Systematic Reviews Application & Importance

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Types of Medical Articles

- Original Article
- Review Article
- Case Reports
- Editorial
- Short Communication (short papers)
- Letter to Editor
- Personal Views

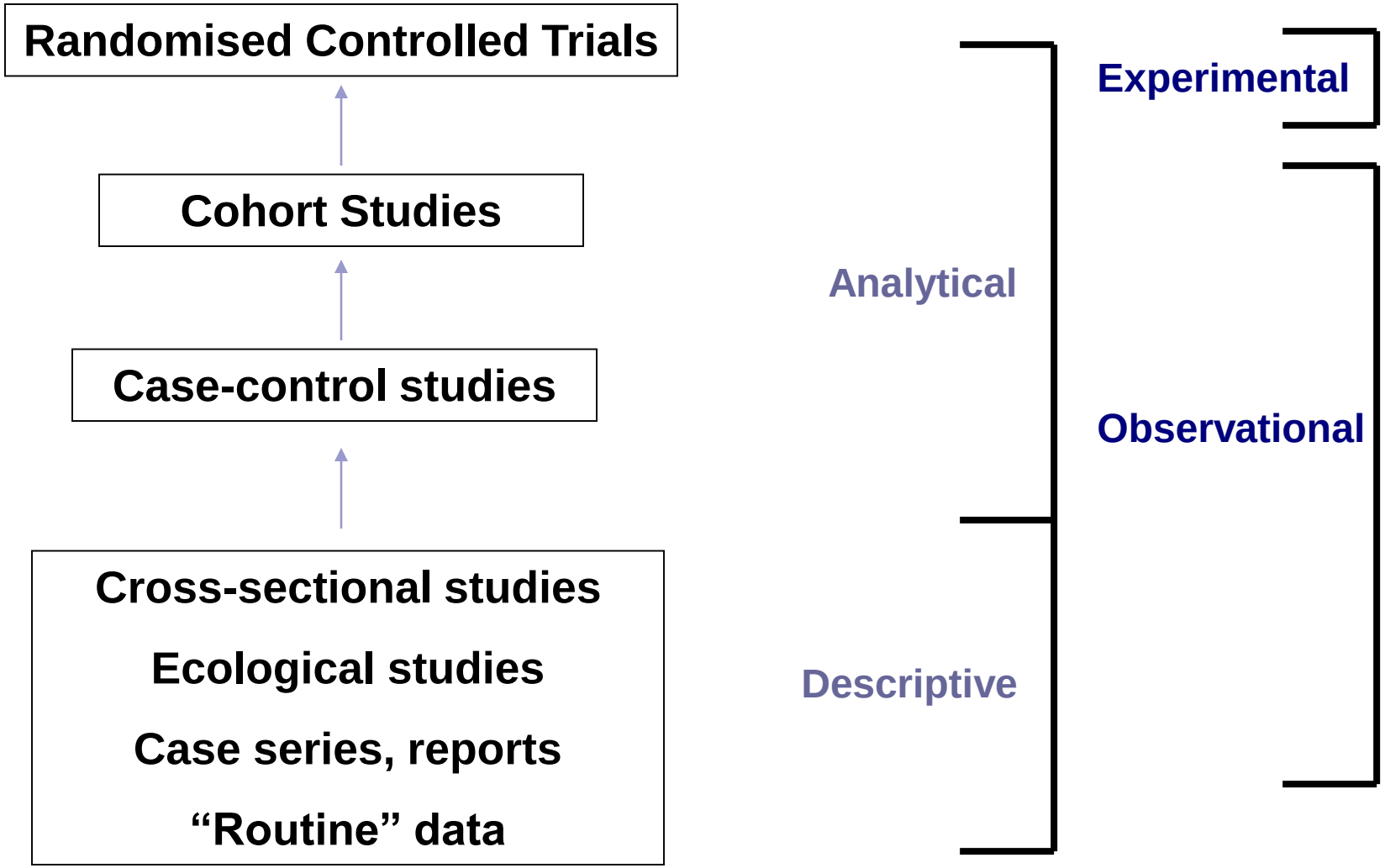
Types of Studies

- Primary Studies
- Secondary Studies

Primary studies

- Experiments
- Surveys (observational studies)

STUDY DESIGNS



Secondary studies

Different from secondary analysis

- Reviews (Overviews)
  - Narrative reviews
  - Systematic reviews & Meta-analyses
- Guidelines
- Decision analyses
- Economic analyses
- Burden of disease
- Modeling of disease

Review Articles

- Traditional Review Articles (Narrative Review)
- Systematic Review (Meta-analysis)

Review article

Label	Description	Methods used (SALSA)			
		Search	Appraisal	Synthesis	Analysis
Critical review	Aims to demonstrate writer has extensively researched literature and critically evaluated its quality. Goes beyond mere description to include degree of analysis and conceptual innovation. Typically results in hypothesis or model	Seeks to identify most significant items in the field	No formal quality assessment. Attempts to evaluate according to contribution	Typically narrative, perhaps conceptual or chronological	Significant component: seeks to identify conceptual contribution to embody existing or derive new theory
Literature review	Generic term: published materials that provide examination of recent or current literature. Can cover wide range of subjects at various levels of completeness and comprehensiveness. May include research findings	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative	Analysis may be chronological, conceptual, thematic, etc.
Mapping review/ systematic map	Map out and categorize existing literature from which to commission further reviews and/or primary research by identifying gaps in research literature	Completeness of searching determined by time/scope constraints	No formal quality assessment	May be graphical and tabular	Characterizes quantity and quality of literature, perhaps by study design and other key features. May identify need for primary or secondary research
Meta-analysis	Technique that statistically combines the results of quantitative studies to provide a more precise effect of the results	Aims for exhaustive, comprehensive searching. May use funnel plot to assess completeness	Quality assessment may determine inclusion/ exclusion and/or sensitivity analyses	Graphical and tabular with narrative commentary	Numerical analysis of measures of effect assuming absence of heterogeneity
Mixed studies review/mixed methods review	Refers to any combination of methods where one significant component is a literature review (usually systematic). Within a review context it refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies	Requires either very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies	Requires either a generic appraisal instrument or separate appraisal processes with corresponding checklists	Typically both components will be presented as narrative and in tables. May also employ graphical means of integrating quantitative and qualitative studies	Analysis may characterise both literatures and look for correlations between characteristics or use gap analysis to identify aspects absent in one literature but missing in the other
Overview	Generic term: summary of the [medical] literature that attempts to survey the literature and describe its characteristics	May or may not include comprehensive searching (depends whether systematic overview or not)	May or may not include quality assessment (depends whether systematic overview or not)	Synthesis depends on whether systematic or not. Typically narrative but may include tabular features	Analysis may be chronological, conceptual, thematic, etc.
Qualitative systematic review/qualitative evidence synthesis	Method for integrating or comparing the findings from qualitative studies. It looks for 'themes' or 'constructs' that lie in or across individual qualitative studies	May employ selective or purposive sampling	Quality assessment typically used to mediate messages not for inclusion/exclusion	Qualitative, narrative synthesis	Thematic analysis, may include conceptual models

ology of reviews, *Maria J. Grant & Andrew Booth*

Review article

Label	Description	Methods used (SALSA)			
		Search	Appraisal	Synthesis	Analysis
Rapid review	Assessment of what is already known about a policy or practice issue, by using systematic review methods to search and critically appraise existing research	Completeness of searching determined by time constraints	Time-limited formal quality assessment	Typically narrative and tabular	Quantities of literature and overall quality/direction of effect of literature
Scoping review	Preliminary assessment of potential size and scope of available research literature. Aims to identify nature and extent of research evidence (usually including ongoing research)	Completeness of searching determined by time/scope constraints. May include research in progress	No formal quality assessment	Typically tabular with some narrative commentary	Characterizes quantity and quality of literature, perhaps by study design and other key features. Attempts to specify a viable review
State-of-the-art review	Tend to address more current matters in contrast to other combined retrospective and current approaches. May offer new perspectives on issue or point out area for further research	Aims for comprehensive searching of current literature	No formal quality assessment	Typically narrative, may have tabular accompaniment	Current state of knowledge and priorities for future investigation and research
Systematic review	Seeks to systematically search for, appraise and synthesis research evidence, often adhering to guidelines on the conduct of a review	Aims for exhaustive, comprehensive searching	Quality assessment may determine inclusion/exclusion	Typically narrative with tabular accompaniment	What is known; recommendations for practice. What remains unknown; uncertainty around findings, recommendations for future research
Systematic search and review	Combines strengths of critical review with a comprehensive search process. Typically addresses broad questions to produce 'best evidence synthesis'	Aims for exhaustive, comprehensive searching	May or may not include quality assessment	Minimal narrative, tabular summary of studies	What is known; recommendations for practice. Limitations
Systematized review	Attempt to include elements of systematic review process while stopping short of systematic review. Typically conducted as postgraduate student assignment	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative with tabular accompaniment	What is known; uncertainty around findings; limitations of methodology
Umbrella review	Specifically refers to review compiling evidence from multiple reviews into one accessible and usable document. Focuses on broad condition or problem for which there are competing interventions and highlights reviews that address these interventions and their results	Identification of component reviews, but no search for primary studies	Quality assessment of studies within component reviews and/or of reviews themselves	Graphical and tabular with narrative commentary	What is known; recommendations for practice. What remains unknown; recommendations for future research

A typology of reviews, *Maria J. Grant & Andrew Booth*

The Ascent of Evidence
(and the exhaustion of Man)

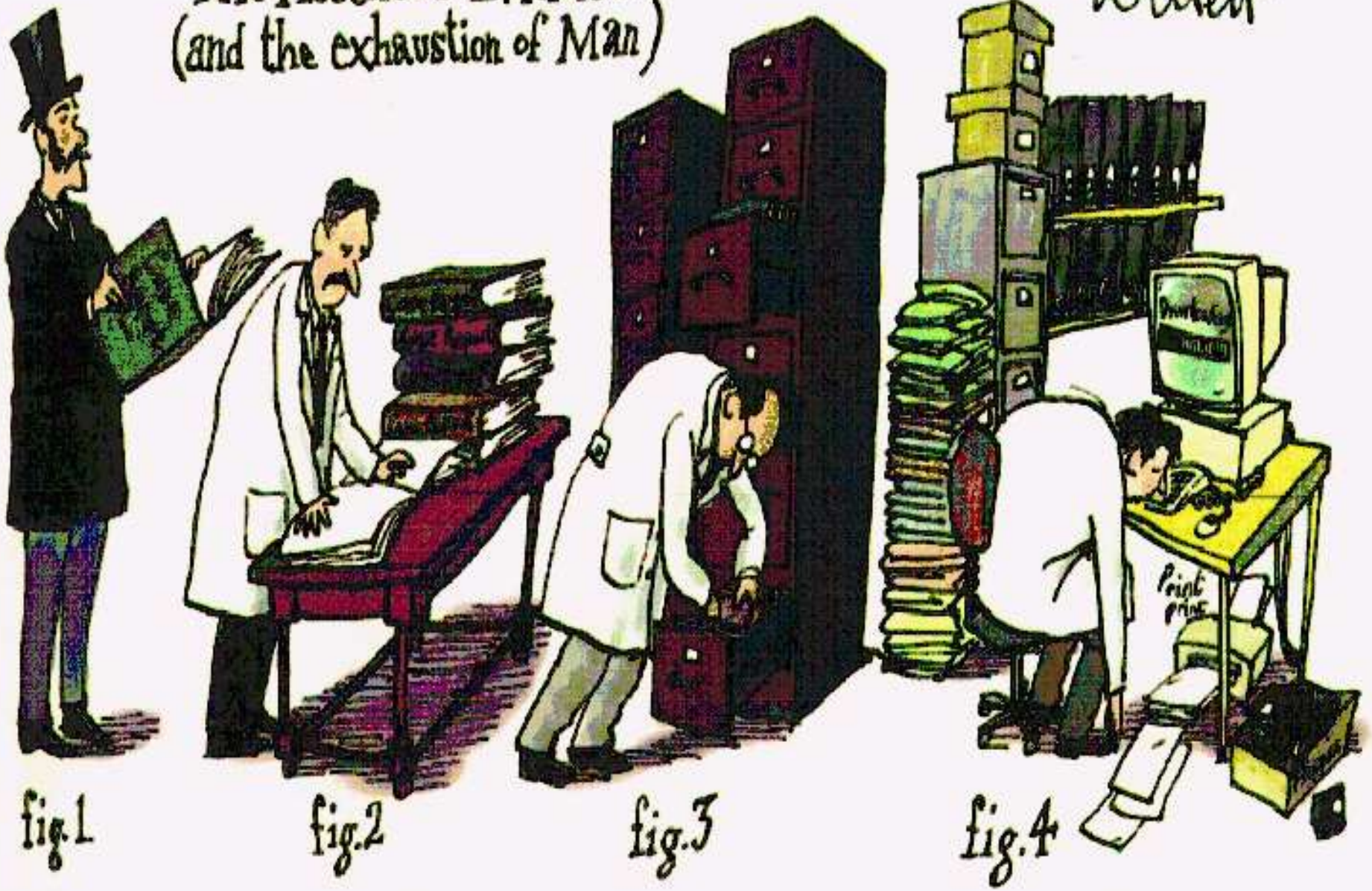


fig.1 fig.2 fig.3 fig.4

Medical Publishing

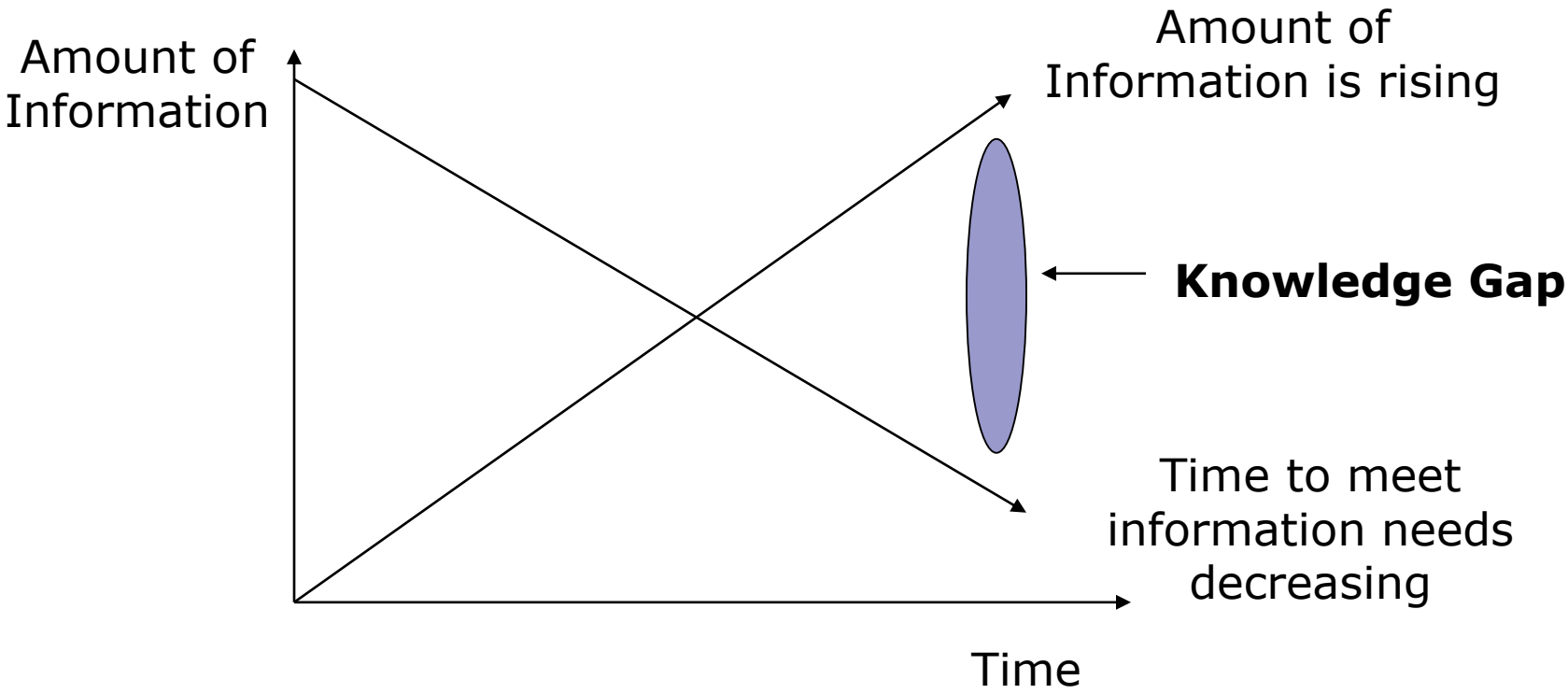
Annually:

- 20,000 journals
- 17,000 new books

MEDLINE:

- +5,000 journals
- +28 Million references
- 10,000,000 new entries yearly

The Problem



The Knowledge Gap

Doubling time of biomedical science was

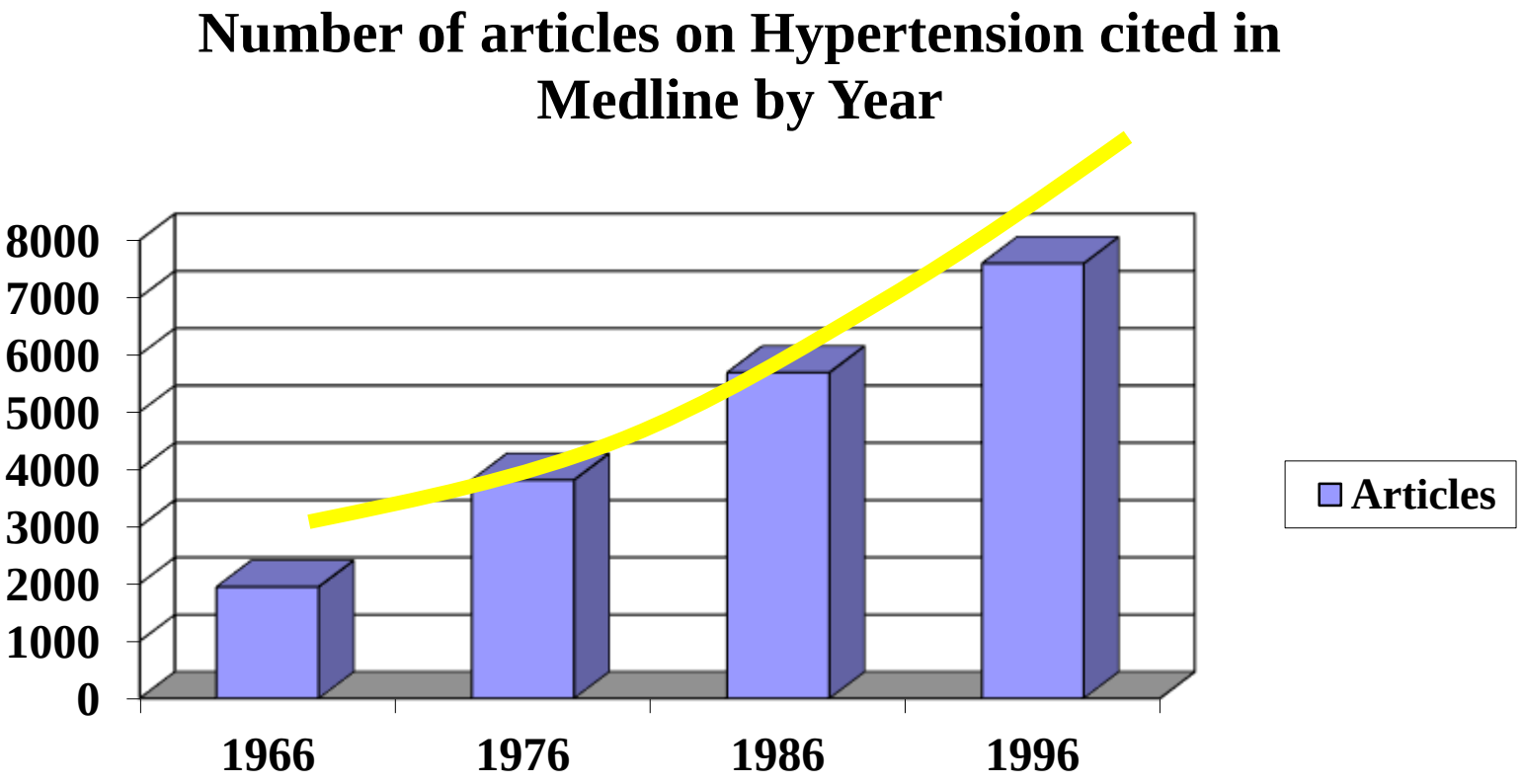
about 19 years in 1991

Doubling time of biomedical science was

about 20 months in 2001

73 day in 2020

Increasing Knowledge



For General Physicians to keep current:

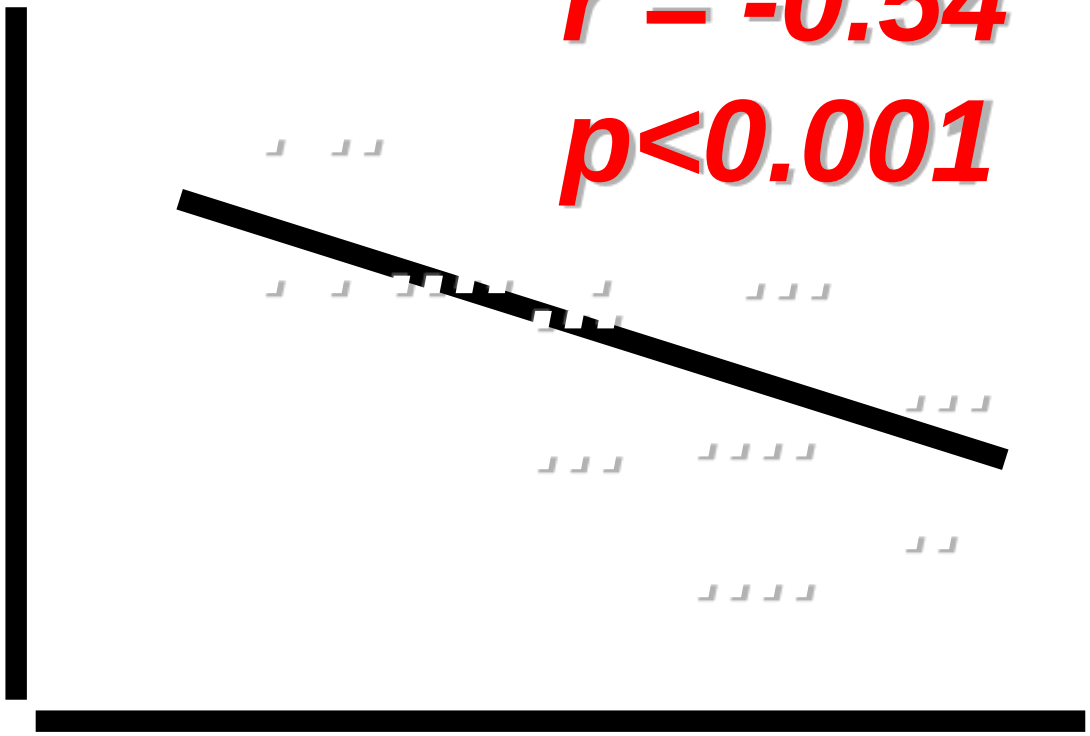
Read 19 new articles per day which appear in medical journals

19 x 2 hrs (Critical Appraisal) = 38 hrs per day

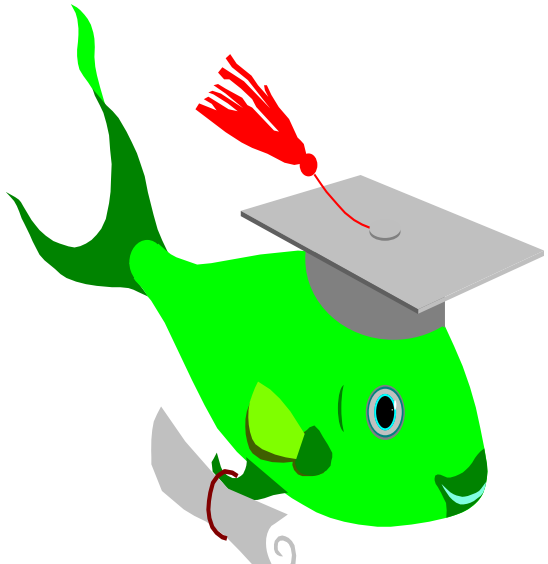
Davidoff F et al. (1995)
EBM; A new journal to help doctors identify
the information they need. BMJ 310:1085-86.

The Slippery Slope

Knowledge of best current HTN care



Years since Med School graduation



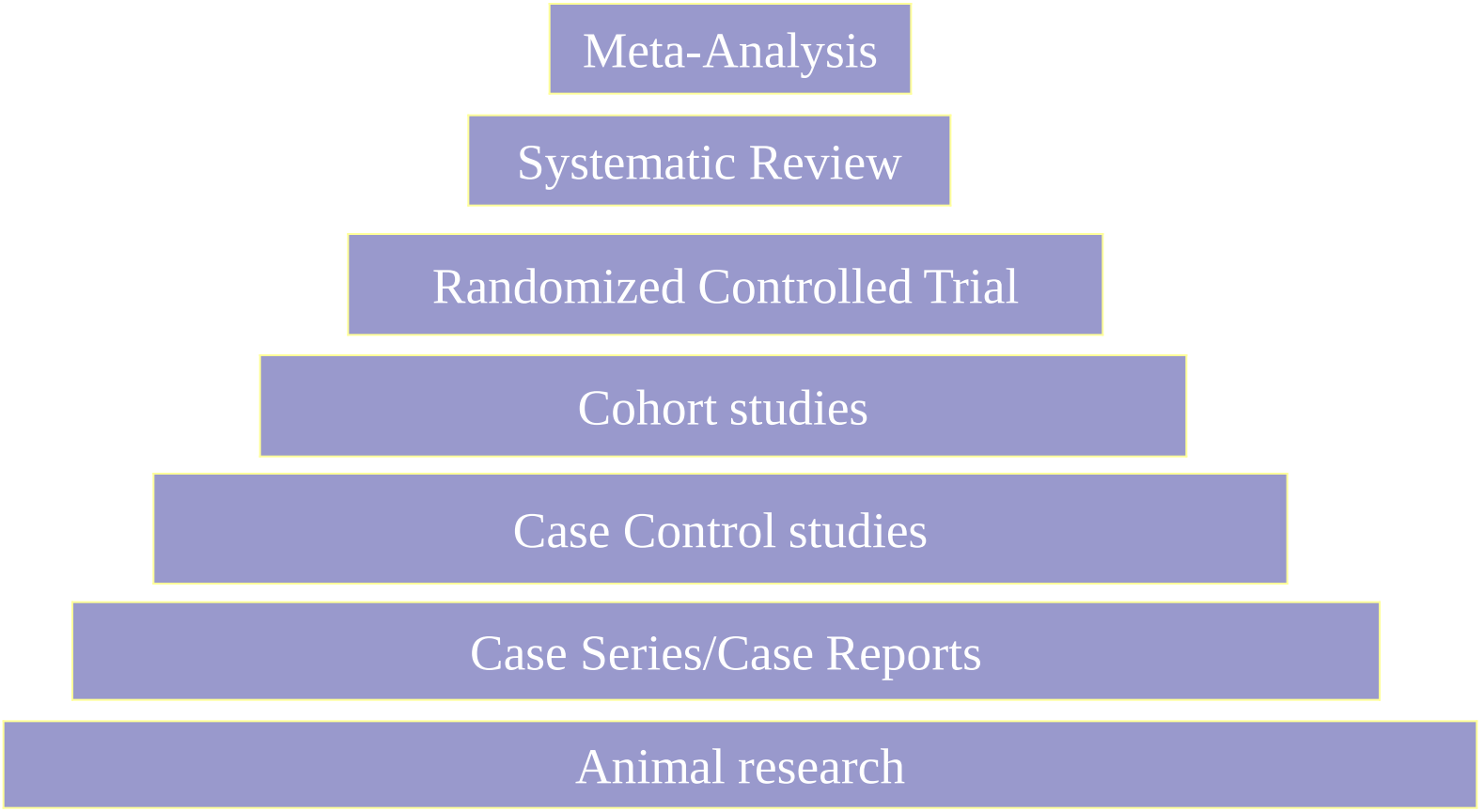
Shin,et al: CMAJ;1993: 969-976

What is ‘level of evidence’?

- The extent to which one can be confident that an estimate of effect or association is correct (unbiased).

Hierarchy of studies

Evidence Pyramid



Levels of Evidence

Level of Evidence	Type of Study
1a	Systematic reviews of randomized clinical trials (RCTs)
1b	Individual RCTs
2a	Systematic reviews of cohort studies
2b	Individual cohort studies and low-quality RCTs
3a	Systematic reviews of case-controlled studies
3b	Individual case-controlled studies
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion based on clinical experience

Adapted from: Sackett DL et al. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. Churchill Livingstone; 2000.

Systematic reviews

- Potsdam Consultation on Meta-analysis (Cook et al, 1995) defined a systematic review as
- **"application of scientific strategies that limit bias to the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic"**

Systematic reviews

- **Systematic review** is a method of
  - locating,
  - appraising,
  - and synthesising evidence
  - while making explicit efforts to limit bias
- > a quarter of a century since Gene Glass coined the term "meta-analysis" to refer to the quantitative synthesis of the results of primary studies

A ‘systematic review’, therefore, aims to be:

- Systematic (e.g. in its identification of literature)
- Explicit (e.g. in its statement of objectives, materials and methods)
- Reproducible (e.g. in its methodology and conclusions

Systematic Review

“Scientific tool which can be used to summaries, appraise, and communicate the results and implications of otherwise unmanageable quantities of research" (NHS CRD, 1996).

Systematic Review

- the process by which similar studies, identified from a comprehensive trawl of numerous sources, are summarized in easy-to-read graphical or tabular form and then their collective message or ''bottom line' presented, together with implications for practice and future research (Booth & Haines, 1998).

They are not conventional Reviews

- Follow a strict methodological and statistical protocol
  - more comprehensive
  - minimising the chance of bias
  - improves transparency, repeatability and reliability

Differences Between Traditional and Systematic Reviews

(Adapted from Cook, D. J. et. al. (1997). Ann. Intern. Med. 126: 376-380)

Feature	Traditional Review	Systematic Review
Question	Often broad in scope	Focused question
Sources & search	Not usually specified, potentially biased	Comprehensive sources & explicit search strategy
Selection	Rarely specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal, uniformly applied
Synthesis	Often a qualitative summary	Quantitative summary* when appropriate
Inferences	Sometimes evidence-based	Evidence-based

*A quantitative summary that includes a statistical synthesis is a meta-analysis

Writing narrative style literature reviews

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Table 2: General framework of narrative reviews

Introduction

- Content: describe the rationale
- Structure: organization of the collected information
- Limits: define the objective(s) and scope

Literature search

- Searching strategy: databases, keywords
- Inclusion/exclusion criteria: types of studies, languages, time periods, others
- Verify the availability of all the selected studies
- Citing and listing the researched references

Central body/Discussion:

Section 1
First key concept:
- discuss and evaluate
- summarize in relation to the research query

Section 2
Another key concept:
- discuss and evaluate
- summarize in relation to the research query

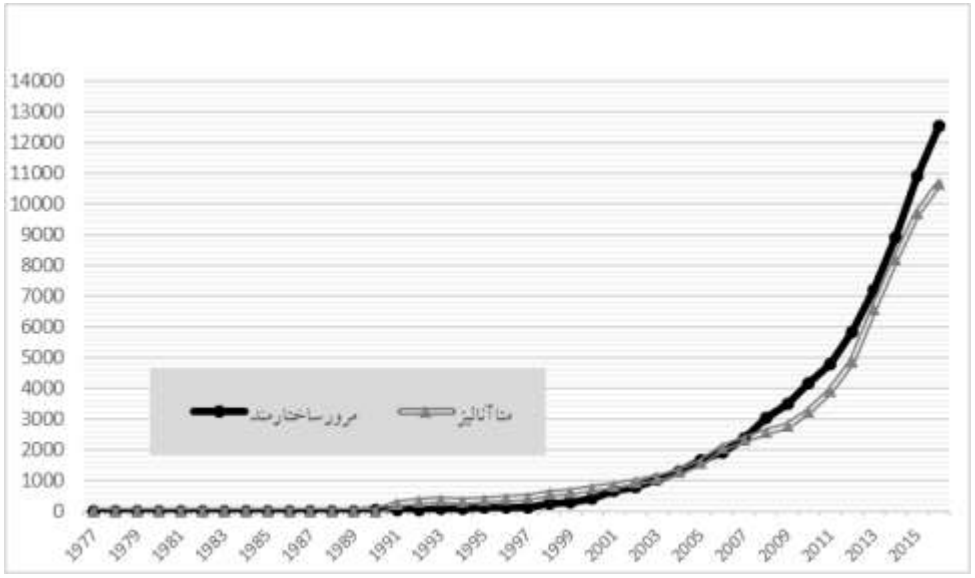
Added sections
- following the same pattern

Conclusions

From each summarised section:
- highlight the main points
- connect with the research needs
- repeat the meaning for the research design

Abstract

- According to the journal style
- Descriptive or structured (IMRAD pattern)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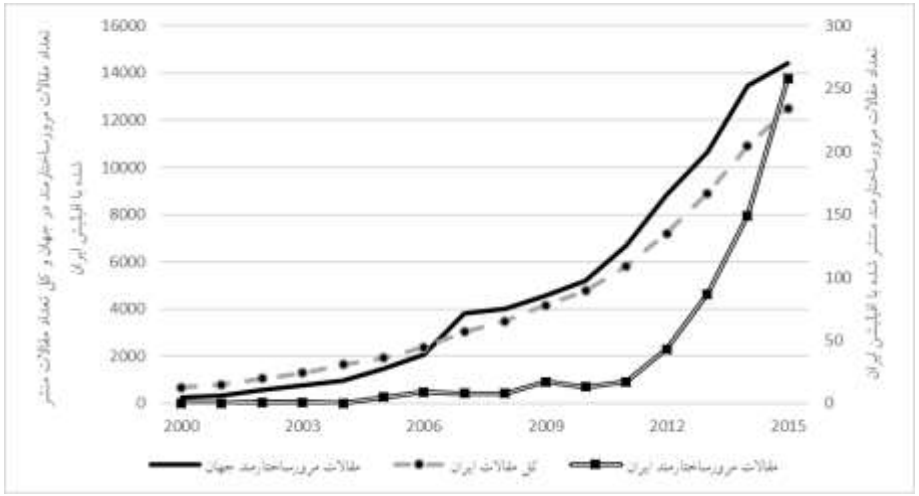
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Stages of a systematic review

- Planning the review – i.e. identifying the need for a review, and documenting the methodology
- Conducting the review – i.e. finding, selecting, appraising, extracting and synthesising primary research studies
- Reporting and dissemination – i.e. writing up and disseminating the results of the review

آشنایی با اجزای یک مرور سیستماتیک

Define the topic or research question

⇩

Identify the relevant information: Inclusion/exclusion criteria and keywords

⇩

Conduct the literature search

⇩

Screen all and exclude the irrelevant studies

⇩

Scrutinize the relevant studies

⇩

Extract data and develop graphic organizers

⇩

Develop evidence synthesis

⇩

Determine if sufficient studies and if meta-analysis is appropriate

⇩ ⇩

If not,

develop meta-synthesis;

report conclusions and recommendations

SYSTEMATIC REVIEW

If yes,

select statistical techniques

⇩

Develop meta-analysis

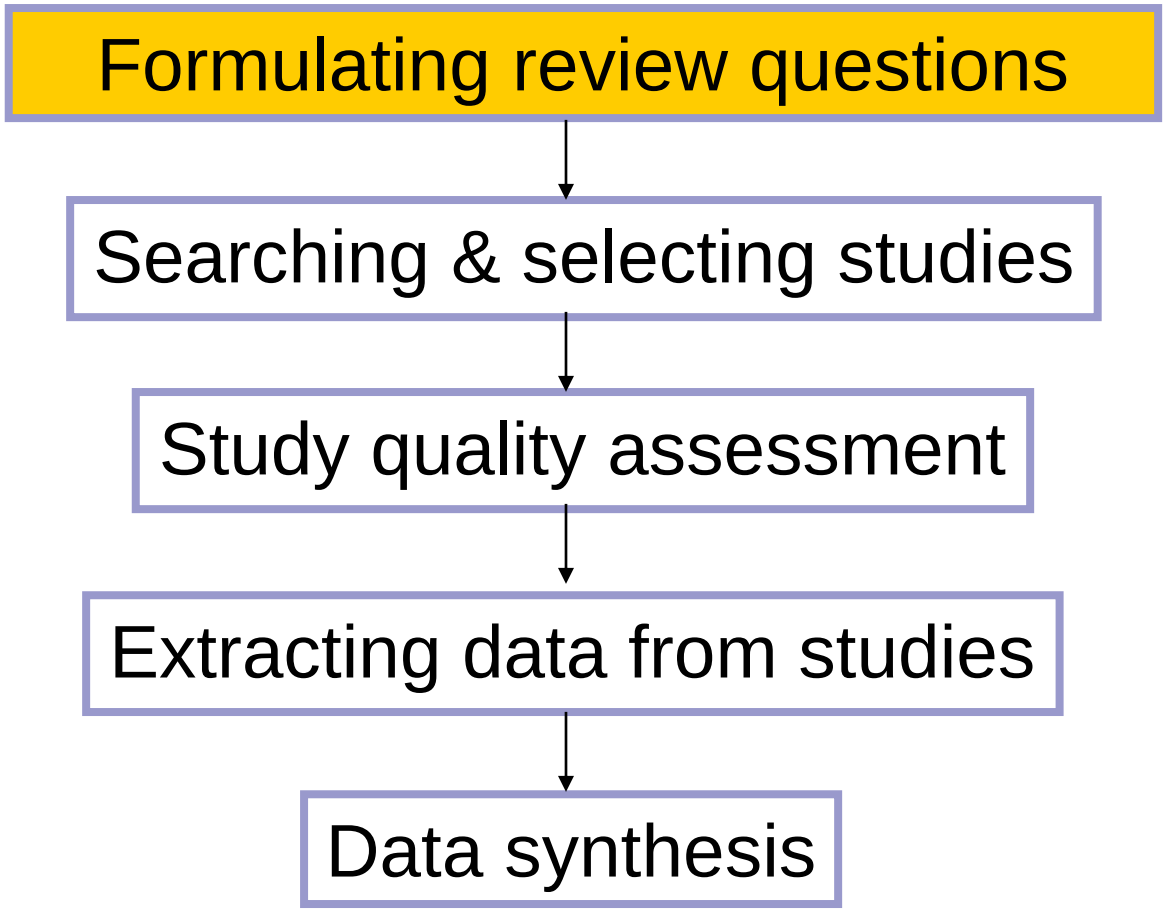
Report results with meta-analysis

Develop conclusions and recommendations

META-ANALYTIC REVIEW

HAVE A BREAK!
10.30-11.00

Steps of Doing a Systematic Review



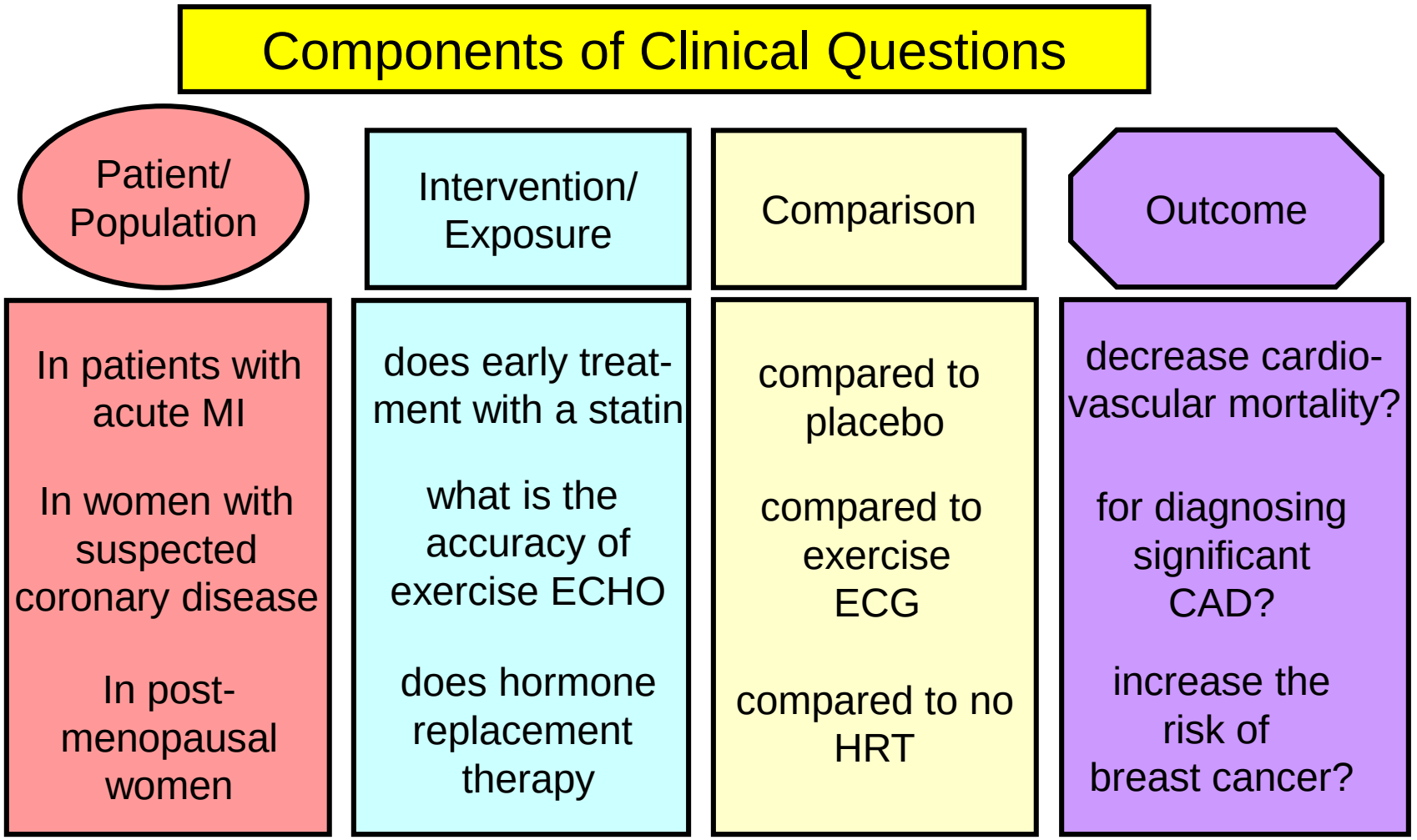
Formulating review questions

- The first and most important decision in preparing a review is to determine its focus
- This is best done by asking clearly framed questions.
- Define a four part clinical question, breaking the question down into its component parts

Question Components: PICO

- What types of **P**atients?
- What types of **I**nterventions?
- What types of **C**omparison?
- What types of **O**utcomes?

Ask Clinical Questions



What types of participants?

- Disease or condition of interest
- Potential co-morbidity
- Setting
- Demographic factors

What types of intervention?

- Treatment
- Diagnostic test
- Causative agent
- Prognostic factor
- Exposure to disease
- Risk behavior

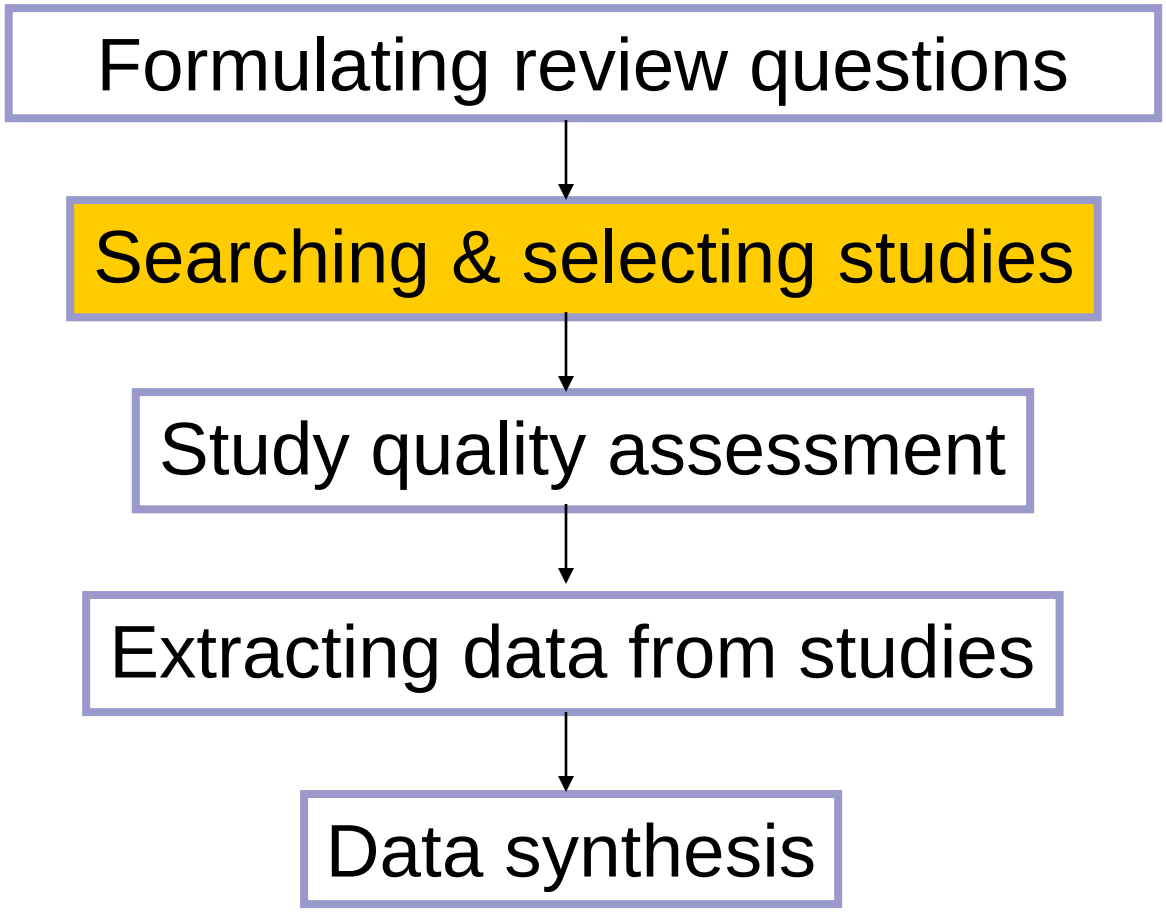
What types of outcomes?

- Mortality/Survival
- Risk of disease
- Disease free period
- Quality of life
- Work absenteeism
- Disability/ Duration and severity of illness
- Pain
- Accuracy of diagnose

Rationale for well-formulated questions

- Determining the structure of a review
- Determining Strategies for locating and selecting studies or data,
- Critically appraising the relevance and validity,
- Helping readers in their initial assessments of relevance.

Steps of Doing a Systematic Review



Selecting studies

- performing a comprehensive, objective, and reproducible search of the literature
- selecting studies which meet the original inclusion and exclusion criteria

can be the most time-consuming and challenging task in preparing a systematic review

Data sources for a systematic review

- **Electronic databases**
  - MEDLINE and EMBASE
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
- **Hand searching**
- **“Grey literature”** (thesis, Internal reports, pharmaceutical industry files, health policy files, conference proceedings)
- **Checking reference lists**
- **Unpublished sources** known to experts in the specialty (seek by personal communication)

Generating a search strategy

- Multiple electronic databases and the internet using a range of Boolean search-terms
- Foreign language searches
- Include grey literature to avoid publication bias (see subsequent slides)
- Search bibliographies and contact experts

Developing a search strategy

- It is always necessary to strike a balance between comprehensiveness and precision when developing a search strategy.

An electronic search strategy generally has three sets of terms:

- 1) terms to search for the health condition of interest;
- 2) terms to search for the intervention(s) evaluated;
- 3) terms to search for the types of study design to be included (such as randomized trials)

Literature Searching: Search terms

- Key words:
  - Reflect the population, intervention and outcome
  - Consider synonyms and alternative spellings
    (e.g., colonise and colonize)
  - Foreign language translations

Vitamin C for preventing and treating the common cold

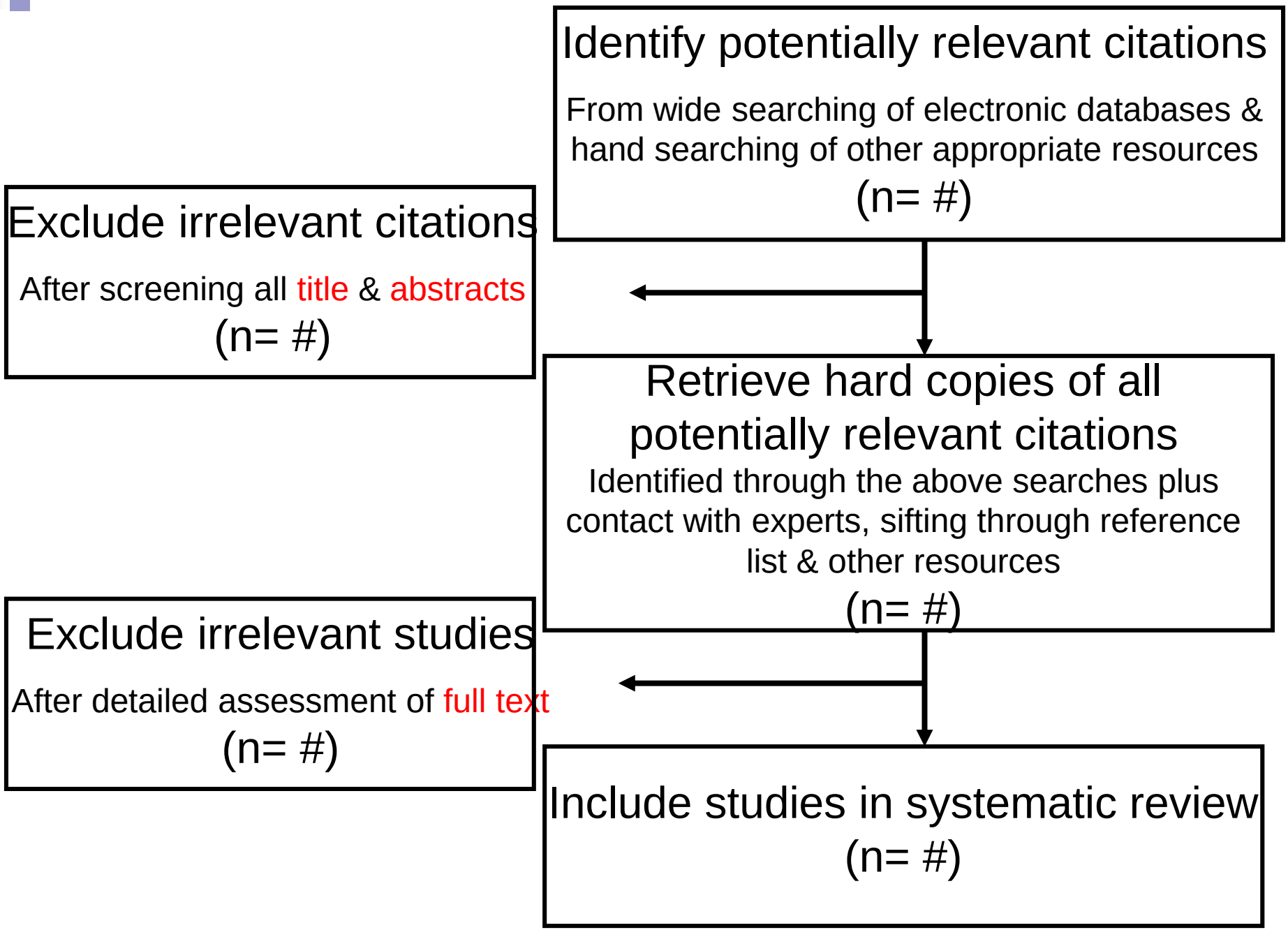
- The following electronic databases were searched for reports of trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2004); MEDLINE (January 1966 to June 2004); and EMBASE (1990 to June Week 23 2004).
- We ran the following search strings in combination with the search strategy developed by the Cochrane Collaboration for identifying randomised controlled trials (Dickersin 1994)
- MEDLINE and CENTRAL were searched using the following search strategy:

- 1 exp Common Cold/
- 2 common cold$.mp.
- 3 exp RHINOVIRUS/
- 4 rhinovir$.mp.
- 5 or/1-4
- 6 exp Ascorbic Acid/
- 7 ascorbic acid.mp.
- 8 vitamin c.mp.
- 9 or/6-8
- 10 5 and 9
- EMBASE search strategy:
- 1 exp Common Cold/
- 2 common cold$.mp.
- 3 exp Rhinovirus/
- 4 rhinovirus infection$.mp.
- 5 or/1-4
- 6 exp Ascorbic Acid/
- 7 vitamin c.mp.
- 8 or/6-7
- 9 5 and 8

Documenting a search strategy

The search strategy should be described in sufficient detail in a review that the process could be replicated:

- Title of database searched (e.g. MEDLINE)
- Date search was run (month, day, year)
- Years covered by the search
- Complete search strategy used, including all search terms


Identify potentially relevant citations
From wide searching of electronic databases & hand searching of other appropriate resources
(n= #)
Exclude irrelevant citations
After screening all title & abstracts
(n= #)
Retrieve hard copies of all potentially relevant citations
Identified through the above searches plus contact with experts, sifting through reference list & other resources
(n= #)
Exclude irrelevant studies
After detailed assessment of full text
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Include studies in systematic review
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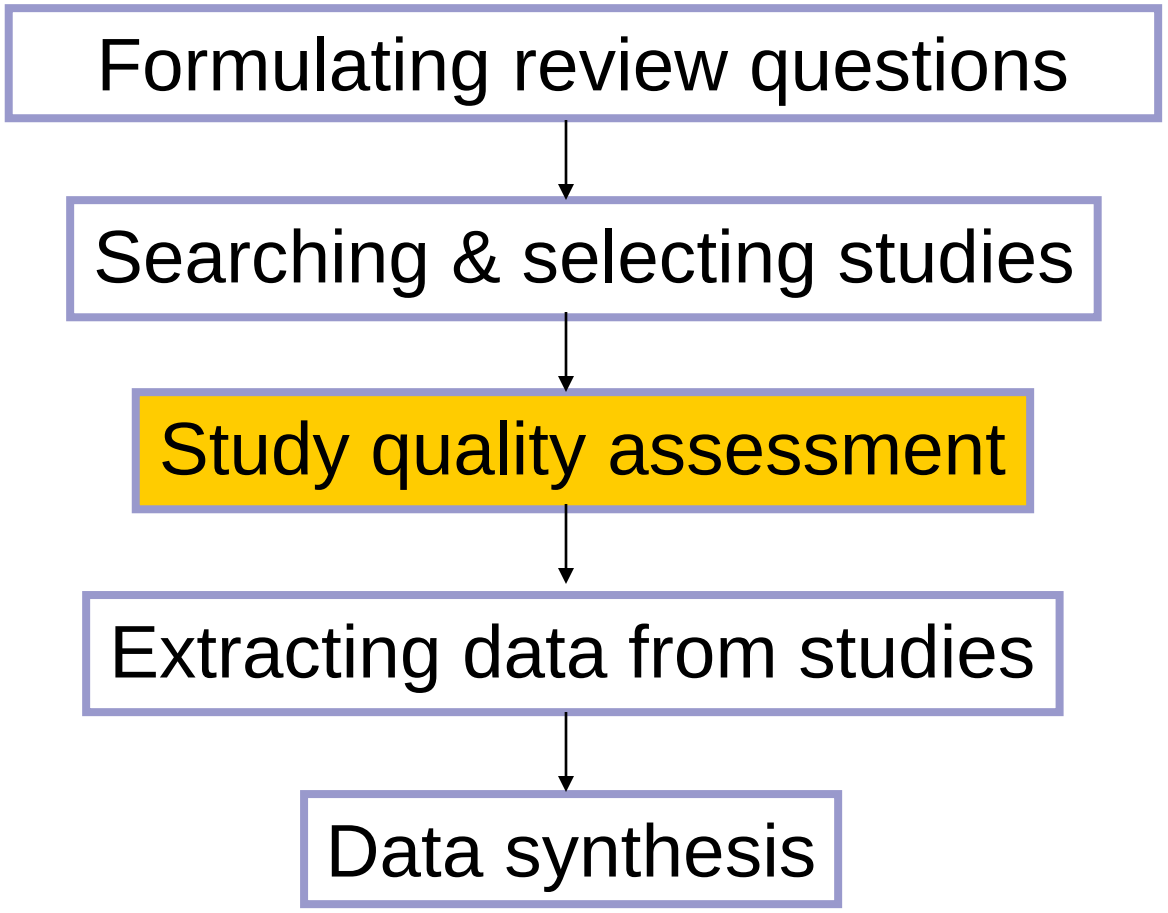
Steps of Doing a Systematic Review



Appraising study quality

- There is no such thing as a perfect study, all studies have weaknesses, limitations, biases
- Interpretation of the findings of a study depends on design, conduct and analysis, as well as on the population, interventions, and outcome measures
- The researchers in a primary study did not necessarily set out to answer your review question

What do we do with quality assessment results?

- Determine minimum quality threshold for inclusion
- Explore differences in quality as an explanation for heterogeneity in study results
- To weight individual study results in relation to their validity or the amount of information they contain
- Guide interpretation and overall recommendations

Assessment of study quality

- Assess each study for:
  - eligibility for inclusion
  - study quality
  - reported findings
- Ideally will involve two independent reviewers

Assessment of study quality

- Validity: the degree to which the trial design, conduct, analysis, and presentation have minimized or avoided systematic biases.

Assessment tools

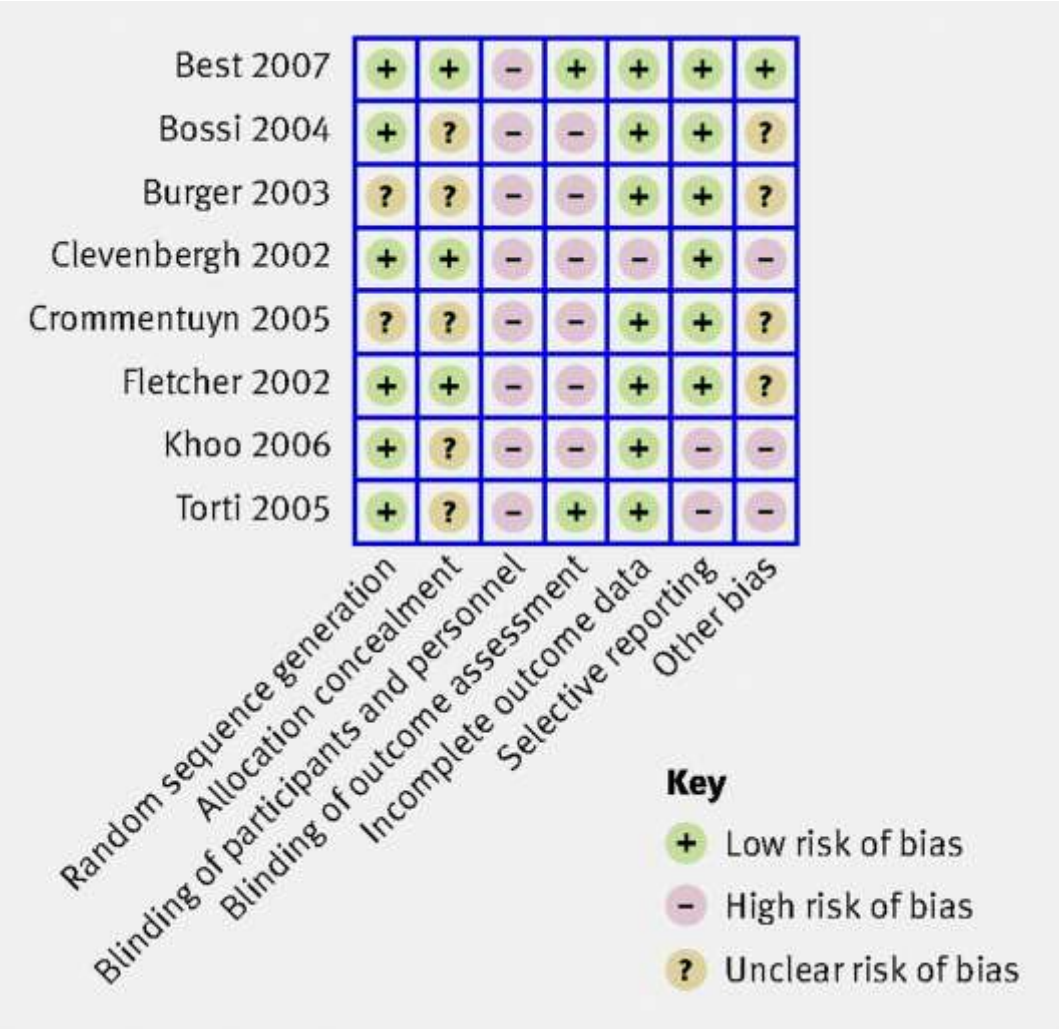
- For RCTs: Cochrane collaboration's tool for assessing risk of bias
- For observational studies: The Newcastle-Ottawa Scale
- GRADE: grading of recommendation assessment, development and evaluation

Quality assessment for interventional studies

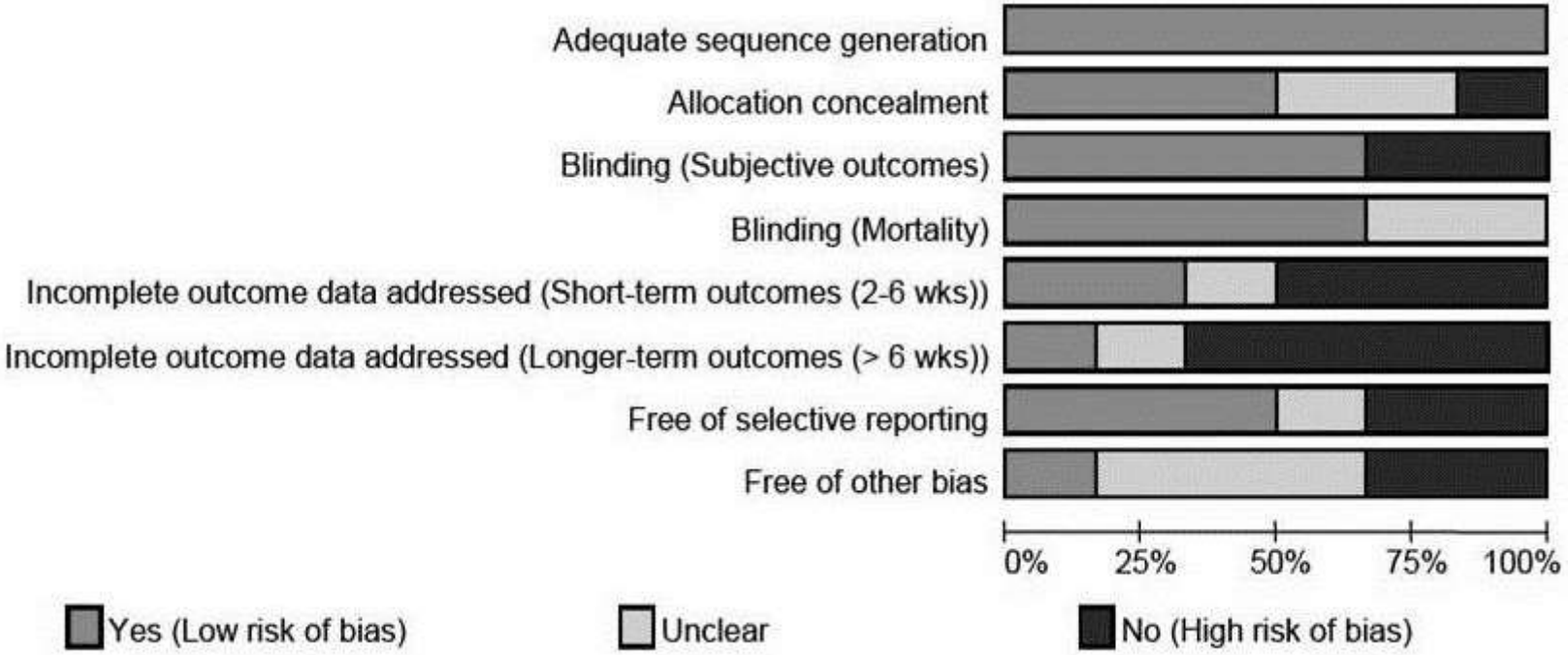
- Cochrane collaboration's tool for assessing risk of bias
  - Selection bias
    - Random sequence generation
    - Allocation concealment
  - Performance bias
    - Blinding
  - Detection bias
    - Blinding of outcome assessment
  - Attrition bias
    - Incomplete outcome data
  - Reporting bias
    - Selective reporting
  - Other biases
    - Other sources of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Fig 1 Example presentation of risk of bias assessments for studies in a Cochrane review of therapeutic monitoring of antiretroviral drugs in people with HIV14.



Julian P T Higgins et al. BMJ 2011;343:bmj.d5928


Adequate sequence generation
Allocation concealment
Blinding (Subjective outcomes)
Blinding (Mortality)
Incomplete outcome data addressed (Short-term outcomes (2-6 wks))
Incomplete outcome data addressed (Longer-term outcomes (> 6 wks))
Free of selective reporting
Free of other bias
0%
25%
50%
75%
100%
Yes (Low risk of bias)
Unclear
No (High risk of bias)

جدول شماره ۲: نمونه‌ای از جدول ارائه شده توسط نرم افزار RevMan برای ارزیابی خطر سوگیری در یک مطالعه مرور ساختارمند

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated." Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).
Allocation concealment (selection bias)	High risk	Quote: "...using a table of random numbers." Comment: Probably not done.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind, double dummy"; "High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution)." Comment: Probably done.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk	Quote: "double blind". Comment: Probably done.
Blinding of outcome assessment (detection bias) (Mortality)	Low risk	Obtained from medical records; review authors do not believe this will introduce bias.
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	High risk	4 weeks: 17/110 missing from intervention group (9 due to 'lack of efficacy'); 7/113 missing from control group (2 due to 'lack of efficacy').
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	High risk	12 weeks: 31/110 missing from intervention group; 18/113 missing from control group. Reasons differ across groups.
Selective reporting (reporting bias)	High risk	Three rating scales for cognition listed in Methods, but only one (with statistically significant results) is reported.

Quality in observational studies

- The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies

- **Cohort studies**
  - **Selection of cohorts**
  - **Comparability of cohorts**
  - **Assessment of outcome**
- **Case-Control studies**
  - **Selection of case and controls**
  - **Comparability of cases and controls**
  - **Ascertainment of exposure**

Development: Identifying Items

- **Identify ‘high’ quality choices with a ‘star’**
- **A maximum of one ‘star’ for each item within the ‘Selection’ and ‘Exposure/Outcome’ categories; maximum of two ‘stars’ for ‘Comparability’**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   - a) truly representative of the average _____ (describe) in the community ☐
   - b) somewhat representative of the average _____ in the community ☐
   - c) selected group of users eg nurses, volunteers
   - d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   - a) drawn from the same community as the exposed cohort ☐
   - b) drawn from a different source
   - c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   - a) secure record (eg surgical records) ☐
   - b) structured interview ☐
   - c) written self report
   - d) no description

4) Demonstration that outcome of interest was not present at start of study
   - a) yes ☐
   - b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   - a) study controls for _____ (select the most important factor) ☐
   - b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   - a) independent blind assessment ☐
   - b) record linkage ☐
   - c) self report
   - d) no description

2) Was follow-up long enough for outcomes to occur
   - a) yes (select an adequate follow up period for outcome of interest) ☐
   - b) no

3) Adequacy of follow up of cohorts
   - a) complete follow up - all subjects accounted for ☐
   - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
   - c) follow up rate < ____% (select an adequate %) and no description of those lost
   - d) no statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ☐
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ☐
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ☐
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ☐
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ☐
   b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ☐
   b) structured interview where blind to case/control status ☐
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ☐
   b) no

3) Non-Response rate
   a) same rate for both groups ☐
   b) non respondents described
   c) rate different and no designation

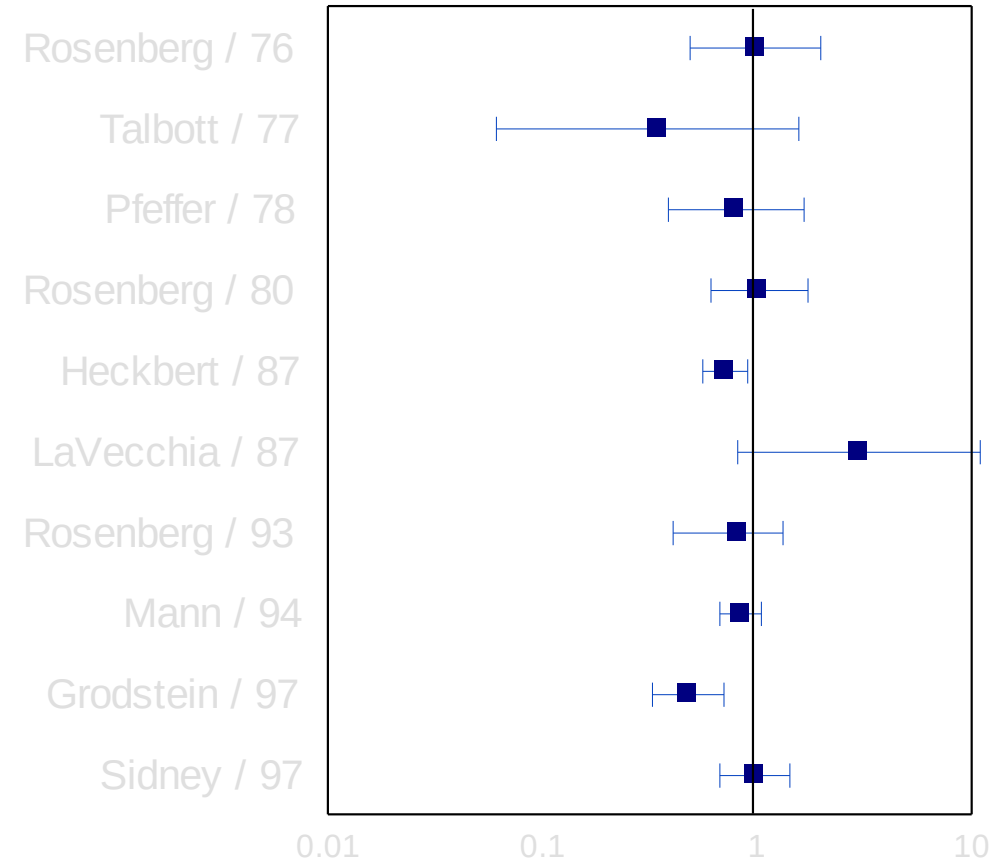
Newcastle-Ottawa Quality Assessment Scale: Case-Control Studies

- Selection (4)
- Comparability (1)
- Exposure (3)
  - A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability

Author	Selection				Comparability		Exposure			Score
Davies[7]	★	★	★			★	★	★		6
Grange[6]	★			★	★		★	★		5
Davies[8]	★	★	★	★	★		★	★		7
Davies[13]	★	★				★	★	★		5
Chan[11]	★	★		★	★		★	★		6
Wilkinson[1]	★	★	★	★	★		★	★		7
Sasidharan[13]	★	★		★	★	★	★	★		7

Nnoaham K, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008; **37**(1): 113-9.

Adjusted Effect Estimates for Coronary Heart Disease (All Events) (HRT: Estrogen Current Use) Case-Control Studies



Selection	Comparability	Exposure
★	★★	★
★★★	★★	★
★★★★	★★	★★★
★★★	★★	★★
★★★★	★★	★★★
★★	★★	★★
★★★★	★★	★★
★★★	★★	★★
★★	★★	★★
★★★★	★★	★★

You can find the manual and scale in:

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

- GRADE differs from other appraisal system for three reasons:
  1. It separate quality of evidence and strenght of recommendation
  2. The quality of evidence is assessed for each outcome
  3. Observational studies can be upgraded if they meet certain criteria

Using GRADE

The GRADE method involves **five** distinct steps:

- ***STEP 1***

  Assign an a-priori ranking of "high" to randomized controlled trials and "low" to observational studies

Randomized controlled trials are initially assigned a higher grade because they are usually less prone to bias than observational studies

- ***STEP 2***

  "Downgrade" or "upgrade" initial ranking

It is common for randomized controlled trials and observational studies to be downgraded because they suffer from identifiable bias. Also, observational studies can be upgraded when multiple high-quality studies show consistent results

Using GRADE

- **Reasons to "downgrade"**

- **Risk of bias**
  - Lack of clearly randomized allocation sequence
  - Lack of blinding
  - Lack of allocation concealment
  - Failure to adhere to intention-to-treat analysis
  - Trial is cut short
  - Large losses to follow-up

- **Inconsistency**

When there is significant and unexplained variability in results from different trials

Using GRADE

- **Reasons to "downgrade"**

- **Indirectness of evidence**
  can refer to several things:
  - An indirect comparison of two drugs.
  - An indirect comparison of population, outcome or intervention

- **Imprecision**
  when wide confidence intervals mar the quality of the data

- **Publication bias**
  when studies with "negative" findings remain unpublished

Using GRADE

- **Reasons to "upgrade"**

- **Large effect**

  When the effect is so large that bias common to observational studies cannot possibly account for the result

- **Dose-response relationship**

  When the result is proportional to the degree of exposure

- **All plausible confounders would have reduced the treatment effect**

  When all possible confounders would only diminish the observed effect and it is thus likely that the actual effect is larger than the data suggests

Using GRADE

STEP 3

- *Assign final grade for the quality of evidence as "high", "moderate", "low" or "very low" for all the critically important outcomes*

Final GRADE ranking		
High	⊕⊕⊕⊕	We are very confident that the effect of the study reflects the actual effect
Moderate	⊕⊕⊕	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different
Low	⊕⊕	The true effect may differ significantly from the estimate
Very low	⊕	The true effect is likely to be substantially different from the estimated effect

Using GRADE

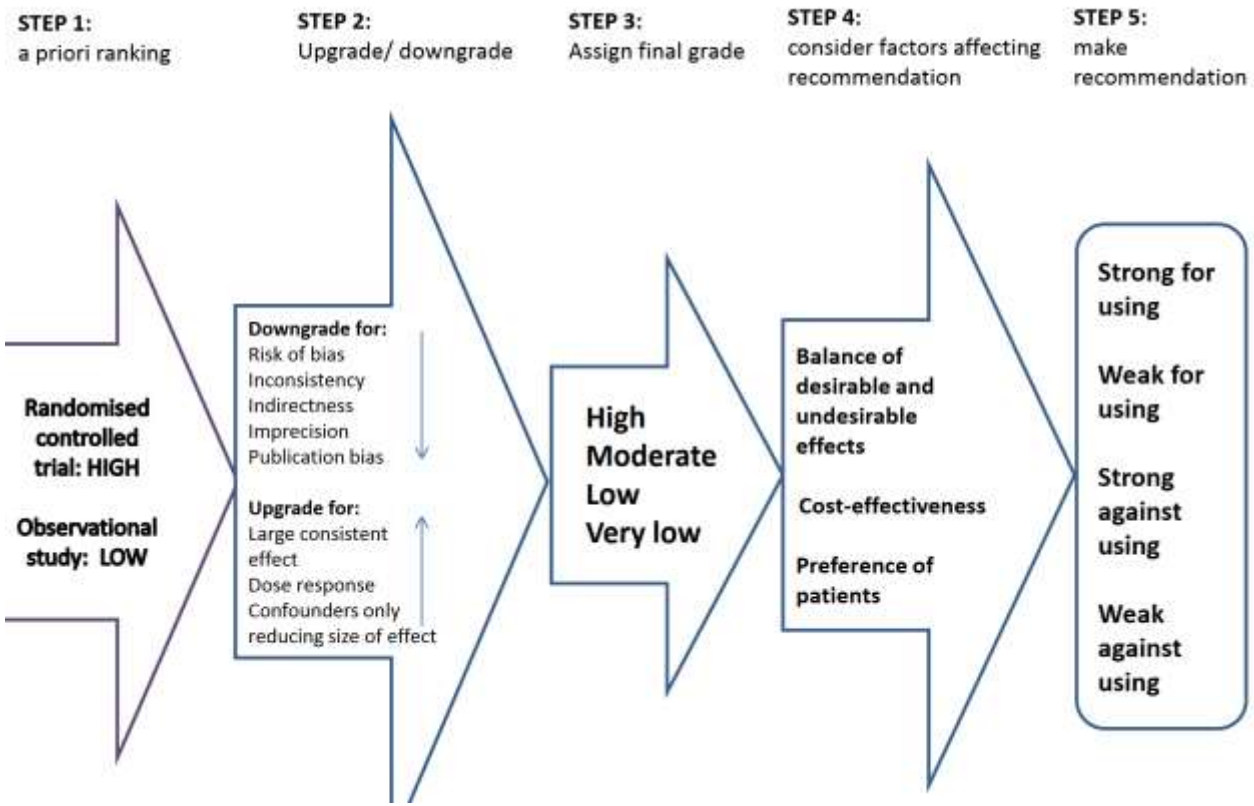
STEP 4

- ***Consider other factors that impact on the strength of recommendation for a course of action***

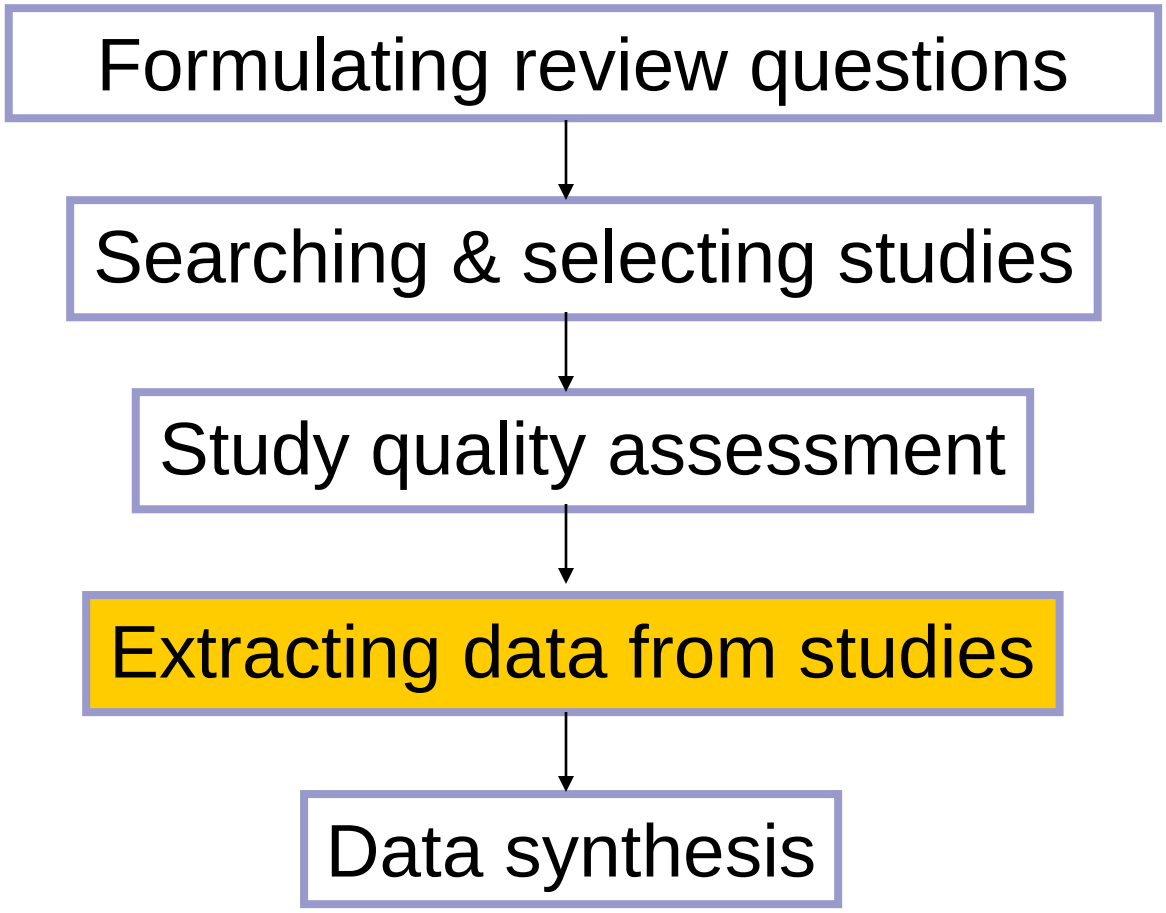
- High-quality evidence does not always imply a strong recommendation. Recommendations must consider factors besides the quality of evidence

- First factor the balance between desirable and undesirable effects.
- Uncontroversial recommendation e.g. antibiotics

- Controversial recommendation: where the benefit to harm ratio is less clear. Patient values and preferences, as well as costs, need to be considered carefully


STEP 1:
a priori ranking
STEP 2:
Upgrade/ downgrade
STEP 3:
Assign final grade
STEP 4:
consider factors affecting recommendation
STEP 5:
make recommendation
Randomised controlled trial: HIGH
Observational study: LOW
Downgrade for:
Risk of bias
Inconsistency
Indirectness
Imprecision
Publication bias
Upgrade for:
Large consistent effect
Dose response
Confounders only reducing size of effect
High
Moderate
Low
Very low
Balance of desirable and undesirable effects
Cost-effectiveness
Preference of patients
Strong for using
Weak for using
Strong against using
Weak against using

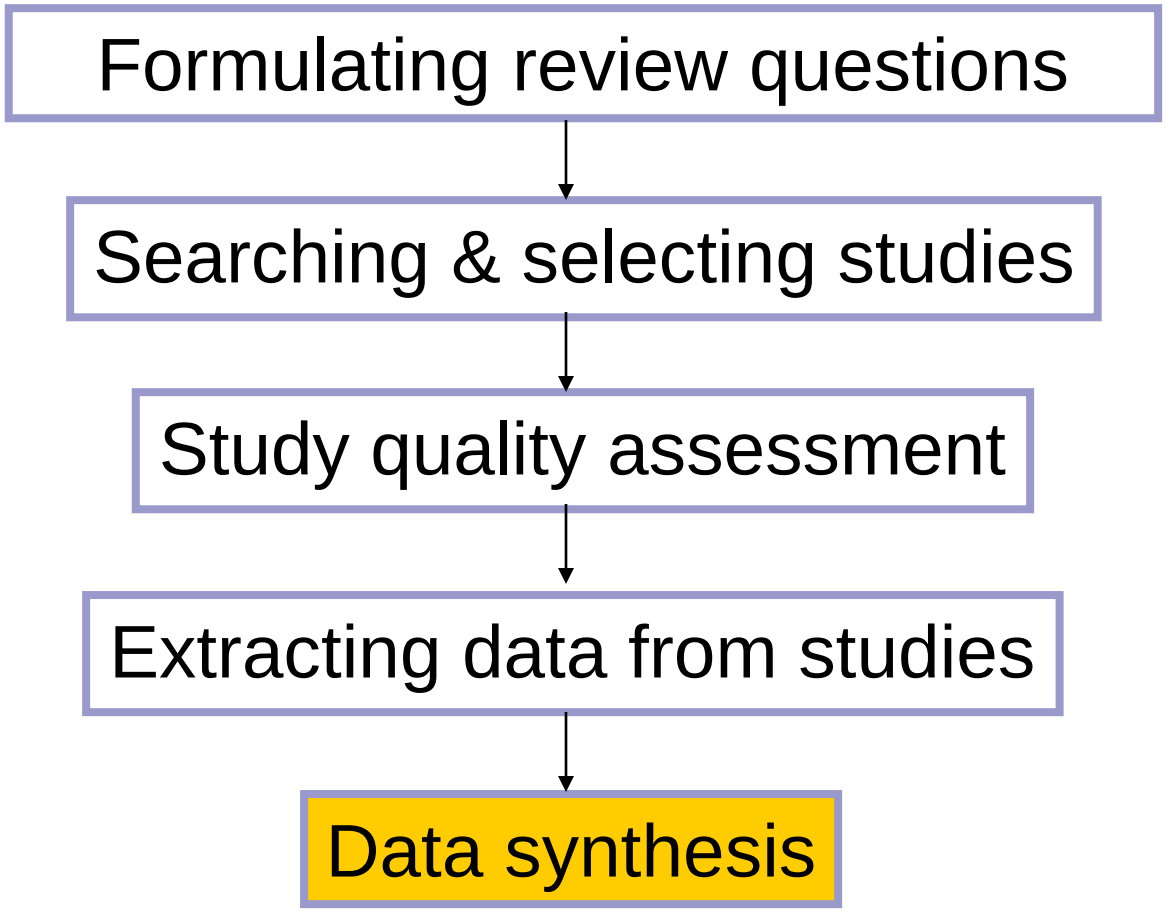
Steps of Doing a Systematic Review



Collecting data

- Data collection forms
  - Methods
  - Participants
  - Interventions
  - Outcome measures and results

Steps of Doing a Systematic Review



Meta-Analysis

- when an overview incorporates a specific statistical strategy for assembling the results of several studies into a single estimate

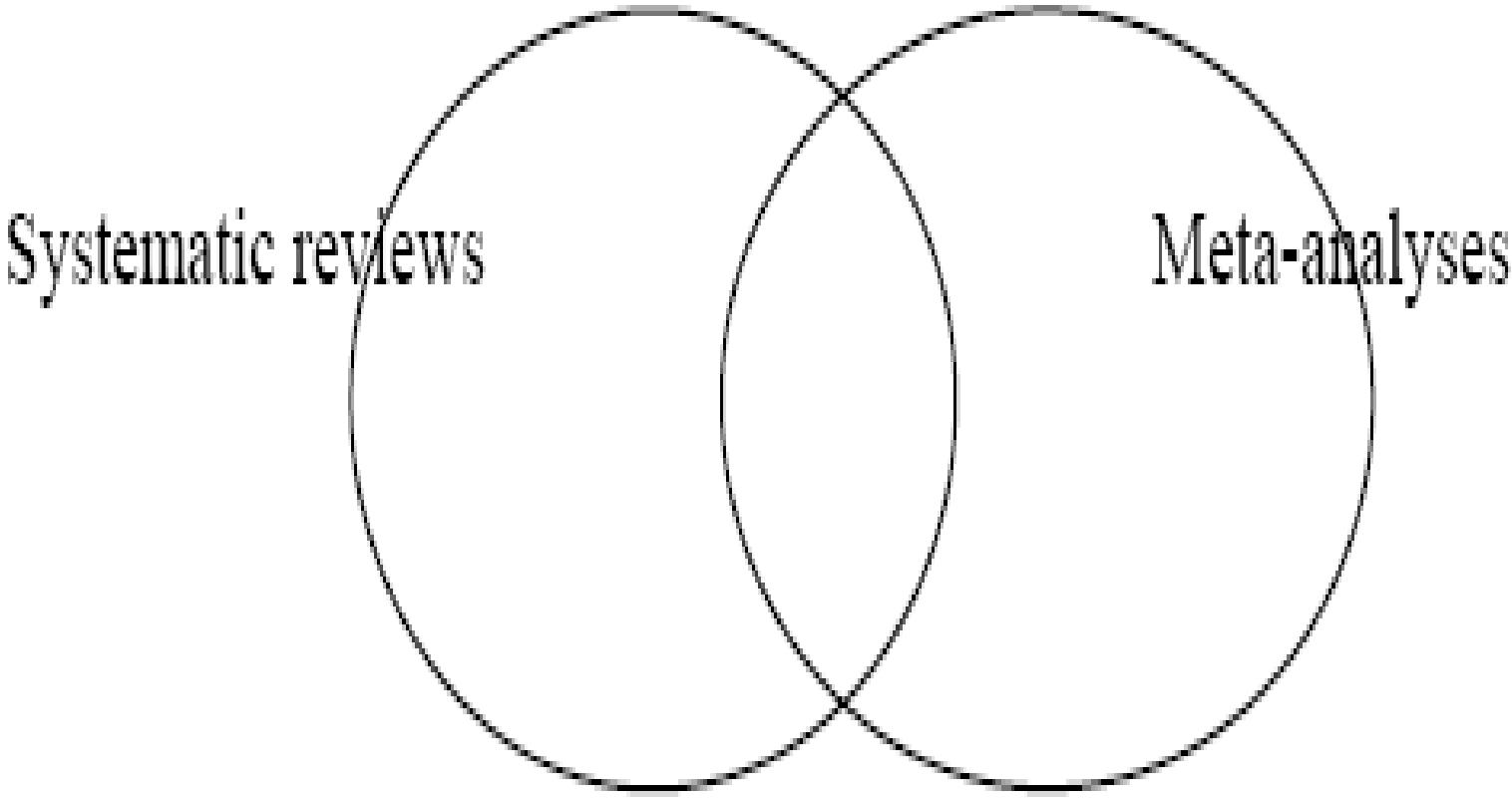
Systematic reviews & Meta-Analysis

- Systematic reviews do not *have* to have a meta-analysis

- There are times when it is not appropriate or possible.

Systematic reviews & Meta-Analysis

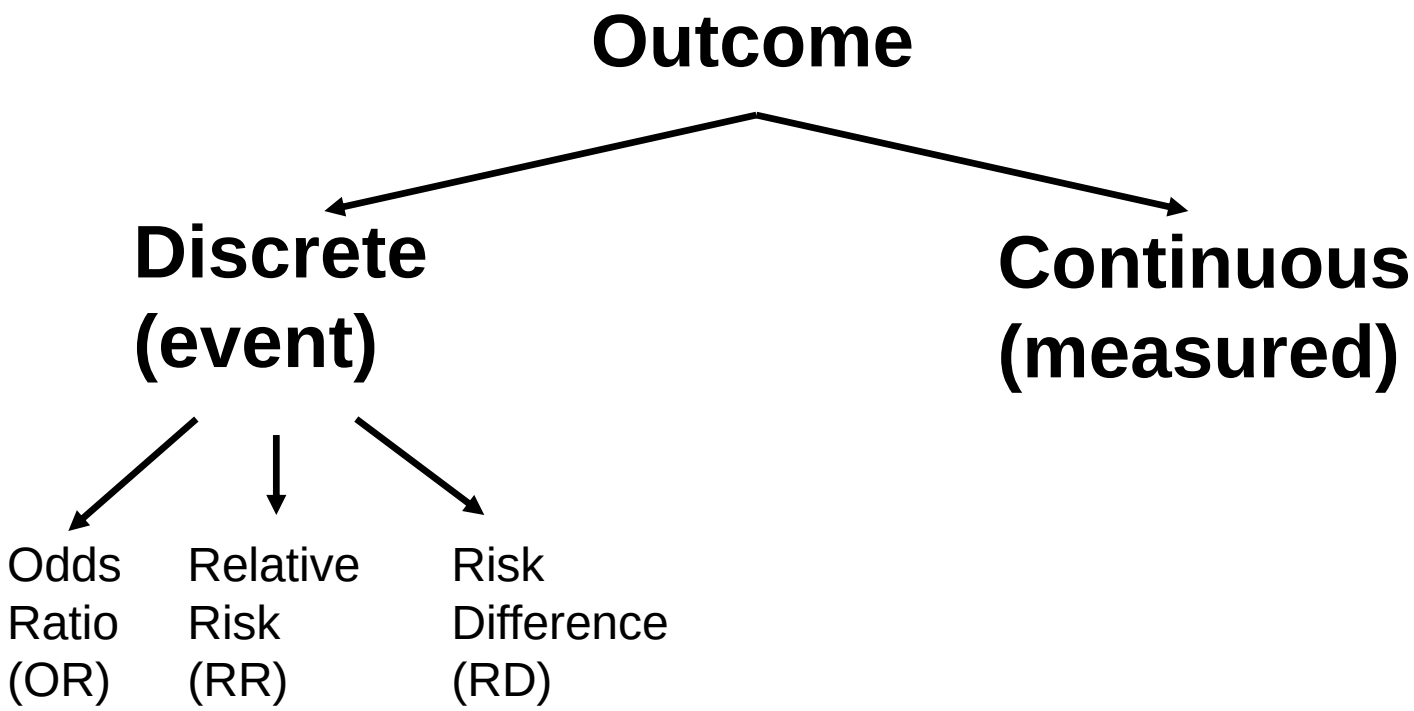
- The term '**meta-analysis**' is often used interchangeable with '**systematic review**'
- It is actually a statistical technique used to combine the results of several studies addressing the same question into a single summary measure (Khan *et al*., 2000).


Systematic reviews
Meta-analyses

Forest Plot

- For each trial
  - estimate (square)
  - 95% confidence interval (CI) (line)
  - size (square) indicates weight allocated
- Solid vertical line of ‘no effect’
  - if CI crosses line then effect not significant (p>0.05)
- Horizontal axis
  - arithmetic: RD, MD, SMD
  - logarithmic: OR, RR
- Diamond represents combined estimate and 95% CI
- Dashed line plotted vertically through combined estimate

Effect Size Measures



What are dichotomous outcomes?

- when the outcome for every participant is one of two possibilities or events
  - alive or dead
  - healed or not healed
  - pregnant or not pregnant

What were the chances of that?

- **Risk** and **odds**
  - express chance in numbers
  - for dichotomous outcomes, express the chance within a group of being in one of two states
  - particular statistical meanings, calculated differently

Risk

- 24 people drank coffee
  6 developed a headache
- risk of a headache

  = 6 headaches / 24 people who could have had one

  = 6/24 = ¼ = 0.25 = 25%

risk = $\frac{\text{no. participants with event of interest}}{\text{total no. participants}}$

Odds

- 24 people drank coffee
  6 developed a headache
- odds of a headache
  = 6 headaches/18 without headaches
  = 6/18 = 1/3 = 0.33 = 1:3 (not usually as %)

odds = $\frac{\text{no. participants with event of interest}}{\text{no. participants without event of interest}}$

Do risks and odds differ much?

- Two examples from caffeine trials

- 5 people with ‘headaches’ out of 65
- chance of having a headache

risk = 5/65 = 0.077 **odds = 5/60 = 0.083**

- 130 people ‘still awake’ out of 165
- chance of still being awake

Comparing two groups

	Headache	No headache	Total
Caffeine	17	51	**68**
Decaf	9	55	**64**
Total	**26**	**106**	**132**

Comparing two groups

- effect measures
  - risk ratio (RR) (relative risk)
  - odds ratio (OR)
  - risk difference (RD) (absolute risk reduction)
- all estimates are uncertain, and should be presented with a confidence interval

Risk ratio

- risk of event with intervention = **17/68**
- risk of event with control = **9/64**

	Headache	No headache	Total
Caffeine	**17**	51	**68**
Decaf	9	55	64
Total	**26**	**106**	**132**

- risk ratio = intervention risk
- **Where risk ratio = 1, there is no difference between the groups**

Expressing it in words

- Risk ratio 1.79
  - the risk of having a headache with treatment was 179% of the risk in the control group
  - intervention increased the risk of headache by 79%

- **or for a reduction in risk:**
  - Risk ratio 0.79
    - the risk of having a headache with treatment was 79% of the risk in the control group
    - intervention reduced the risk of headache by 21%

Odds ratio

- odds of event with intervention = **17/51**
- odds of event with control = **9/55**
- odds ratio = intervention odds
- control odds
- =**17/51** = 0.33 = 2.06
- **9/55** 0.16

	Headache	No headache	Total
Caffeine	**17**	**51**	68
Decaf	9	55	64
Total	**26**	**106**	**132**

Where odds ratio = 1, there, is no difference between the groups

Expressing it in words

- Odds ratio 2.06
  - intervention doubled the odds of headache
  - intervention increased the odds to 206% of the odds in the control group
  - intervention increased the odds of headache by 106%

- **or for a reduction in odds:**
  - Odds ratio 0.06
    - intervention reduced the odds of headache to 6% of the odds in the control group
    - intervention reduced the odds of headache by 94%

Risk difference

	Headache	No headache	Total
Caffeine	17	51	68
Decaf	9	55	64
Total	26	106	132

- risk of event with intervention = **17/68**
- risk of event with control

  = **9/64**

- risk difference = risk with intervention – risk with control

- =**17/68 – 9/64**
- = 0.25 – 0.14 = 0.11

- **Where risk difference = 0, there is no difference between the groups**

Expressing it in words

- Risk difference 0.11
  - intervention increased the risk of headache by 11 percentage points
  - 14 out of 100 people experienced a headache in the control group. 11 more people experienced a headache with caffeine.

- **or for a reduction in risk:**
  - Risk difference -0.11
    - intervention reduced the risk of headache by 11 percentage points
    - 14 out of 100 people experienced a headache in the control group. 11 fewer people experienced a headache with caffeine.

Now it's your turn!

	Event	No Event	Total
Intervention	2	8	10
Control	5	5	10
Total	**7**	**13**	**20**

1. calculate:
   - risk ratio for the effect of treatment on chance of event
   - odds ratio for the effect of treatment on chance of event
2. express the results in words

The answers

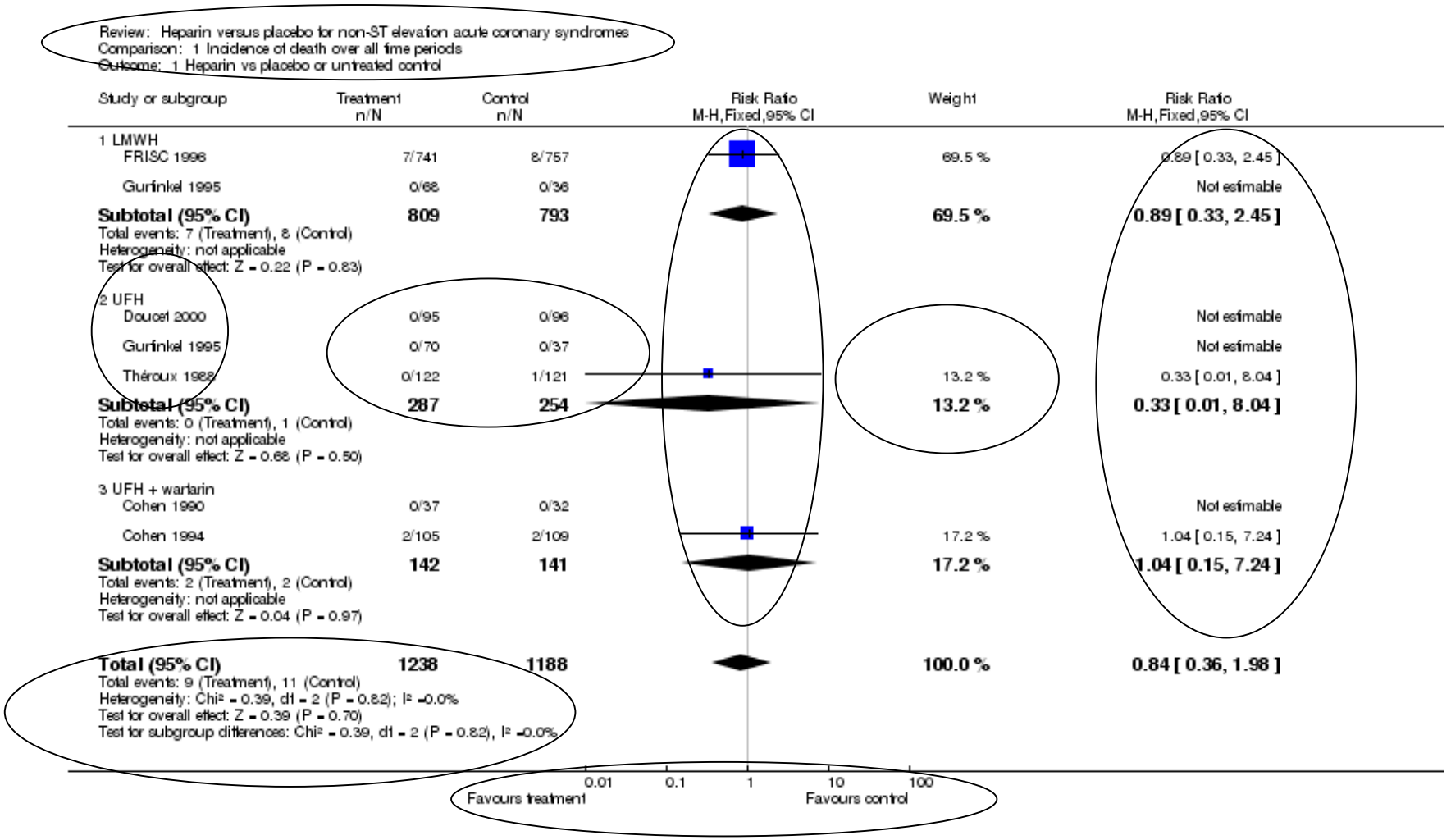
- Risk ratio $= \frac{2/10}{5/10} = \frac{0.2}{0.5} = 0.4$

$$= \frac{2/8}{5/5} = \frac{0.25}{1} = 0.25$$

- Odds ratio

Communication

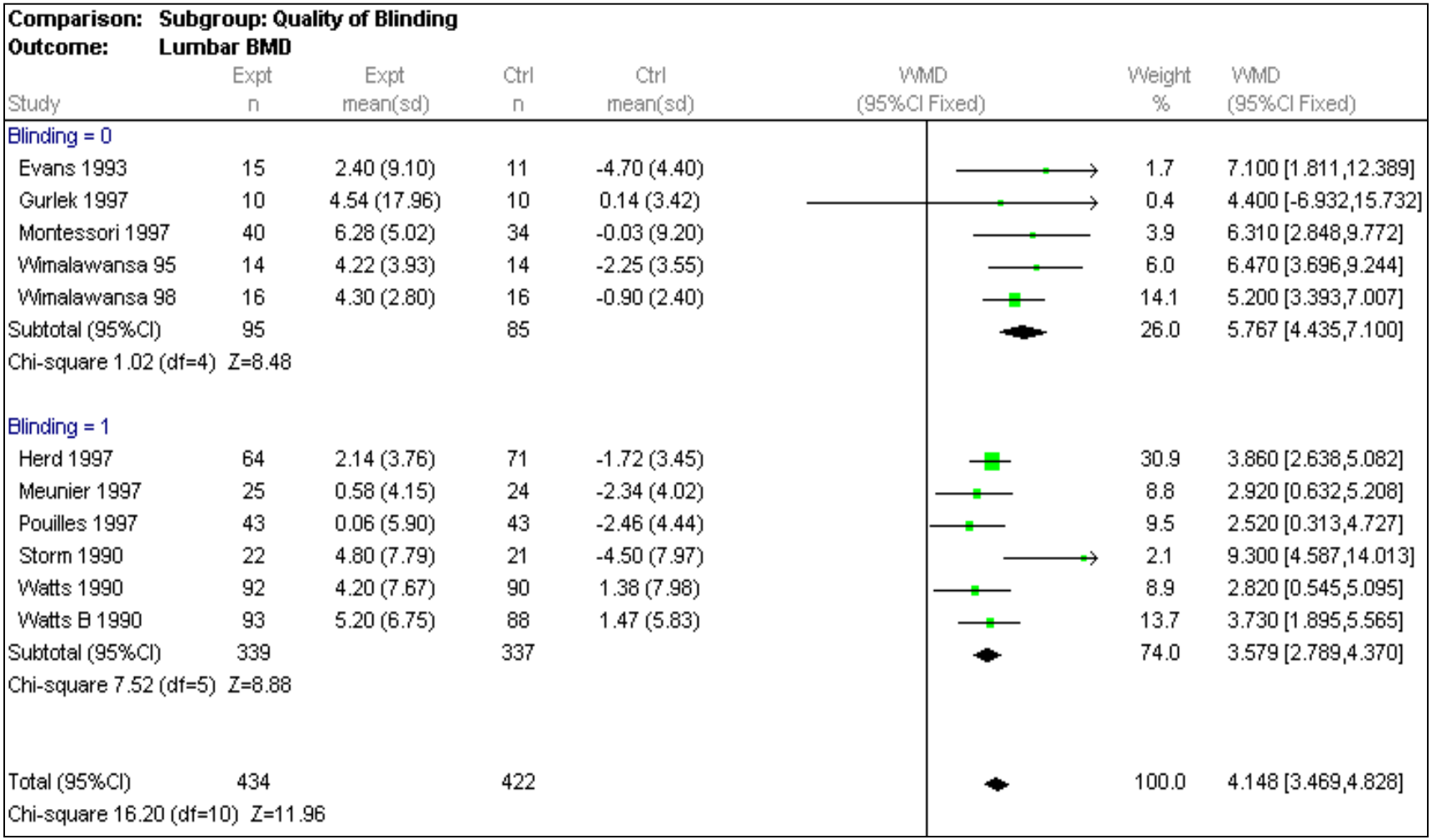
- OR is hard to understand, often misinterpreted
- RR is easier, but relative
  - can mean a very big or very small change
- RD is easiest
  - absolute measure of actual change in risk
  - easily converted to natural frequencies or NNT



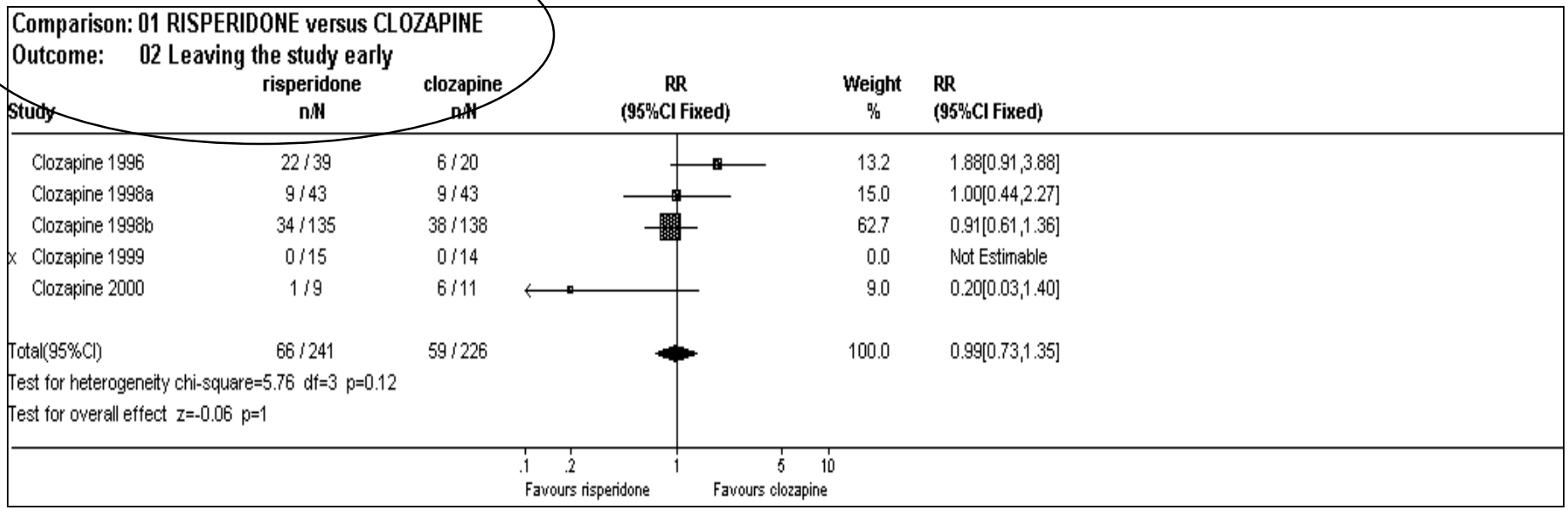
1.1. Comparison 1 Incidence of death over all time periods, Outcome 1 Heparin vs placebo or untreated control.

Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Magee K. Heparin versus placebo for non-ST elevation acute coronary syndromes. Cochrane Database of Systematic Reviews 2014, 6. Art. No.: CD003462. DOI: http://dx.doi.org/10.1002/14651858.CD003462.pub3

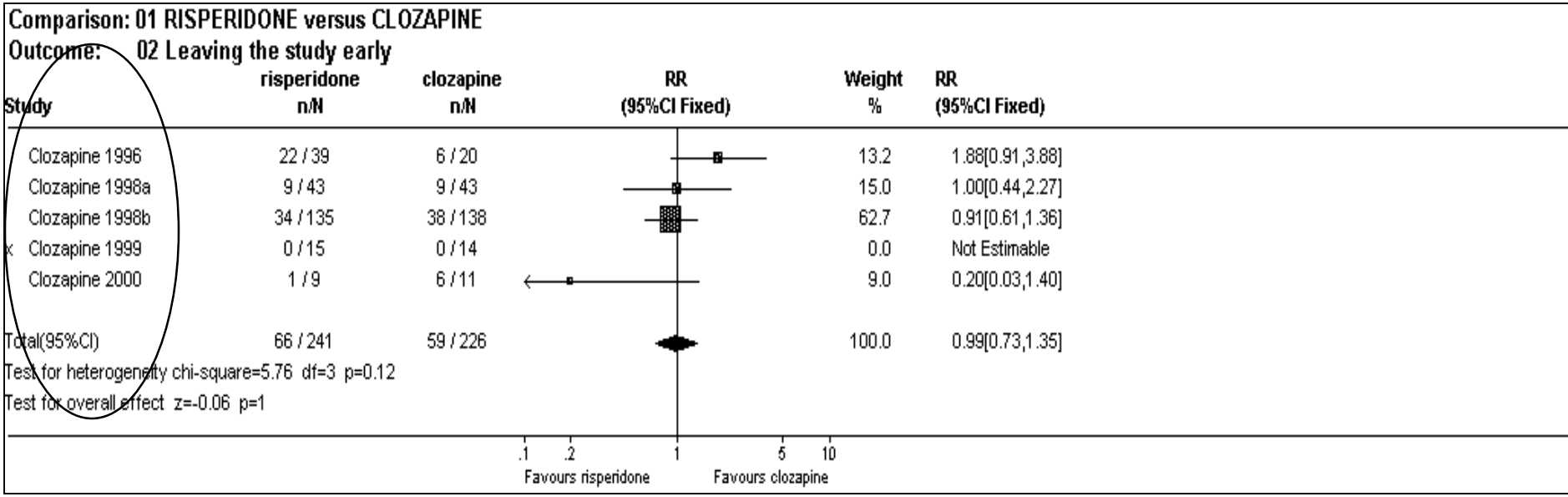
Forest plot


Comparison: Subgroup: Quality of Blinding
Outcome: Lumbar BMD
Study
Expt n
Expt mean(sd)
Ctrl n
Ctrl mean(sd)
WMD (95%CI Fixed)
Weight %
WMD (95%CI Fixed)
Blinding = 0
Evans 1993 15 2.40 (9.10) 11 -4.70 (4.40) 1.7 7.100 [1.811,12.389]
Gurlek 1997 10 4.54 (17.96) 10 0.14 (3.42) 0.4 4.400 [-6.932,15.732]
Montessori 1997 40 6.28 (5.02) 34 -0.03 (9.20) 3.9 6.310 [2.848,9.772]
Wimalawansa 95 14 4.22 (3.93) 14 -2.25 (3.55) 6.0 6.470 [3.696,9.244]
Wimalawansa 98 16 4.30 (2.80) 16 -0.90 (2.40) 14.1 5.200 [3.393,7.007]
Subtotal (95%CI) 95 85 26.0 5.767 [4.435,7.100]
Chi-square 1.02 (df=4) Z=8.48
Blinding = 1
Herd 1997 64 2.14 (3.76) 71 -1.72 (3.45) 30.9 3.860 [2.638,5.082]
Meunier 1997 25 0.58 (4.15) 24 -2.34 (4.02) 8.8 2.920 [0.632,5.208]
Pouilles 1997 43 0.06 (5.90) 43 -2.46 (4.44) 9.5 2.520 [0.313,4.727]
Storm 1990 22 4.80 (7.79) 21 -4.50 (7.97) 2.1 9.300 [4.587,14.013]
Watts 1990 92 4.20 (7.67) 90 1.38 (7.98) 8.9 2.820 [0.545,5.095]
Watts B 1990 93 5.20 (6.75) 88 1.47 (5.83) 13.7 3.730 [1.895,5.565]
Subtotal (95%CI) 339 337 74.0 3.579 [2.789,4.370]
Chi-square 7.52 (df=5) Z=8.88
Total (95%CI) 434 422 100.0 4.148 [3.469,4.828]
Chi-square 16.20 (df=10) Z=11.96

Forest plot


Comparison: 01 RISPERIDONE versus CLOZAPINE
Outcome: 02 Leaving the study early
Study
risperidone n/N
clozapine n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Clozapine 1996 22 / 39 6 / 20 13.2 1.88[0.91,3.88]
Clozapine 1998a 9 / 43 9 / 43 15.0 1.00[0.44,2.27]
Clozapine 1998b 34 / 135 38 / 138 62.7 0.91[0.61,1.36]
x Clozapine 1999 0 / 15 0 / 14 0.0 Not Estimable
Clozapine 2000 1 / 9 6 / 11 9.0 0.20[0.03,1.40]
Total(95%CI) 66 / 241 59 / 226 100.0 0.99[0.73,1.35]
Test for heterogeneity chi-square=5.76 df=3 p=0.12
Test for overall effect z=-0.06 p=1
.1
.2
1
5
10
Favours risperidone
Favours clozapine

Forest plot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.2
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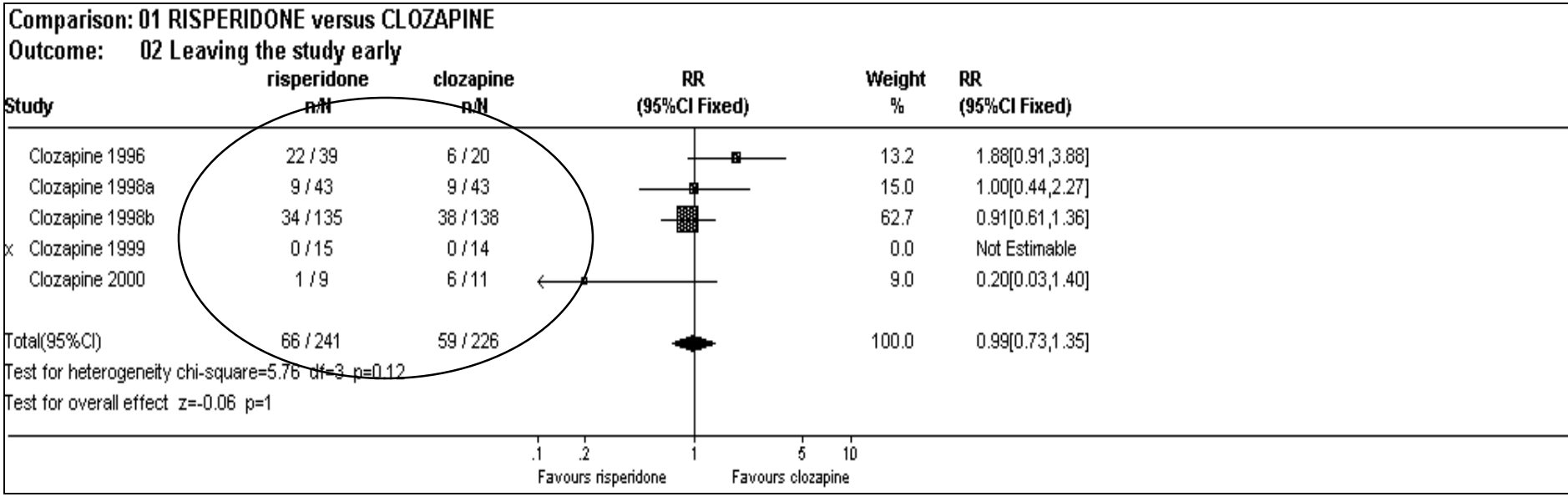
Forest plot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RR (95%CI Fixed)
Clozapine 1996 22 / 39 6 / 20 13.2 1.88[0.91,3.88]
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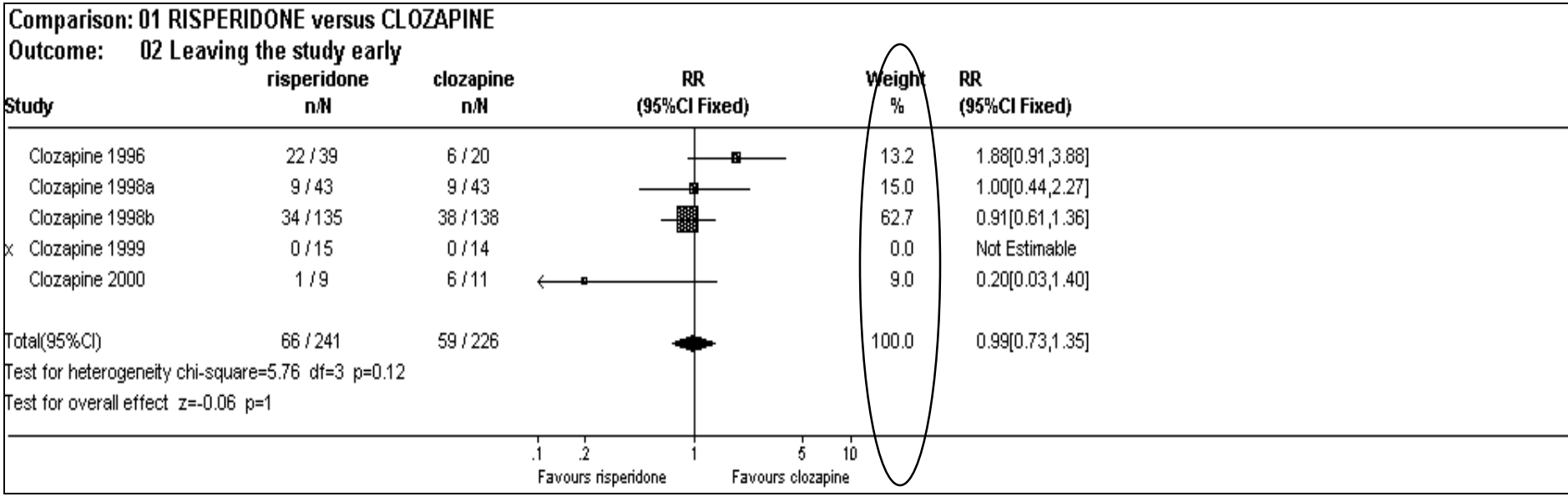
Total(95%CI) 66 / 241 59 / 226 100.0 0.99[0.73,1.35]
Test for heterogeneity chi-square=5.76 df=3 p=0.12
Test for overall effect z=-0.06 p=1
.1
.2
1
5
10
Favours risperidone
Favours clozapine

Forest plot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RR (95%CI Fixed)
Weight %
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Total(95%CI) 66 / 241 59 / 226 100.0 0.99[0.73,1.35]
Test for heterogeneity chi-square=5.76 df=3 p=0.12
Test for overall effect z=-0.06 p=1
.1
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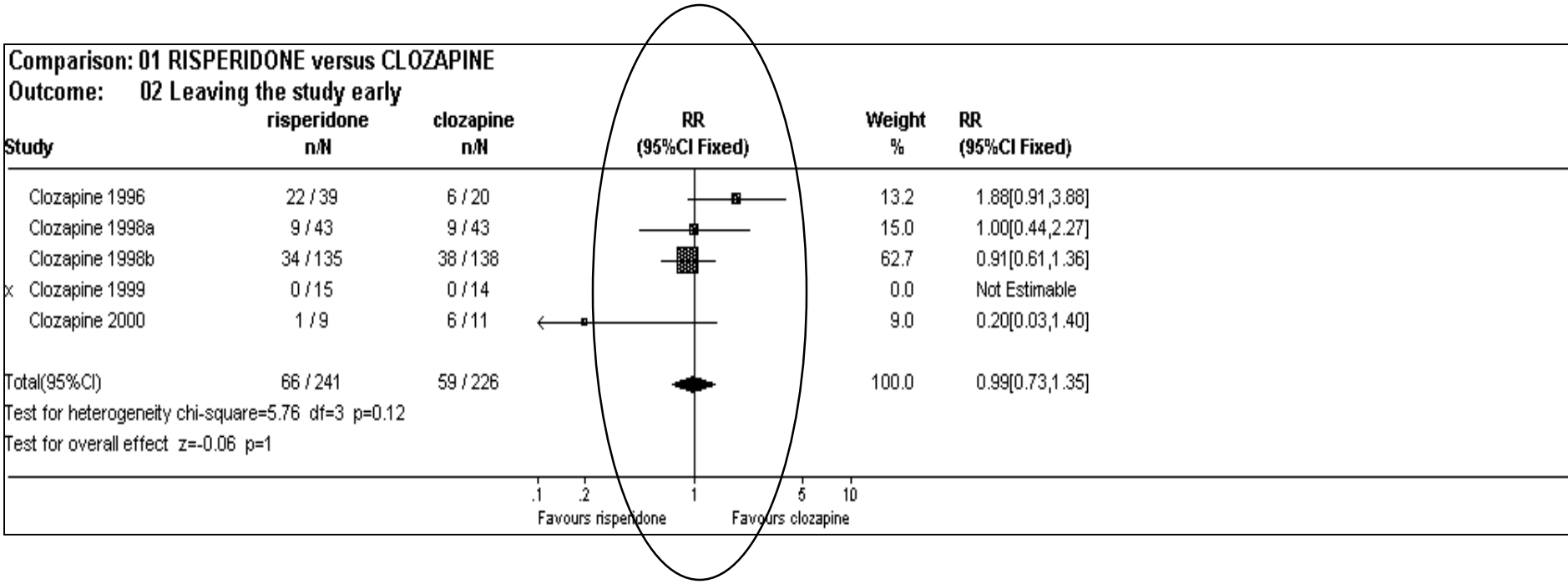
Favours risperidone
Favours clozapine

Forest plot


Comparison: 01 RISPERIDONE versus CLOZAPINE
Outcome: 02 Leaving the study early
Study
risperidone n/N
clozapine n/N
RR (95%CI Fixed)
Weight %
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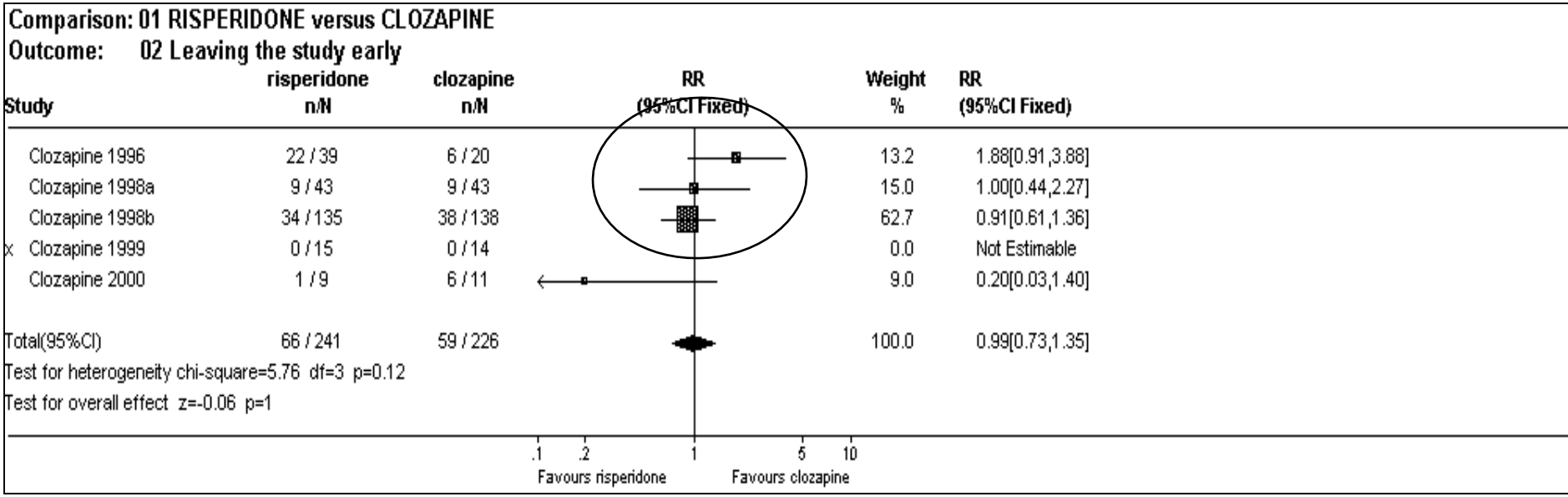
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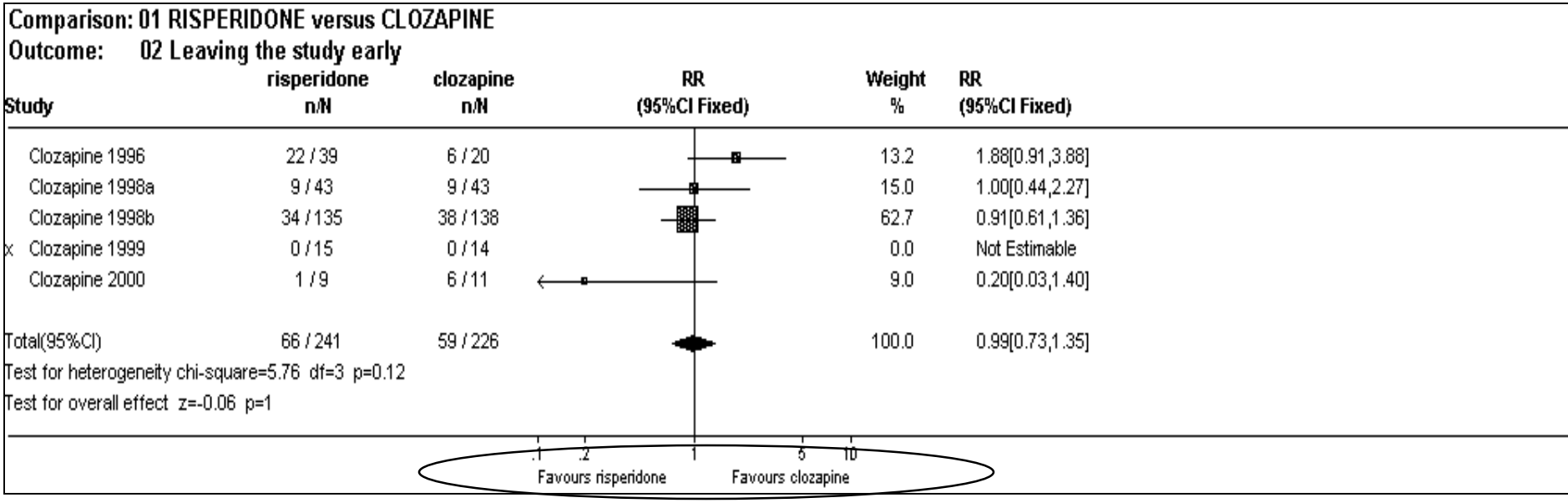
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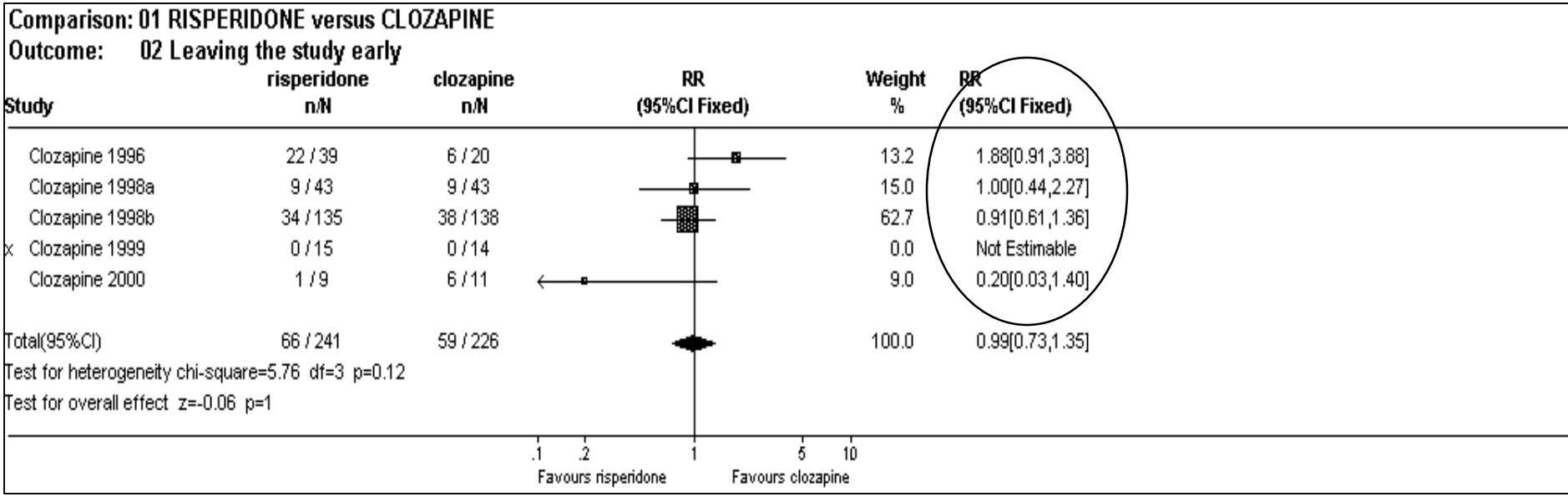
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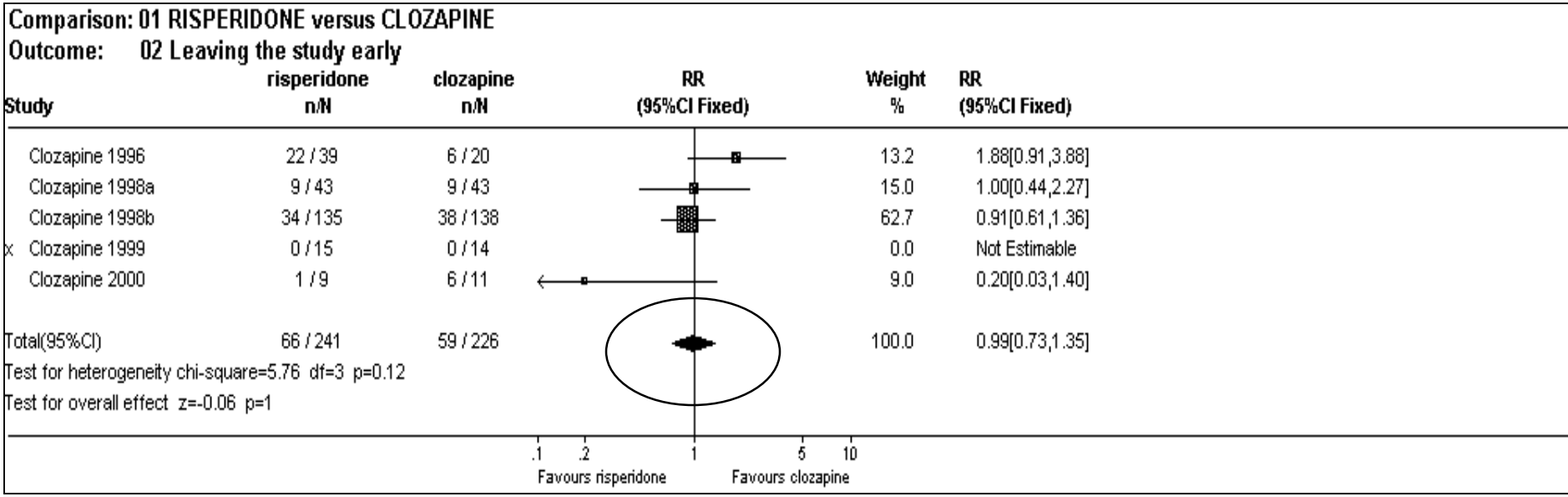
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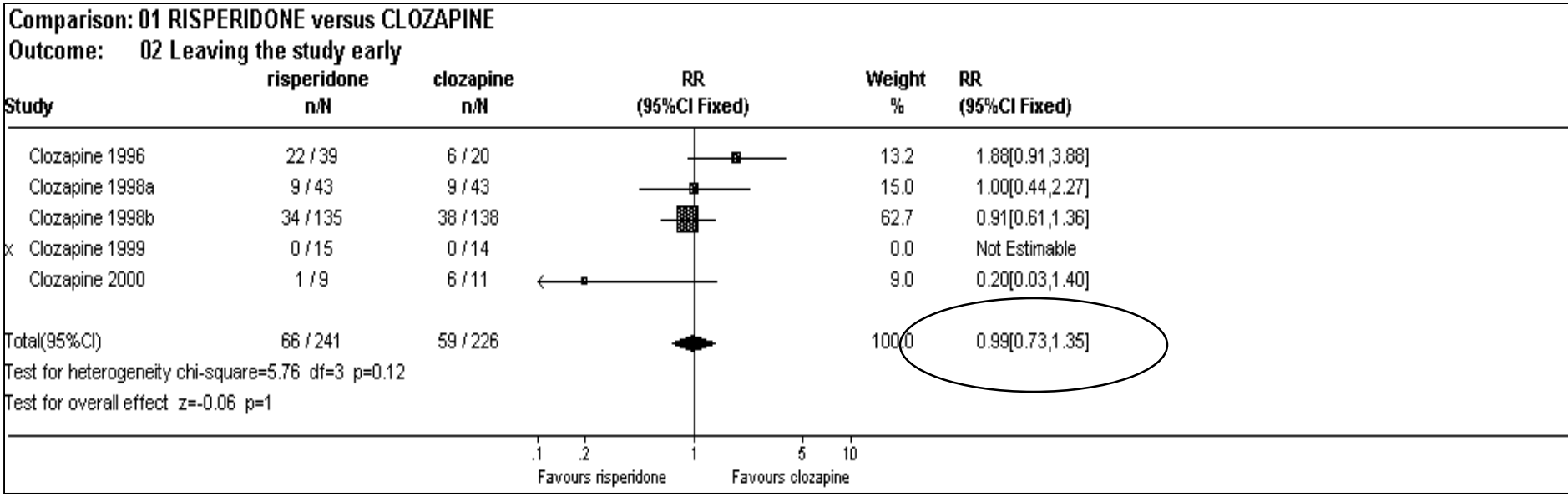
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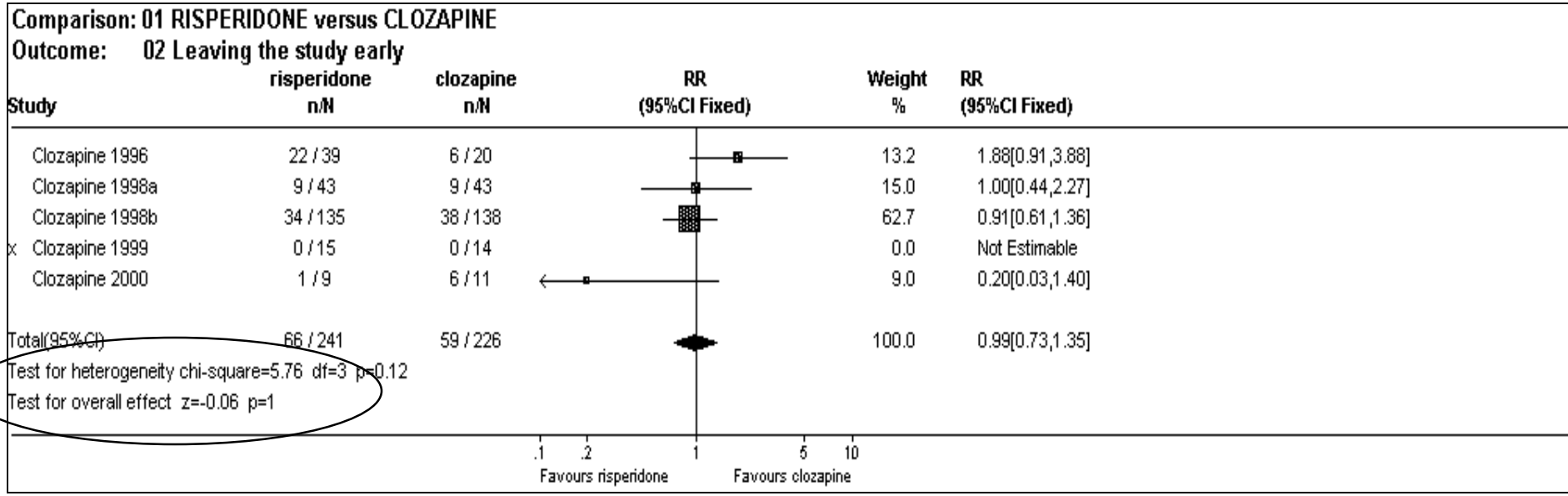
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fnajafi@kums.ac.ir