Publication Bias in Systematic Reviews

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Publication bias

- The likelihood of finding studies is related to the results of those studies

Publication Bias

- "Publication bias refers to the greater likelihood that studies with positive results will be published"

- *JAMA* 2002;287:2825-2828

Publication Bias

- Positive trials are more likely to be submitted for publication
- Positive trials are more likely to be published
- Positive trials are more likely to be published quickly

- Stern and Simes *BMJ 1997;*315:640-645

Publication Bias

- Sterling study: 97% of papers published in 4 psychology journals showed statistically significant results at alpha level 5% !
- Dickersin study: compared published RCTs with unpublished ones .results:55%pub,15% unpub, favoring new therapy!
- Mahoney stuD:75 reviewers asked to review different versions of a fictitious manuscript. ”introduction” & ”methods” : identical, ”results” & “discussion” : different (+/ambiguous /-). results of reviewers evaluation : manuscripts with “positive” results received higher average scores!

Publication Bias

- 1)…if they had reached sig.
- 2) positive result
- 3) interesting results for both reviewers & authors!
- 4) language bias (ENG) in being included in a meta-analysis.

How to Bypass Publication Bias

- Searching Libraries for Thesis & Research Reports
- Searching Registries
- Searching Grey Literature
- Searching especial Journals like:

"*Journal of Negative results in Biomedicine*"

Funnel plots

- A funnel plot is a scatter plot of treatment effect (Effect Size) against a measure of study size.

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Funnel plots

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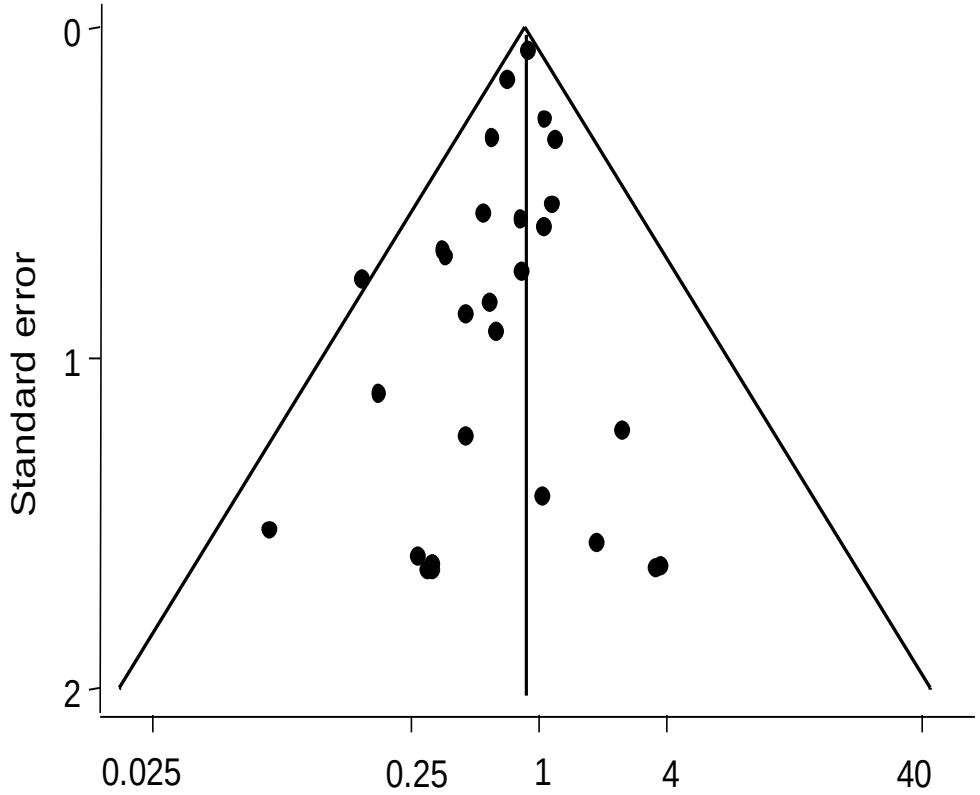
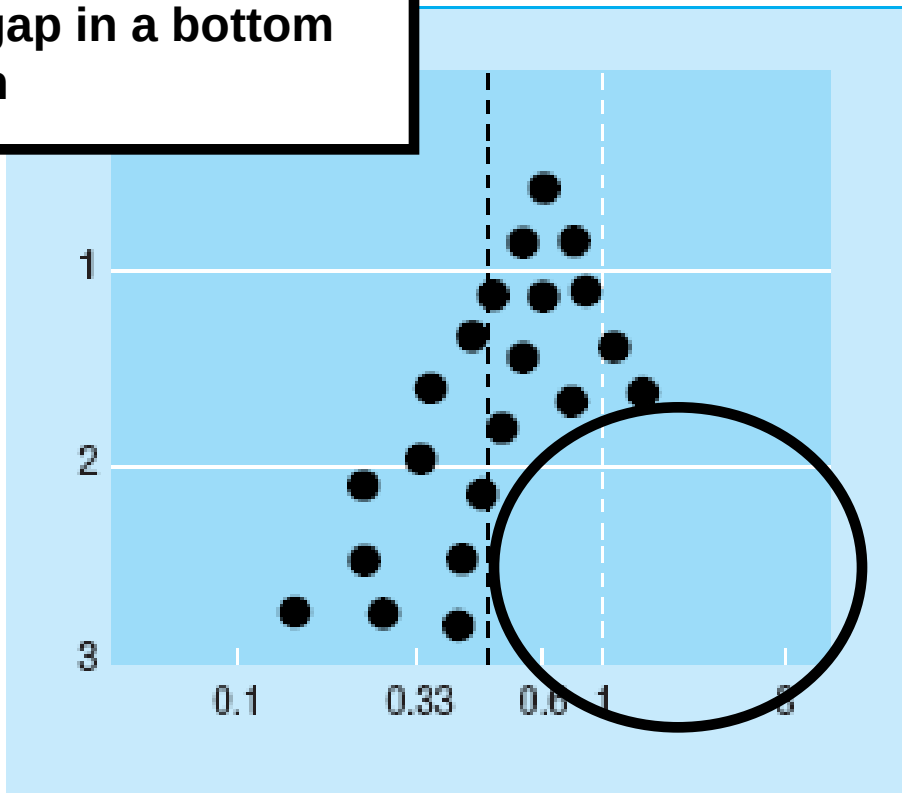


Why Funnel?

- Precision in the estimation of the true treatment effect increases as the sample size increases.
- Small studies scatter more widely at the bottom of the graph
- In the absence of bias the plot should resemble a symmetrical inverted funnel

Publication Bias

Asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph



Publication Bias

- In this situation the effect calculated in a meta-analysis will overestimate the treatment effect
- The more pronounced the asymmetry, the more likely it is that the amount of bias will be substantial.

Possible sources of asymmetry in funnel plots

1. Selection biases
   - Publication bias
   - Location biases
2. Poor methodological quality of smaller studies
   - Poor methodological design
   - Inadequate analysis
   - Fraud
3. True heterogeneity
   - Size of effect differs according to study size (for example, due to differences in the intensity of interventions or differences in underlying risk between studies of different sizes)
4. Chance

Publication bias Approaches

- Attempt to Retrieve all Studies
- Worst Case Adjustment
  - Number of unpublished negative studies to negate a "positive" meta-analysis:
  - $X = [N \times (ES) / 1.645]^2 - N$
    - where: N = number of studies in meta-analysis,
    - ES = effect size
- Example:
  - If N = 25, and ES = 0.6 then X = 58.2
  - Almost 60 unpublished negative studies would be required to negate the meta-analysis of 25 studies.

Poor methodological quality

- Smaller studies are, on average, conducted and analyzed with less methodological rigor than larger studies.
- Trials of lower quality also tend to show larger treatment effects
- Trials which, if conducted and analyzed properly, would have been ‘negative’ may thus become ‘positive’

Meta-Analysis

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Meta-Analysis

- Meta-analysis is a statistical analysis of a collection of studies
- Meta-analysis methods focus on contrasting and comparing results from different studies in anticipation of identifying consistent patterns and sources of disagreements among these results
- Primary objective:
  - Synthetic goal (estimation of summary effect)

    vs.
  - Analytic goal (estimation of differences)

Systematic Review & Meta-analyses

- A systematic review need not contain any meta-analyses.

- If there is considerable variation in results, it may be misleading to quote an average value

What is heterogeneity?

Variability in effect size estimates which exceeds that expected from sampling error alone.

Heterogeneity

Sources of variety of varieties are:

- Study diversity
- Methodological diversity
- Statistical heterogeneity

Sources of Variation over Studies

- Inter-study variation may exist
- Sampling error may vary among studies (sample size)
- Characteristics may differ among studies (population, intervention)

Heterogeneity

How to Identify it:

- Common sense

  are the populations, interventions and outcomes in each of the included studies sufficiently similar

- Statistical tests

Statistical Tests of Homogeneity (heterogeneity)

- Homogeneity calculations
  - H_o = studies are homogeneous
  - Based on testing the sum of weighted differences between the summary effect and individual effects
  - Calculate Mantel Haenszel Q, where:

$$Q = \sum[weight_i \times (lnOR_{mh} - lnOR_i)^2]$$

  - If $p < 0.05$, then there is significant heterogeneity.

Statistical Tests of Homogeneity (heterogeneity)

- Power of such statistical tests is low

  (a non-significant test does not rule out clinically important heterogeneity)

Statistical Models

For Calculating overall effects, there are two Statistical Models:

- Fixed effects model (FEM)
- Random effects model (REM)

How to deal with Heterogeneity

- If homogenous, use fixed effects model
  - random will give same results
  - fixed is computationally simpler
- If heterogeneous…then first ask why?!
  - In the face of heterogeneity, focus of analysis should be to describe possible sources of variability
  - attempt to identify sources of important subgroup differences

How to Deal with Heterogeneity

1. No Heterogeneity:

   Use Fixed Effects Model

2. If Heterogeneity is there:

   Do not ‘pool at all’

3. Explore heterogeneity through:

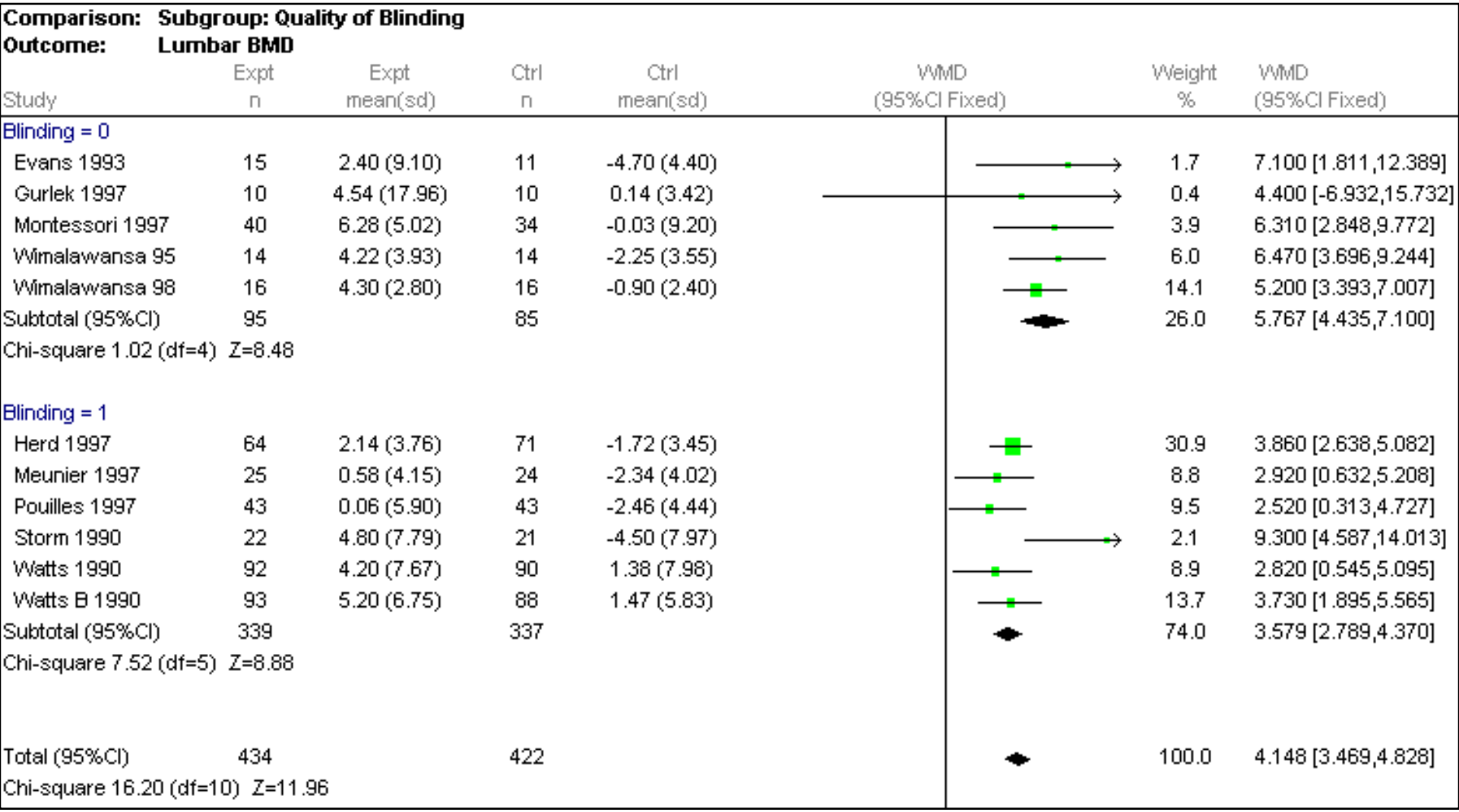
   Subgroup analysis

   Meta-regression

4. If Heterogeneity still persist:

   Use Random Effects Model

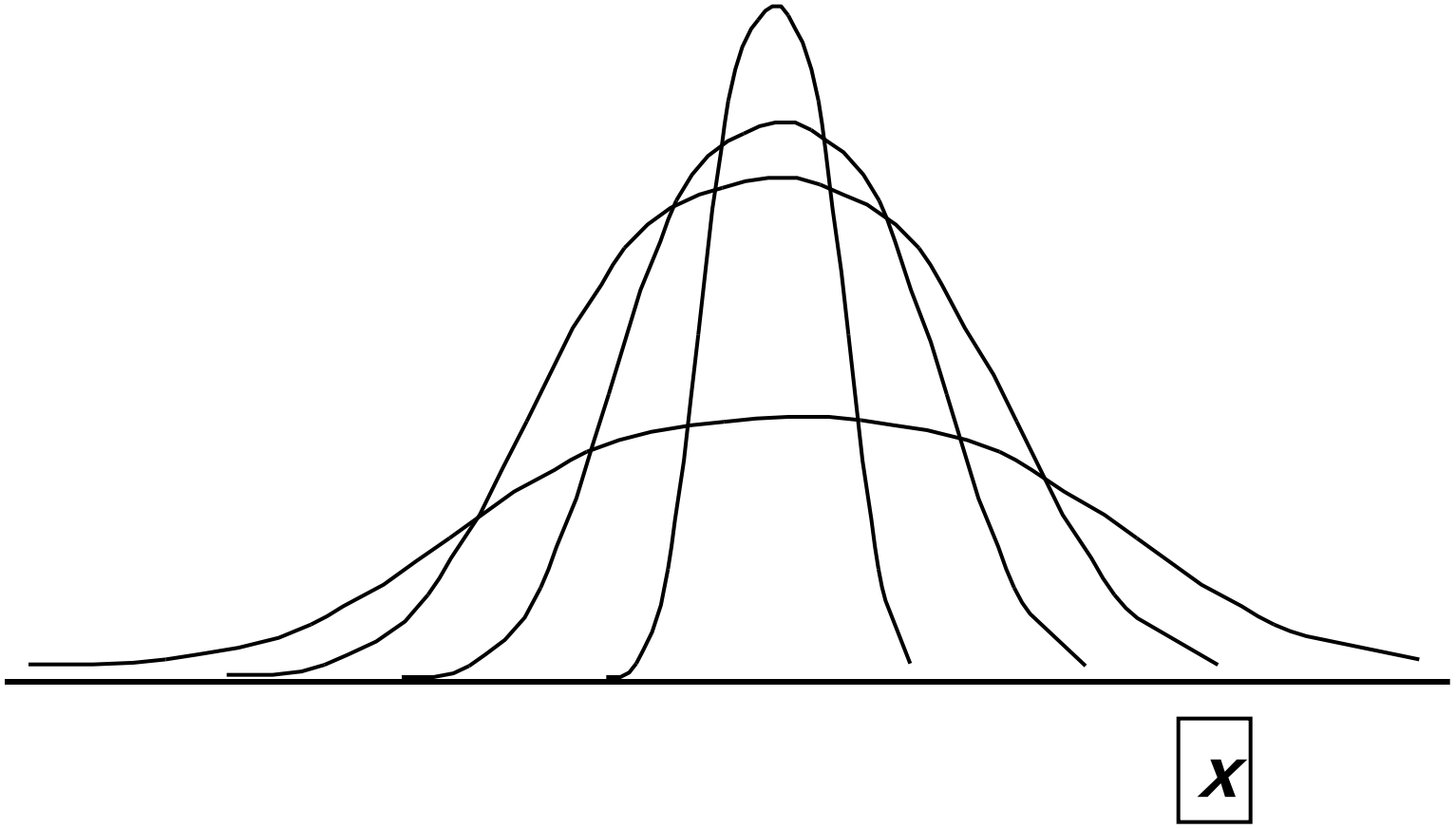
Exploring Heterogeneity



Fixed effects model

- All trials are measuring a single, true effect
- The reason for any difference between the effect in an individual trial and this true effect is chance

Fixed-Effects Model



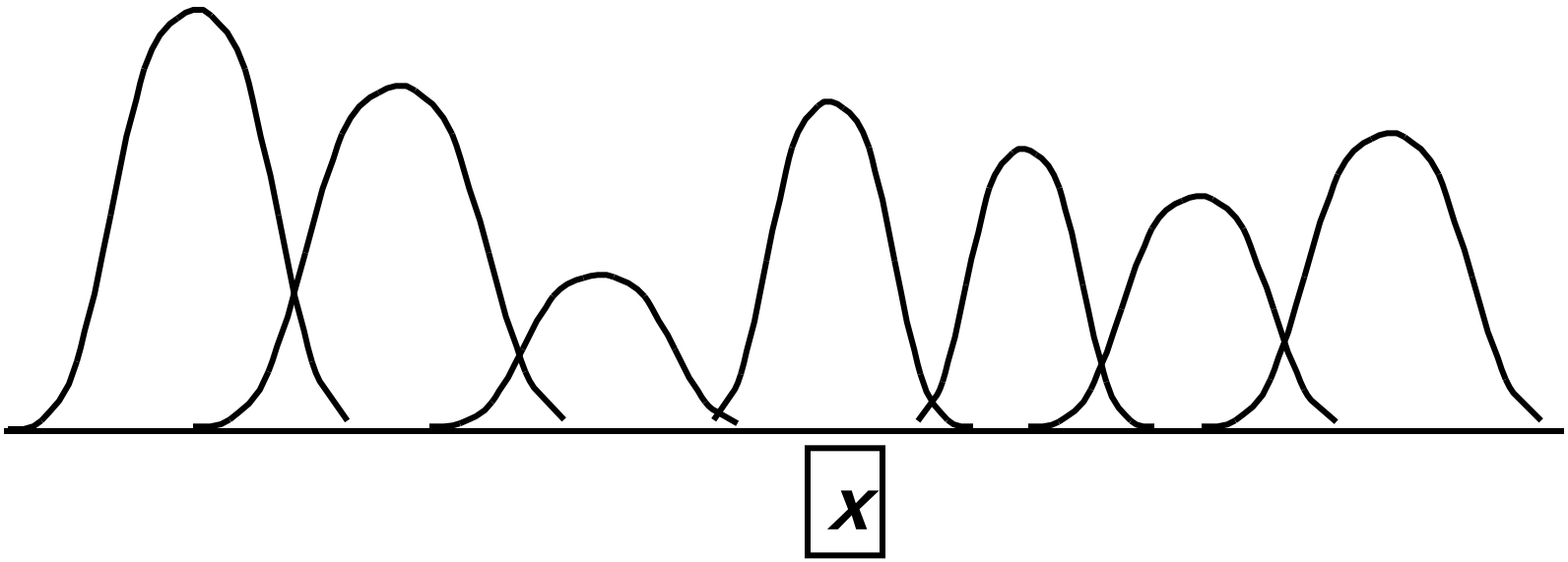
Fixed Effects Model

- Require from each study
  - effect estimate; and
  - standard error of effect estimate
- Combine these using a weighted average:
  - pooled estimate = $\frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}}$
  - where weight = 1 / variance of estimate
- Assumes a common underlying effect behind every trial

Random Effects models

- consider both *between-study* and *within-study* variability.
- Each trial is measuring a different, true effect
- The true effects for each trial are normally distributed
- There is a true average effect
- The reason for any difference between the effect in an individual trial and this average effect is both the difference between the true effect for the trial and this average, and chance.

Random-Effects Model



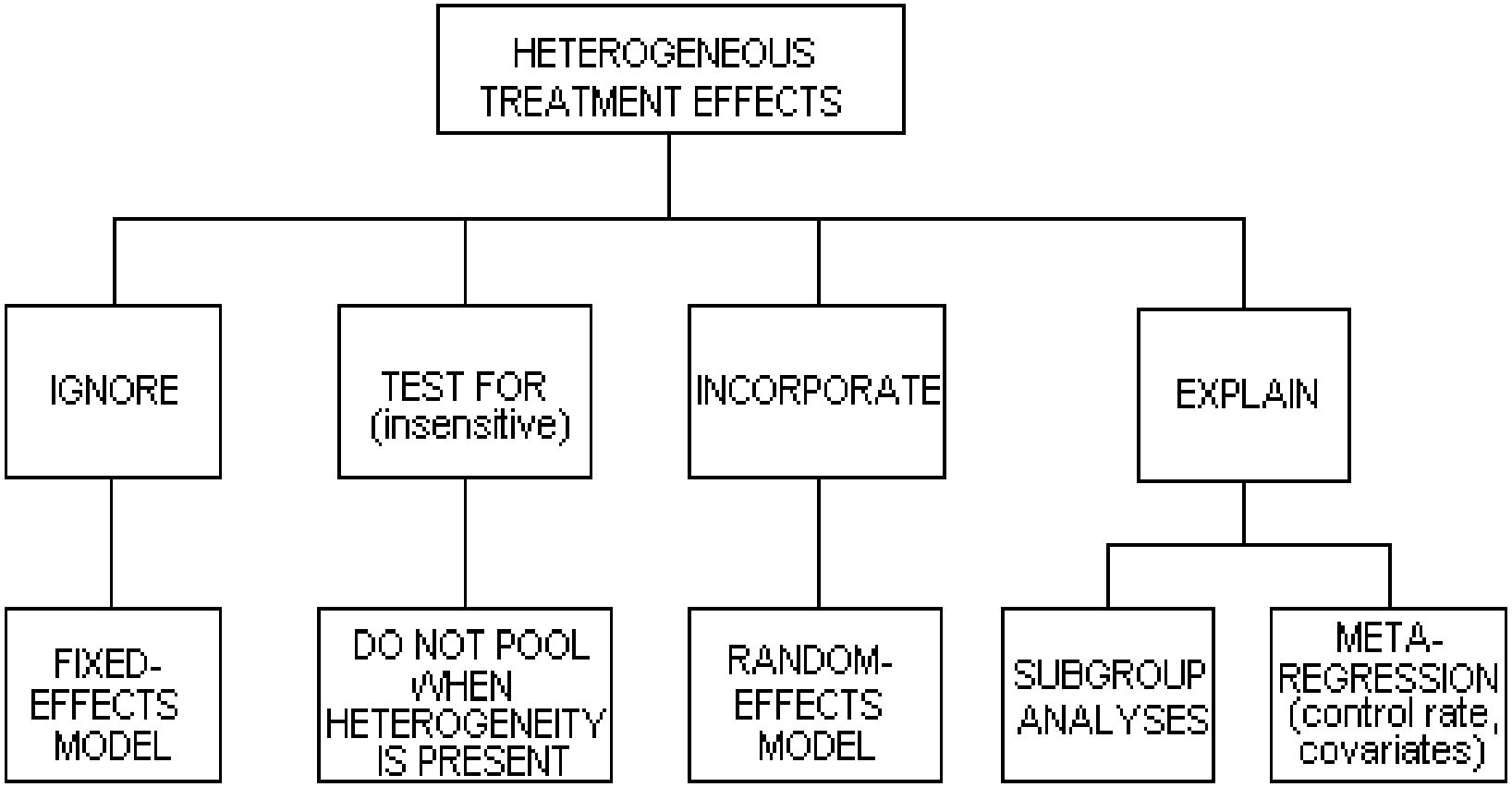
Random-Effects Model

- Assume true effect estimates really vary across studies
- Two sources of variation:
  - within studies (between patients)
  - between studies (heterogeneity)
- What the software does is Revise weights to take into account both components of variation:
- Weight = $\frac{1}{\text{Variance + heterogeneity}}$

Random-Effects Model

- When heterogeneity exists we get:
  - a different pooled estimate (but not necessarily) with a different interpretation
  - a wider confidence interval
  - a larger p-value

Generic Inferential Framework

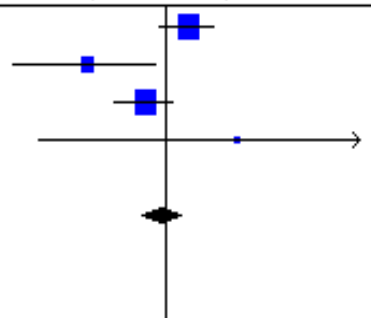


Fixed vs. Random Effects: Discrete Data

Fixed Effects

Comparison: **Fluoride vs Placebo - Overall**
Outcome: **No. People with new vertebral fractures - 2 years**

Study	Expt n/N	Ctrl n/N	Relative Risk (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Meunier	69 / 208	37 / 146		42.6	1.31 [0.93,1.84]
Pak	6 / 54	16 / 56		15.4	0.39 [0.16,0.92]
Riggs 1990	33 / 101	42 / 101		41.1	0.79 [0.55,1.13]
Sebert	2 / 35	1 / 41		0.9	2.34 [0.22,24.76]
Total (95%CI)	110 / 398	96 / 344		100.0	0.96 [0.76,1.21]
Chi-square 9.17 (df=3) Z=0.33					



Random Effects

Comparison: **Fluoride vs Placebo - Overall**
Outcome: **No. People with new vertebral fractures - 2 years**

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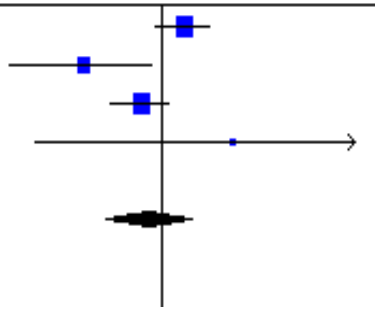
Meunier	69 / 208	37 / 146		38.1	1.31 [0.93,1.84]
Pak	6 / 54	16 / 56		20.3	0.39 [0.16,0.92]
Riggs 1990	33 / 101	42 / 101		37.2	0.79 [0.55,1.13]
Sebert	2 / 35	1 / 41		4.4	2.34 [0.22,24.76]
Total (95%CI)	110 / 398	96 / 344		100.0	0.87 [0.51,1.46]
Chi-square 9.17 (df=3) Z=0.53					



اگر میل داشتید Email بزنید !

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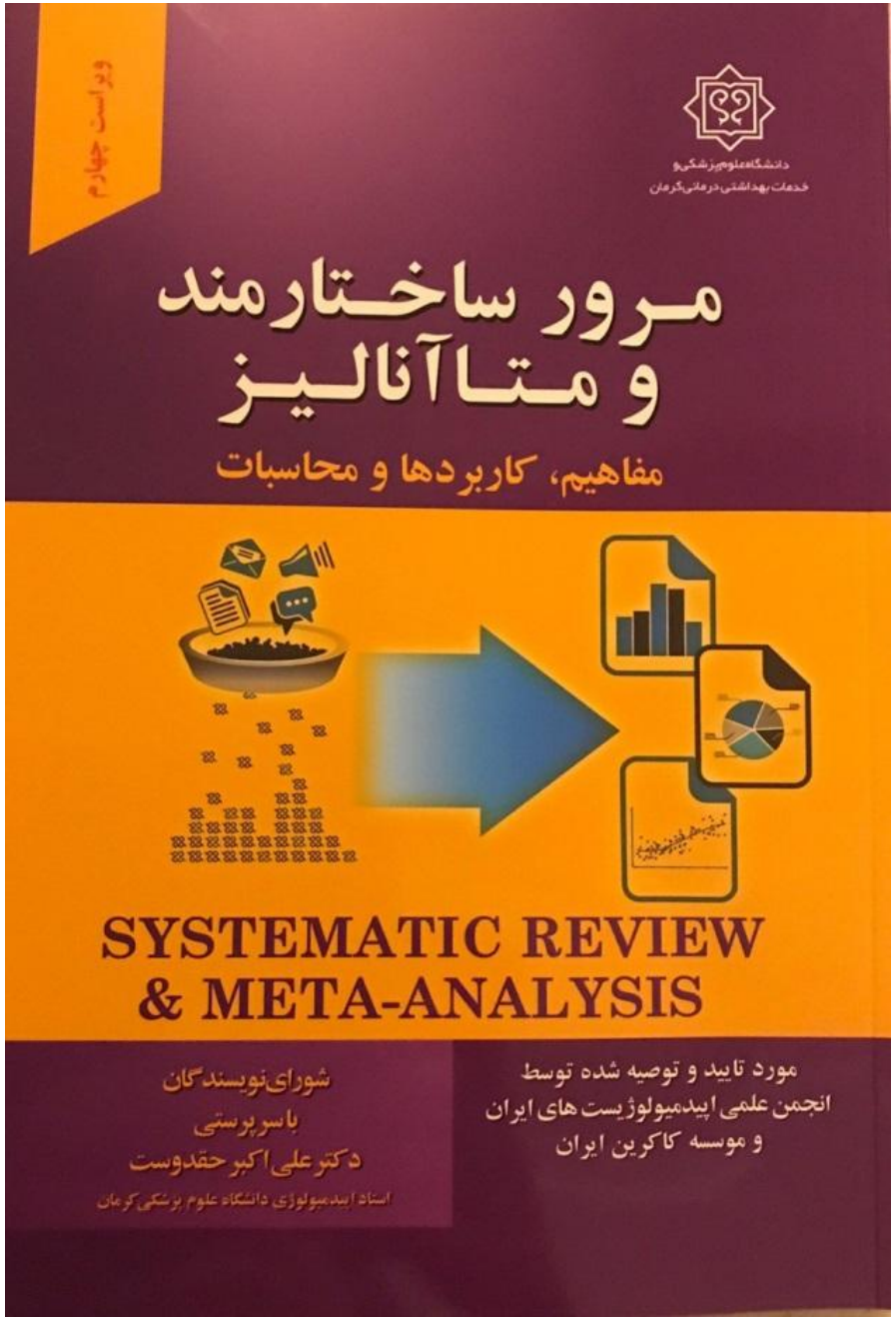
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دانشگاه علوم پزشکی و
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مرور ساختارمند
و متاآنالیز
مفاهیم، کاربردها و محاسبات
SYSTEMATIC REVIEW
& META-ANALYSIS
مورد تایید و توصیه شده توسط
انجمن علمی اپیدمیولوژیست های ایران
و موسسه کاکرین ایران
شورای نویسندگان
با سرپرستی
دکتر علی اکبر حقدوست
استاد اپیدمیولوژی دانشگاه علوم پزشکی کرمان