Analytical Methods: Summary measures

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Analytical Methods

- Always start the meta-analysis with a "visual meta-analysis" (i.e., a great table 1 and forest plot).
  - A clinician should be able to interpret the results
- Step 1: Calculate a summary measure = "weighted mean effect estimate"
  - You can combine anything, but use judgment
- Step 2: Assess for heterogeneity
  - Heterogeneity is not always a problem
- Step 3: Assess for publication bias
  - Both visual and statistical methods
- Step 4: Perform subgroup/sensitivity analyses
  - Ideally specify these a priori

How do you create a summary measure?

- Clinical example: 5 year old girl presents with ear pain and is found to have an acute otitis media.
- Should she get antibiotics?

Research Questions:

1. In children with OM, are antibiotics effective for pain relief?
2. In children with OM, do antibiotics reduce the rate of complications (mastoiditis, hearing problems)?

3 studies are identified (examining effect of Abx on Pain)

- Study 1: N = 100 RR=1.41
- Study 2: N=200 RR=0.98
- Study 3: N=300 RR=1.01
- You could take the average effect: (1.41 + 0.98 + 1.01) / 3 = 1.13
- Is this a good summary measure?

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Summary measure weighted by sample size

- Provide "weight" for studies based on their sample size

Study	N	RR
1	100	1.41
2	200	0.98
3	300	1.01
Total	600	

$$\text{summary effect estimate} = \frac{\Sigma (N_i \times \text{effect estimate}_i)}{\Sigma(N_i)} = \frac{640}{600} = 1.07$$

More refined: Provide "weight" by using inverse of variance

Study	N	RR	Var RR	Weight
1	100	1.41	3.0	0.33
2	200	0.98	0.1	10
3	300	1.01	0.05	20
Total	700			

$$\text{Summary effect estimate} = \frac{\Sigma (\text{weight}_i \times \text{effect estimate}_i)}{\Sigma(\text{weight}_i)} = \frac{30.5}{30.3} = 1.00$$

The summary measure

- To perform a meta-analysis we compute an effect size and variance for each study, and then compute a weighted mean of these effect sizes.
- Odds ratios, rate ratio, risk ratios, risk differences, standardized mean differences or correlations are the measure of association in various study design.

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What is an Effect Size?

- Effect size – a way of expressing results in a common metric
- Units – standard deviation

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Table 3.1 Roadmap of formulas in subsequent chapters.

Effect sizes based on means (Chapter 4)
Raw (unstandardized) mean difference (*D*)
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Effect sizes based on correlational data (Chapter 6)
Correlation (*r*)
Based on studies with one group

- Results extracted from study reports may need to be converted to a consistent, or usable, format for analysis .

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Effect Size

- ES = $\frac{X_1 - X_2}{SD_{pooled}}$

1. ES increases as difference between means increases
2. ES increases as SD decreases
3. ES is expressed in units of SD
4. Summary ES combines the weighted ES from each study.

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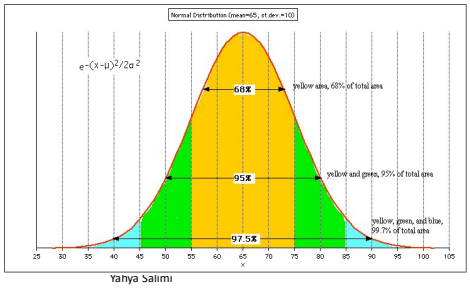
Effect Size



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Analytical model

- To compute the weighted mean we generally assign more weight to the more precise studies, but the rules for assigning weights depend on our assumptions about the distribution of true effects.

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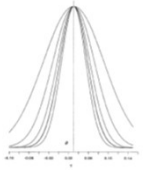
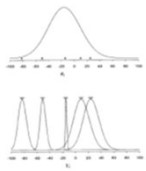
Fixed-effects model



Fixed-effects meta-analysis assumes that the intervention has a single true effect.

$$\frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \qquad W_i = \frac{1}{s_i^2}$$

Random-effects model



Random-effects meta-analysis assumes that the effect of the intervention varies across studies.

$$W_i(\tau) = \frac{1}{s_i^2 + \tau^2} \qquad \frac{\sum_{i=1}^{k} W_i(\tau) Y_i}{\sum_{i=1}^{k} W_i(\tau)}$$

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Fixed-effect model

- Under the fixed-effect model we assume that there is one true effect size that underlies all the studies in the analysis, and that all differences in observed effects are due to sampling error.

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Random-effects model

- Under the random-effects model we allow that the true effect size might differ from study to study.
- The term "Random" reflects the fact that the studies included in the analysis are assumed to be a random sample of all possible studies that meet the inclusion criteria for the review.
- For example, the effect size might be higher (or lower) in studies where the participants are older, or more educated, or healthier than in other studies, or when a more intensive variant of an intervention is used.

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Fixed-effects model OR Random-effects model

Which should I choose?

- Good news – most software produces both
- Both theoretical and practical reasons for choosing
  - Generalizability
    - What is the focus of this meta-analysis?
    - Can I assume this is the whole population?

The mistake to avoid

- Some researchers start the analysis by selecting the fixed-effect model. They then test perform a statistical test for heterogeneity in effect sizes (the Q-test).
- If the test for heterogeneity is not statistically significant, they conclude that the fixed-effect model is consistent with the data, and use this model in the analysis.
- If the test for heterogeneity is statistically significant they conclude that the fixed-effect model is not consistent with the data, and use the random-effects model in the analysis.

Why does it matter which model we use?

- If we should be using the random-effects model and (by mistake) employ the fixed-effect model, then it's likely that:
- The estimate of the mean will be incorrect
- The standard error will be incorrect
- The test of significance for the mean will be incorrect
- The confidence interval about the mean effect will be too narrow

In sum

- The selection of the correct statistical model is critically important.
- We should choose the model that fits the sampling frame.
- We should not choose a model based on the statistical test for heterogeneity

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Fixed-effect model

- Based on the fixed-effect model, there are several methods to estimate the weighted mean (or pooled) effect size.
- -Inverse-variance weighted estimation method (i.e. inverse of each study's variance)
- -Peto method
- -Mantel-Haenszel method
- -Maximum likelihood estimation method

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Fixed-effect model

	Yes	No	Total
Treatment	a1	b1	n1
Control	a2	b2	n2

	IVW	M-H
OR (i.e. ES):	(a1*b2)/(b1*a2)	(a1*b2)/(b1*a2)
Weight:	1/(1/a1+1/b1+1/a2+1/b2)	(b1+a2)/(a1+b1+a2+b2)

Peto

OR (i.e. ES): $\frac{observed_i - \text{expected}_i}{I_i}$

Weight: $I_i = \frac{(a1_i + b1_i) * (a2_i + b2_i) * (a1_i + a2_i) * (b1_i + b2_i)}{n_i^2 * (n_i - 1)}$

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Random-effects model

- •Based on the random-effects model, methods to estimate the weighted mean ES (i.e. based on how to calculate tau-squared)
- -Weighted least squares estimation method (called DerSimonian-Laired (DL) method)
- -Maximum likelihood estimation method
- -Restricted maximum likelihood estimation method

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Example

- Antibiotics for acute bronchitis.
- After search and application of inclusion/exclusion criteria, 8 studies were included.

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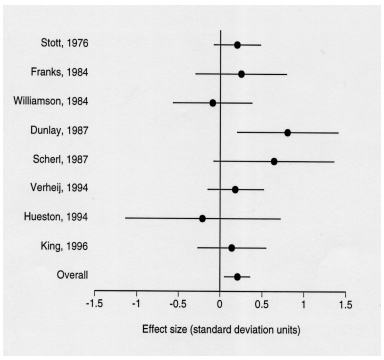
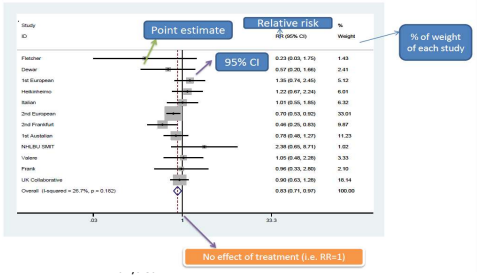
RCTs in Acute Bronchitis

Study, yr	N	Abx	Outcome	Result*
Stott, 76	207	Doxy	Days of Yellow Spit	0.6 (-0.2 to 1.4)
Franks, 84	54	TMP/S	Cough Amount Score	0.2 (-0.2 to 0.6)
Williamson, 84	69	Doxy	Days of Purulent Sputum	-0.2 (-1.2 to 0.8)
Dunlay, 87	45	Erythro	Sputum production score	0.5 (0.1 to 0.9)
Scherl, 87	31	Doxy	Days of sputum	1.9 (-0.2 to 4.0)
Verheij, 94	140	Doxy	Days of productive cough	0.5 (-0.4 to 1.4)
Hueston, 94	23	Erythro	Days of productive cough	-0.4 (-2.4 to 1.6)
King, 96	91	Erythro	Days of sputum production	0.7 (-1.3 to 2.7)

* Positive numbers indicate antibiotics are superior to placebo



Forest plot



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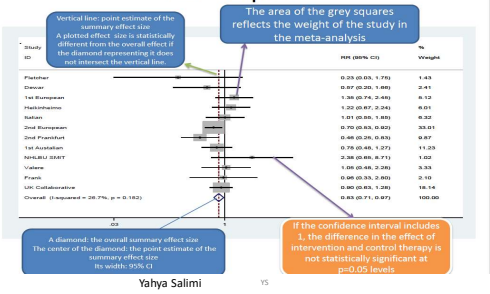

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Mantel-Haenszel Method (Fixed Effects Model)

	Diseased	Not diseased
Treated (exposed)	a_i	c_i
Not treated (unexposed)	b_i	d_i

$$OR_i = \frac{a_i / c_i}{b_i / d_i} = \frac{a_i \times d_i}{b_i \times c_i}$$

$$\ln OR_{mh} = \frac{\Sigma (w_i \times \ln OR_i)}{\Sigma w_i}$$

$$\text{variance } \ln OR_i = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}$$

$$\text{variance } OR_{mh} = \frac{1}{\Sigma w_i}$$

$$\text{weight}_i = (w_i) = \frac{1}{\text{variance } \ln OR_i}$$

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Randomized Trials of Antibiotic Rx for acute OM to prevent TM perforation

Study 1	Perforation	No Perforation
Antibiotic	1	114
Placebo	3	116

Study 2	Perforation	No Perforation
Antibiotic	7	65
Placebo	12	65

1. Calculate OR and lnOR for each study:

$OR_1 = \frac{1 \times 116}{3 \times 114} = 0.34$ $\ln OR_1 = -1.08$

$OR_2 = \frac{7 \times 65}{12 \times 65} = 0.58$ $\ln OR_2 = -0.54$

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Randomized Trials of Antibiotic Rx for acute OM to prevent TM perforation

2. Calculate variance $\ln OR_i$ for each study:

$$\text{Var ln } OR_1 = \frac{1}{1} + \frac{1}{1} + \frac{1}{1} + \frac{1}{1} = 1.35$$

$$\text{Var ln } OR_2 = \frac{1}{7} + \frac{1}{12} + \frac{1}{65} + \frac{1}{65} = 0.26$$

3. Calculate w_i for each study:

$$w_1 = \frac{1}{1.35} = 0.74$$

$$w_2 = \frac{1}{0.26} = 3.85$$

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Randomized Trials of Antibiotic Rx
for acute OM to prevent TM perforation

Study 1	Perforation	No Perforation
Antibiotic	1	114
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4. Calculate the w_i x ln OR_i for each study:

$w_1 \times \ln OR_1 = 0.74 \times -1.08 = -0.80$

$w_2 \times \ln OR_2 = 3.85 \times -0.54 = -2.08$

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Randomized Trials of Antibiotic Rx
for acute OM to prevent TM perforation

5. Calculate the sum of the w_i

$w_1 + w_2 = 0.74 + 3.85 = 4.59$

Summary $\ln OR_{mh} = \frac{\Sigma (w_i \times \ln OR_i)}{\Sigma w_i} = \frac{-0.80 + -2.08}{4.59} = -0.63$

$= OR_{mh} = 0.53$

Calculate variance $OR_{mh} = \frac{1}{\Sigma w_i} = \frac{1}{4.59} = 0.22$

8. Calculate 95% CI $= e^{\ln ORmh \pm (1.96 \times \sqrt{\text{variance lnORmh}})}$

$= e^{-.63 \pm (1.96 \times \sqrt{0.22})} = 0.21 - 1.34$

Summary OR = 0.53 (95% CI 0.21 – 1.34)

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Dersimonian and Laird Method
(Random Effects Model)

Similar formula to Mantel-Haenszel:

$$\ln OR_{dl} = \frac{\Sigma (w_i \times \ln OR_i)}{\Sigma w_i} \qquad w_i = \frac{1}{\text{variance}_i + D}$$

- Where D gets larger as the OR (or effect estimate) of the individual studies vary from the summary estimate

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Different types of data

- Different scales (example)
  - Ordinal data
  - Binary data
  - Continuous outcomes

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RCTs in Acute Bronchitis: Different Scales

Study, yr	N	Abx	Outcome	Result
Stott, 76	207	Doxy	Days of Yellow Spit	0.6 (-0.2 to 1.4)
Franks, 84	54	TMP/S	**Cough Amount Score**	0.2 (-0.2 to 0.6)
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Problem

- How do you combine studies with slightly different outcomes?

- Option 1: - don't do it
- Option 2: Transform all outcomes to an effect size

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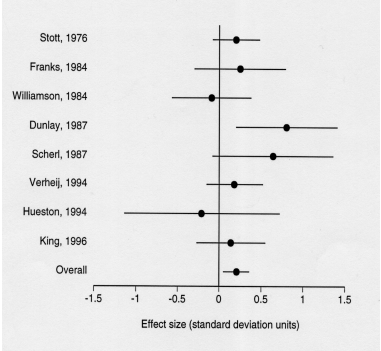

Main Result

- Summary ES = 0.21 (95% CI 0.05 to 0.36)

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But…All you need to know is:

- When combined, individual study effect estimates are weighted by their inverse variance
- Variance is related to sample size AND # of events (dichotomous) and precision (continuous)
- Fixed effects just combines all weighted estimates, while random effects "penalizes" estimates for variation between studies

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Thank you
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