Systematic Reviews Application & Importance

Payam Kabiri, MD. PhD.
Clinical Epidemiologist

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

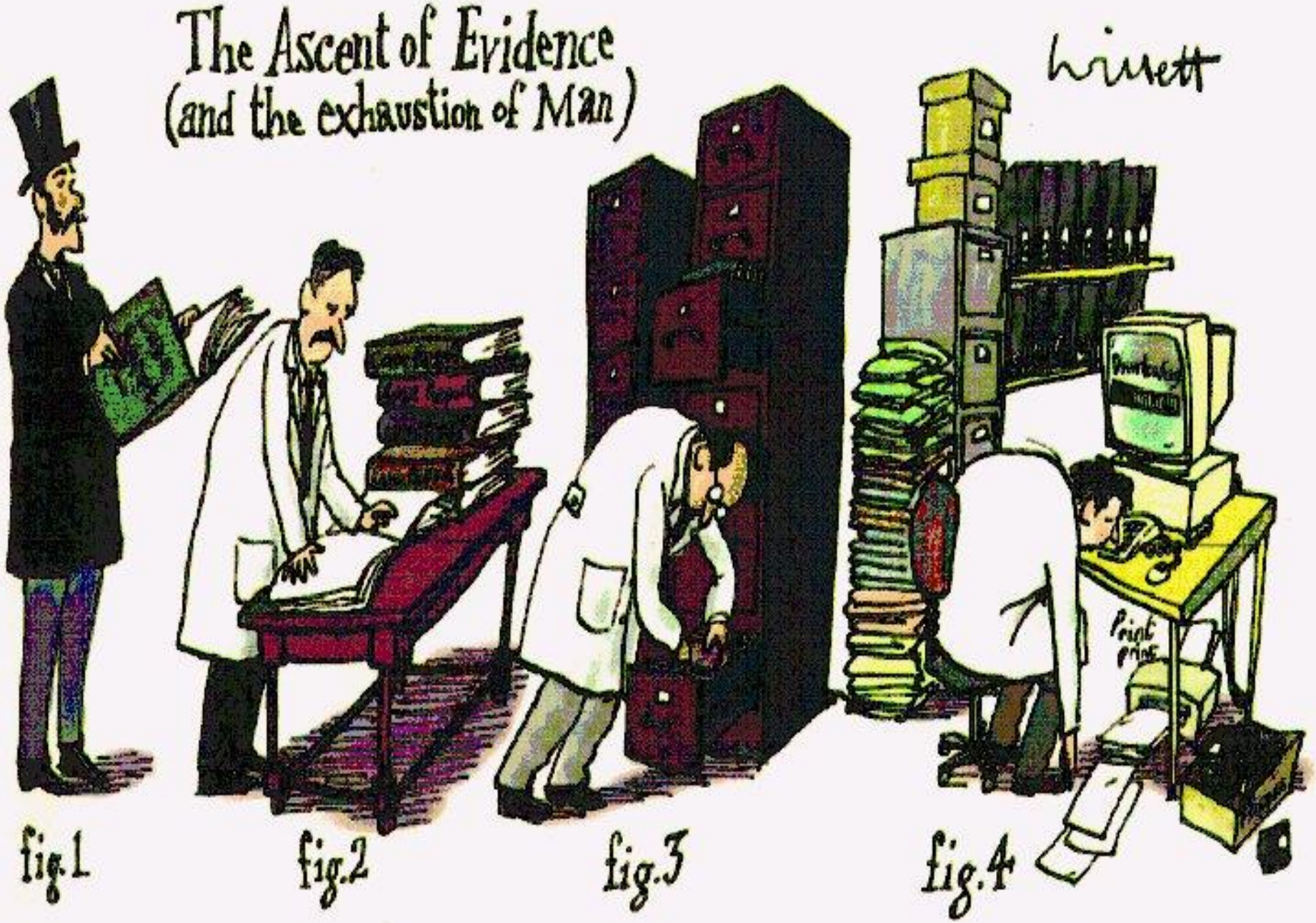
- Experiments
- Clinical trials
- Surveys

Secondary studies

- Reviews (Overviews)
  - Narrative reviews
  - Systematic reviews & Meta-analyses
- Guidelines
- Decision analyses
- Economic analyses

Review Articles

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


The Ascent of Evidence
(and the exhaustion of Man)
Hewett
fig.1
fig.2
fig.3
fig.4

Medical Publishing

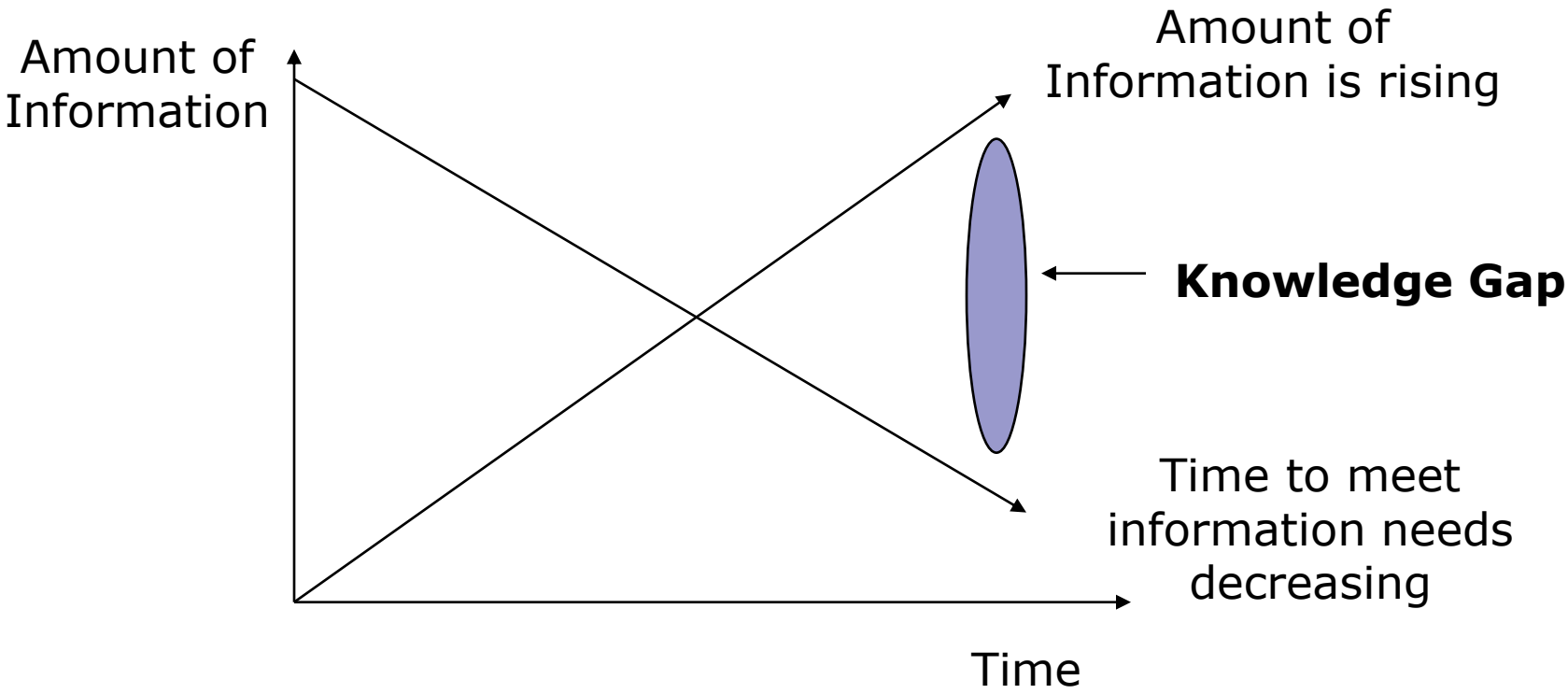
Annually:

- 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

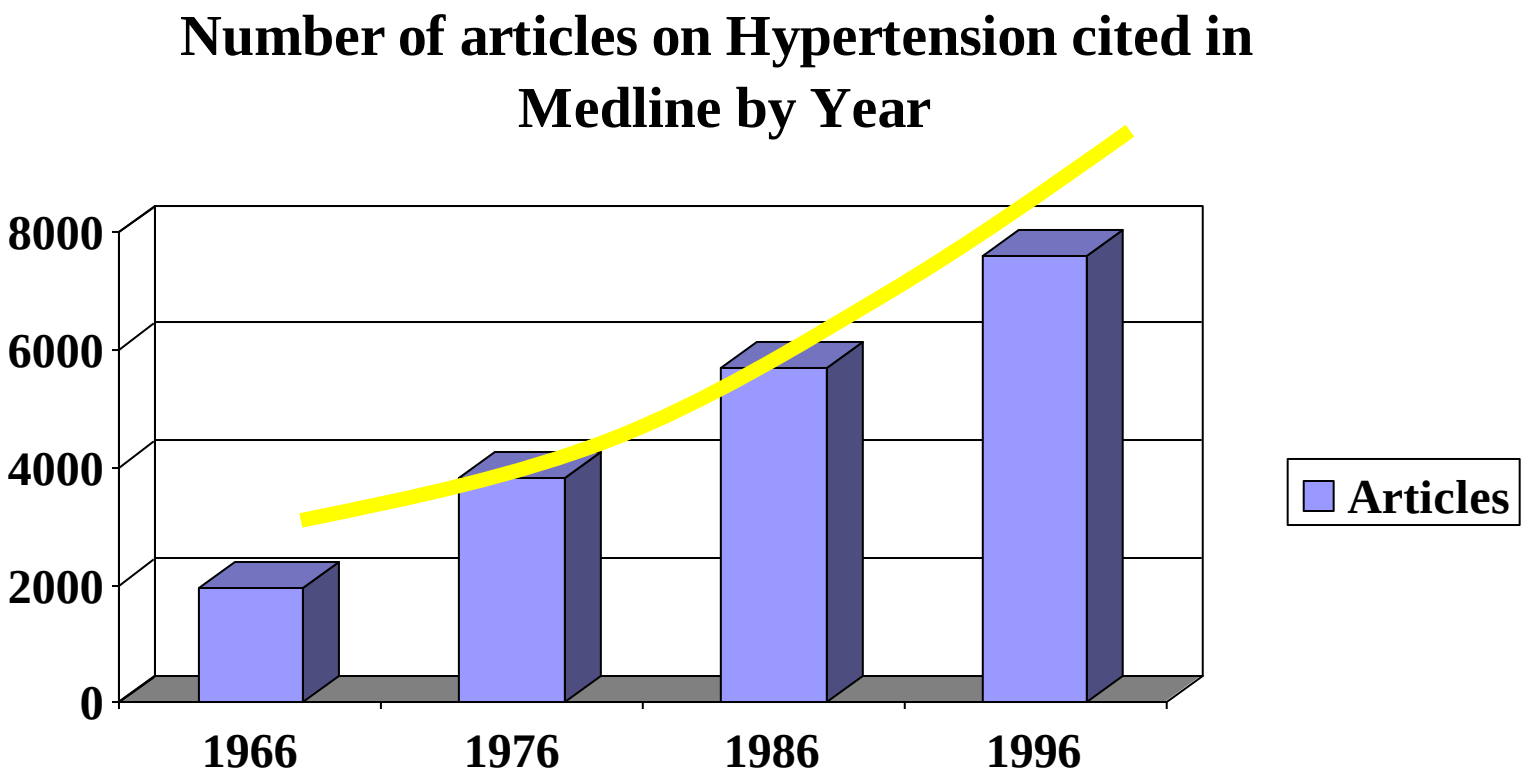
Doubling time of biomedical science was

about 19 years in 1991

Doubling time of biomedical science was

about 20 months in 2001

Increasing Knowledge



For General Physicians to keep current:

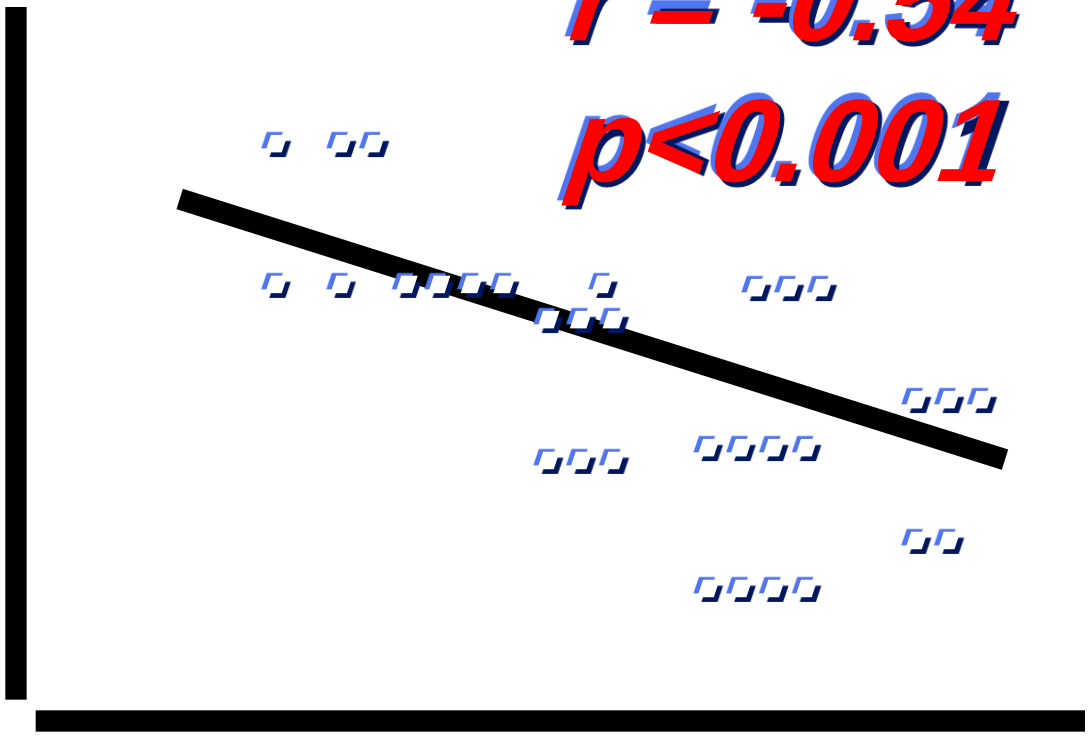
Read 19 new articles per day which appear in medical journals

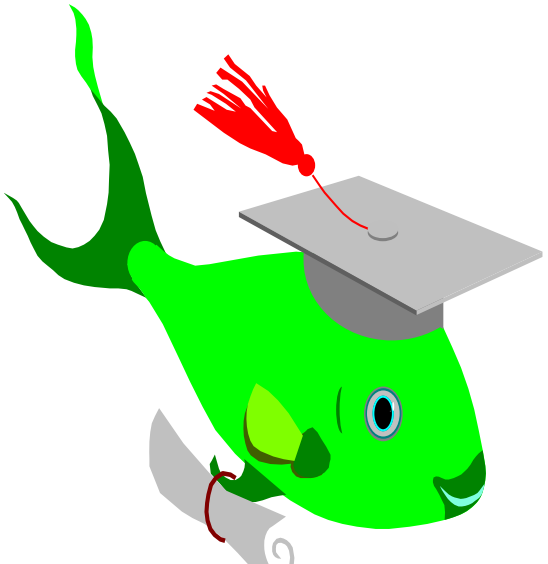
19 x 2 hrs (Critical Appraisal) = 38 hrs per day

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

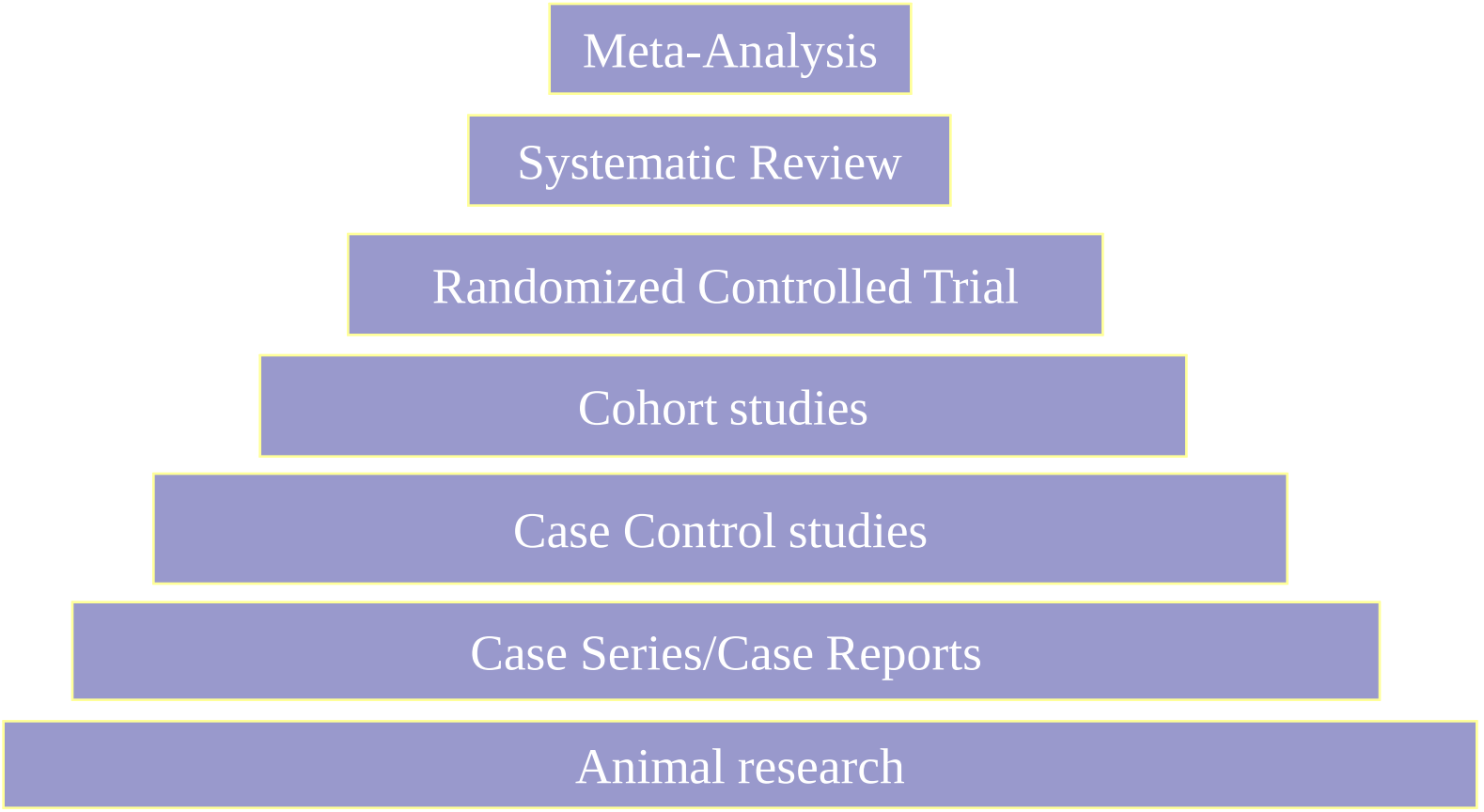
Shin,et al: CMAJ;1993: 969-976

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

- Postdam 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

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

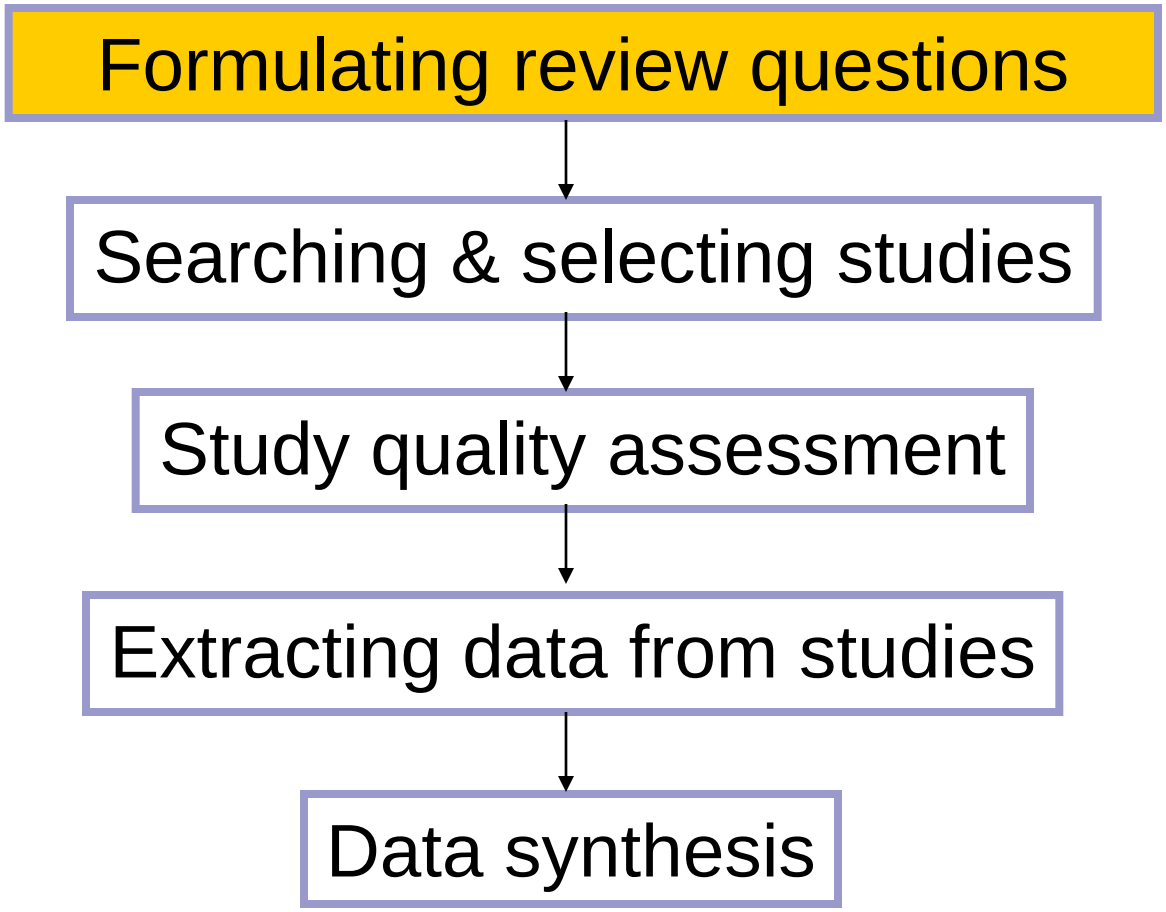
Differences Between Traditional and Systematic Reviews

(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

Steps of Doing a Systematic Review



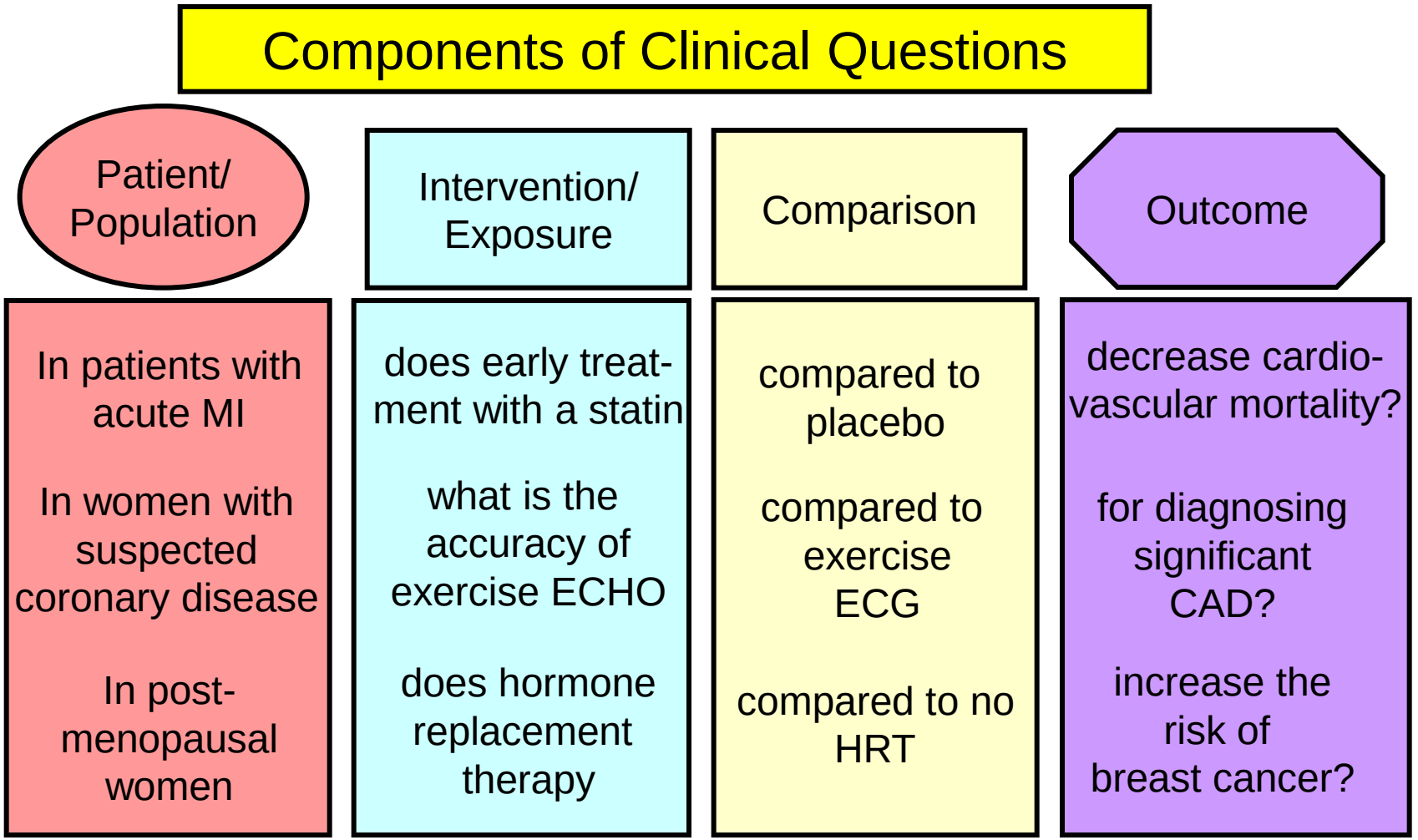
Formulating review questions

- 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

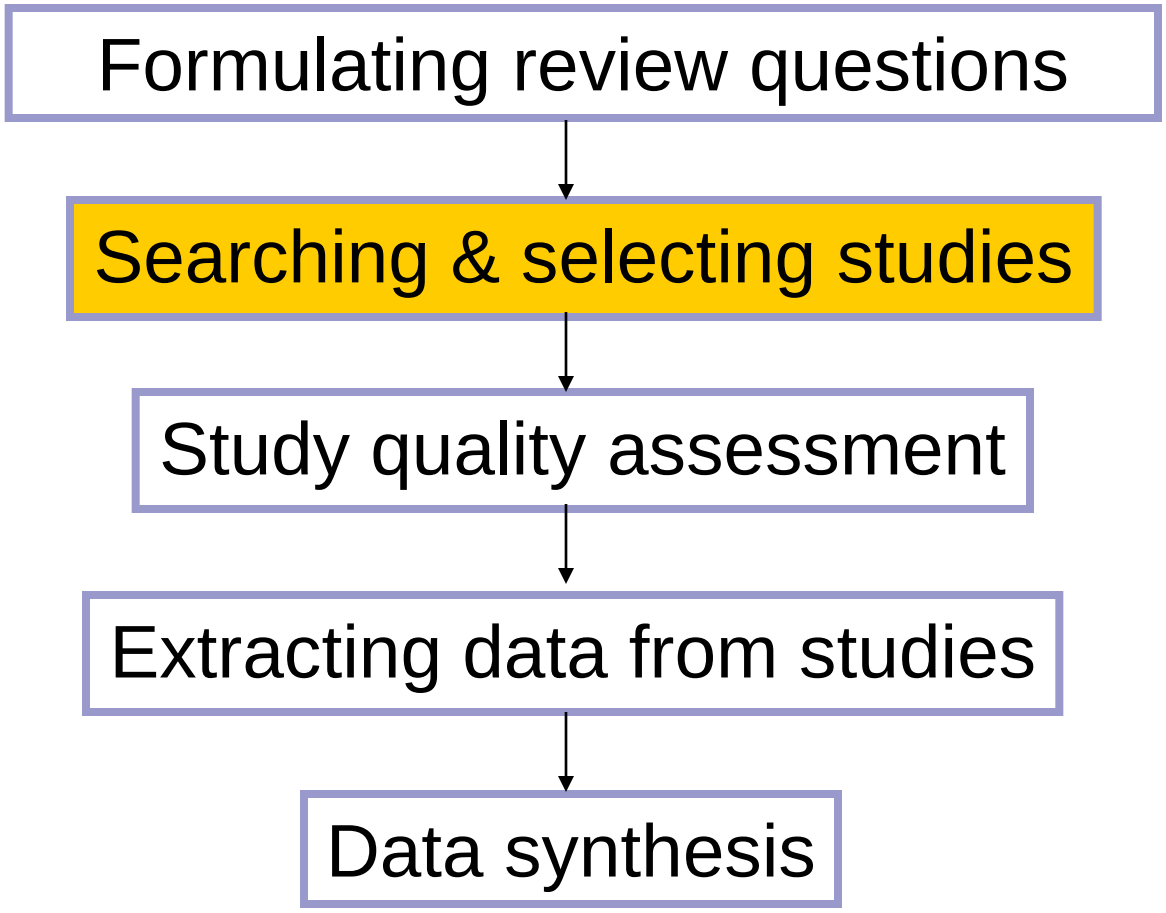
What types of outcomes?

- 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)
- **Checking reference lists**
- **Unpublished sources** known to experts in the specialty (seek by personal communication)
- **Raw data** from published trials

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

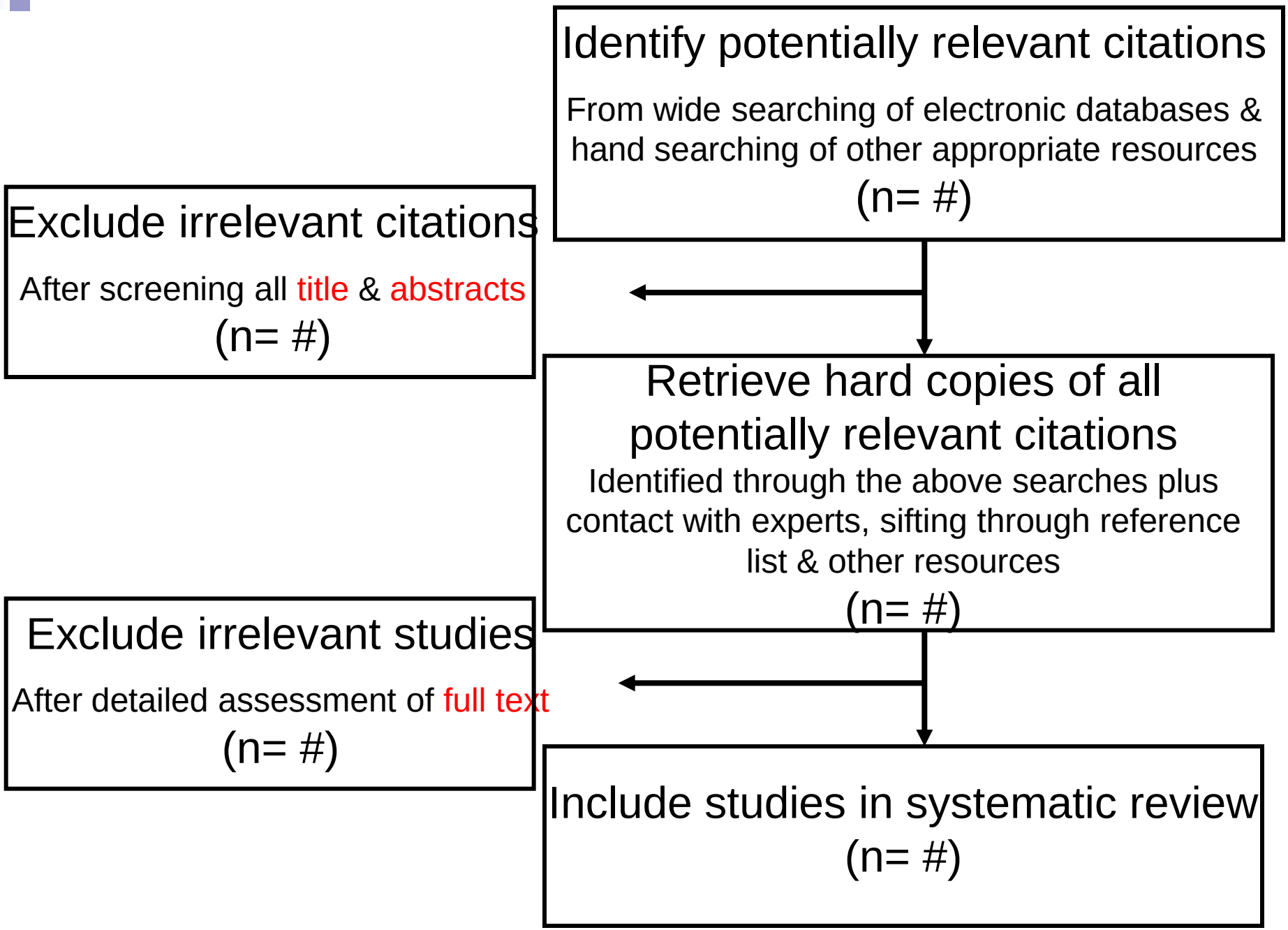
- The following electronic databases were searched for reports of trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2004); MEDLINE (January 1966 to June 2004); and EMBASE (1990 to June Week 23 2004).
- We ran the following search strings in combination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

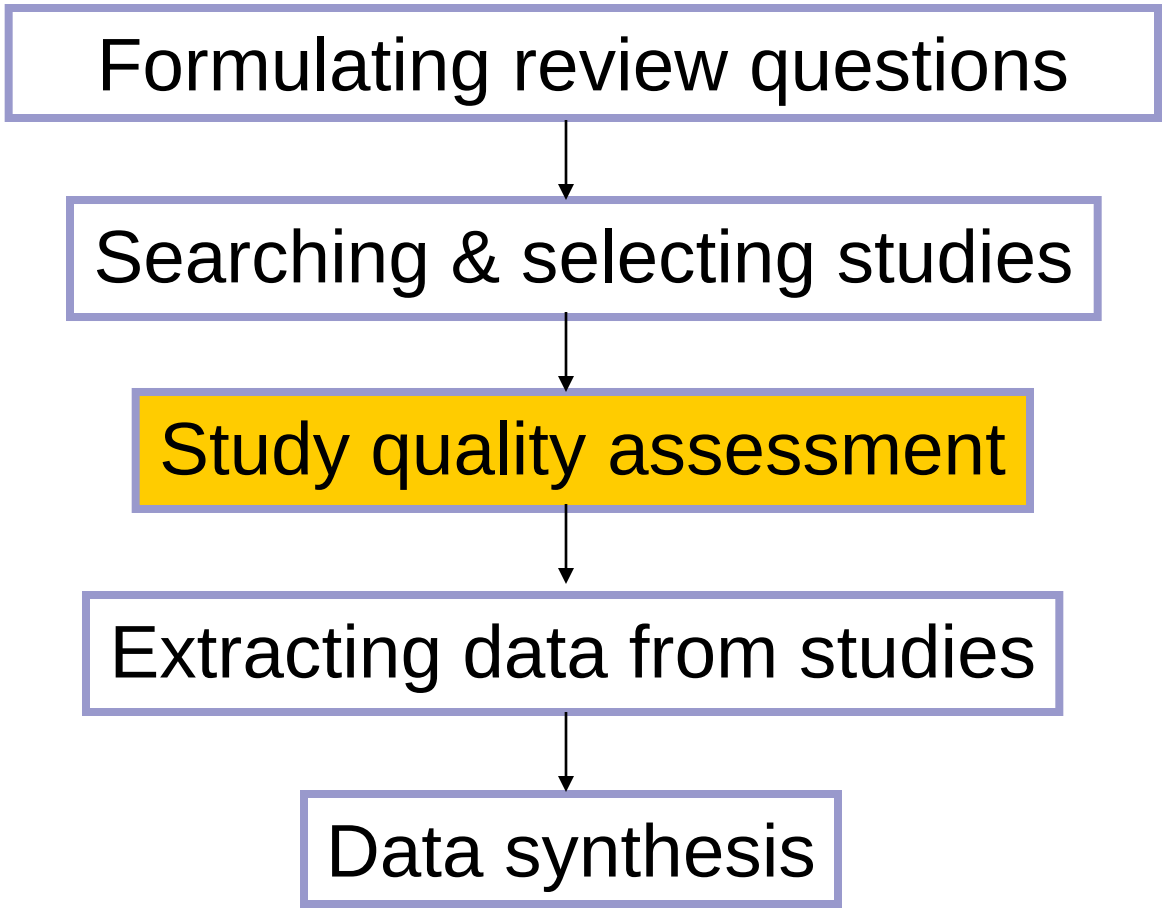
Documenting a search strategy

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
(n= #)
Include studies in systematic review
(n= #)

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

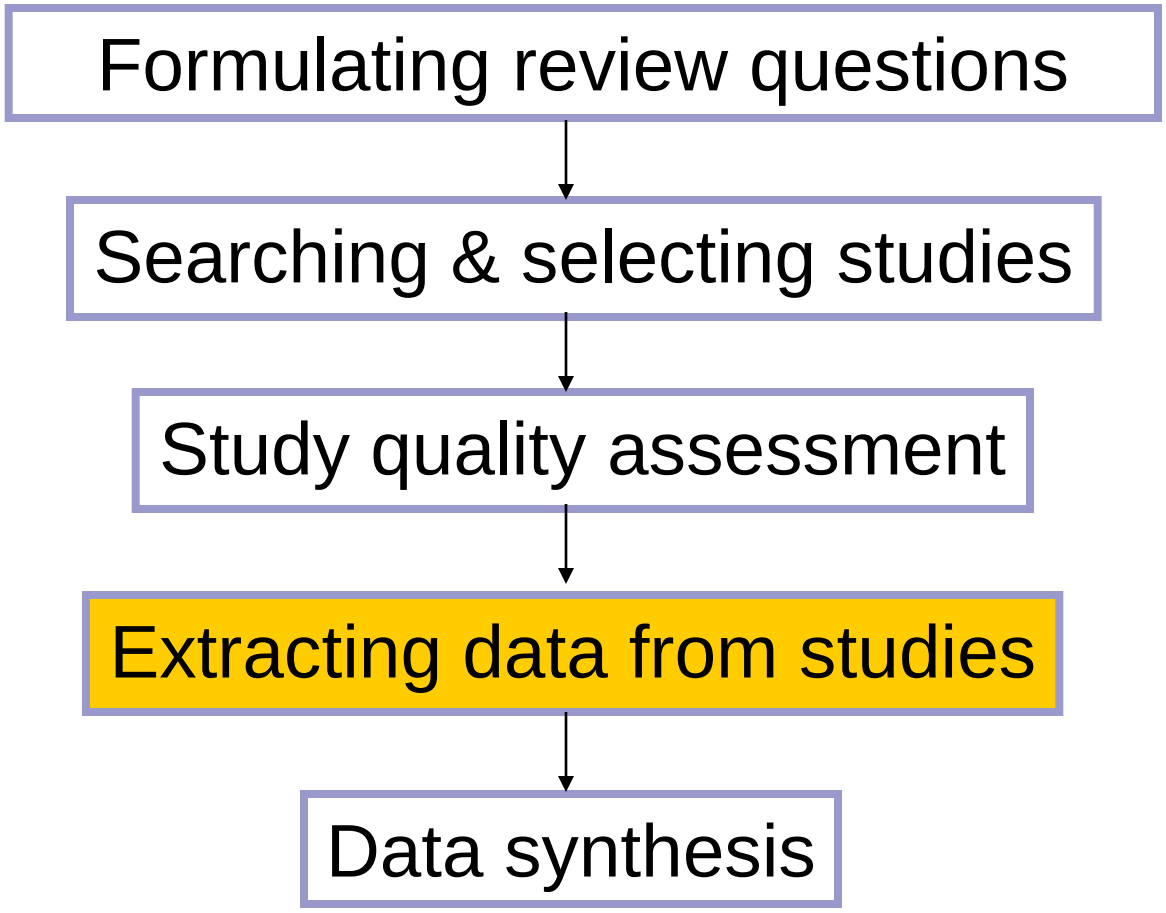
Assessment of study quality

- 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.

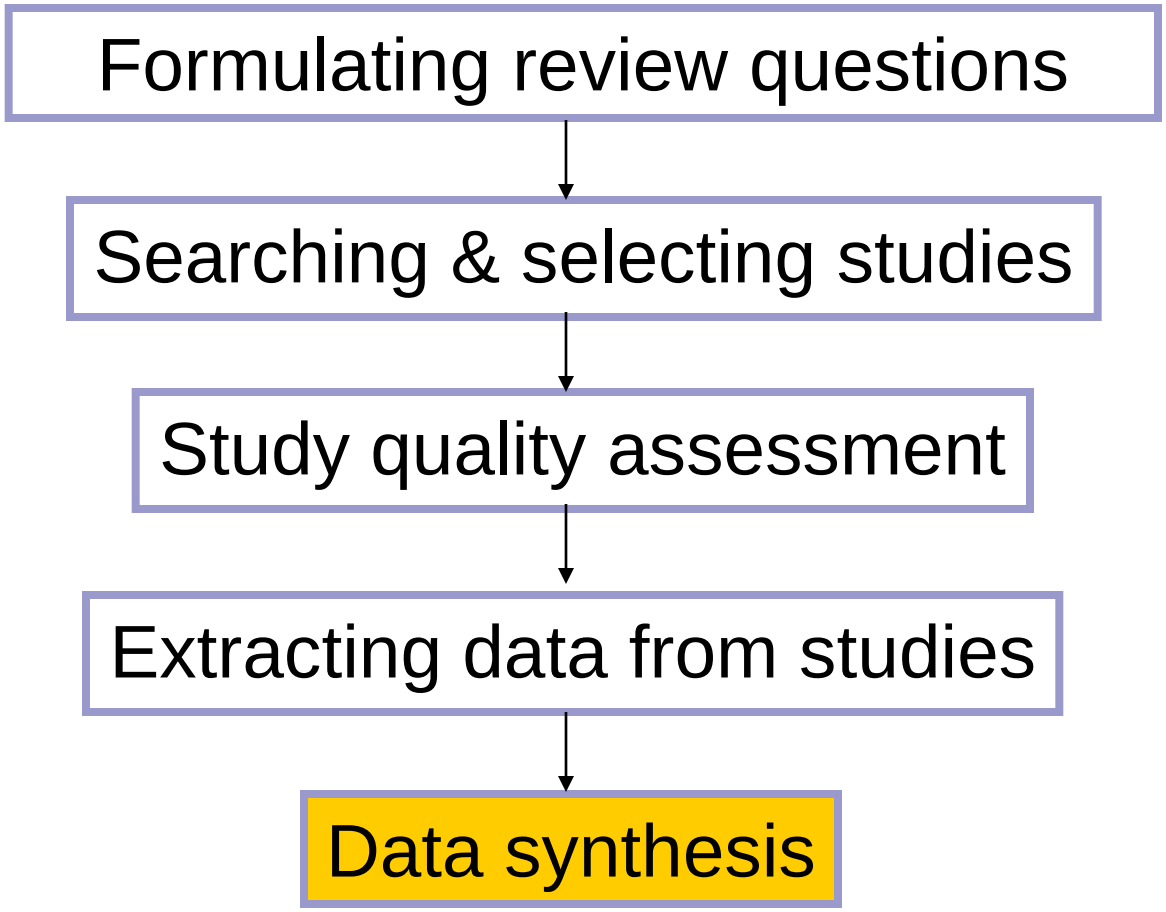
Steps of Doing a Systematic Review



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

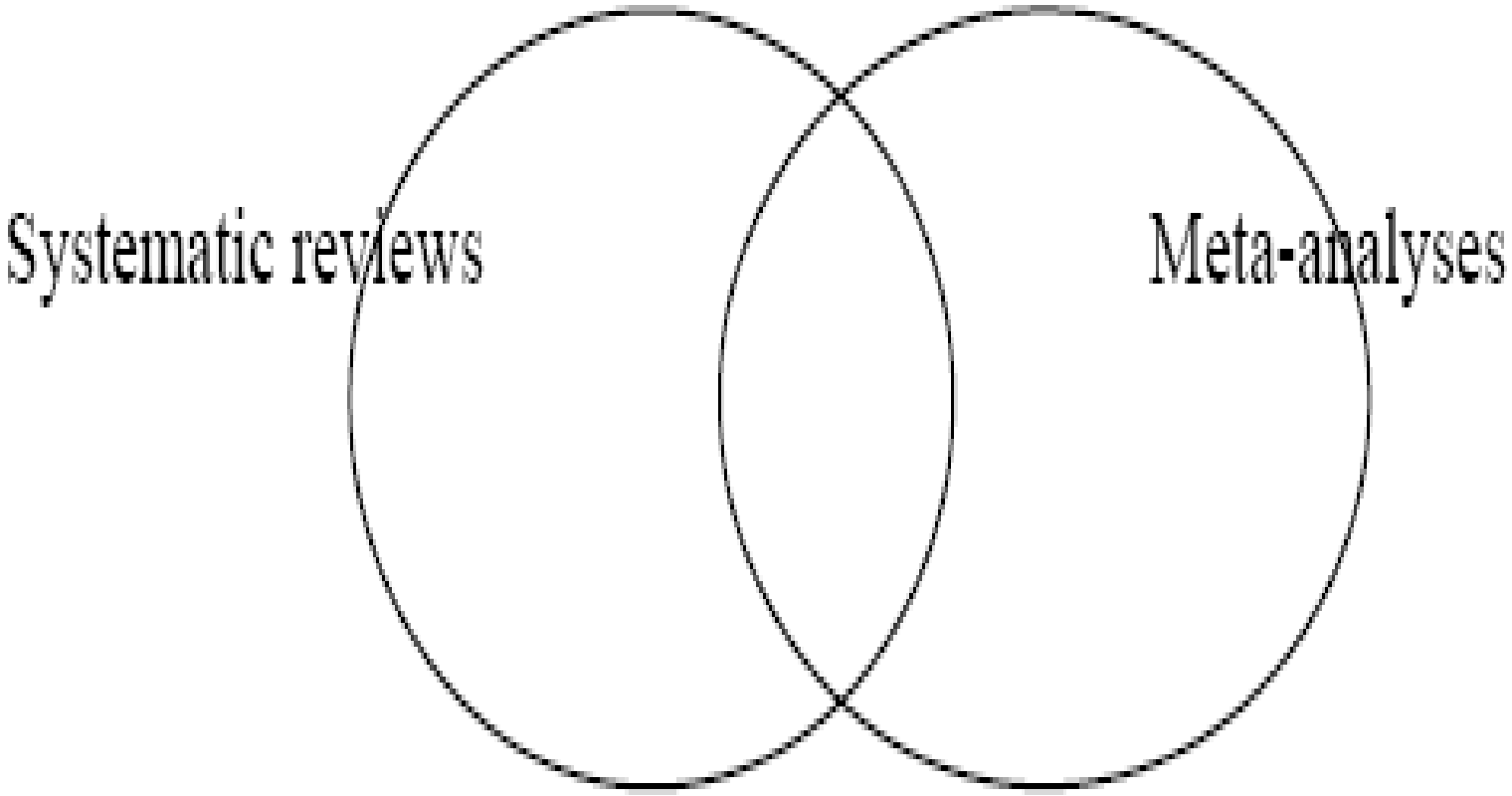
Systematic reviews & Meta-Analysis

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

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

Systematic reviews & Meta-Analysis

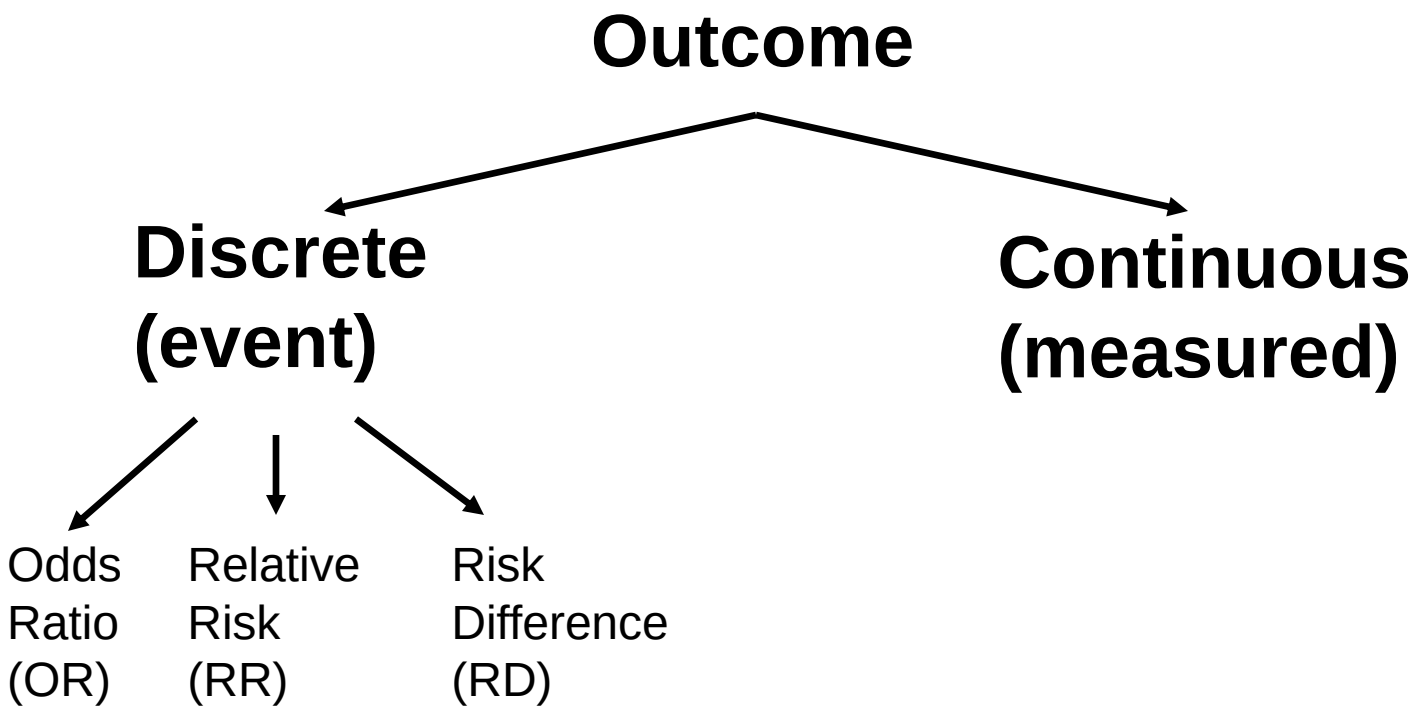
- The term '**meta-analysis**' is often used interchangeable with '**systematic review**'
- It is actually a statistical technique used to combine the results of several studies addressing the same question into a single summary measure (Khan *et al*., 2000).


Systematic reviews
Meta-analyses

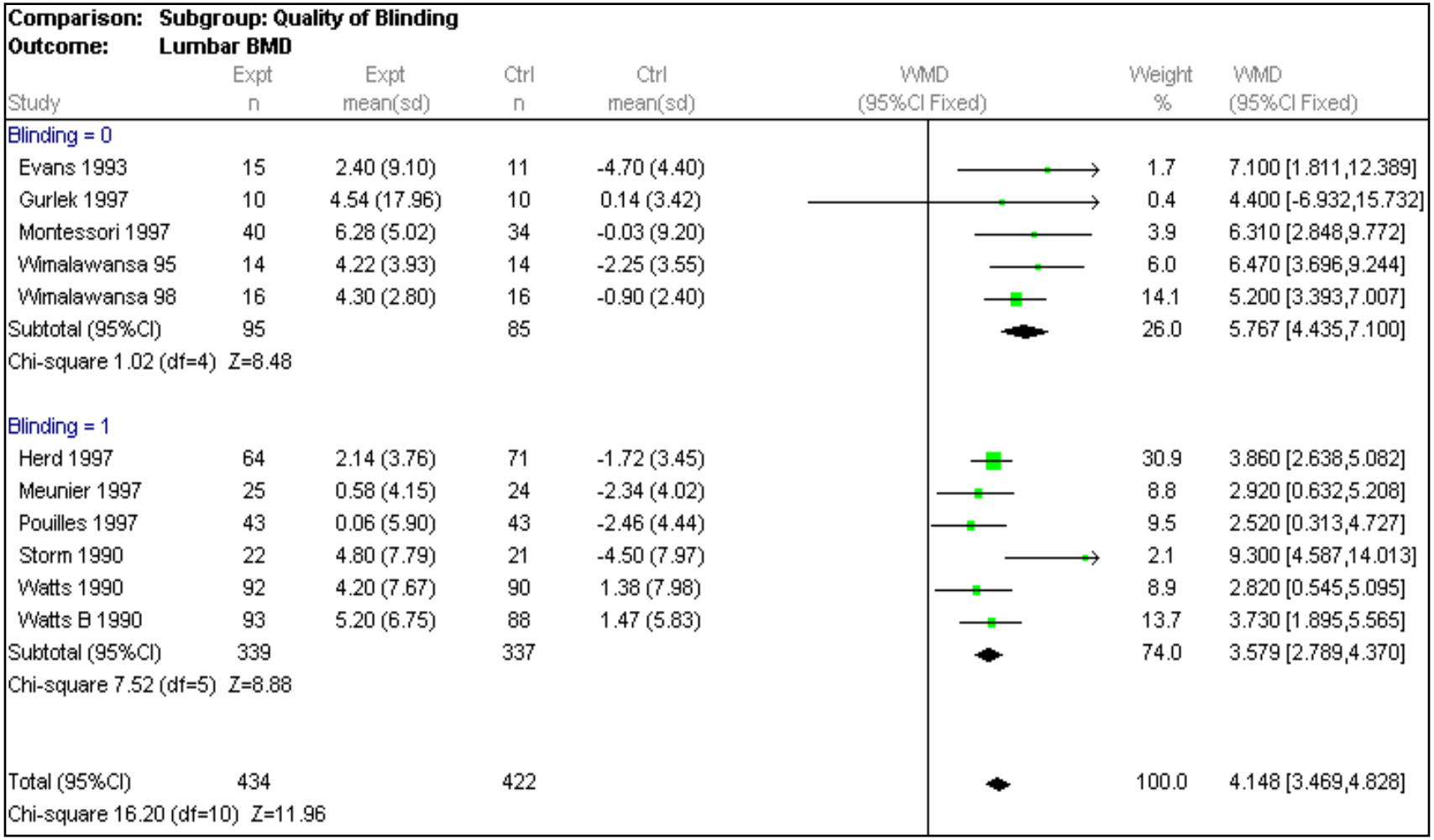
Forest Plot

- 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

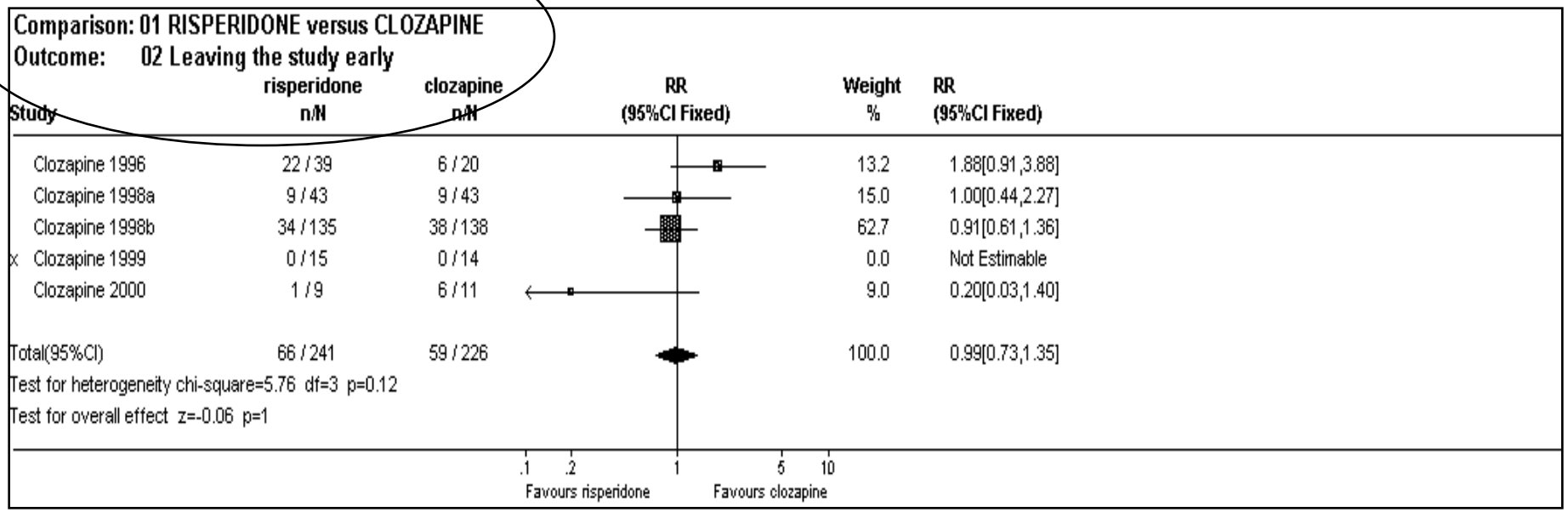
Effect Size Measures



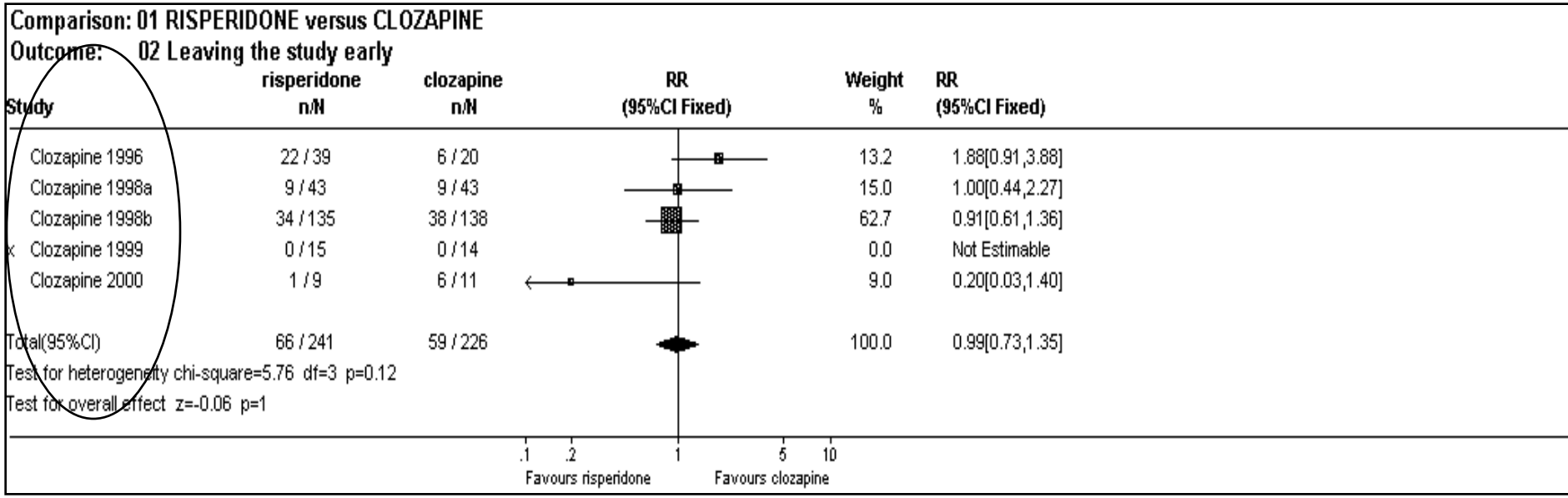
Forest plot


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

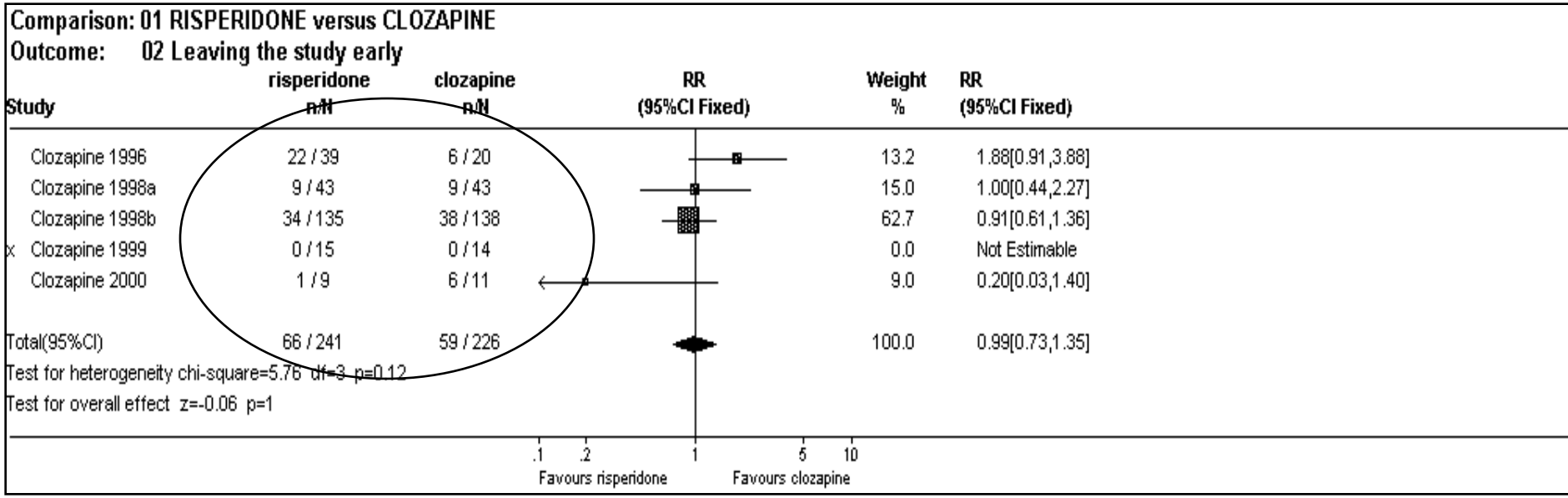
Forest plot


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

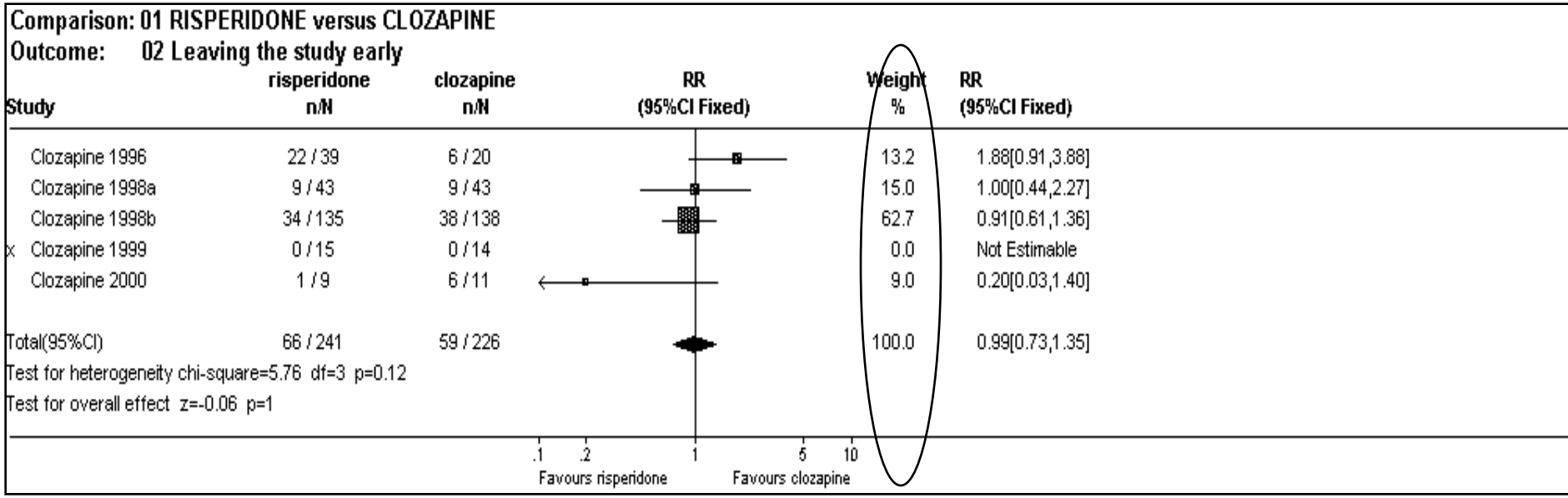
Forest plot


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

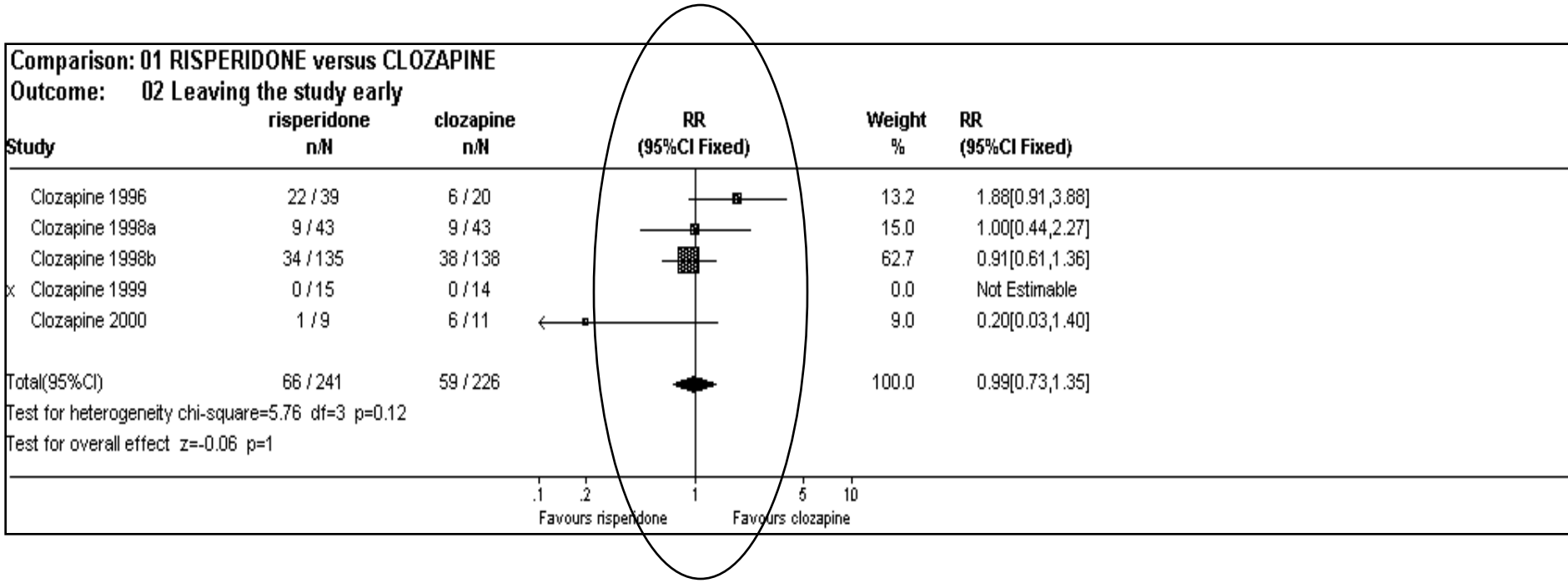
Forest plot


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

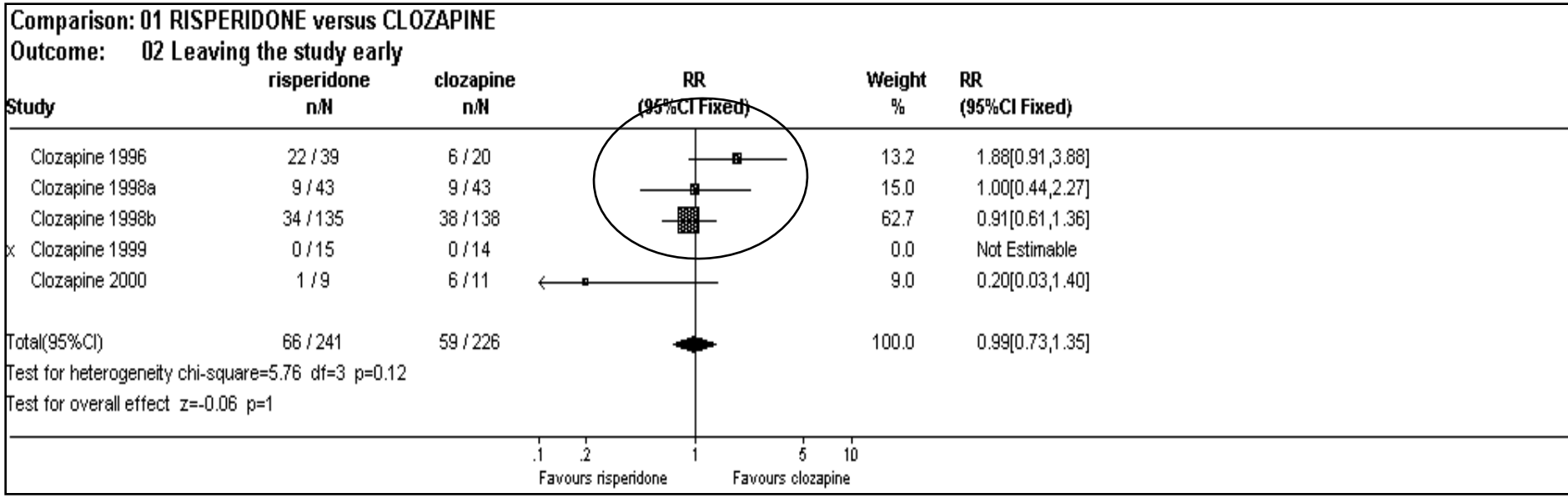
Forest plot


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

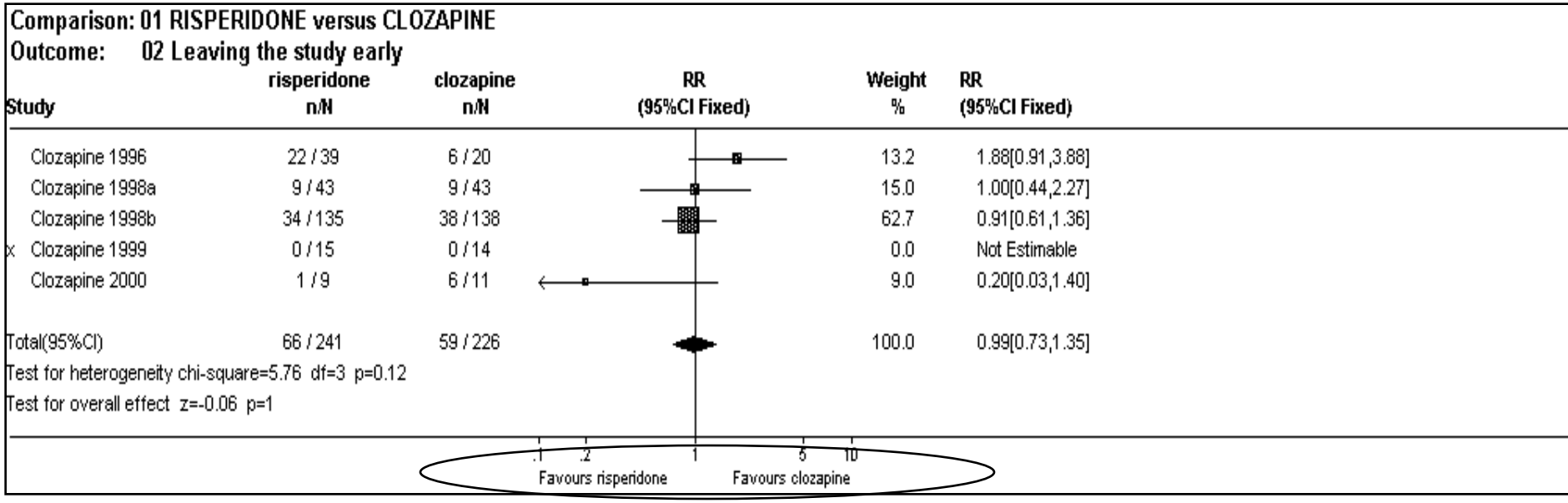
Forest plot


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

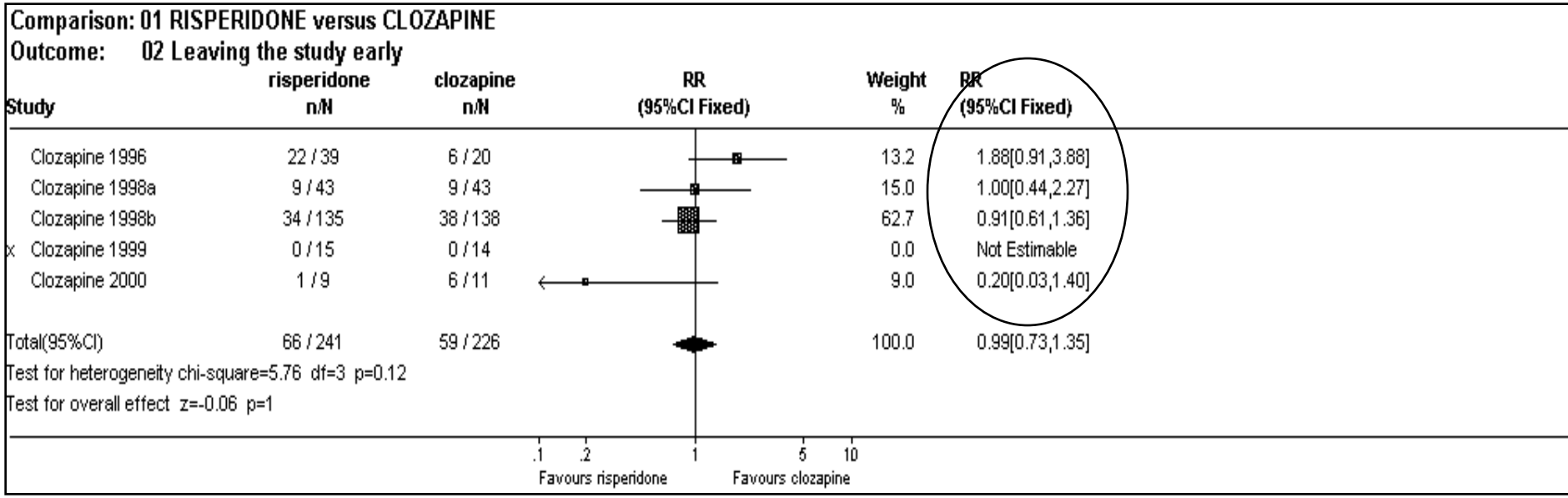
Forest plot


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

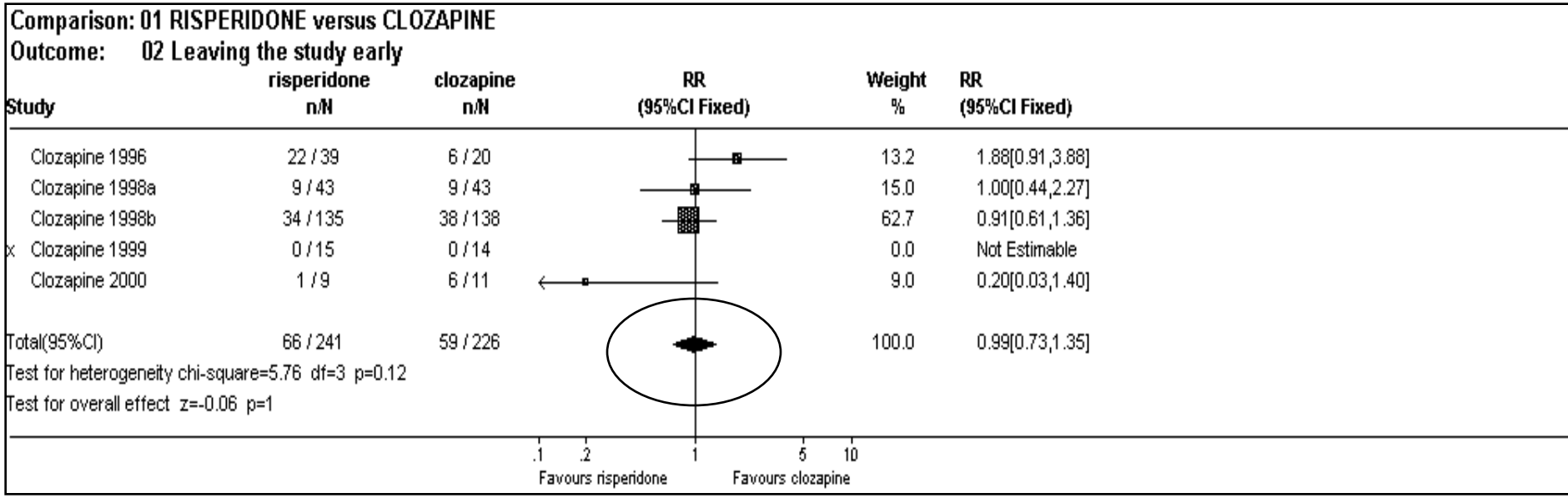
Forest plot


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

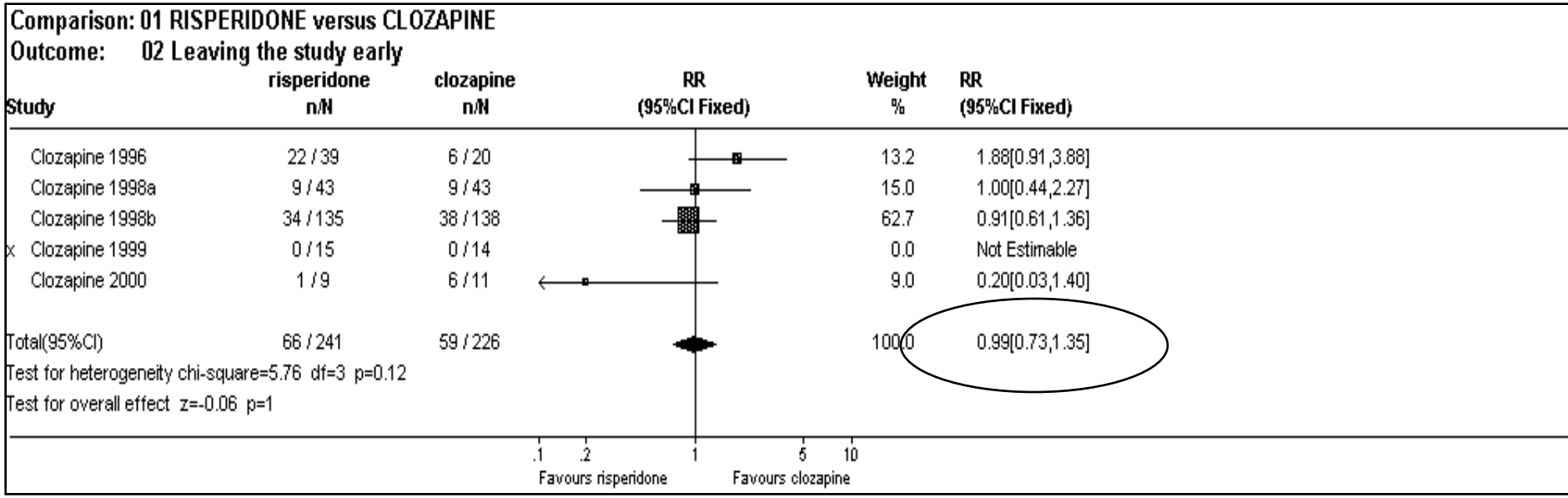
Forest plot


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

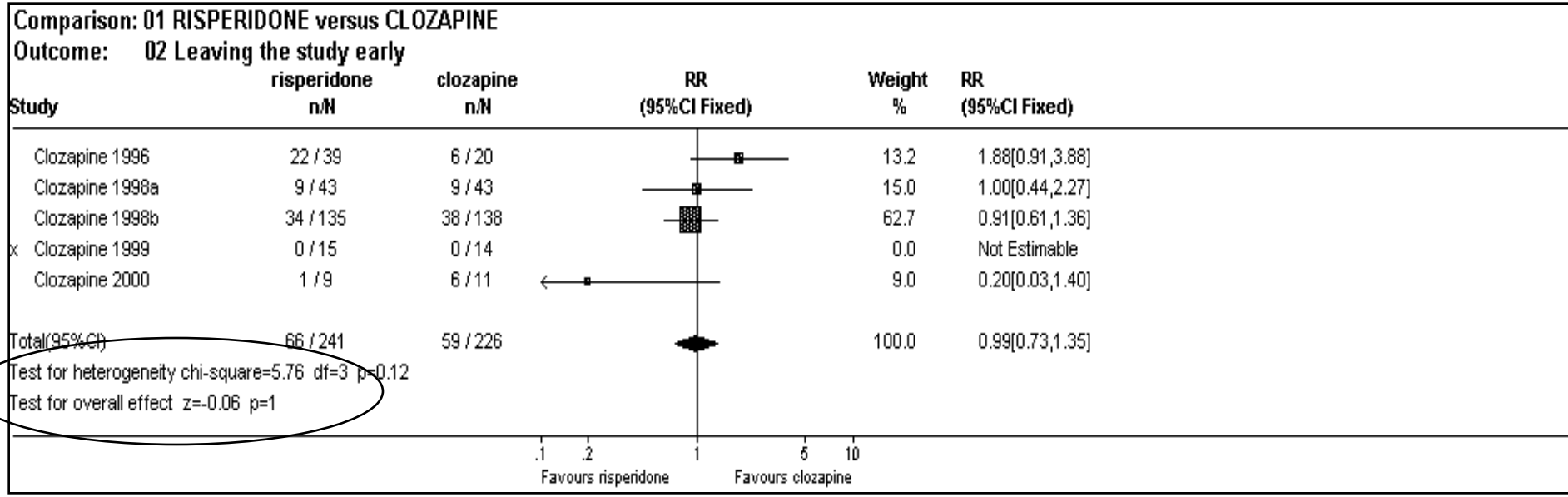
Forest plot


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


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


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

اگر میل داشتید Email بزنید !

kabiri@tums.ac.ir