi potrebbero provenire da popolazioni di studi diverse

I pesi sono ridistribuiti in modo più omogeneo tra studi grandi e piccoli (il peso non è dovuto solo alla variabilità intra-studio)

Gli intervalli di confidenza del parametro sono aumentati

Popolazioni di riferimento molteplici, eterogenee

Quale modello?

Fixed effect

Random effect

Potente (IC ristretti)

Assume un solo parametro, non facile in ambito biomedico

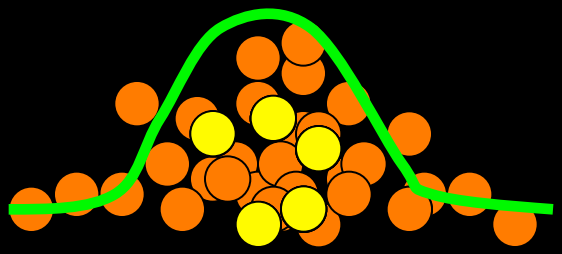
Più facile per sottogruppi

Semplicistico

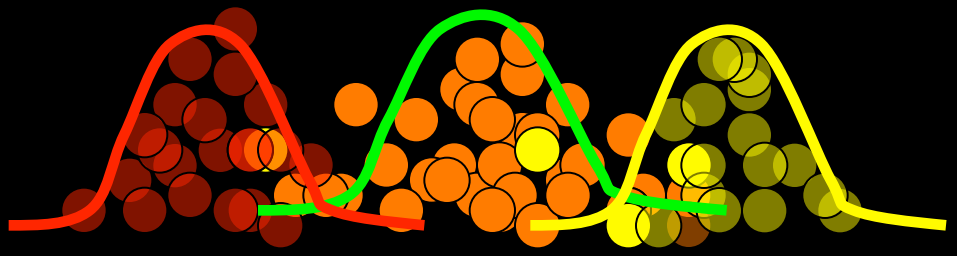
Dà luogo a un aggiustamento dei pesi grezzo (ridistribuzione senza tener conto di nessuna co-variata)

IC realistici

I^2= 20% - 50%



I^2= 50% - 70%

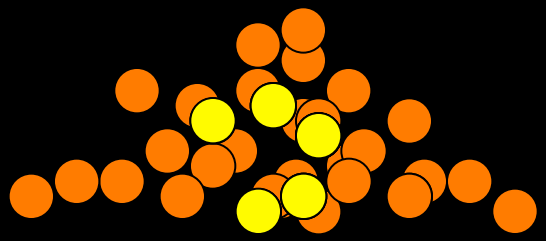


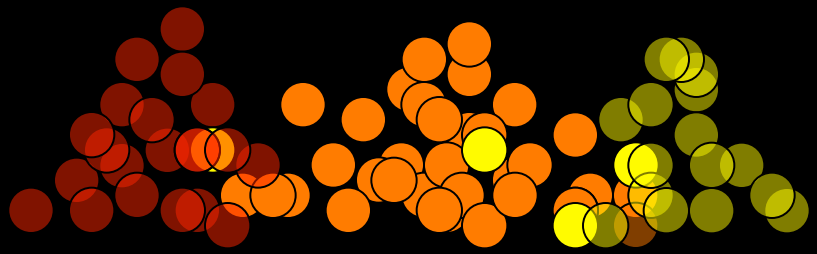
I^2= > 70%

Quale modello?

Fixed effect

Random effect



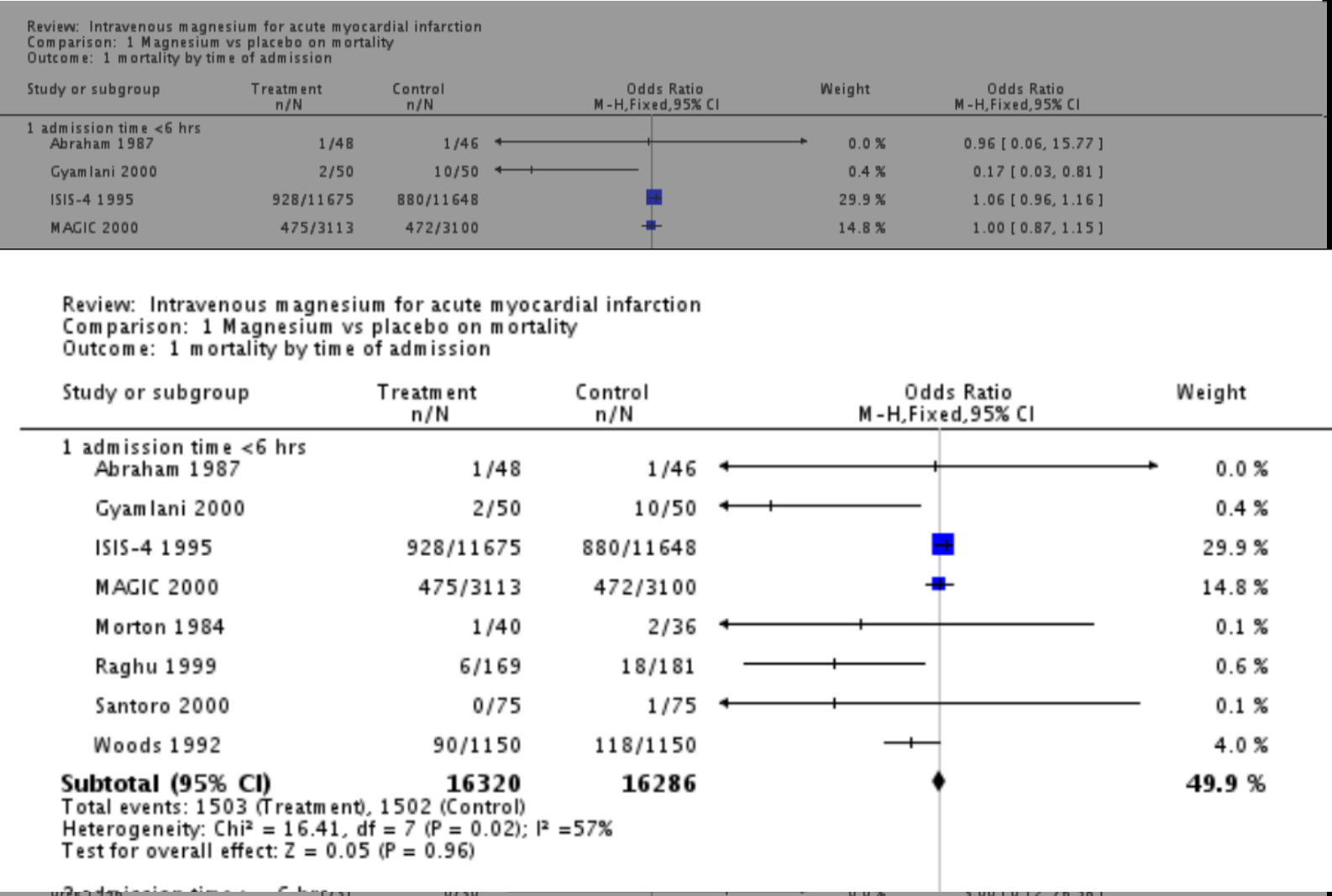


Per decidere

Q - I^2

Ma anche:

- E' ragionevole assumere una media costante?
- La variabilità tra gli studi (inter-studio) può essere attribuita al (solo) caso?
- I protocolli degli studi sono diversi?

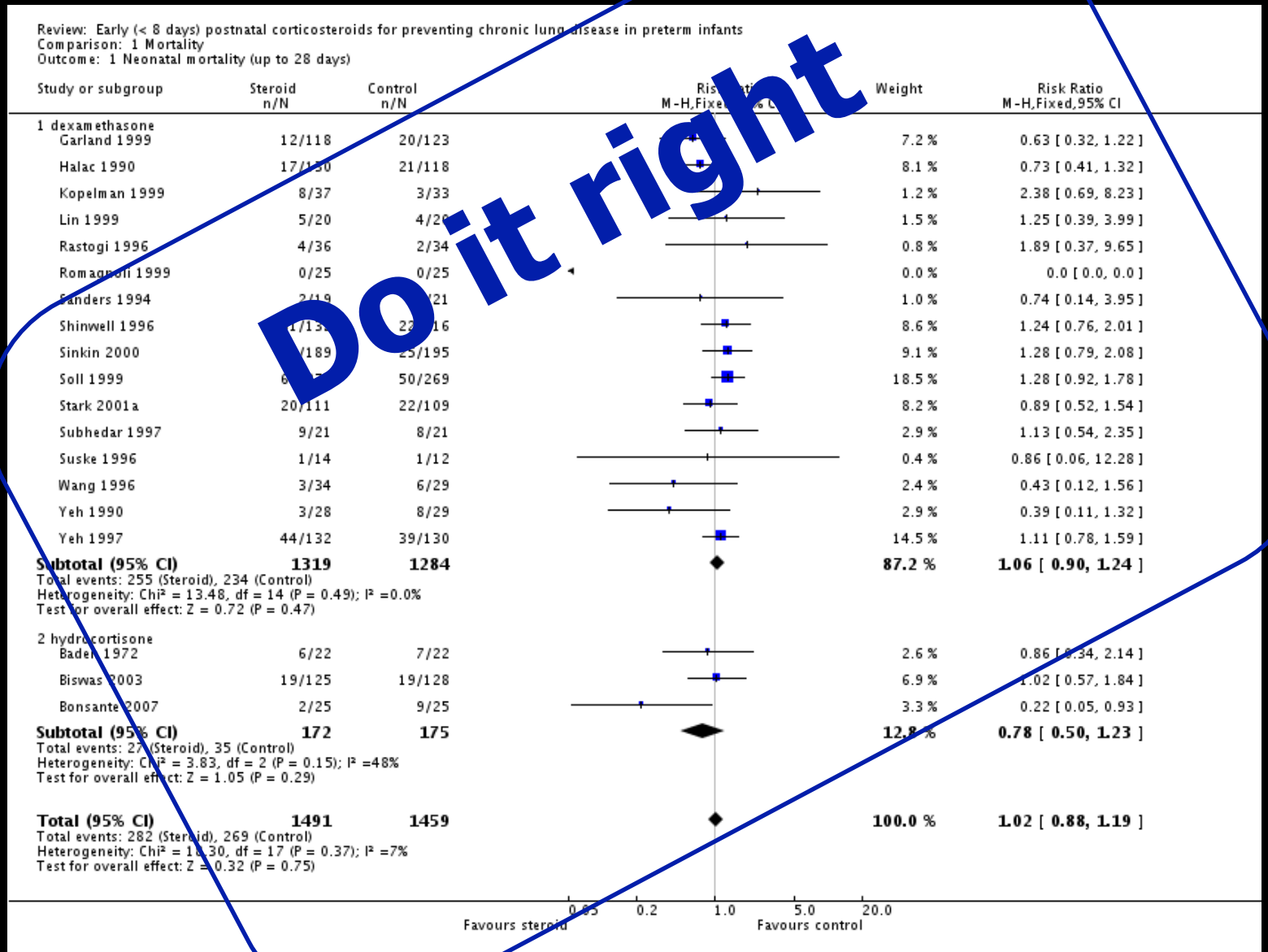


Review: Intravenous magnesium for acute myocardial infarction
Comparison: 1 Magnesium vs placebo on mortality
Outcome: 1 mortality by time of admission

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 admission time <6 hrs					
Abraham 1987	1/48	1/46		0.0 %	0.96 [0.06, 15.77]
Gyamlani 2000	2/50	10/50		0.4 %	0.17 [0.03, 0.81]
ISIS-4 1995	928/11675	880/11648		29.9 %	1.06 [0.96, 1.16]
MAGIC 2000	475/3113	472/3100		14.8 %	1.00 [0.87, 1.15]
Morton 1984	1/40	2/36		0.1 %	0.44 [0.04, 5.02]
Raghu 1999	6/169	18/181		0.6 %	0.33 [0.13, 0.86]
Santoro 2000	0/75	1/75		0.1 %	0.33 [0.01, 8.20]
Woods 1992	90/1150	118/1150		4.0 %	0.74 [0.56, 0.99]
Subtotal (95% CI)	**16320**	**16286**		**49.9 %**	**1.00 [0.93, 1.08]**

Total events: 1503 (Treatment), 1502 (Control)
Heterogeneity: Chi² = 16.41, df = 7 (P = 0.02); I² =57%
Test for overall effect: Z = 0.05 (P = 0.96)

Knowledge synthesis



Do it right

WHAT?

Cosa è emerso di particolarmente saliente e rilevante?

(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?

(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso