



Beyond research papers: reviews and meta-analysis

Shobna Bhatia

**Department of Gastroenterology
T N Medical College & B Y L Nair
Hospital, Mumbai**

Definitions

- **Meta-analyses are studies of studies**
 - Kassirer JP, NEJM 1992
- **Logical framework to a research review: similar measures from comparable studies are listed & available effect measures combined where possible**
 - Dickersin, Berline, Epidemiol Rev 1992
- **Meta-analysis - mathematical synthesis of results of >2 primary studies that addressed the same hypothesis in the same way**
 - Greenhalgh, BMJ 1997

Definitions

- **Types of reviews**

- Narrative review
- Systematic review

- **Meta-analysis**

- Statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable.'

Purpose

- **Avoid time and expense of conducting a clinical trial**
- **Make comparisons of interventions more objective and accurate**
- **Identify areas in which insufficient research has been performed or in which additional research may not be necessary**
- **Increase statistical power by combining many smaller studies.**

Aims

- **More information from existing data**
- **Pooling results of many smaller studies**
- **Apply one or more statistical techniques**
- **Evaluate therapeutic effectiveness, plan new studies, give guidelines**
- **Benefits or hazards not detected in small studies can be found**

Information explosion

- 1940 --> 2300 biomedical journals
- 1995 --> 25000 biomedical journals
- Approx. 9000 RCTs/year
- Over 2 million articles are published annually
- More than 17,000 biomedical books are published annually
- **Single studies rarely provide definitive answers to clinical questions**

Systematic reviews

- **Scientific investigations in themselves**
- **Pre-planned methods (Protocol)**
- **Original studies (Subjects)**
- **Synthesize results of multiple primary investigations by using strategies that limit bias and random error (Methods)**
 - Cook DJ et al, 1998

Primary vs secondary research

- **Results of a particular research study cannot be interpreted unless they are considered together with results of other studies addressing the same or similar questions**
- **Research synthesis -- “science is cumulative”**

Similar methodology

- **Primary Research**
 - Question / Hypothesis
 - Criteria for selection of 'subjects'
 - Study population
 - Sampling
 - Data collection
 - Data management and analysis
 - Structured report
- **Secondary Research**
 - Question / Objective
 - Criteria for selection of 'studies'
 - Study 'pool'
 - Study selection
 - Data extraction
 - Data management and analysis
 - Structured report

Narrative vs systematic review

Feature	Narrative	Systematic
Question	Broad	Focused
Sources/Search	Usually unspecified Potentially biased	Specified Explicit Criterion based
Selection	Unspecified	Uniformly applied
Appraisal	Variable	Rigorous/Critical
Synthesis	Usually qualitative	Quantitative
Inferences	Sometimes evidence-based	Evidence-based

Statistical reasoning

- Limit bias
- ↑↑ Overall Sample Size
- ↑↑ Statistical Power
- ↑↑ Precision of the Estimate
- Provide robust estimate
- Identify crucial areas and questions that have not been adequately addressed with past research

Manuscript writing

- **Similar structure as primary research**
- **IMRAD**
 - Title
 - Abstract / Summary
 - Introduction: Why was this work undertaken?
 - Methods: How was it done?
 - Results: What did you find?
 - Discussion: what does it imply?

Introduction

- **Purpose**
- **Rationale / Background**
- **Problem / Relevance /
Justification / Need**
- **Brief Review of Literature**
- **Expected Implications**

Aim

- **Summarize a large and complex body of literature on a topic**
- **Resolve conflicting reports in literature**
- **Clarify or quantify strengths and weaknesses of studies on a topic**
- **Document need for a major clinical trial**

Purpose

- **Improve precision of an estimated treatment effect**
- **Detect smaller treatment effects than have been reported.**
- **Investigate variations in treatment effects through subgroup (or stratified) analysis.**
- **Improve generalizability of known treatment effects.**

Methods

- **Sources of Relevant Studies**
- **Search Strategies**
- **Selection of Studies**
- **Appraisal of Studies**
- **Data Extraction**
- **Statistical Analysis - Strategy**

Sources

- **Electronic Databases**
- **Online Journals**
- **Manual Search**
- **Reference Lists**
- **Study Registries**
- **Current Awareness Publications**
- **Text Books and Reference Books**
- **Monographs and Recent Advances**
- **Dissertations and Thesis**

Sources

- **Pharmaceutical & Appliance Companies**
- **Funding Agencies**
- **Professional Organizations**
- **Personal Contact**
- **Personal Knowledge**
- **E Journals**
- **Foreign Language Literature**
- **Unpublished Studies?**
- **Abstracts?**

Selection and appraisal

- **Relevance of studies to review question**
- **Judge features of design and analysis**

Differences in inclusion

	Conn & Blitzer		
	Included	Excluded	Total
Messer			
Included	25	46	71
Excluded	17	113	130
Total	42	159	201

Papers included and excluded in meta-analysis of RCTs relating peptic ulcer to steroid therapy by Conn & Blitzer and Messer et al

Duplicate publication

- **Data access vs data excess**
- **Example**
 - Single trial of risperidone for chronic schizophrenia was reported in seven different publications with different authorship

Flip side of publication bias

- **Negative trials less likely to be published**
- **Consequences are similar in both cases**
 - Excessively precise and inflated effect size estimates

Quantitative methods

- **Statistical methods to combine results (Effect Measures) of multiple studies**
- **Statistical methods involved appear to be mathematically complex**

Quantitative Methods

- **Four basic questions**
 - Are results of different studies similar?
 - To the extent that they are similar, what is the best overall estimate?
 - How precise and robust is this estimate?
 - Can dissimilarities be explained?

Quantitative Methods

- **Stepwise tasks**
 - Deciding whether to combine data and defining what to combine
 - Evaluating statistical heterogeneity of data
 - Estimating a common effect
 - Exploring and explaining heterogeneity
 - Assessing the potential for bias

Results

- **Typical presentation: graphic form**
- **Tables**
- **Effect measures: point estimates and 95% CI**
- **Data in 2x2 table format**
- **Study characteristics**
- **Co-variates (Codes)**
- **Summary Estimates (5 % CI)**
- **Heterogeneity statistics**

Types of analyses

- **Subgroup Analysis**
- **Quality Assessment (Scores)**
- **Cumulative Meta-Analysis, Stepwise Deletion**
- **Meta-Regression Results**
- **Sensitivity Analysis**
- **Cross Design Synthesis**
- **Publication Bias (Funnel Plot)**

Publication Bias

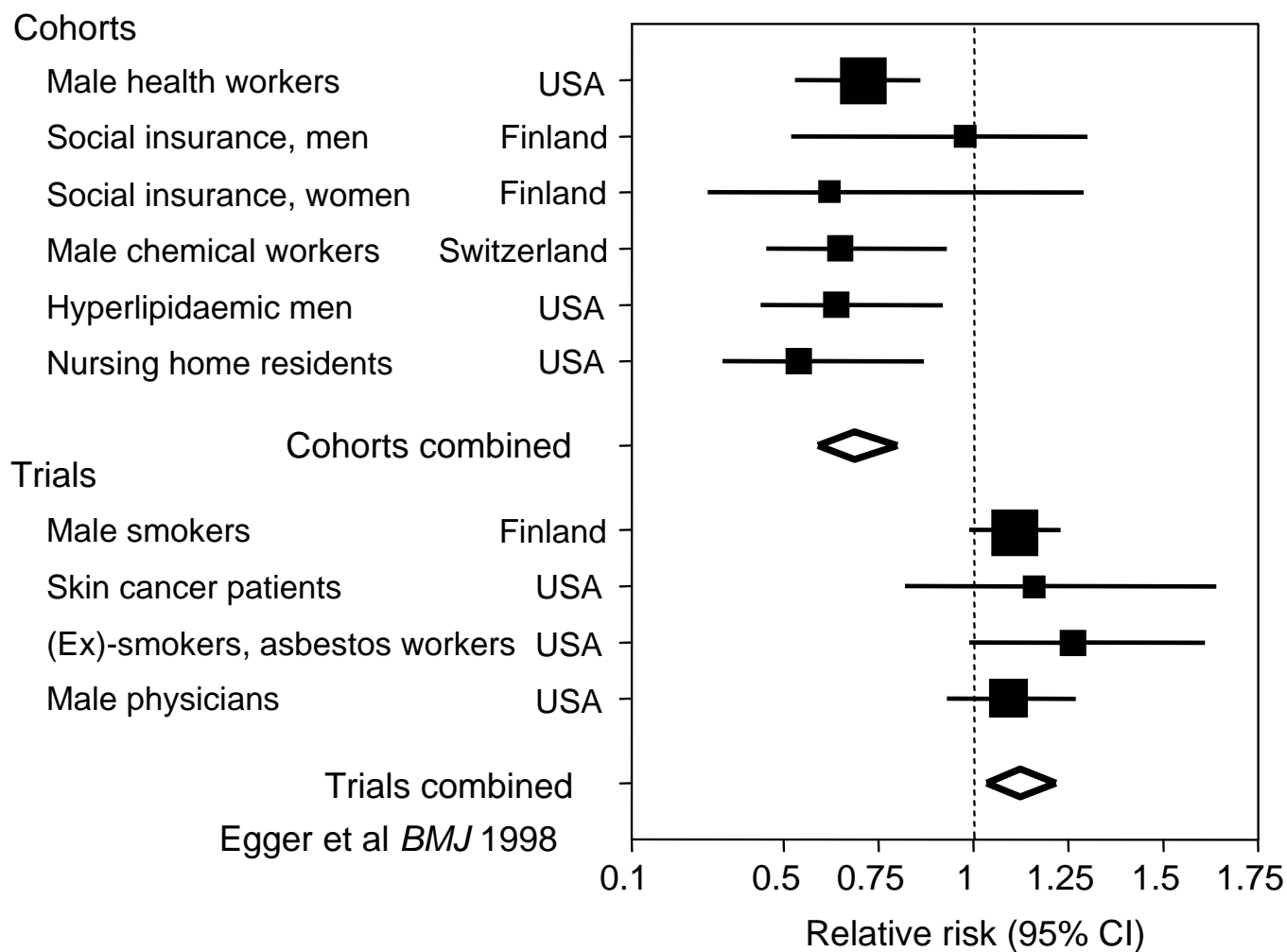
- ***Selection bias***
 - Publication bias
 - Location bias
 - English language bias
 - Citation bias
 - Multiple publication bias

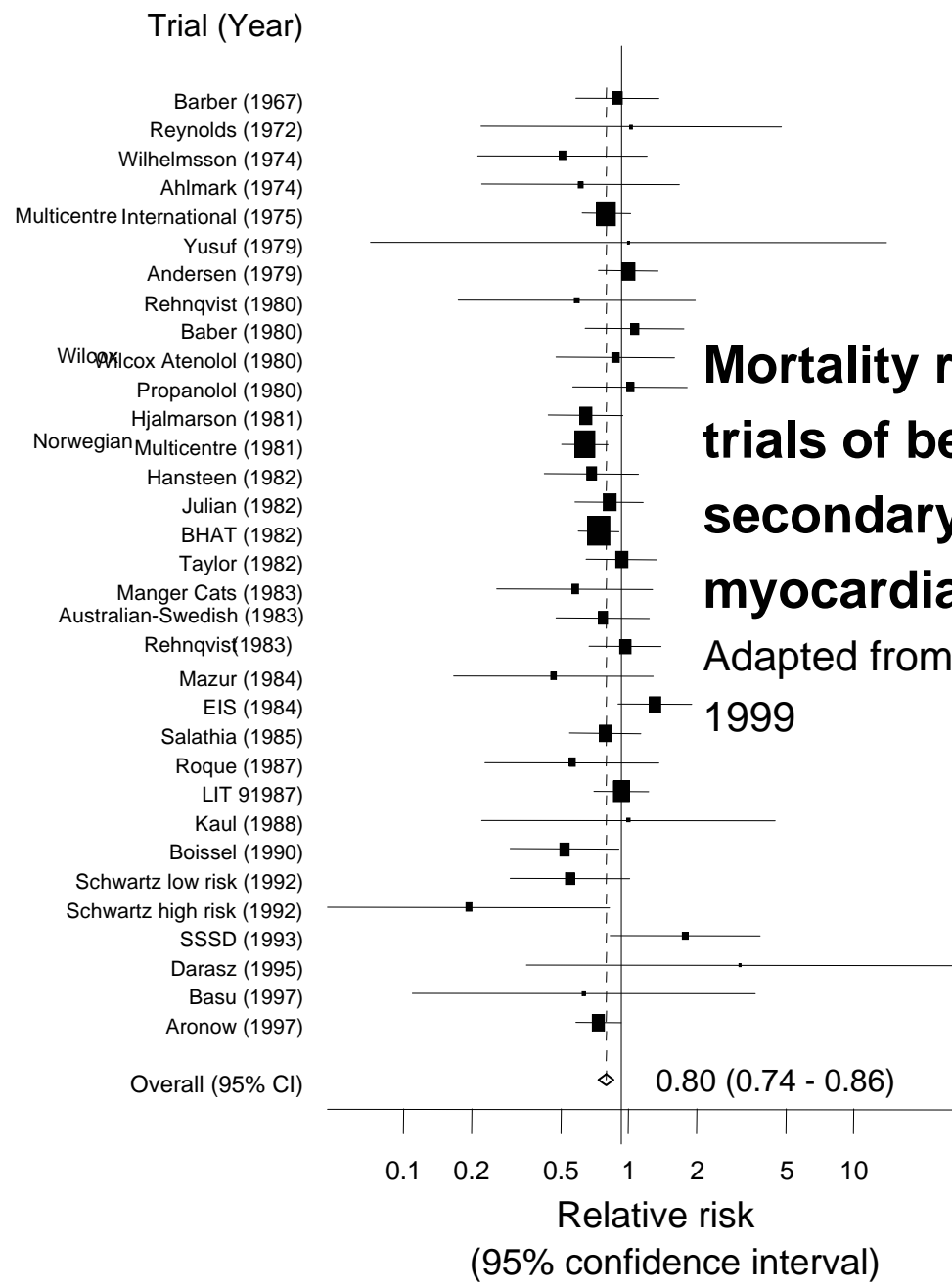
-
- ***True heterogeneity***
 - Size of effect differs according to study size
 - Intensity of intervention
 - Differences in underlying risk
 - **Data irregularities**
 - Poor methodological design of small studies
 - Inadequate analysis
 - Fraud

Arrange studies

- **Publication date**
- **Sample size**
- **Quality of study**
- **Duration of treatment**
- **Size of treatment dose**
- **Study design**
- **Effect measures**

Beta-carotene and cardiovascular mortality





Discussion

- **Summary estimates (implications)**
- **Results of large trials and MA**
- **Results of earlier MA vs current MA**
- **Selection and appraisal criteria**
- **Analytical strategy**
- **Heterogeneity**
- **Biases (Selection bias, data extraction bias, source of support, ecologic bias, publication bias)**
- **Strengths and limitations**

Conclusion

- **Meta analyses and systematics reviews**
- **Best available evidence**
- **Influence decision making in clinical practice and public health**