Systematic Reviews & Meta-Analysis

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objectives

- What is Systematic review(SR)?
  - How?
- What is META analysis?
  - How?

What is a Systematic Review?

- "A review that is conducted according to clearly stated, scientific research methods, and is designed to minimize biases and errors inherent to traditional, narrative reviews."

Margaliot, Zvi, Kevin C. Chung. Systematic Reviews: A Primer for Plastic Surgery Research. PRS Journal. 120/7 (2007)

comparison

- **Traditional Approach**
  - **Expert Opinion- From personal experience**
  - **Narrative review**
  - **Consensus statements (group expert opinion)**
- **Systematic reviews**
  - **Standard reviews with SOP**
  - **Explicit quantitative synthesis of ALL the available evidence**

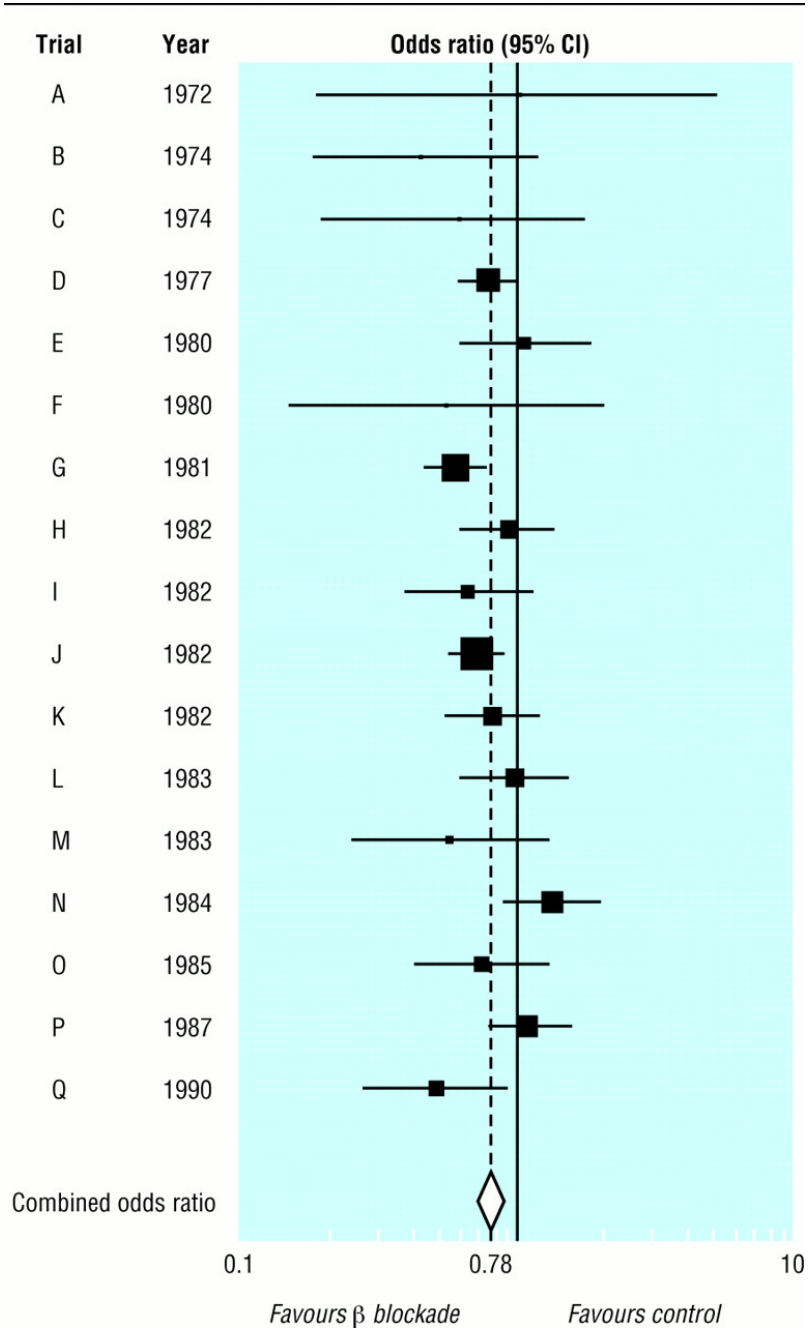
What is the significance of Systematic Reviews?

- The large amount of medical literature for make an informed decision.

- "A systematic review is a more scientific method of summarizing literature because specific protocols are used to determine which studies will be included in the review." minimize bias

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD, "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol. 31A No.10 December 2006. p.1671

using evidence more systematically



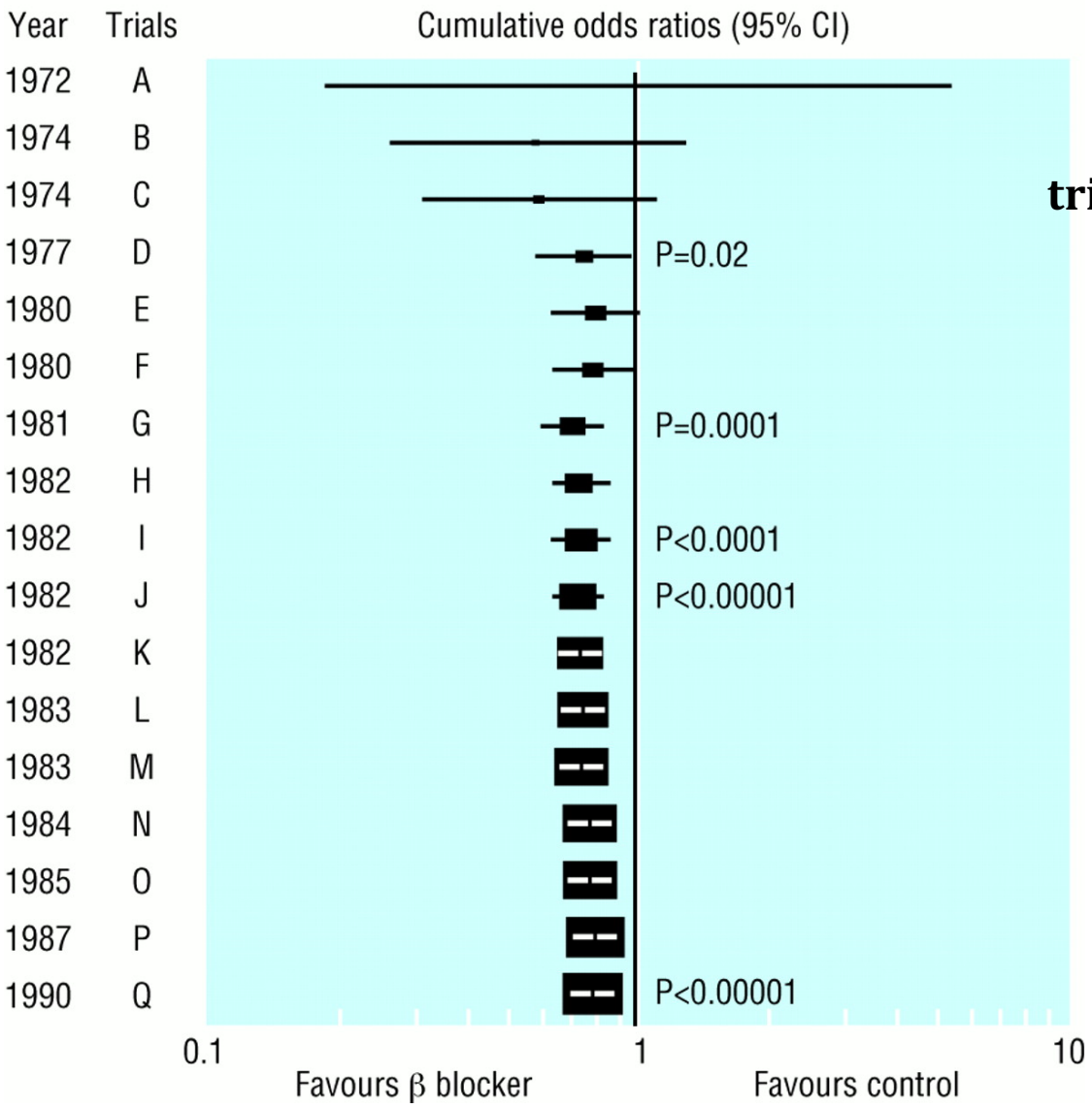
Total mortality from trials of β-blockers in 2° prevention after MI.

Black square & horizontal line correspond to odds ratio (OR) & 95% confidence interval (CI) for each trial. The size of the black square reflects the weight of each trial. The diamond represents the combined OR & 95 CI, showing a 22% reduction in odds of death

Egger, M. et al. BMJ 1997;315:1533-1537

BMJ

using evidence more systematically



Cumulative meta-analysis of total mortality results from trials of oral β-blockers after MI.

Size of squares reflect amount of statistical information available at a given point in time

Egger, M. et al. BMJ 1997;315:1371-1374

BMJ

Key Characteristics of Sys Reviews

- 1.Clearly stated title and objectives
- 2.Comprehensive searching strategy for all relevant studies (unpublished and published)
- 3.Explicit and justified criteria for the inclusion or exclusion of studies
- 4. assessment of characteristics of each study included and an methodological quality
- 5.Comprehensive list of all studies excluded and justification for exclusion
- 6.Clear analysis of the results of the eligible studies
  - statistical synthesis of data (meta-analysis) if appropriate and possible; or qualitative synthesis
- 7.Structured report of the review clearly stating the aims, describing the methods and materials and reporting the results

Linda N. Meurer, MD, MPH Department of Family and Community Medicine. "Systematic Synthesis of the Literature: Introduction to Meta-analysis". Power Point Presentation.

An author of a good Systematic Review…

- Formulates a Question
- Conducts a Literature Search
- Refines the search by applying predetermined inclusion and exclusion criteria
- Extracts the appropriate data and assess their quality and validity
- Synthesizes, interprets, and reports data

Focus of the Question

- The structured question will determine the inclusion and exclusion criteria:
  - What is the population of interest?
  - What are the interventions?
  - What are the outcomes of interest?
  - What study designs are appropriate?

Literature Search Challenges

- **Database Bias** - "No single database is likely to contain all published studies on a given subject."
- **Publication Bias** - selective publication of articles that show positive treatment of effects and statistical significance.
  - Hence, it is important to search for unpublished studies through a manual search of conference proceedings, correspondence with experts, and a search of clinical trials registries.
- **language bias** - occurs when reviewers exclude papers published in languages other than the native language ,like English or Chinese.
- **Citation bias** - occurs when studies with significant or positive results are referenced in other publications, compared with studies with inconclusive or negative findings

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1837

Data Collection (cont.)

- Collected data includes:
  - Study characteristics
  - Sample demographics
  - Outcome data

Quality Assessment

- "The validity of a systematic review ultimately depends on the scientific method of the retrieved studies and the reporting of data."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Quality Assessment (cont.)

- Randomized Controlled Trials (RCT):
  - RCT are considered to be more rigorous than observational studies
  - A review based on well-designed RCT will likely be more valid and accurate than a review based on observational studies or case reports

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Quality Assessment (cont.)

- "The most common way to assess and report study quality has been using a composite, numerical scoring instrument."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Quality Assessment (cont.)

- "More than 35 different quality assessment instruments have been published in the literature, and most are designed for randomized clinical trials."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Jadad score & Chalmers score

- "The Jadad score and the T.C. Chalmers score are two examples of quality assessment instruments."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Jadad score

- **Randomization (2 points possible)**
  - 1 point if study described as randomized
  - Add 1 point if randomization method described and appropriate (e.g. random numbers generated)
  - Deduct 1 point randomization described and inappropriate
- **Double-blinding (2 points possible)**
  - 1 point if study described as double-blinded
  - Add 1 point if method of double-blinding described and appropriate
  - Deduct 1 point if double-blinding described and inappropriate
- **Withdrawals (1 point possible)**
  - Give 1 point for a description of withdrawals and drop-outs

Linda N. Meurer, MD, MPH Department of Family and Community Medicine. "Systematic Synthesis of the Literature: Introduction to Meta-analysis". Power Point Presentation.

Jadad Score Example

Study	Randomization	Blinding	Drop-out
1	++	+	++
2	+	++	0
3	++	0	+
4	+	++	++
5	0	++	+

Data Synthesis

- "Once the data have been extracted and their quality and validity assessed, the outcomes of individual studies within a systematic review may be pooled and presented as summary outcome or effect"

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1840

Data Synthesis (cont.)

- The authors summarize heterogeneous data qualitatively
  - "Data that are very conflicting and widely variable should not, under most circumstances, be combined numerically."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1840

When can data in a systematic review be synthesized numerically?

- When data are NOT too sparse, of too low quality or too heterogeneous
  - For example: the patients, interventions and outcomes in each of the included studies are sufficiently similar
- meta analysis can be conducted

Meta-Analysis

Quantitative systematic review

History of Meta analysis

- A historical instance of Meta-analysis dates back to the twelfth century in China, a famous philosopher, Chu Hsi (朱熹, 1130~1200), built up his philosophical theory by summarizing a series of related literatures. He called this research methodology 'Theory of Systematic Rule'(道統論) (See reference http://ir.lib.ntnu.edu.tw/retrieve/52215/).

History of Meta analysis

- While in the Western World, the historical roots of meta-analysis may be traced back to 17th century studies of astronomy, a paper published in 1904 by the statistician Karl Pearson in the *British Medical Journal*
- data from several studies of typhoid inoculation
- It was the first time a meta-analytic approach was used to aggregate the outcomes of multiple clinical studies.

History of Meta analysis

- In 1978, Gene V. Glass statistically aggregated the findings of 375 psychotherapy outcome studies
  - Glass (and colleague Smith) concluded that psychotherapy did indeed work
- Glass called his method “meta-analysis”

Meta-analysis (cont.)

- "Protocols for the reporting of meta-analysis results were developed for RCTs (Quality of Reports of Meta-analysis [QUOROM] and Observational Studies in Epidemiology [MOOSE]."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1672

advantages

- Results can be generalized to a larger population,
- The precision and accuracy of estimates can be improved as more data is used. This, in turn, may increase the statistical power to detect an effect.
- Inconsistency of results across studies can be quantified and analyzed. For instance, does inconsistency arise from sampling error, or are study results (partially) influenced by between-study heterogeneity.
- Hypothesis testing can be applied on summary estimates,
- Moderators can be included to explain variation between studies,
- The presence of publication bias can be investigated,

Protocols

- The purpose of QUOROM and MOOSE guidelines is to provide proper procedures for conducting a meta-analysis and to standardize the methods of reporting a meta-analysis.

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1672

Statistical issues in Meta-analysis

- the analysis of the heterogeneity of the study-specific effect sizes
- the calculation of a pooled estimate & the confidence interval of effect size
- a sensitivity analysis
- Publication bias

Case control study

Cohort study

Smoking is hazard to your health

- The smokers in cancer cases are more than that inn control.
- Odds ratio

- The number of lung cancer cases in smokers is greater than that in nonsmokers.
- Risk ratio
- The average life span for smokers is less than that for nonsmokers.
- Difference of mean

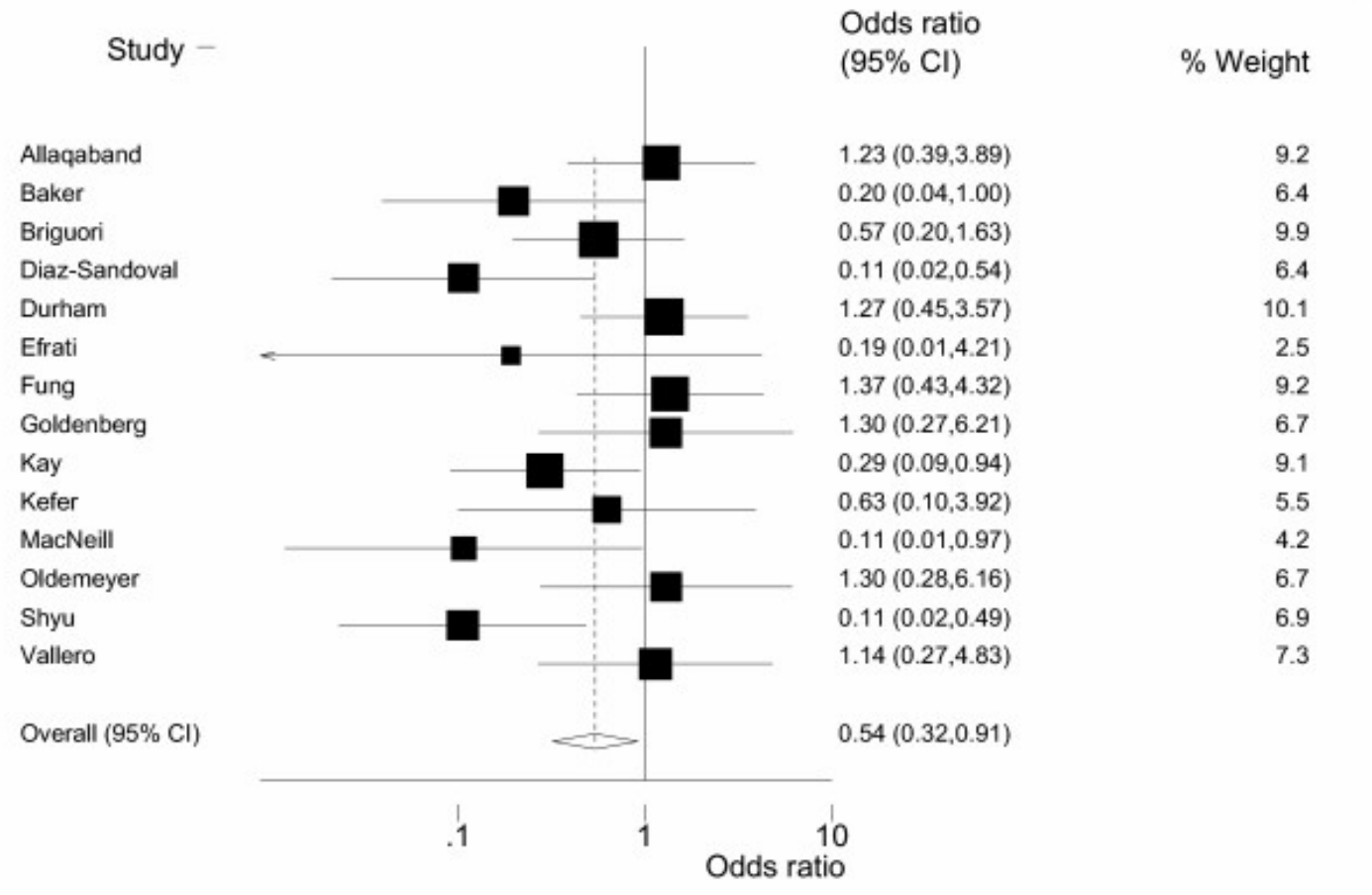
Effect Sizes

- difference
  - standardized mean difference/pre-post differences
- ratio
  - odds ratio/risk ratio
- Coefficient
  - correlation/regression

A Forest Plot(Q to T)

- is a graphical display designed to illustrate the relative strength of treatment effects in multiple quantitative scientific studies addressing the same question.
- It was developed for use in medical research as a means of graphically representing a meta-analysis of the results of randomized controlled trials.

Forest Plot for OR



Forest Plot for SMD

Heterogeneity

- To Pool dogs and cats?
- In epidemiological research different study designs are in use and none of them can be considered as a gold standard as the randomized clinical trial for therapy studies.
- Therefore it is necessary to evaluate the comparability of the single designs before summarizing the results.
- Differences could be explored in a formal sensitivity analysis but also by graphical methods (funnel plot).

The Fixed Effects Model

- "The fixed-effects model assumes that the true effect of treatment is the same for every study."
- 10 measurements for the same tree

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1675

The Random Effects Model

- "The random effects model assumes that the true effect estimate for each study vary."
- 10 measurement from 10 trees in the same forest

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1672

Meta-analysis: Reporting the Results

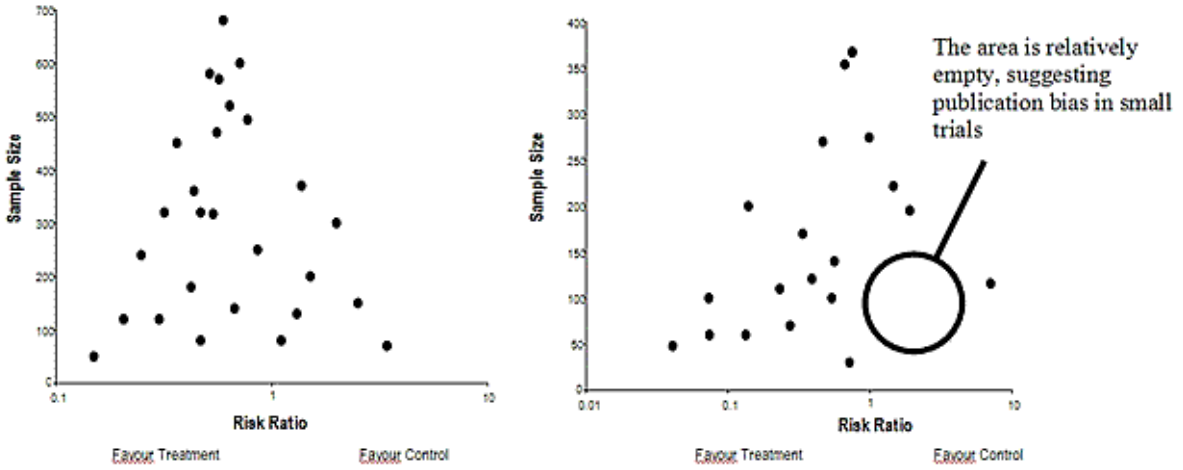
- A meta-analysis should include:
  - A title, abstract, an introduction
  - Methods, results, and discussion sections

A Funnel Plot

- "A funnel plot is used as a way to assess publication bias in meta-analysis."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1676

Plots the effect size against the sample size of the study or the standard error of effect size(related to n).



Example: Research Issue

- ***Let's say we want to know whether :***
- ***streptokinase is protective for death from acute myocardial infarction.***
- ***How should we set up a search strategy? We will search pub-med only***

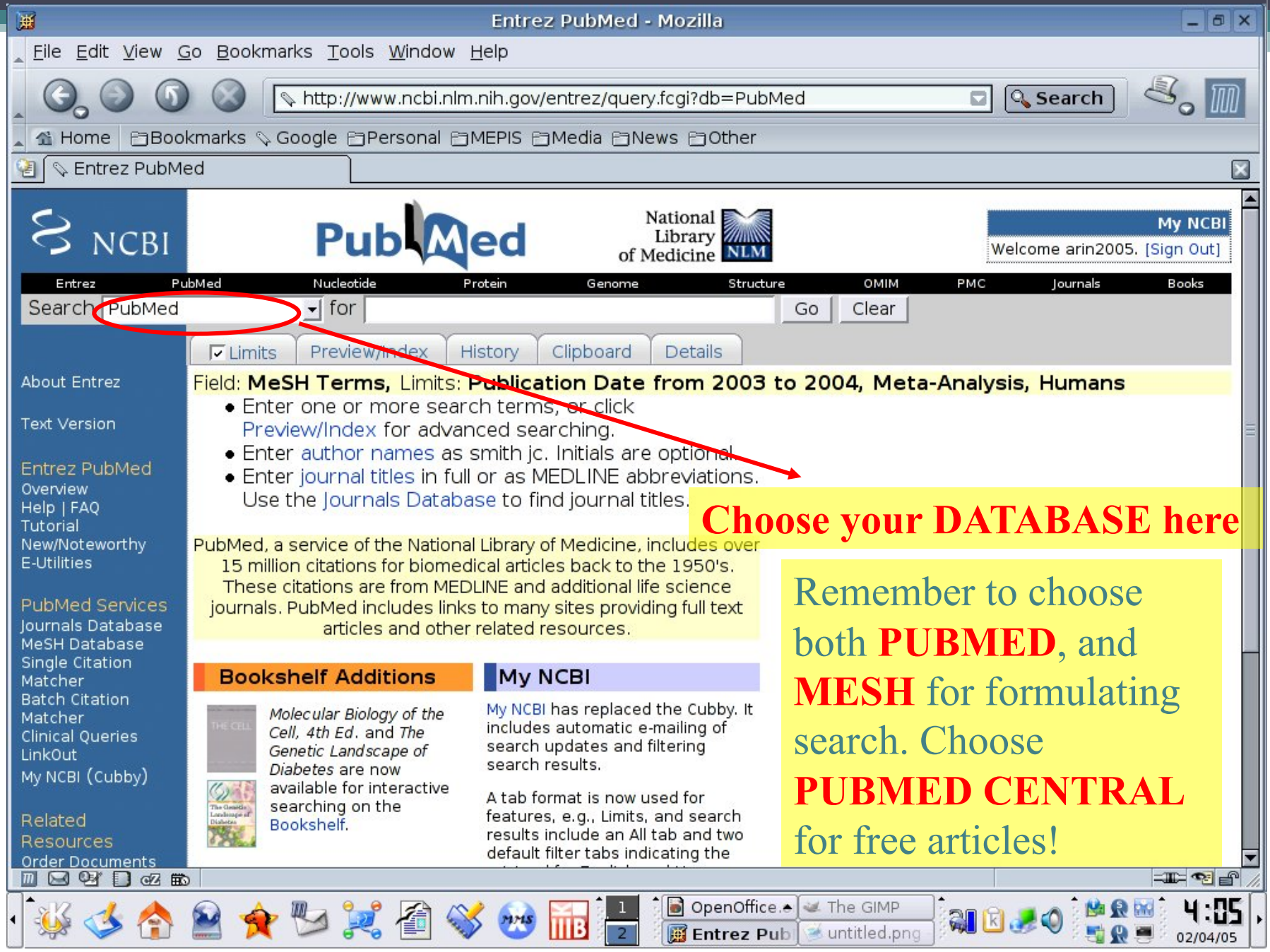
Example

Streptokinase & death from acute myocardial infarction. protective or not?

Searching -Key words

- **"streptokinase"[text word] OR "acute myocardial infarction"[text word] produces ALL articles that contain EITHER streptokinase OR acute myocardial infarction anywhere in the text – inclusive, many**
- **streptokinase [text word] AND "acute myocardial infarction" [text word] will capture only those subsets that have BOTH streptokinase AND acute myocardial infarction anywhere in the text – restrictive, few**

Next, we shall look at the PUBMED Screen …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Clinical Queries
LinkOut
My NCBI (Cubby)
Related Resources
Order Documents
Field: MeSH Terms, Limits: Publication Date from 2003 to 2004, Meta-Analysis, Humans
Enter one or more search terms, or click Preview/Index for advanced searching.
Enter author names as smith jc. Initials are optional.
Enter journal titles in full or as MEDLINE abbreviations. Use the Journals Database to find journal titles.
Choose your DATABASE here
PubMed, a service of the National Library of Medicine, includes over 15 million citations for biomedical articles back to the 1950's. These citations are from MEDLINE and additional life science journals. PubMed includes links to many sites providing full text articles and other related resources.
Bookshelf Additions
Molecular Biology of the Cell, 4th Ed. and The Genetic Landscape of Diabetes are now available for interactive searching on the Bookshelf.
My NCBI
My NCBI has replaced the Cubby. It includes automatic e-mailing of search updates and filtering search results.
A tab format is now used for features, e.g., Limits, and search results include an All tab and two default filter tabs indicating the
Remember to choose both PUBMED, and MESH for formulating search. Choose PUBMED CENTRAL for free articles!
OpenOffice.
The GIMP
Entrez Pub
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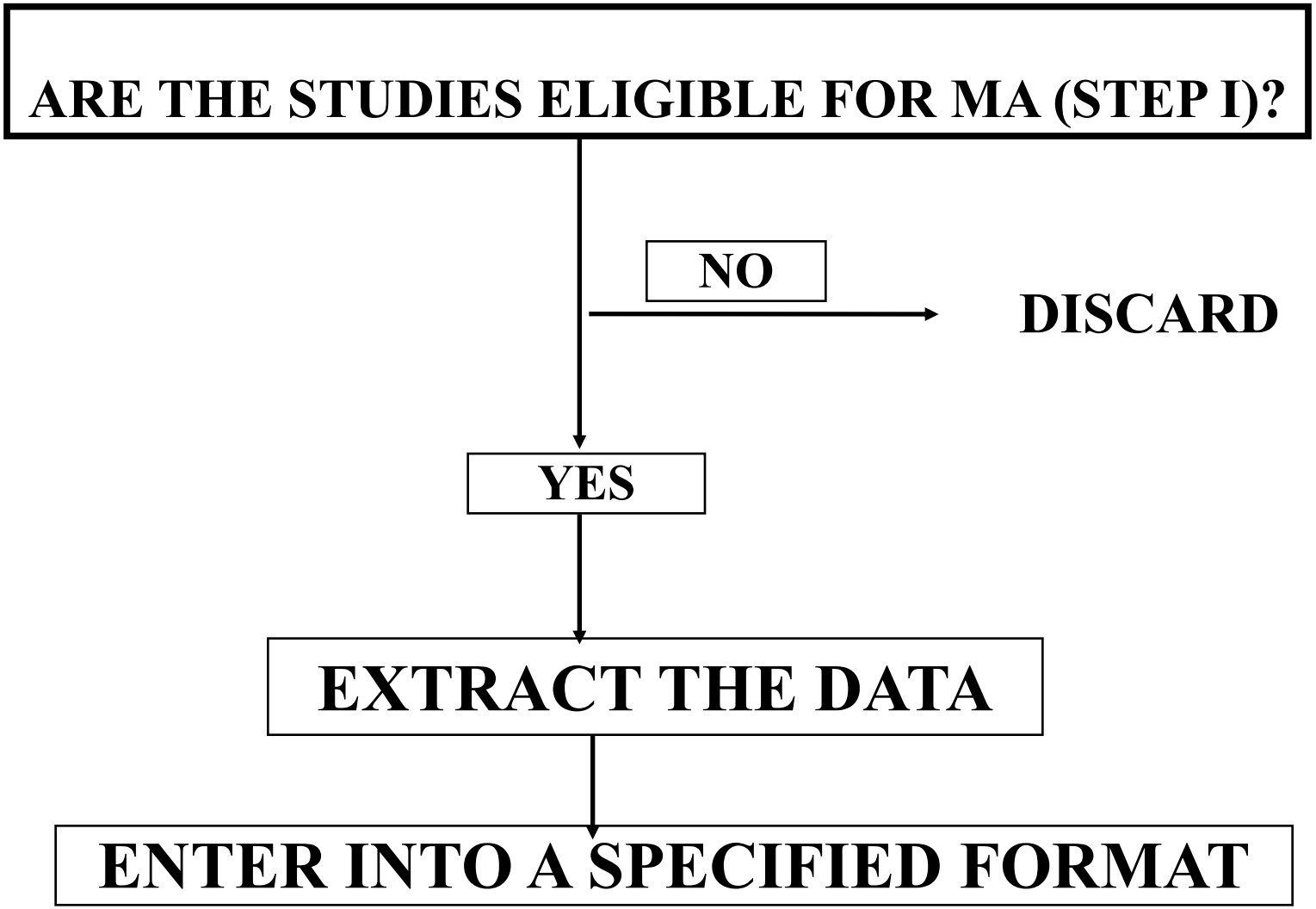
02/04/05

Keep some, throw out others

- **Cannot include all studies**
- **Keep the ones with**
  - **high levels of evidence**
  - **good quality**
  - **check with QUOROM guidelines**
- **Usually, MA done with RCTs**
- **Case series, and case reports definitely out**
- **Selection problems are major problems**
  - **read the article you got and printed**

MA = Meta Analysis; RCT = Randomized Controlled Trial

Plan of Action



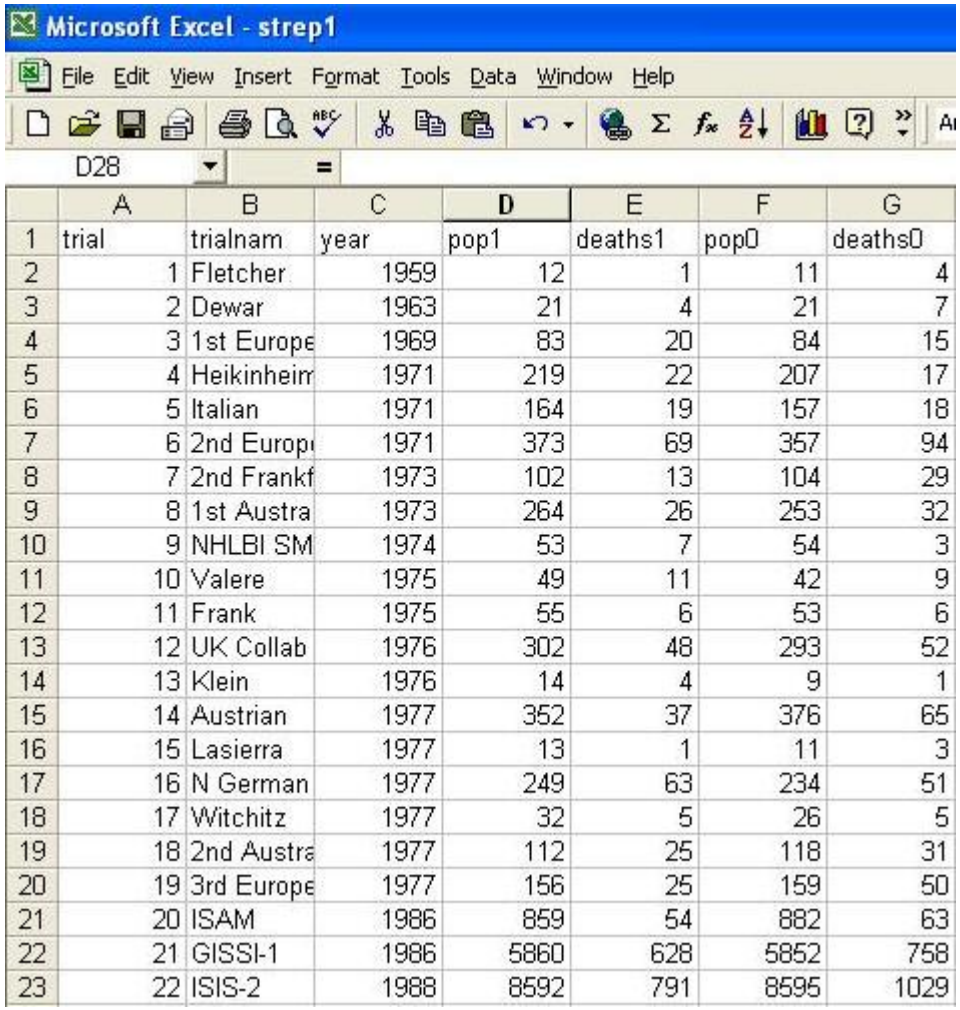
How to Extract Data: Guidelines

- **Create a spreadsheet (Excel, or OpenOffice Calc)**
- **For each study, create the following columns:**
  - **name of the study**
  - **name of the author, year published**
  - **number of participants who received intervention**
  - **number of participants who were in control arm**
  - **number who developed outcomes in intervention**
  - **number who developed outcomes in control arm**

Let's do that to our streptokinase myocardial infarction study, next …

Spreadsheet Data for Strepto Study

We got like 22 studies to do our meta analysis, after all



	A	B	C	D	E	F	G
1	trial	trialnam	year	pop1	deaths1	pop0	deaths0
2	1	Fletcher	1959	12	1	11	4
3	2	Dewar	1963	21	4	21	7
4	3	1st Europe	1969	83	20	84	15
5	4	Heikinheim	1971	219	22	207	17
6	5	Italian	1971	164	19	157	18
7	6	2nd Europ	1971	373	69	357	94
8	7	2nd Frankf	1973	102	13	104	29
9	8	1st Austra	1973	264	26	253	32
10	9	NHLBI SM	1974	53	7	54	3
11	10	Valere	1975	49	11	42	9
12	11	Frank	1975	55	6	53	6
13	12	UK Collab	1976	302	48	293	52
14	13	Klein	1976	14	4	9	1
15	14	Austrian	1977	352	37	376	65
16	15	Lasierra	1977	13	1	11	3
17	16	N German	1977	249	63	234	51
18	17	Witchitz	1977	32	5	26	5
19	18	2nd Austra	1977	112	25	118	31
20	19	3rd Europe	1977	156	25	159	50
21	20	ISAM	1986	859	54	882	63
22	21	GISSI-1	1986	5860	628	5852	758
23	22	ISIS-2	1988	8592	791	8595	1029

We created seven columns

trial: ***trial identity code***

trialname: **name of trial**

year: **year of the study**

pop1: **study population**

deaths1: **deaths in study**

popo: **control population**

deathso: **deaths in control**

Analyze Data Statistically

- **Combine data to arrive at a summary, 3 measures**
  - **Effect Size (Odds Ratio)**
  - **Variance with 95% Confidence Interval**
  - **Test of heterogeneity**
- **Two Graphs**
  - **Forest Plot**
  - **Funnel Plot**
- **Examine why the studies are heterogeneous, if they are**
- **Use Statistical Packages, several choices**

Let's see what we got for streptokinase versus deaths from AMI

Summary Estimates

Mantel Haenszel
OR=**0.77**

95% Confidence Interval
[**0.72, 0.83**]

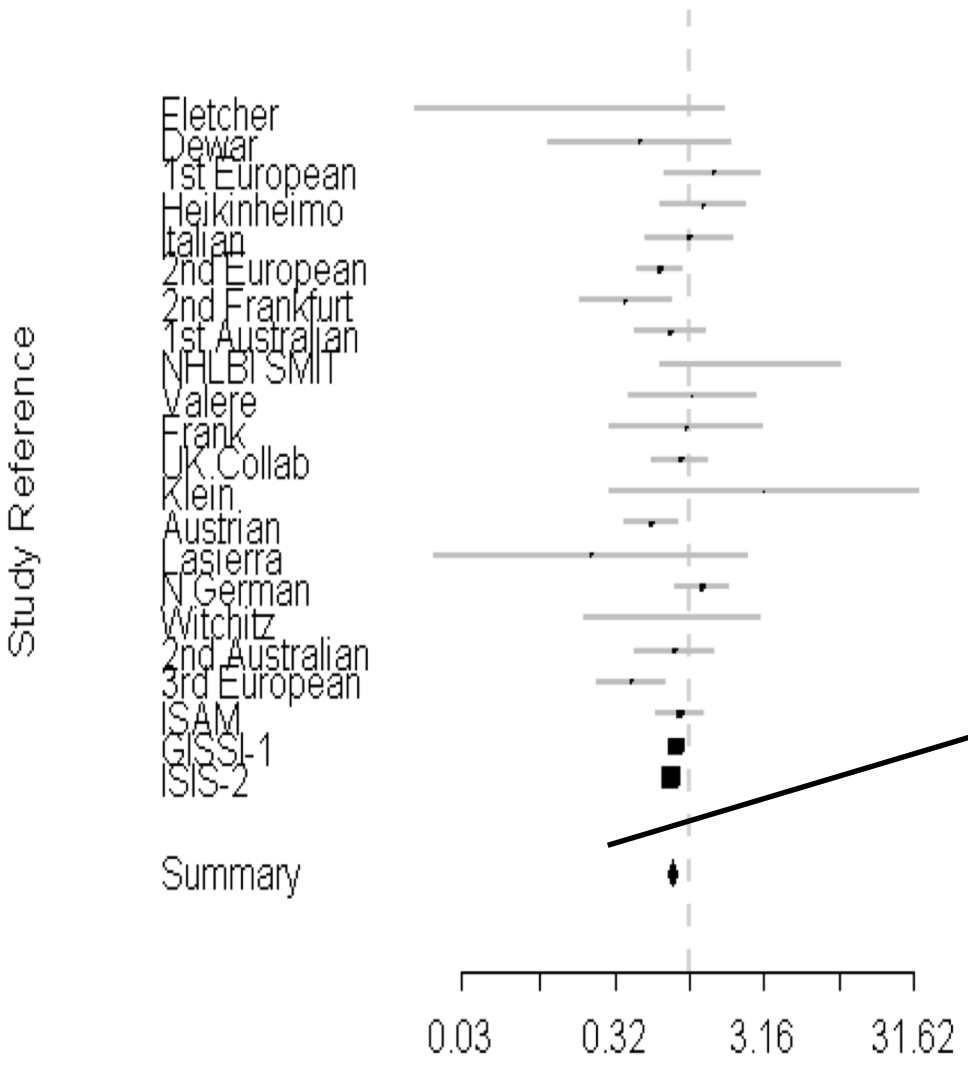
Test of Heterogeneity:
Chi-square (df=21) = **31.5**
P-Value = **0.07**

The pooled Odds Ratio shows that those receiving streptokinase at AMI are about 77% at risk of death (23% less likely to die)

That in 95 out of 100 such meta analyses, the pooled Odds Ratio would lie between 0.72 and 0.83, indicating a statistically significant protective effect

That these studies were not significantly heterogeneous

Forest Plot



The dotted line passes across null, or 1.0

The Risk Estimate of each study is lined up on each side of the dotted line, with 95% CI spread as the line

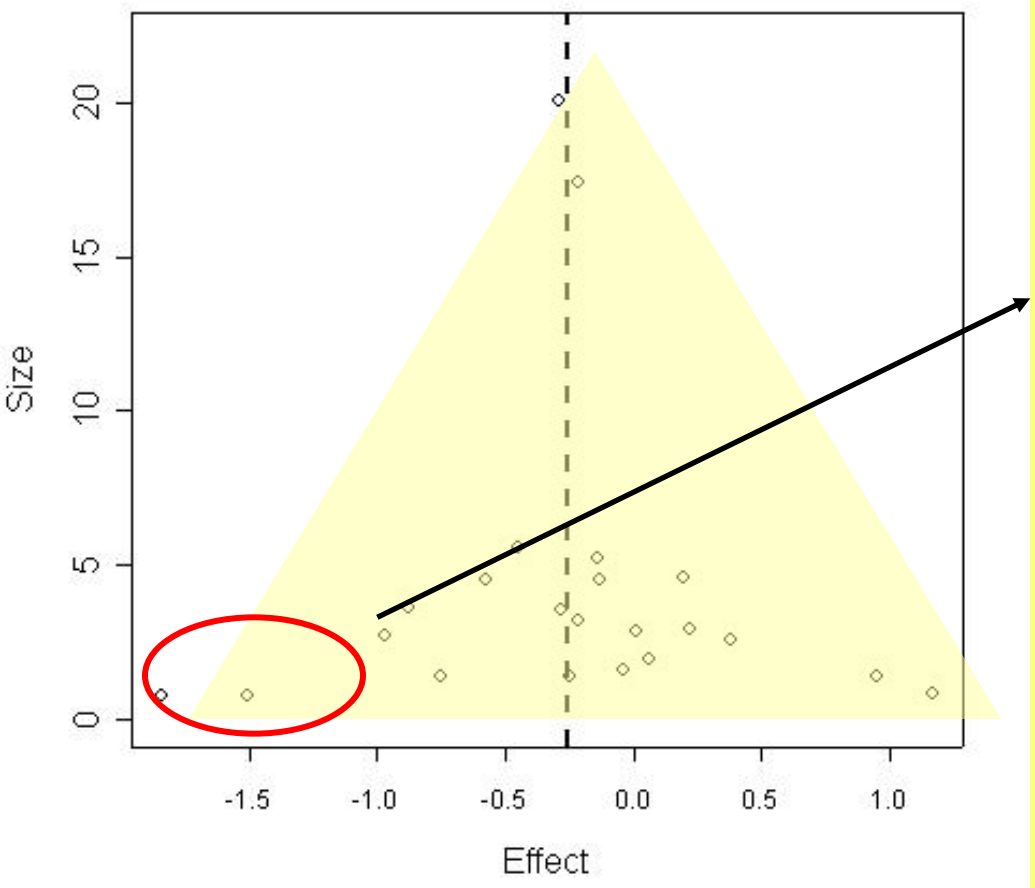
The diamond in the below is the summary estimate

The two ends of the diamond indicate 95% CI

The size of the black square box indicates weight of the study

They call it a forest plot so that you don't miss the wood for the trees!

Funnel Plot: what and how to read



Plots the effect size against the sample size of the study

To study a funnel plot, look at its LOWER LEFT corner, that's where negative or null studies are located

If EMPTY, this indicates "PUBLICATION BIAS"

Note that here, the plot fits in a funnel, and that the left corner is not all that empty, but we cannot rule out publication bias

Fixed Effects or Random Effects Model?

Fixed Effects Model

- conduct if it is reasonable to assume underlying Rx effect is SAME for all studies
- Pooling: Mantel Haenszel OR
- Test: test of heterogeneity
- If significant, go for random effects model
- short 95% CI for summary
- smaller summary estimate
- OR=0.77 [0.72,0.83]

Random Effects Model

- Conduct if test of heterogeneity is significant (shows heterogeneity)
- Assume that TRUE log odds ratio comes from a normal distribution
- Method: DerSimonian Lair's method (DSL) of calculating Odds' Ratio
- OR=0.78 [0.69,0.88]

Bias in Meta-analysis

- **Poor Quality of Trials**
  - To avoid them, learn more at CONSORT statement

  [http://www.consort-statement.org]
- **Publication Bias**
  - study showing beneficial **effects of new treatment** more likely to be published than one showing no effect
  - negative trials assumed to contribute less; never show up in the literature base
  - use several approaches to avoid this
  - Use Funnel Plots to examine the influence of publication bias

Quality Control in MA:QUOROM Table

Table 1 Quality of reporting of systematic reviews (meta-analyses)

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a systematic review (meta-analysis) of RCTs		
Abstract		Use a structured format		
		Describe		
	Objectives	The clinical question explicitly		
	Data sources	The databases (ie list) and other information sources		
	Review methods	The selection criteria (ie population, intervention, outcome and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie point estimates and confidence intervals); and subgroup analyses		
	Conclusion	The main results		
		Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review		
Methods	Searching	The information sources, in detail (eg databases, registers, personal files, expert informants, agencies, hand-searching) and any restrictions (years considered, publication status, language publication)		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)		
	Validity assessment	The criteria and process used (eg masked conditions, quality assessment, and their findings)		
	Data abstraction	The process or processes used (eg completed independently, in duplicate)		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definition, Etc, and how clinical heterogeneity was assessed		
	Quantitative data synthesis	The principal measures of effect (eg relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias		
Results	Trial flow	Provide a systematic review profile summarising trial flow (see Fig. 1)		
	Study characteristics	Present descriptive data for each trial (eg age, sample size, intervention, dose, duration, follow-up period)		
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome; present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2x2 tables of counts, means and SDs, proportions)		
Discussion		Summarise key findings; discusses clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg population bias); and suggest a future research agenda		

- **Detailed Guidelines**
- **A Good Checklist**
- **Use it for reporting**
- **Meta Analysis**
- **Systematic reviews**

Statistical Software for Meta Analysis

- **Huge Checklist**

[http://faculty.ucmerced.edu/wshadish/]

- **Free Software:**
  - **EpiMeta: from Epi Info**
  - **Revman: from Cochrane Collaboration**
  - **"meta" package in R for statistical computing**
- **Non-free**
  - **meta module in STATA**

Summarizing…

- **Defined meta analysis**
  - **quantitative research synthesis**
- **Outlined basic steps**
  - **Information retrieval**
  - **Data Abstraction**
  - **Data Analysis**
  - **Model Selection: Fixed Effects or Random effects**
- **Outlined some issues and listed software**

Recommended Resources:

- "Reading Medical Articles," in Statistics in Medicine. Robert H. Riffenburgh. 2nd edition. Boston: Academic Press, 2006.
- Meta-analysis: New Developments and Applications in Medical and Social Sciences. Ralph Schulze, Heinz Holling, Dankmar Bohning (eds.) Toronto: Hogrefe & Huber Publishers, 2003.
- "Finding and Using Health Statistics" - an online course offered by the National Library of Medicine
- Margaliot, Zvi, Kevin C. Chung. Systematic Reviews: A Primer for Plastic Surgery Research. PRS Journal. 120/7 2007 .
- Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. vol. 31A no.10 December 2006.

Homework for lab section

- pls. describe the structure of the paper you printed briefly like this:
  - title and objectives
  - searching strategy
  - inclusion and exclusion criteria
  - scale for quality assessment
  - effect size to be pooled(Extract the data tables or just describe)
  - publication bias or not
  - conclusion

Requirement:

1. By your word; handwriting is encourged.
2. Copy is forbidden if the score for the section will be zero for original version and copies

Thank you!

essay/activity for SE

- **Read the 2 reviews of *** , Evaluate each review in terms of** title and objectives
- searching strategy
- inclusion and exclusion criteria
- scale for quality assessment
- effect size to be pooled(Extract the data tables or just describe)
- publication bias or not
- conclusion

- **Which review is good, which is bad?**