



دانشگاه علوم پزشکی و خدمات بهداشتی درمانی ارومیه

Systematic Reviews & Meta-Analysis

Dr. Z. Niazkhani, MD., MSc., PhD
Dr. H. Pirnejad, MD., MSc., PhD



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.”

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



What is the significance of Systematic Reviews?

- The large amount of medical literature requires clinicians and researchers alike to rely on systematic reviews in order to make an informed decision.
- Systematic Reviews minimize bias. “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.”

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



Why are Systematic Reviews Necessary?

- “The volume of published material makes it impractical for an individual clinician to remain up to date on a variety of common conditions. This is further complicated when individual studies report conflicting conclusions, a problem that is prevalent when small patient samples and retrospective designs are used.”

Margaliot, Zvi, Kevin C. Chung. “Systematic Reviews: A Primer for Plastic Surgery Research”. PRS Journal. 120/7 (2007) p.1834



Key Characteristics of Systematic Reviews

- Clearly stated title and objectives
- Comprehensive strategy to search for relevant studies (unpublished and published)
- Explicit and justified criteria for the inclusion or exclusion of any study
- Clear presentation of characteristics of each study included and an analysis of methodological quality
- Comprehensive list of all studies excluded and justification for exclusion

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



Characteristics of Systematic Reviews (cont.)

- Clear analysis of the results of the eligible studies
 - statistical synthesis of data (meta-analysis) if appropriate and possible;
 - or qualitative synthesis
- 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



Hypothesis

- “A systematic review should be based on principles of hypothesis testing, and the hypotheses must be conceived a priori.”

Margalioth, Zvi, Kevin C. Chung. Systematic Reviews: A Primer for Plastic Surgery Research. PRS Journal. 120/7 (2007) p. 1836



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?



Inclusion/Exclusion Criteria

- “Once the study question is formalized, the authors must compose a comprehensive list of inclusion and exclusion criteria.”
- “To avoid selection bias, inclusion and exclusion criteria should be agreed upon and formalized before data extraction and analysis.”

Margaliot, Zvi, Kevin C. Chung. “Systematic Reviews: A Primer for Plastic Surgery Research.” PRS Journal. 120/7 (2007) p.1836



Literature Search

- “A comprehensive and reproducible literature search is the foundation of a systematic review.”

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



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.

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



Literature Review Challenges (cont.)

- **English-language bias** - occurs when reviewers exclude papers published in languages other than English
- **Citation bias** - occurs when studies with significant or positive results are referenced in other publications, compared with studies with inconclusive or negative findings



Data Collection

- “The list of data to be extracted should be agreed upon a priori consensus during the design stage of the study.”

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



Data Collection (cont.)

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



Data Collection (cont.)

- “It is necessary to design a review-specific data extraction form, so that the same data are extracted from each study and missing data are clearly apparent.”

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



Data Collection (cont.)

- “To ensure that data extraction is accurate and reproducible, it should be performed by at least two independent readers.”

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



Quality Assessment

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

Margalioth, 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

Margalioth, 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.”

Margaliof, 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.”

Margalioth, 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



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”

Margalioth, 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.”

Margaliof, 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

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

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



Meta-Analysis (cont.)

- “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 (cont.)

- “If a meta-analysis is to be included in a systematic review, an experienced statistician or an epidemiologist should be consulted during all phases of the study.”

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



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



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



Steps of Meta-analysis

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



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.”

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: Performing the Literature Search

- “The literature search is a critical step in the meta-analysis and often the most difficult part.”

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: The Literature Search (cont.)

- “The researcher should search more than just MEDLINE to ensure a comprehensive search.”

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. 1673



Meta-analysis: The Literature Search (cont.)

- Search for published studies in MEDLINE, EMBASE, and CINAHL.
- Search for unpublished clinical trials in the Cochrane Central Register of Controlled Trials



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.”

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. 1673



Meta-analysis: Study Selection (cont.)

- Meta-analysis needs to be documented
 - “One should keep track of the studies included and excluded at each step of the selection process to document the selection 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. 1673



Meta-analysis: Study Selection (cont.)

- “The QUOROM guidelines for reporting a meta-analysis requests that investigators provide a flow diagram of the selection 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. 1673



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



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



Meta-analysis: Data

- What are the examples of data commonly extracted?
 - Study design, descriptions of study groups, diagnostic information, treatments, length of follow-up evaluation, and outcome measures.



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.”

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



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.”

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.”

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



The Introduction

- “The introduction should indicate the clinical question of interest, the hypothesis being tested, the types of treatment or exposure being studied, the study designs to be included, and a description of the study population.”

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 Methods Section

- “The methods section should
 - describe the literature search, specifically the databases used, and if the search was restricted in any way.
 - The selection process for articles, quality assessment, methods of data abstraction, and synthesis.”

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



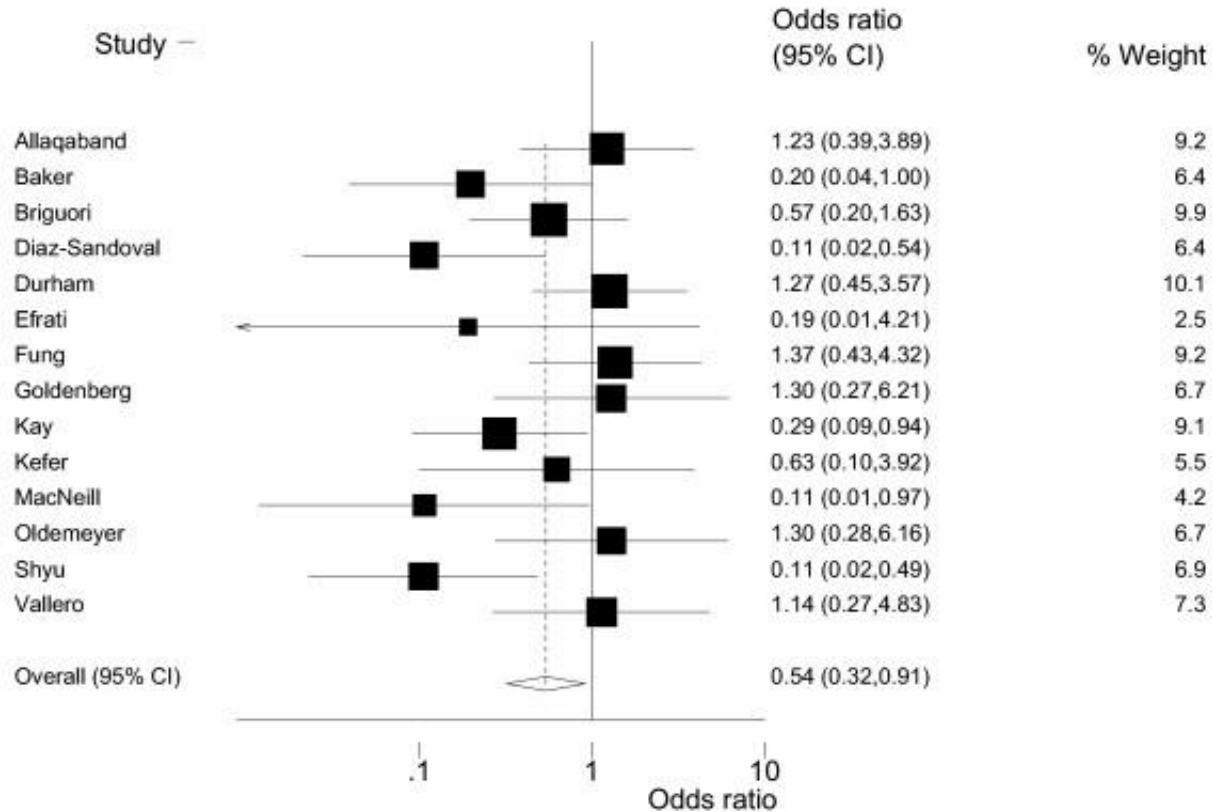
The Results Section

- The results section should
 - Include a flow chart of studies included
 - A figure displaying the results from each individual study (forest plot), results of heterogeneity testing, overall summary statistic, and results of a sensitivity analysis and meta-regression, if performed.

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



A Forest Plot

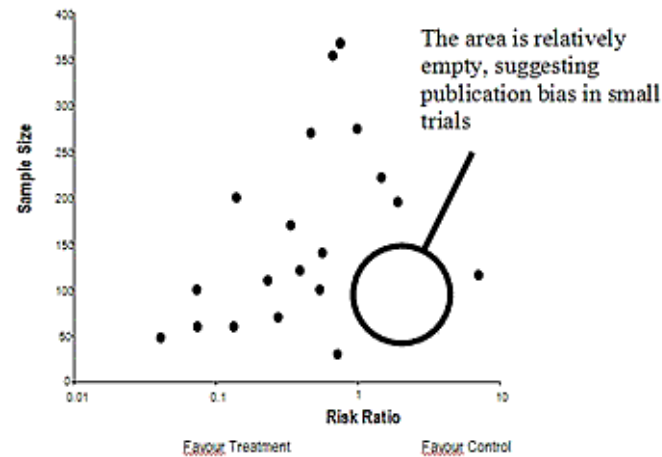
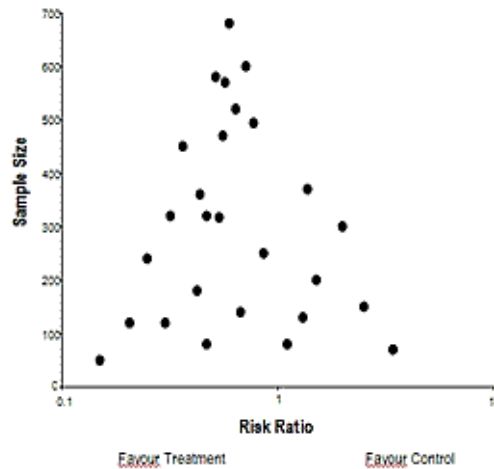




A Funnel Plot

- “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





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.



Questions?

Thank you!