
جمعه سلام

کارگاه آموزشی

Meta-Analysis

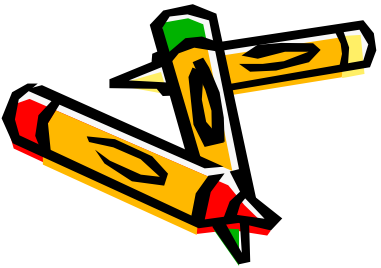
A step-by-step workshop

دکتر حسن مهراد مجد

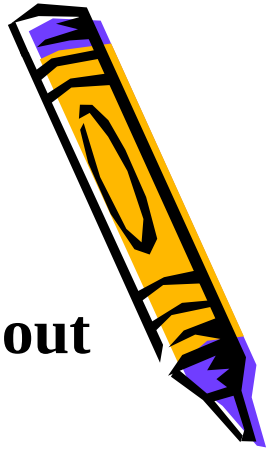
استادیار پزشکی مولکولی دانشگاه علوم پزشکی مشهد

Major Topics Covered

I. Overview of Meta-Analysis
II. Steps for Conducting A Meta-Analysis

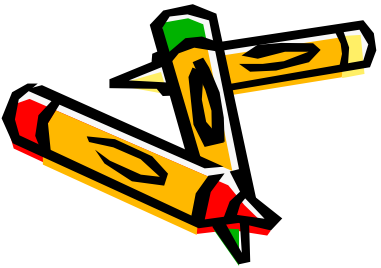


What is meta analysis?



Quantitative approach for systematically combining results of previous research to arrive at conclusions about the body of research.

- Quantitative : numbers
- Systematic : methodical
- combining: putting together
- previous research: what's already done
- conclusions: new knowledge



- "Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect."

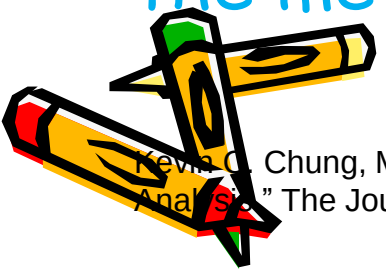
- "While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis."

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

Meta-analysis need protocols

- "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]."

- 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

MOOSE Checklist

Diabetes mellitus increases the risk of active tuberculosis : a systematic review of 13 observational studies

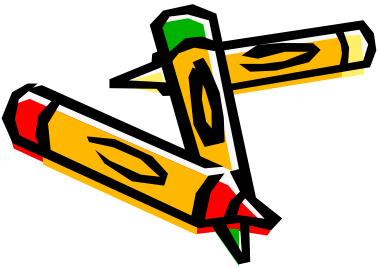
Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Diabetes mellitus is a condition that could affect one's risk of active tuberculosis disease. Diabetes prevalence is on the rise, while tuberculosis burden remains stagnant. The potential public health impact of diabetes on TB remains to be summarized quantitatively.
√	Hypothesis statement	Diabetes increases the risk of active tuberculosis.
√	Description of study outcomes	Active tuberculosis disease
√	Type of exposure or intervention used	Diabetes mellitus
√	Type of study designs used	We included case-control studies, prospective cohort studies, cross-sectional studies, comparisons of study populations with age standardization; We excluded studies of reverse association.
√	Study population	We placed no restriction.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators CJ and MM are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	PubMed from 1965 – March 2007 EMBASE from 1974 – March 2007 See Box 1 in the article
√	Databases and registries searched	PubMed and EMBASE
√	Search software used, name and version, including special	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications

Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement checklist

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis [or systematic review] of RCTs[24]		
Abstract		Use a structured format[27]		
		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[28] (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status,[29] language of publication[30,31])		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)[32]		
	Validity assessment	The criteria and process used (eg, masked conditions, quality assessment, and their findings[33-36])		
	Data abstraction	The process or processes used (eg, completed independently, in duplicate)[33,34]		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c,[37] 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;[38] a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias[39]		
Results	Trial flow	Provide a meta-analysis profile summarising trial flow (see figure)		
	Study characteristics	Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)		

Steps of Meta-analysis

- Define the Research Question
- Perform the literature search
- Select the studies
- Extract the data
- Analyze the data
- Report the results



Define research/review question
In consultation/collaboration with the clinical community, commissioners and patient/public representatives

Develop review protocol
Pre-specify the type of studies to be included, the methods of collating, appraising and analysing data

Identify relevant studies
Develop a comprehensive search strategy and undertake systematic searches of the literature

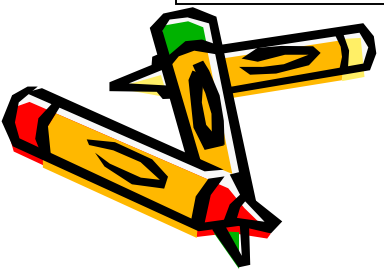
Assess eligibility
Select those studies which meet the pre-defined inclusion criteria

Data extraction /checking
Develop data extraction from into which study information and outcome data can be extracted, checked & verified

Study assessment/appraisal
Assess the quality and validity of the included studies using the pre-defined method.

Synthesis
Narratively and/or statistically summarise/describe the data, exploring similarities and differences between studies.

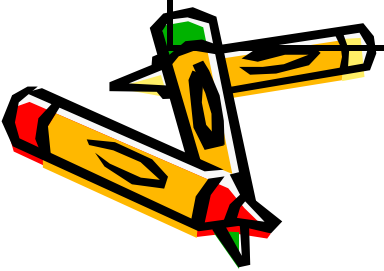
Knowledge translation
Review details and results are disseminated to relevant target audiences using appropriate formats



Meta-analysis: The Research Question

"Common questions addressed in meta-analysis are whether one treatment is more effective than another or if exposure to a certain agent will result in disease."

Problem, population	Intervention	Comparison	Outcome	Types of studies
Young people under 25 years of age	a) Television b) Radio c) Newspapers d) Bill boards e) Posters f) Leaflets g) Booklets	a) School-based interventions b) No intervention	a) objective measures of smoking (saliva thiocyanate levels, alveolar CO) b) self-reported smoking behaviour	a) RCT b) Controlled before and after studies c) Time series designs

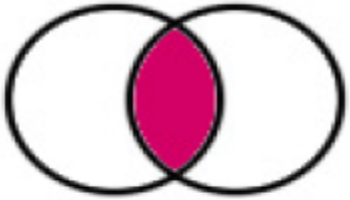
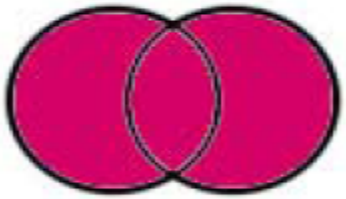
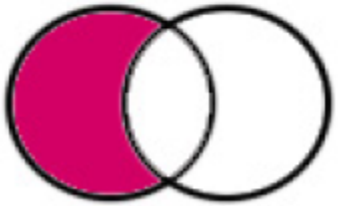


Meta-analysis: Performing the Literature Search

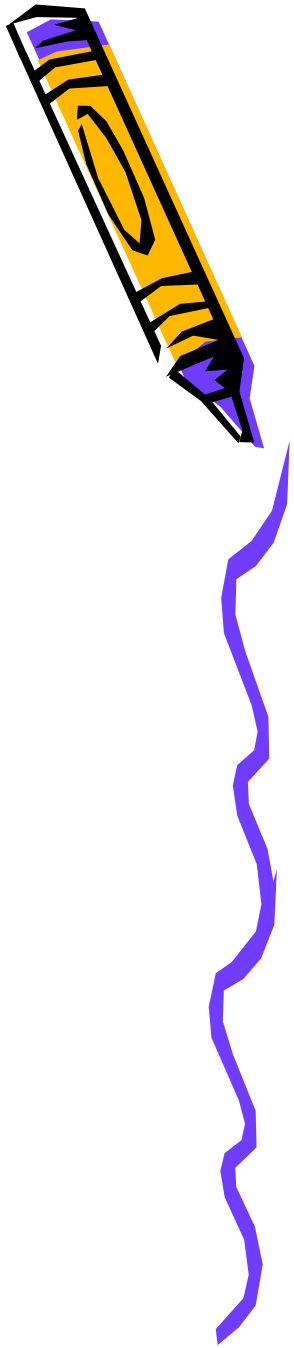
Formulate your question appropriately

- If you are searching pubmed Use Medical Subject Headings (MeSH) [1]
  - Lookup word in text word, abstract, title [2]
  - Combine [1] with [2] using boolean logic
  - Set up proper filters
- For Others, use text word, abstract

Boolean operators

Operator	Symbols	Example search	The search will find…	Venn diagrams – results are the shaded areas
AND	+	dogs AND cats	items containing both dogs and cats	
OR	/	dogs OR cats	items containing either dogs or cats or both	
NOT	-	dogs NOT cats	items containing dogs but not cats – *caution,* its easy to exclude relevant items	

Example???



“streptokinase” OR “acute myocardial infarction”

produces ALL articles that contain

EITHER streptokinase OR acute myocardial infarction

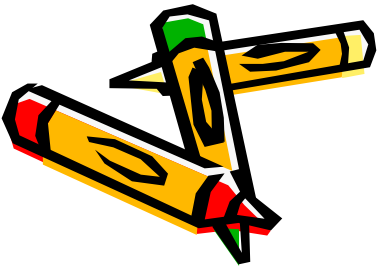
anywhere in the text – inclusive, many

streptokinase AND “acute myocardial infarction”

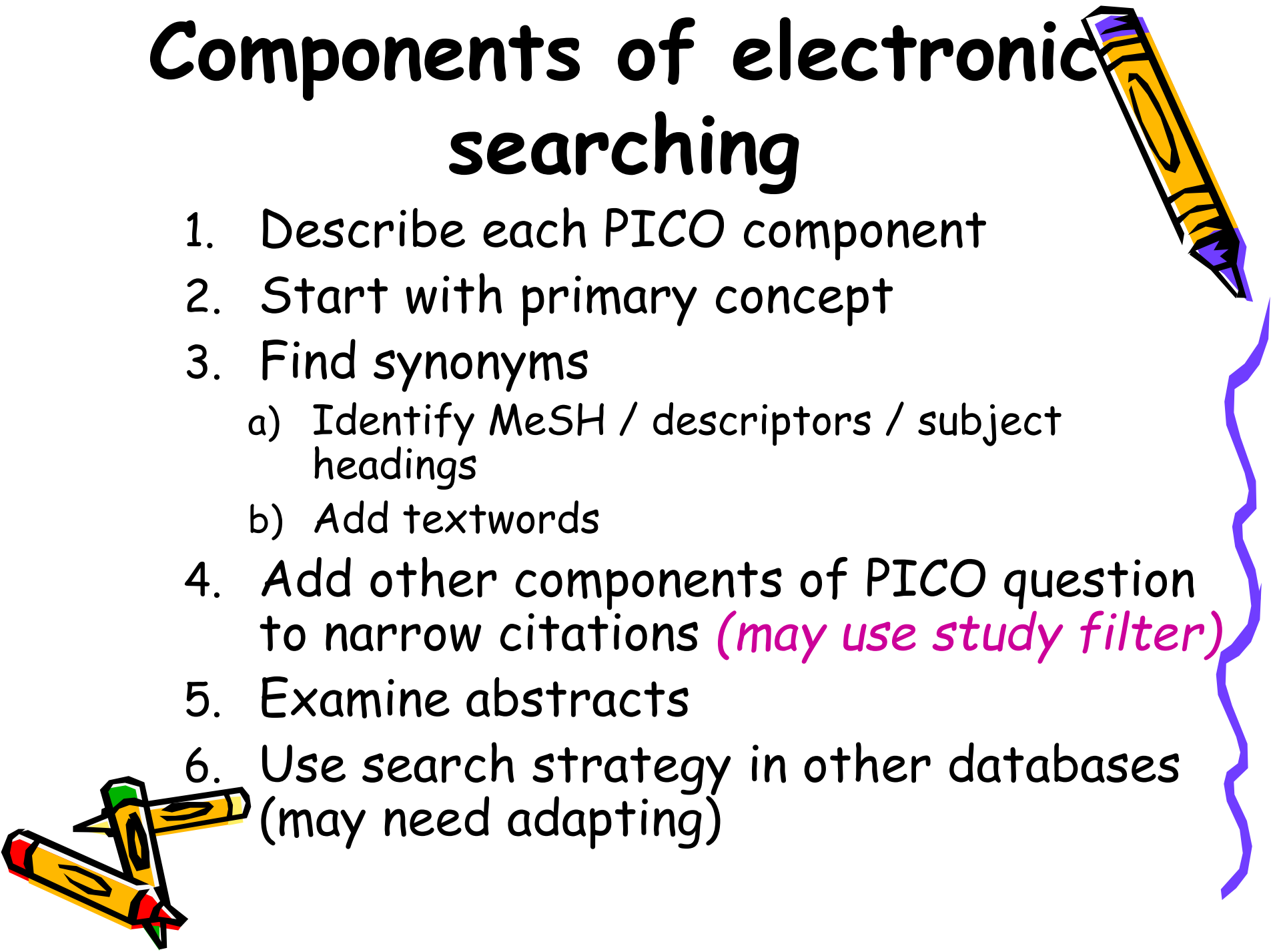
will capture only those subsets that have

BOTH streptokinase AND acute myocardial infarction

anywhere in the text – restrictive, few

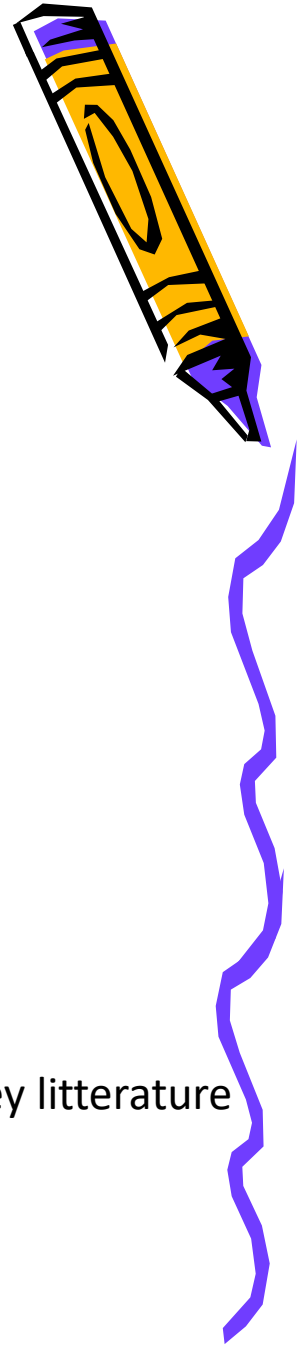


Components of electronic searching



1. Describe each PICO component
2. Start with primary concept
3. Find synonyms
   a) Identify MeSH / descriptors / subject headings
   b) Add textwords
4. Add other components of PICO question to narrow citations *(may use study filter)*
5. Examine abstracts
6. Use search strategy in other databases (may need adapting)

Literature Search



- Be methodical: **plan first**
- List of popular databases to search
  - Pubmed/Medline
  - Embase
  - Cochrane Review
  - ISI Web of Science
  - SCOPUS

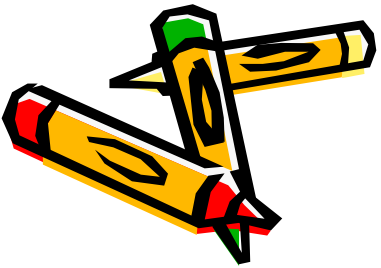
Database bias!!!

- Other strategies you may adopt
  - Trial registries (clinicaltrials.gov)
  - Abstracts from meetings
  - Hand search (go to the library…)
  - Personal references
  - References from published reviews/meta-analysis/trials
  - Contact experts
  - Web, eg. Google (http://scholar.google.com)

Grey litterature

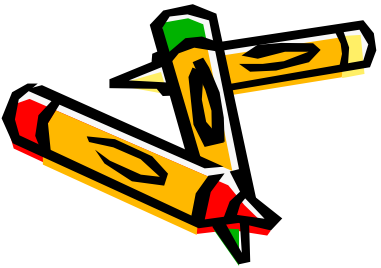
Meta-analysis: Study Selection

- "The inclusion and exclusion criteria for studies needs to be defined at the beginning, during the design stage of the meta-analysis."
  - "Factors determining inclusion in the analysis are study design, population characteristics, type of treatment or exposure, and outcome measures."



Selection of Studies

- Reference manager software package
  - Endnote – RefMan – ProCite – Mendeley
- Import results and screen
  - Assess titles/abstracts against your predetermined criteria
  - If in doubt include
  - Retrieve full text articles of initial selections
- Assess full text for inclusion
  - Requires judgement (>1 reviewer)
  - Check reviewer agreement (3rd review to resolve)
  - Use a selection form to ensure consistency and record decisions



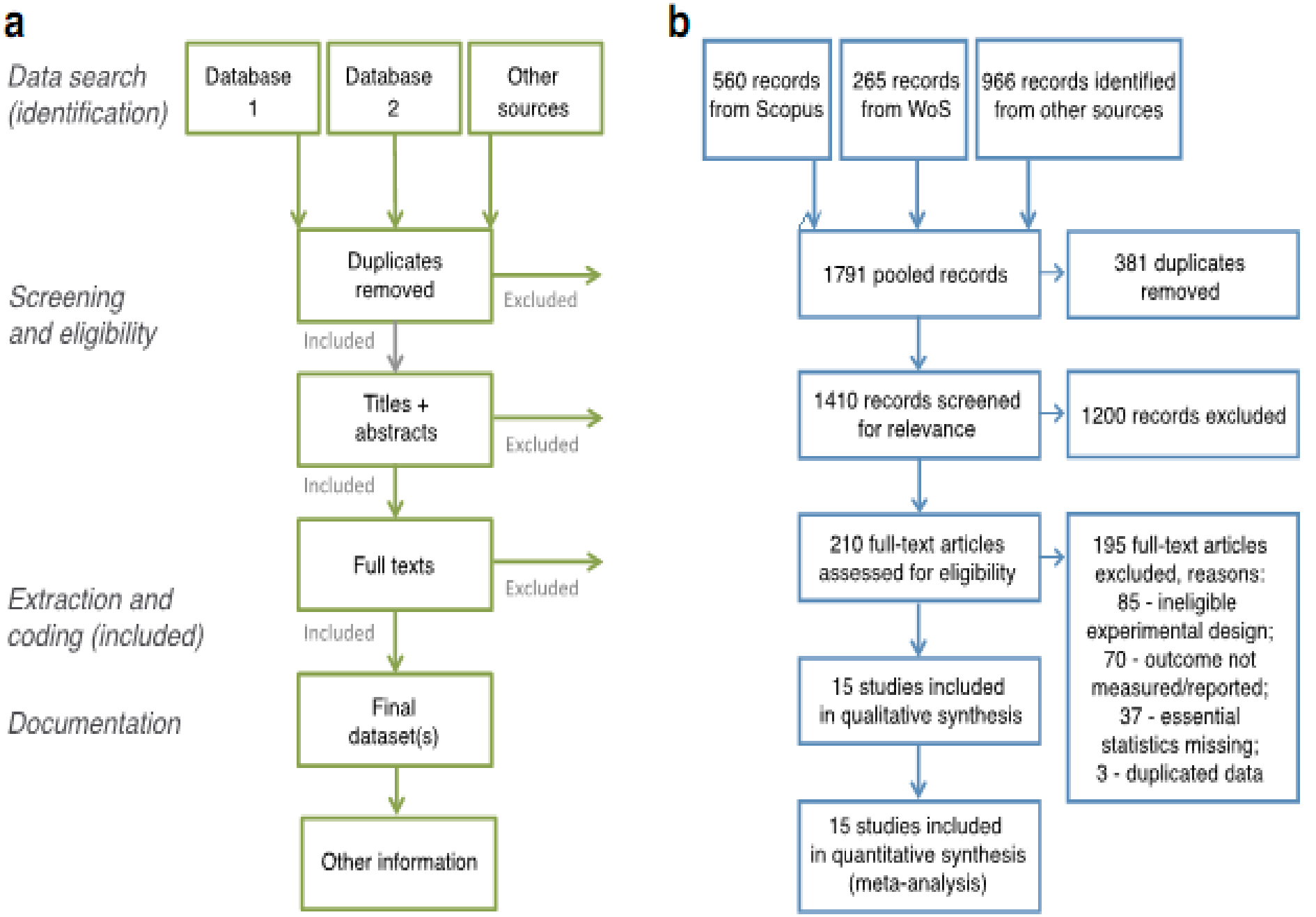
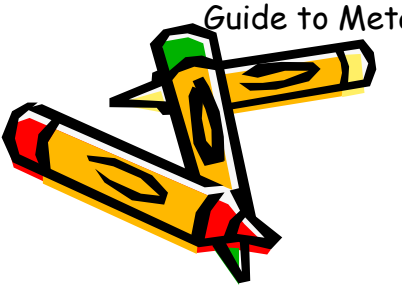


Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (PRISMA). **a** The main components of a systematic review or meta-analysis.

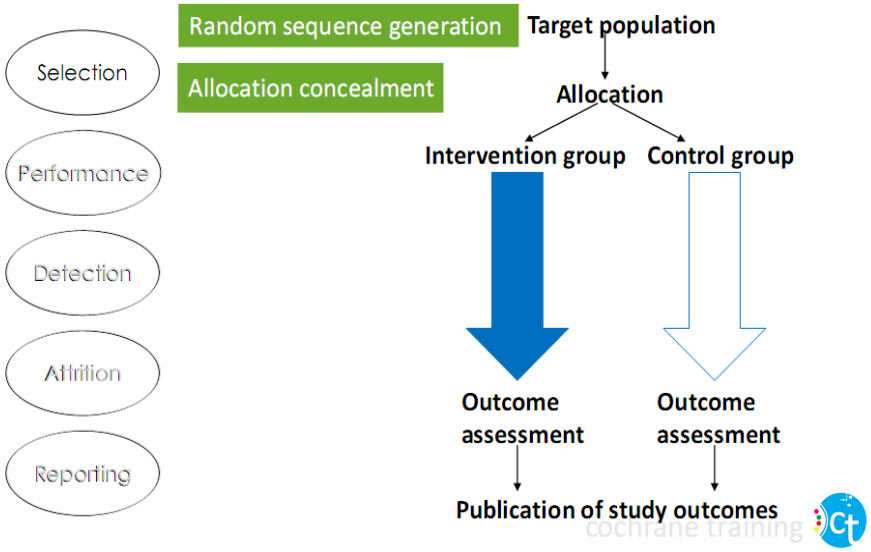
The Validity of a Meta-analysis

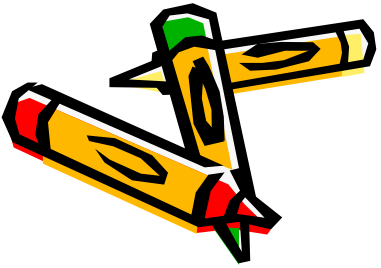
- "The validity of a meta-analysis depends on the quality of the studies included, and an assessment of quality is a necessary part of the process."

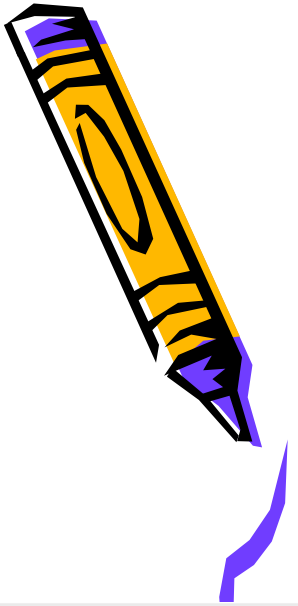
Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1674

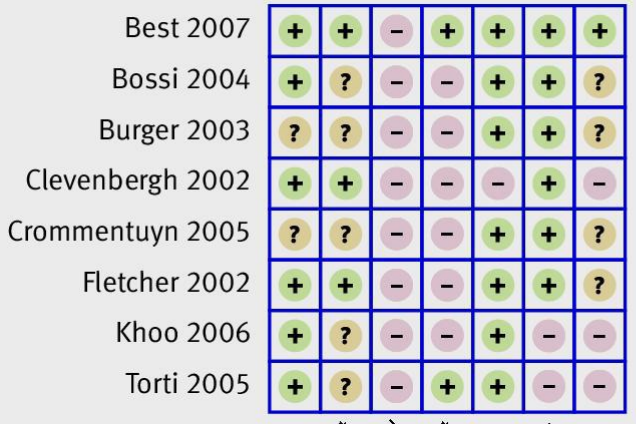


Sources of bias





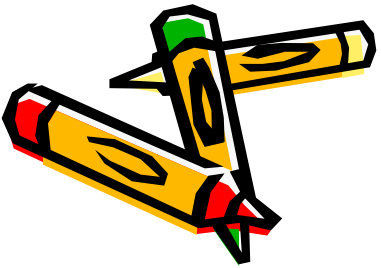




Meta-analysis: Extracting the Data

- "The type of data to be extracted from each study should be determined in the design phase and a standardized form is constructed to record the data."

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. 1674



Plan of Action

ARE THE STUDIES ELIGIBLE FOR MA (STEP I)?

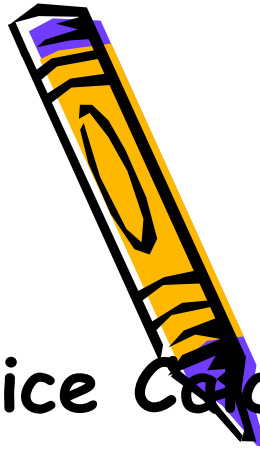
NO → **DISCARD**

YES

ABSTRACT THE DATA

ENTER INTO A SPECIFIED FORMAT

How to Abstract 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

Microsoft Excel - strep1

File Edit View Insert Format Tools Data Window Help

D28 =

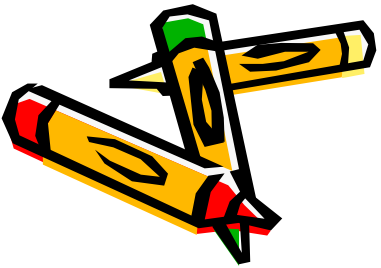
	A	B	C	D	E	F	G
1	trial	trialnam	year	pop1	deaths1	pop0	deaths0
2	1	Fletcher	1959	12	1	11	4
3	2	Dewar	1963	21	4	21	7
4	3	1st Europe	1969	83	20	84	15
5	4	Heikinheim	1971	219	22	207	17
6	5	Italian	1971	164	19	157	18
7	6	2nd Europ	1971	373	69	357	94
8	7	2nd Frankf	1973	102	13	104	29
9	8	1st Austra	1973	264	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

Table 1 | Characteristics of trials included in meta-analysis (see web appendix for references)

Study	Age range (mean)*	No of patients analysed		Severity of sore throat	Intervention	Control	Antibiotics used	Analgesia	Outcomes
		Intervention	Control						
O'Brien et al 1993 (US)[w8]	12–65 (26.4)	26†	25†	Severe (GABHS not tested, 100% exudative)	Dexamethasone 10 mg (IM)	Saline 1 ml (IM)	Penicillin G or erythromycin	Unregulated, no differences recorded, type not reported	Reduction in pain VAS, time to onset of pain relief, time to complete pain resolution
Marvez-Valls et al 1998 (US)[w4]	14-65 (29.1)	46	46	Severity not stated (53% GABHS‡, 100% exudative)	Betamethasone 8 mg/2 ml§ (IM)	Saline, 2 ml (IM)	Penicillin G or erythromycin (similar proportion in each group)	Unregulated, unrecorded, paracetamol or ibuprofen recommended	Reduction in pain VAS, time to onset of pain relief, time to complete pain resolution, days missed from school or work, percentage of recurrence

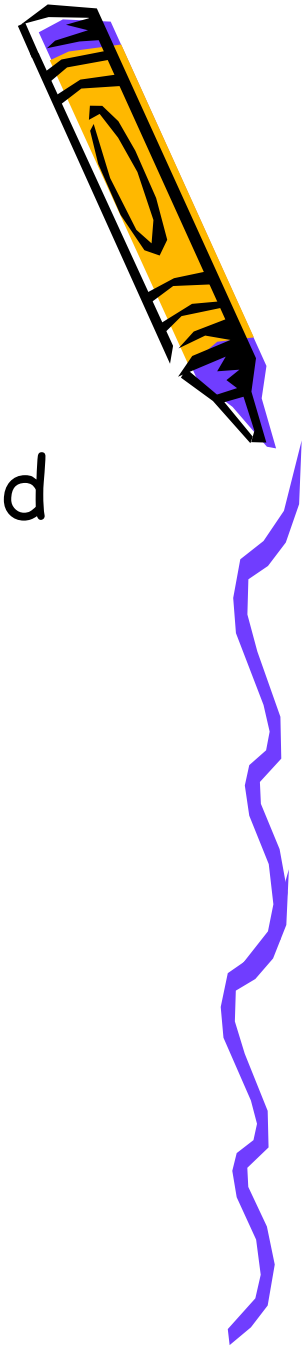
Meta-analysis: Data

- "The difficulty with data extraction is that studies often use different outcome metrics, which make combining the data awkward. The data should be converted to a uniform metric for pooling."

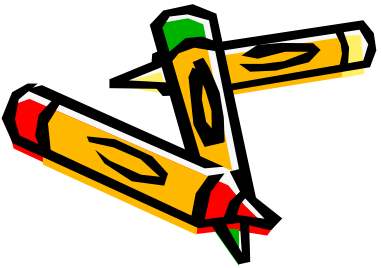


$$\text{Standardized difference} = \frac{\text{difference between the means in the two treatment groups}}{\text{population standard deviation}}$$

Meta-analysis: Analyzing the Data



- There are 2 statistical models used in a meta-analysis:
  - Fixed effects
  - Random effects

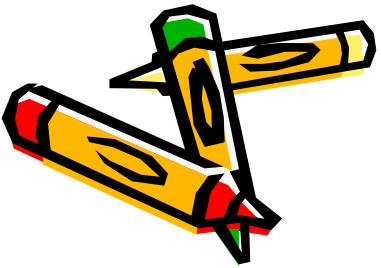


The Fixed Effects Model

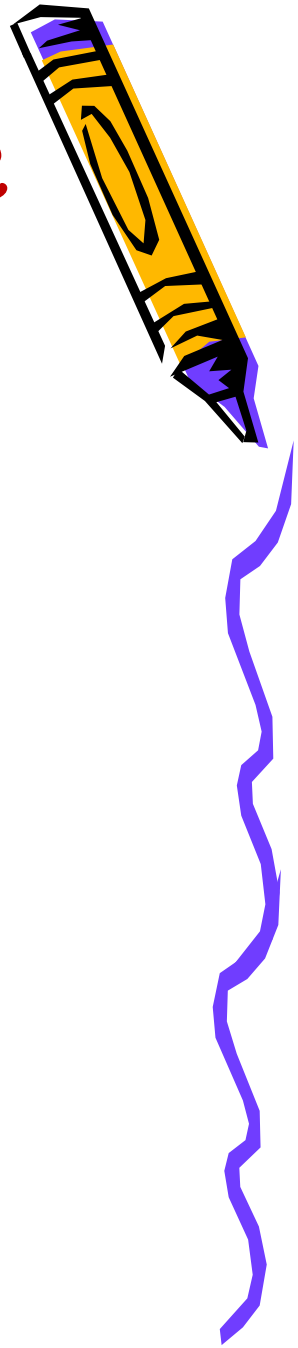
- "The fixed-effects model assumes that the true effect of treatment is the same for every study."

The Random Effects Model

- "The random effects model assumes that the true effect estimate for each study vary."

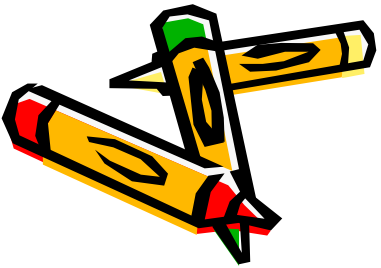


Meta-analysis: Reporting the Results

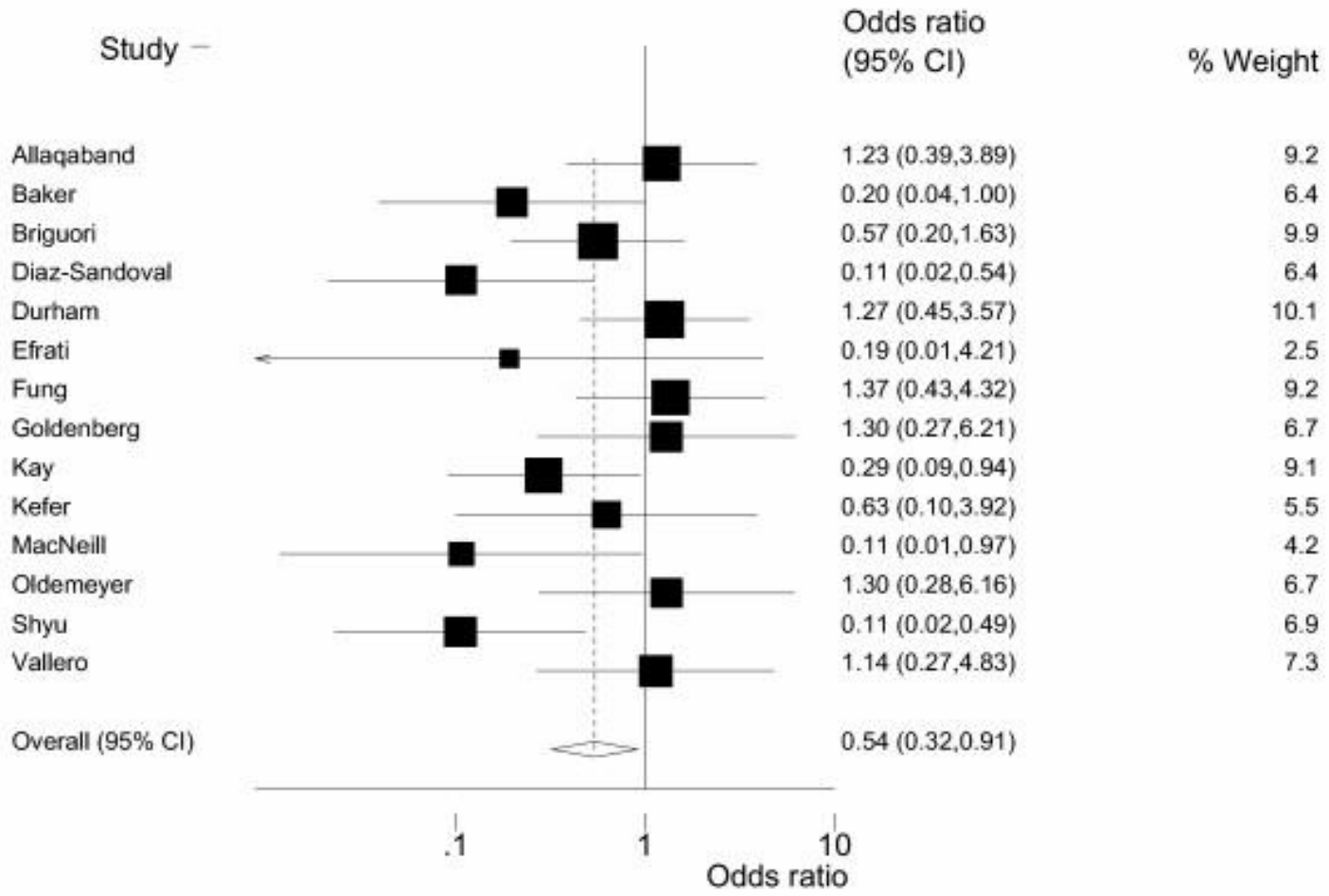


A meta-analysis should include:

- A title, abstract, an introduction –
- Methods, results, and discussion – sections

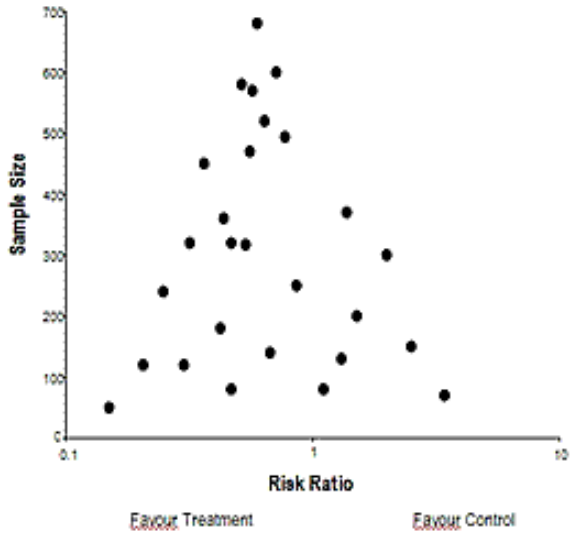


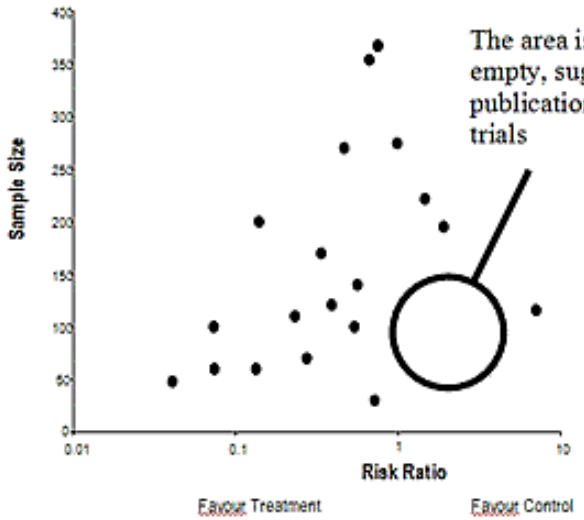
A Forest Plot



A Funnel Plot

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






Thanks for
your attention