



# Systematic Reviews Application & Importance

Payam Kabiri, MD. PhD.  
Clinical Epidemiologist

# انواع مقالات در علوم پزشکی

- Original Article
- Review Article
- Case Reports
- Editorial
- Short Communication  
(short papers)
- Letter to Editor
- مقاله پژوهشی اصیل
- مقاله مروری
- مقاله گزارش مورد
- سرمقاله (سخن سردبیر)
- مقاله کوتاه
- نامه به سردبیر

# انواع مقالات مروری در علوم پزشکی

- ◆ **Traditional** Review Articles  
(Narrative Review)

■ مقالات مروری سنتی  
مرور روایتی

- ◆ **Systematic** Review  
(Meta-analysis)

■ مقالات مروری نظام‌مند  
مرور ساختاردار



# 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

# The Ascent of Evidence (and the exhaustion of Man)

Wissett



fig.1



fig.2



fig.3



fig.4



# Medical Publishing

Annually:

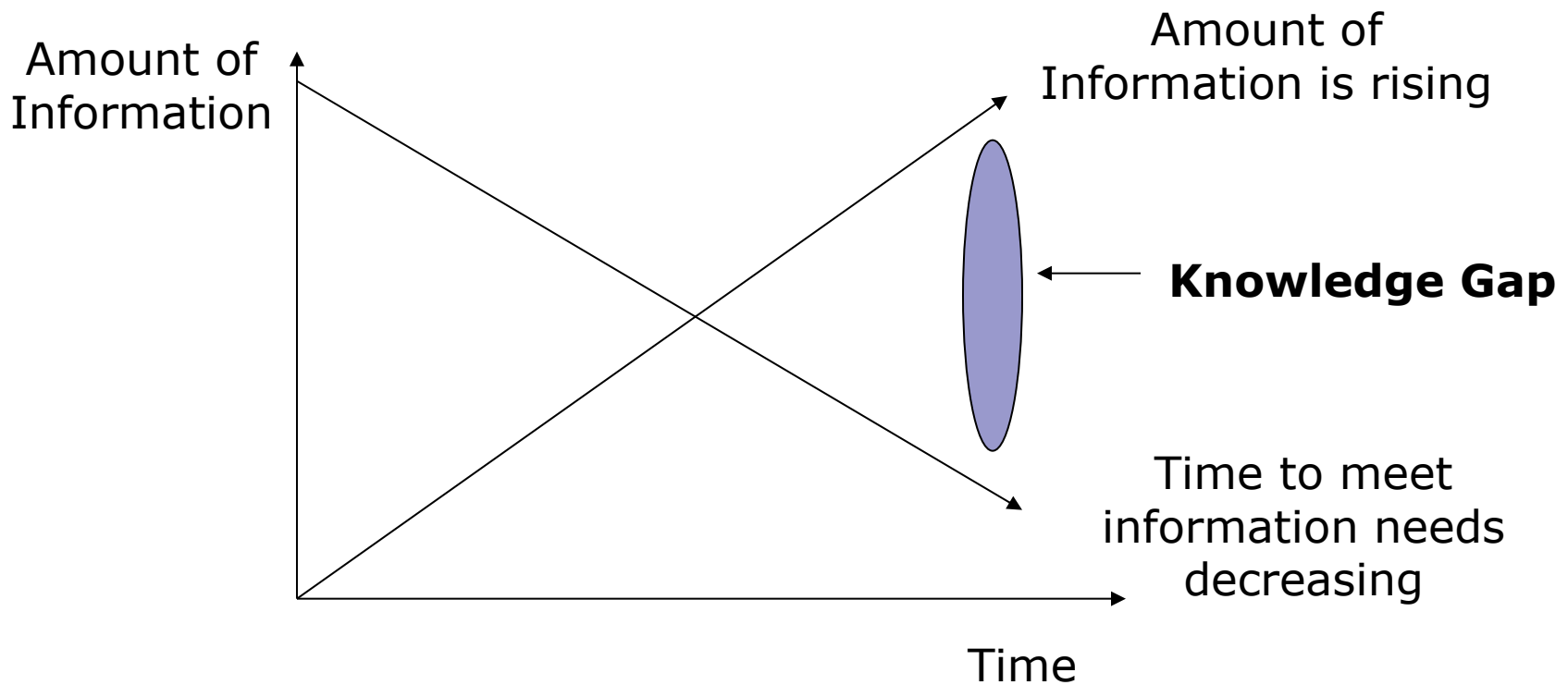
- 20,000 journals
- 17,000 new books

MEDLINE:

- +5,000 journals
- +29 Million references
- 10,000,000 new entries yearly



# The Problem



The Knowledge Gap



Doubling time of  
biomedical science was

**about 19 years in 1991**

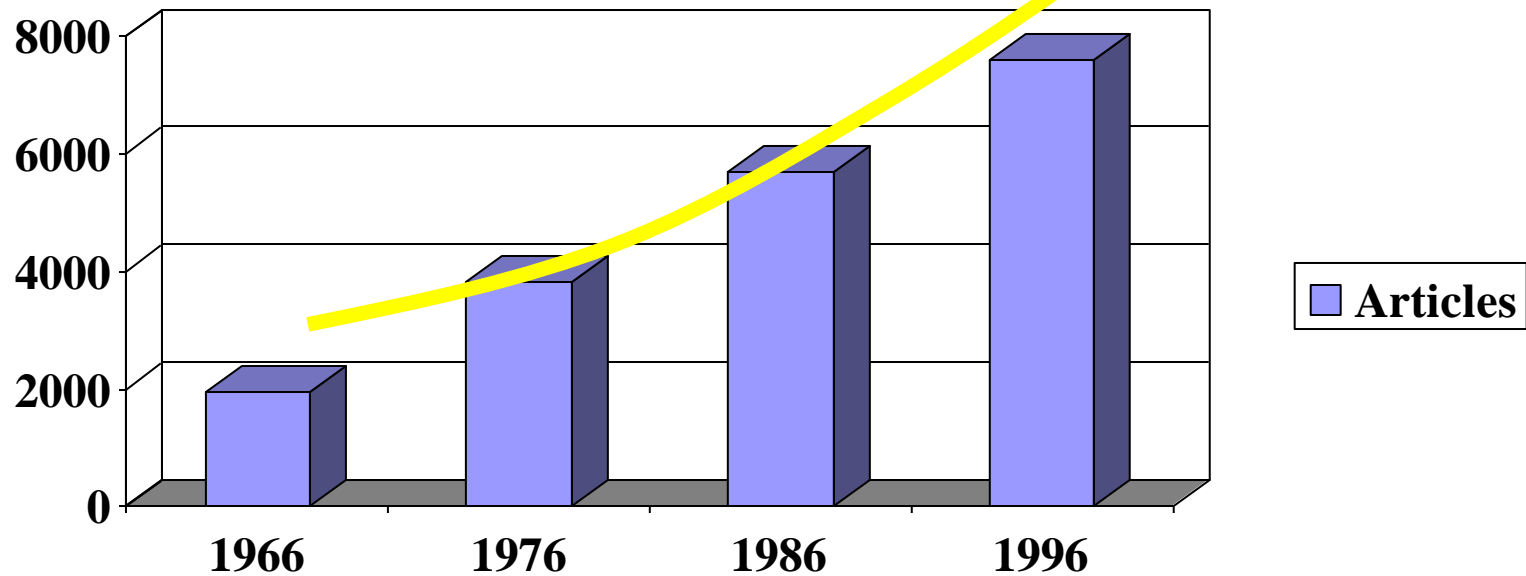


Doubling time of  
biomedical science was

**about 20 months in 2001**

# Increasing Knowledge

**Number of articles on Hypertension cited in Medline by Year**



# For General Physicians to **keep current:**

Read 19 new articles per day which appear in medical journals

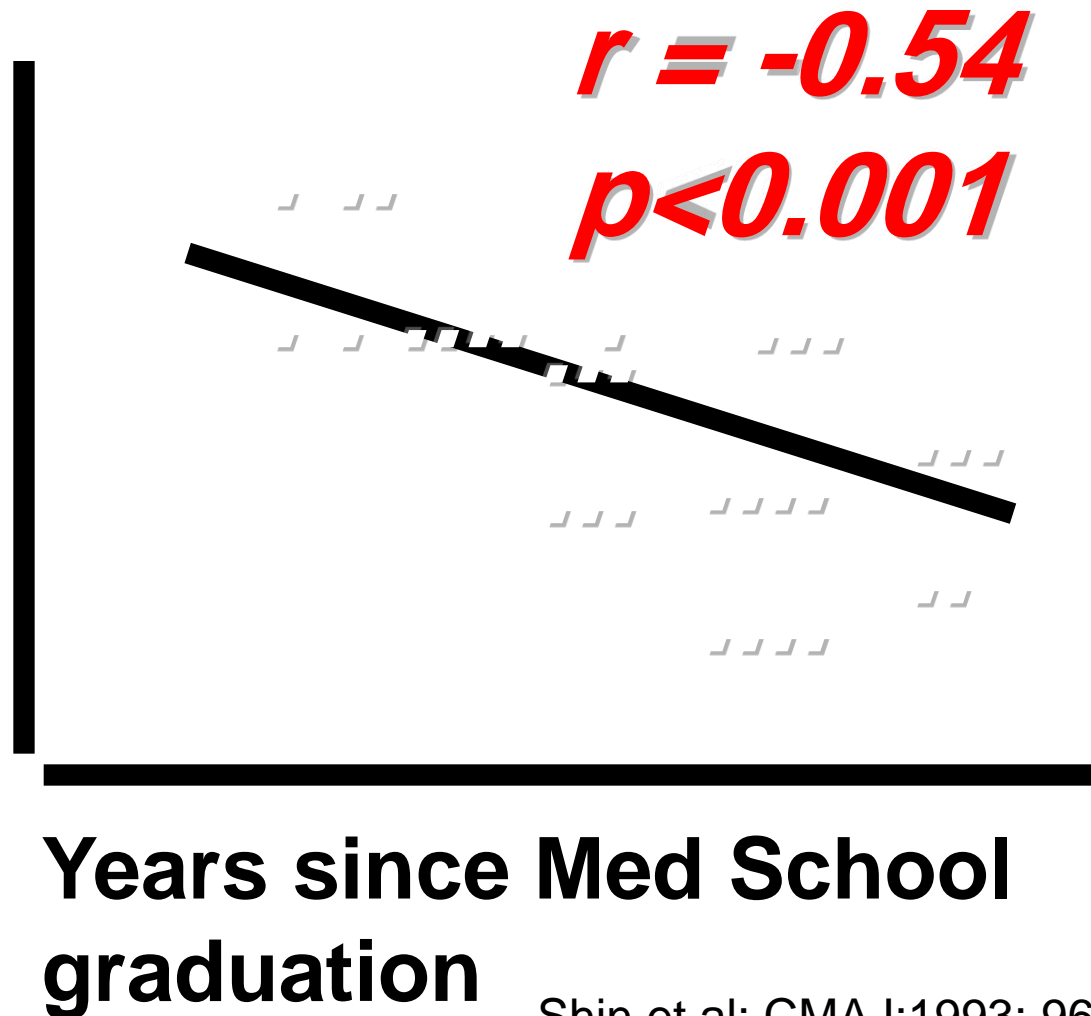
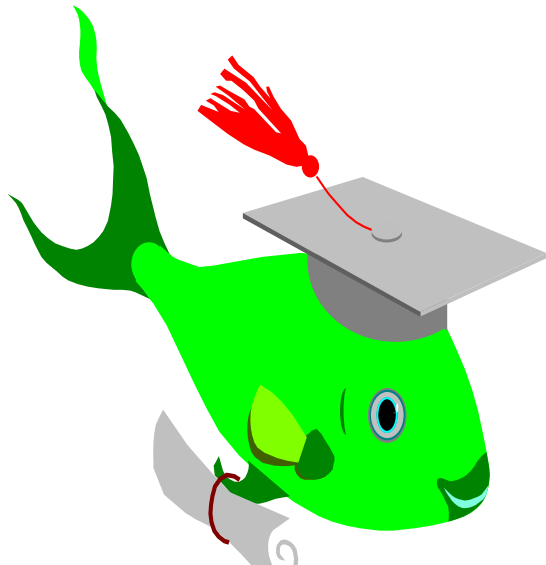
19 x 2 hrs (Critical Appraisal) = **38 hrs per day**

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



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

Systematic Review

Randomized Controlled Trial

Cohort studies

Case Control studies

Case Series/Case Reports

Animal research

# Levels of Evidence


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

# 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	<b>Traditional</b> Review	<b>Systematic</b> 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

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis





# Formulating review questions

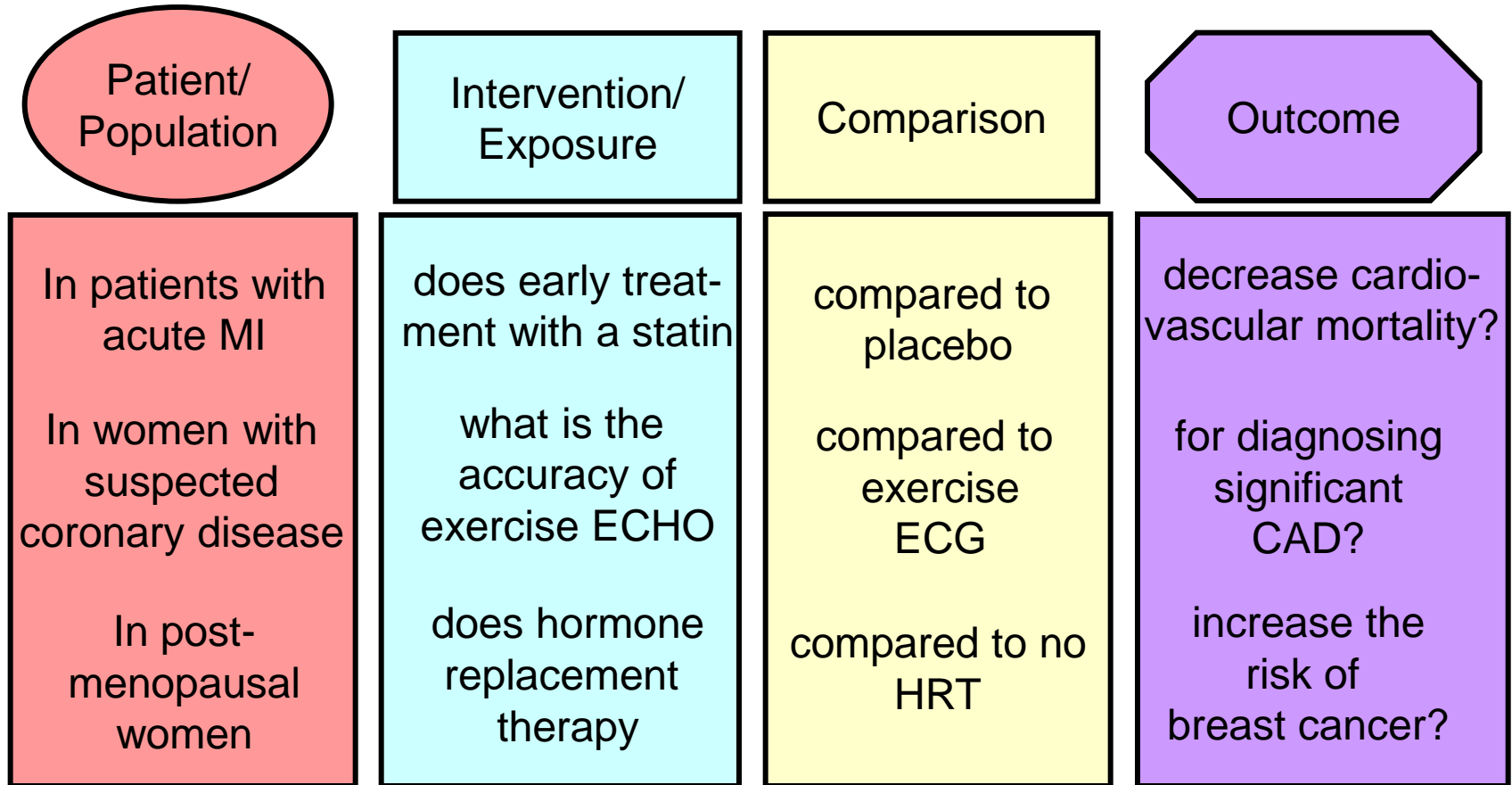
- The first and most important decision in preparing a review is to determine its focus
- This is best done by asking clearly framed questions.
- Define a four part clinical question, breaking the question down into its component parts

# 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

## Components of 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

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis



# 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

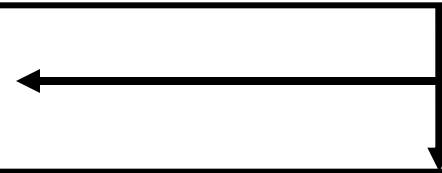
From wide searching of electronic databases & hand searching of other appropriate resources

(n= #)

Exclude irrelevant citations

After screening all **title** & **abstracts**

(n= #)



Retrieve hard copies of all potentially relevant citations

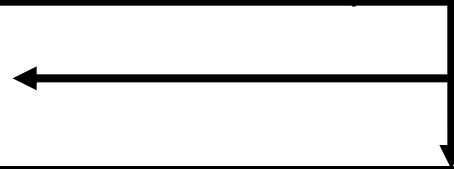
Identified through the above searches plus contact with experts, sifting through reference list & other resources

(n= #)

Exclude irrelevant studies

After detailed assessment of **fulltext**

(n= #)



Include studies in systematic review

(n= #)

# Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis



# 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

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis





# Collecting data

- Data collection forms

- Methods
- Participants
- Interventions
- Outcome measures and results

# Steps of Doing a Systematic Review

Formulating review questions

Searching & selecting studies

Study quality assessment

Extracting data from studies

Data synthesis

# 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).





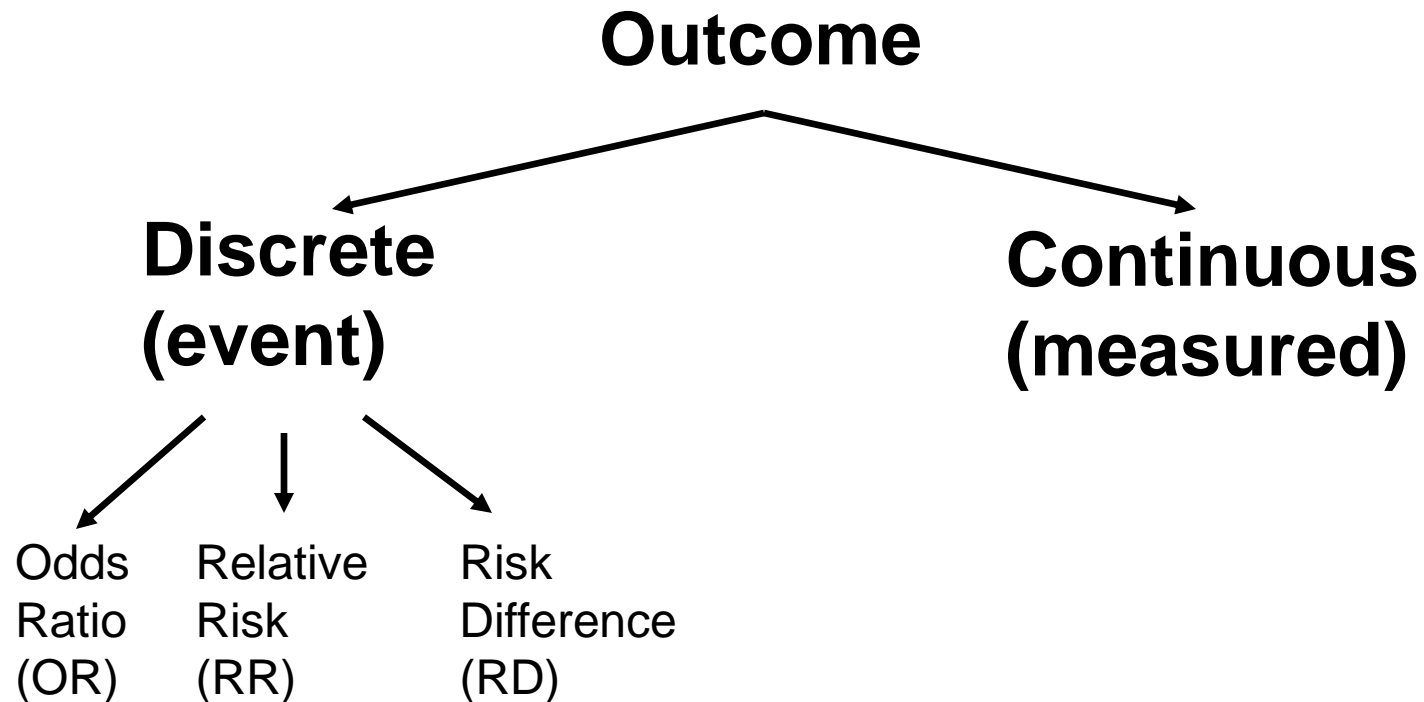
Systematic reviews

Meta-analyses

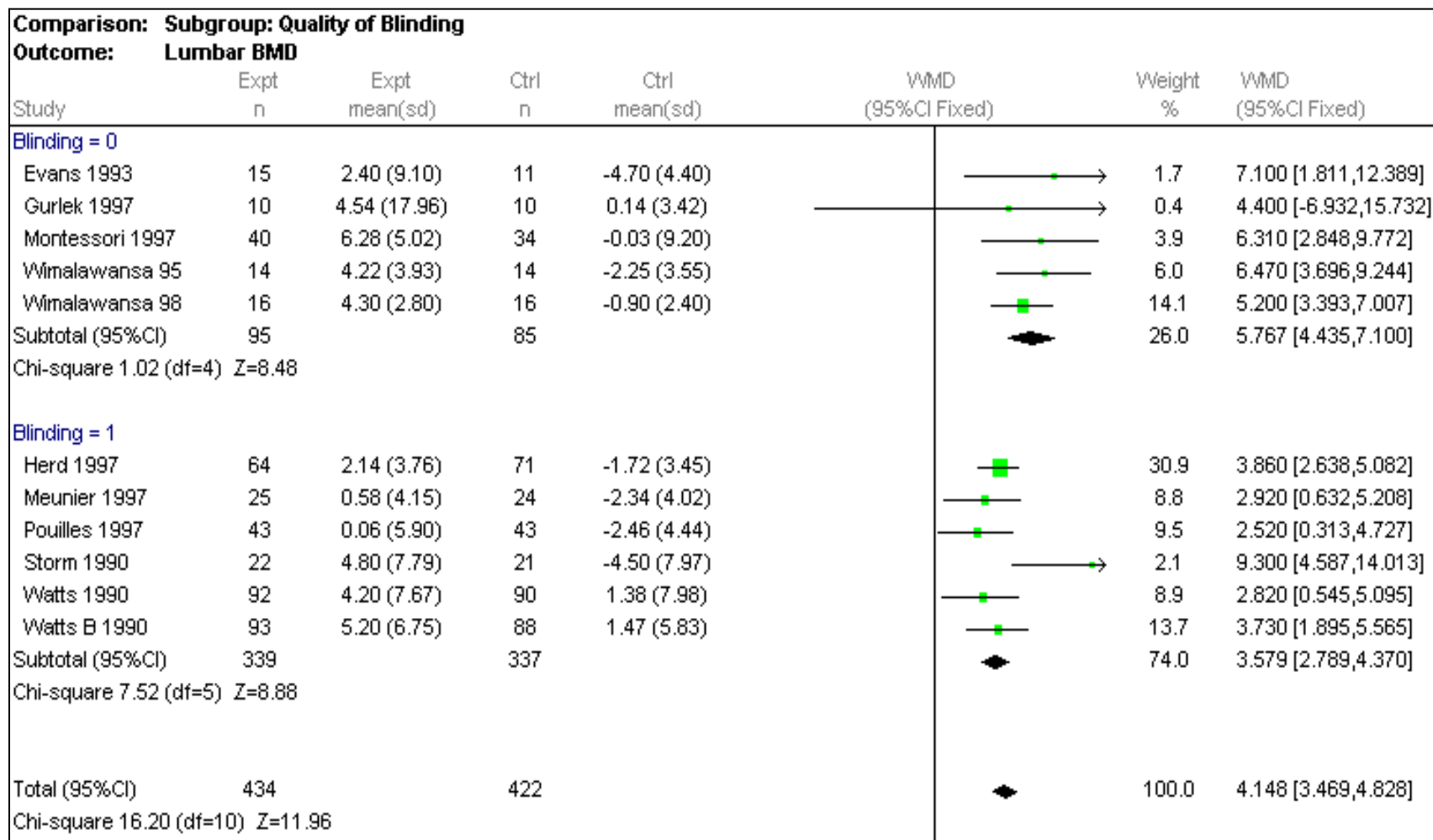
# Forest Plot

- ◆ 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



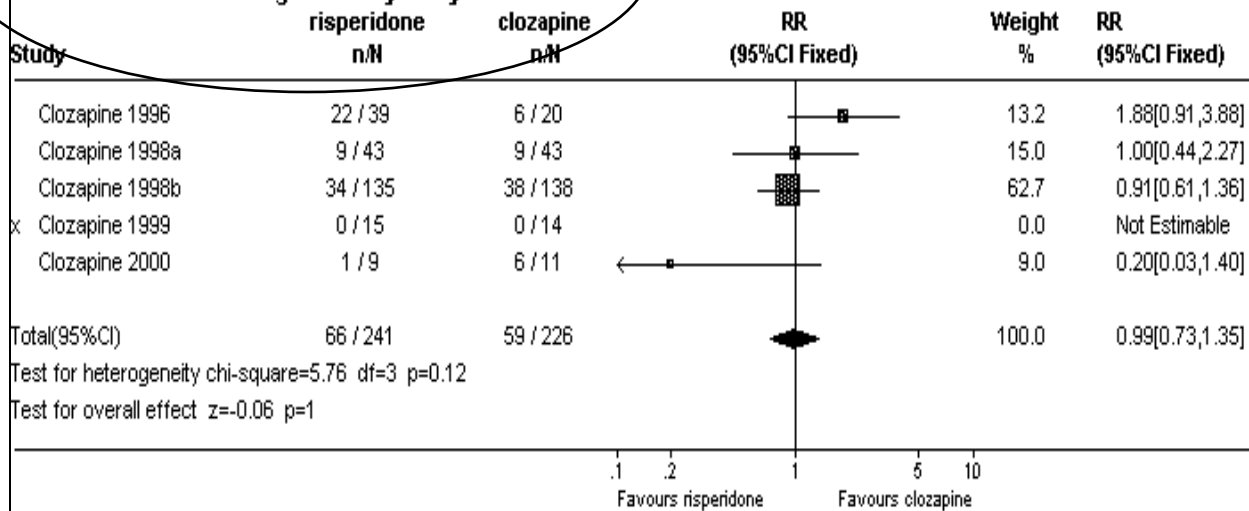
# Forest plot



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

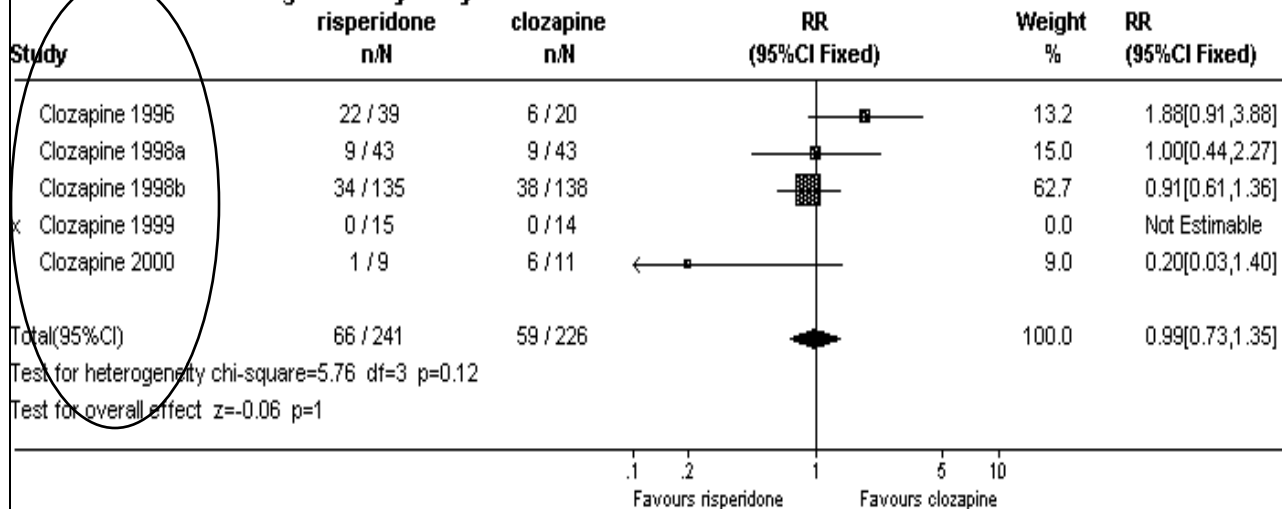
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

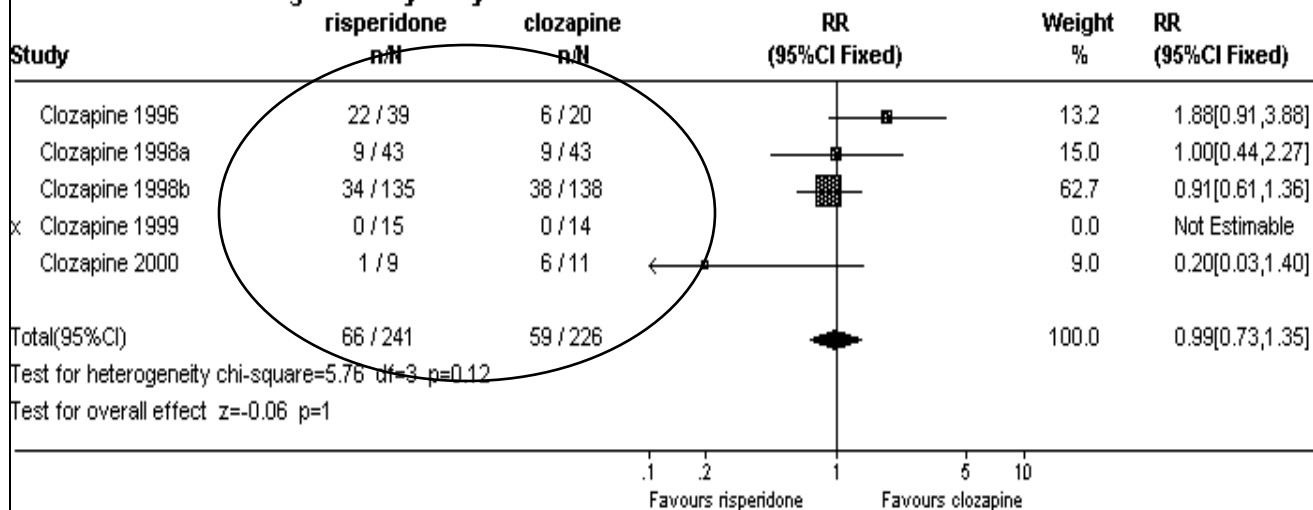
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

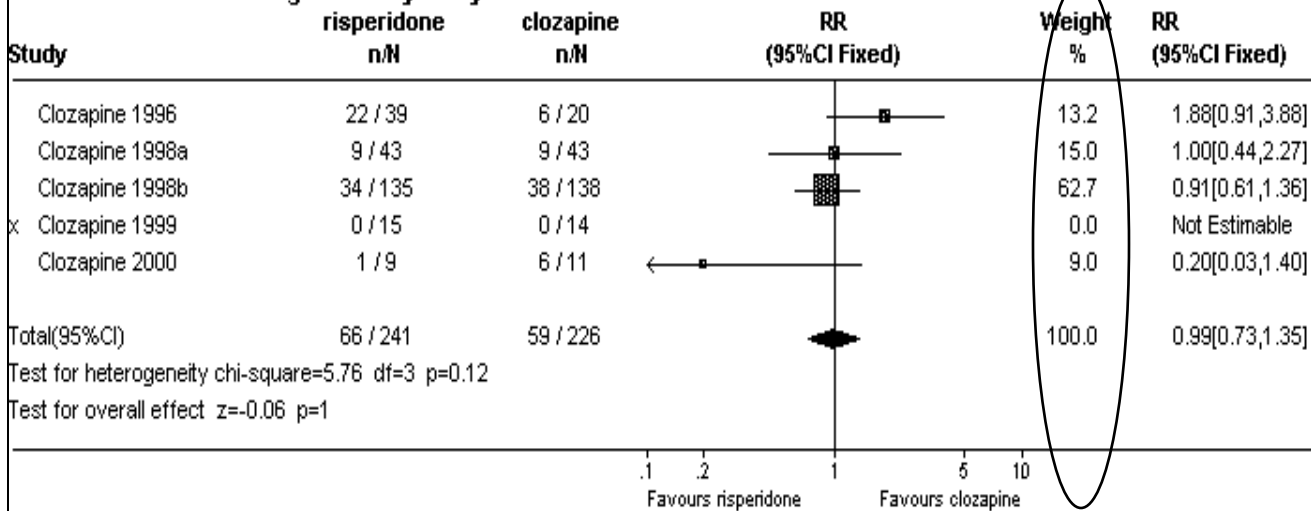
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early

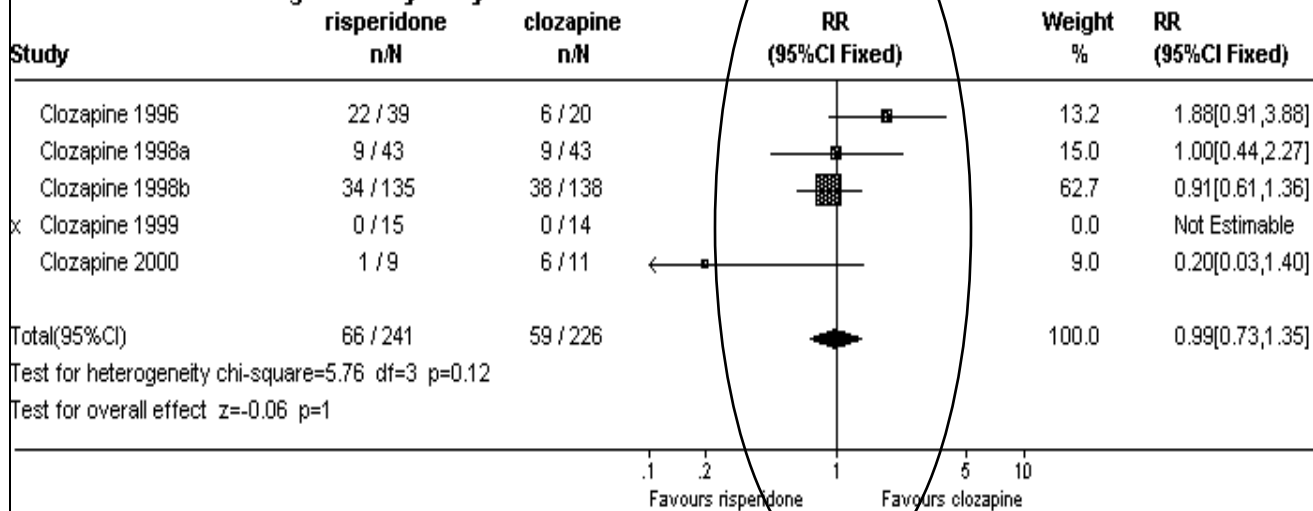




# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

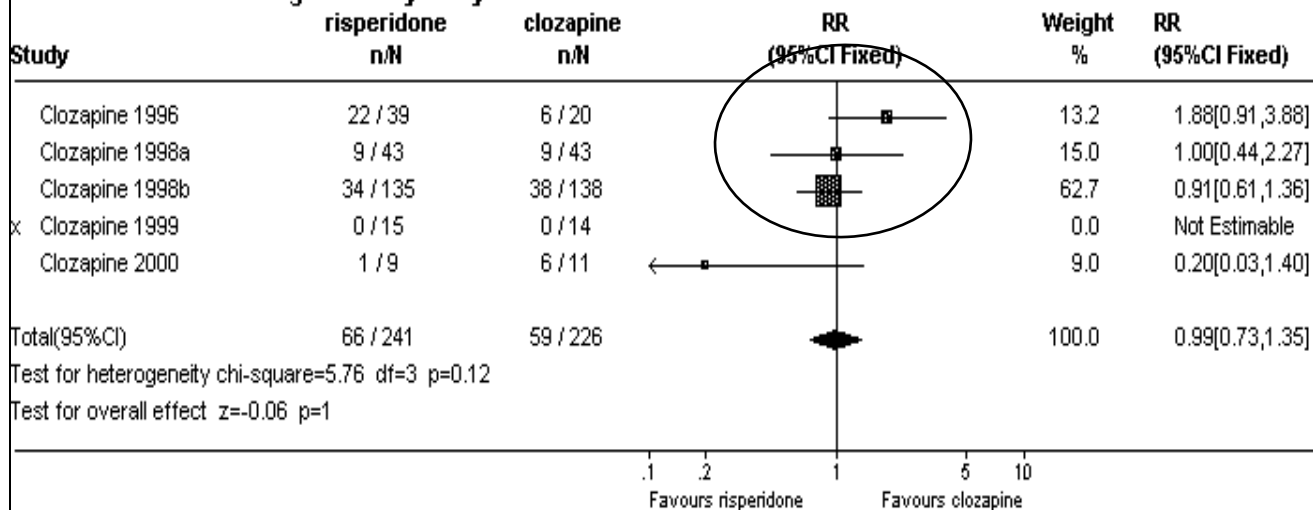
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early



# Forest plot

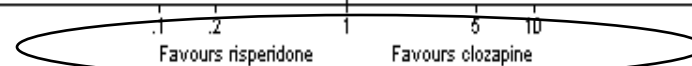
Comparison: 01 RISPERIDONE versus CLOZAPINE

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]
Clozapine 1999	0 / 15	0 / 14	Not Estimable	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

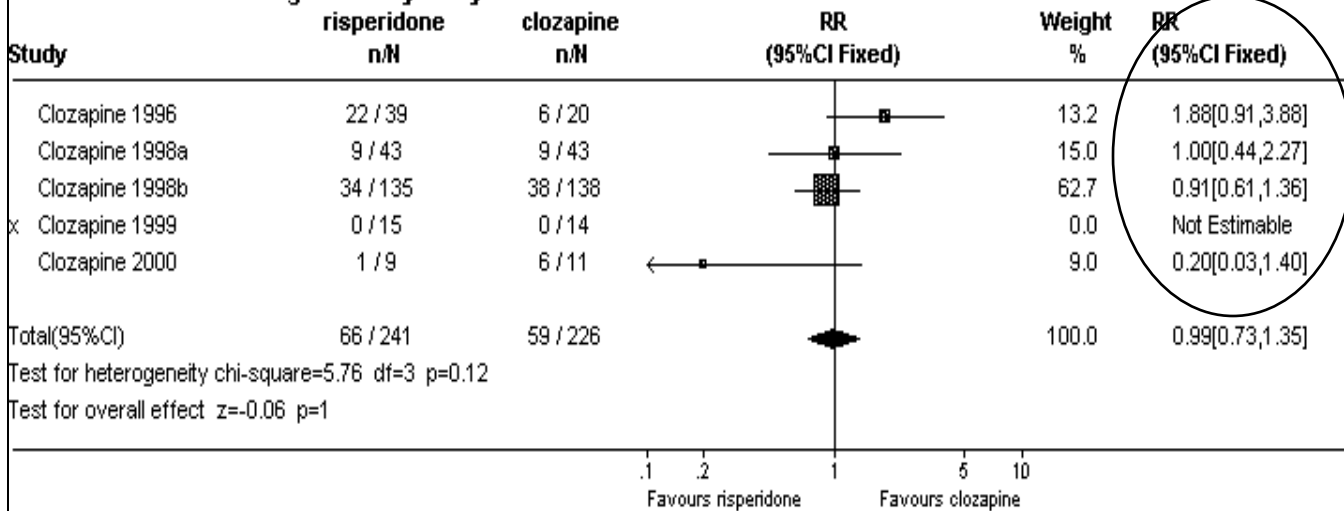
Test for overall effect z=-0.06 p=1



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

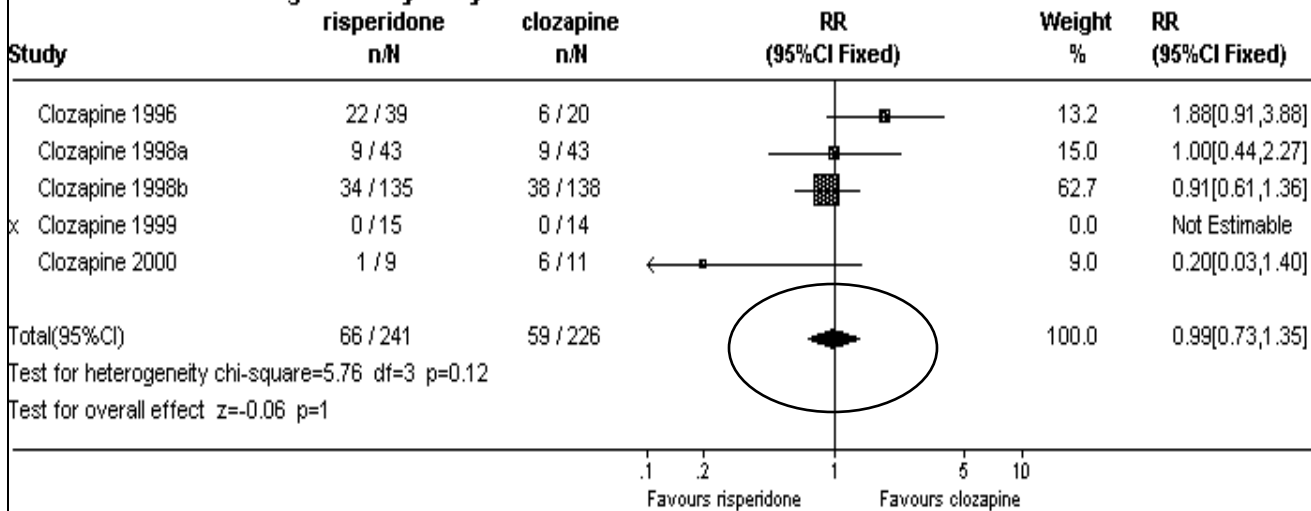
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

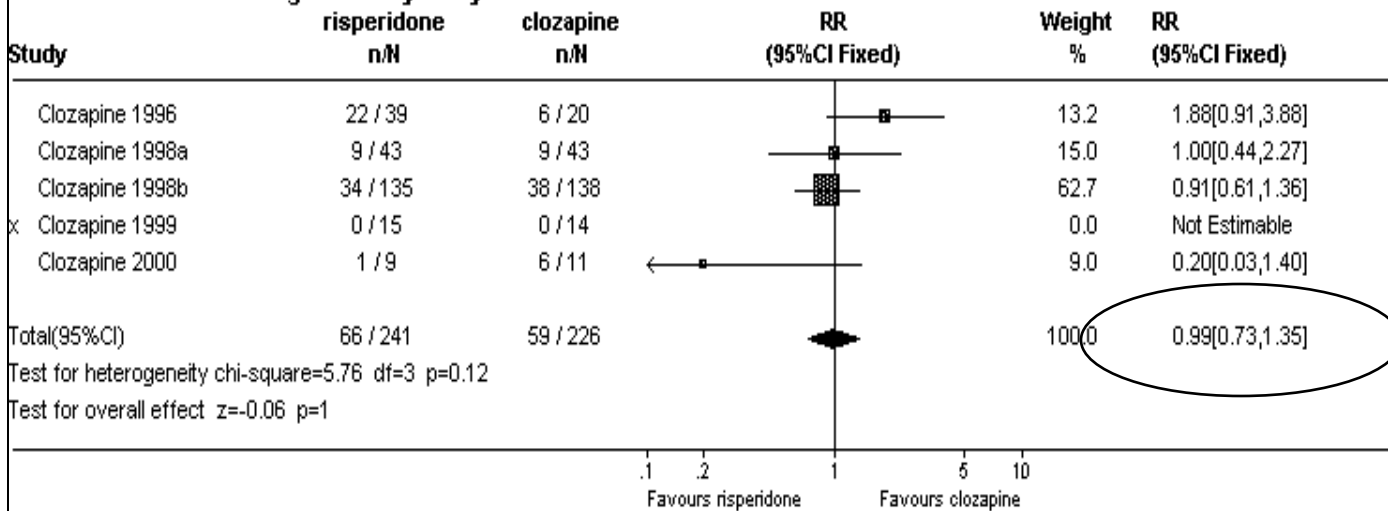
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

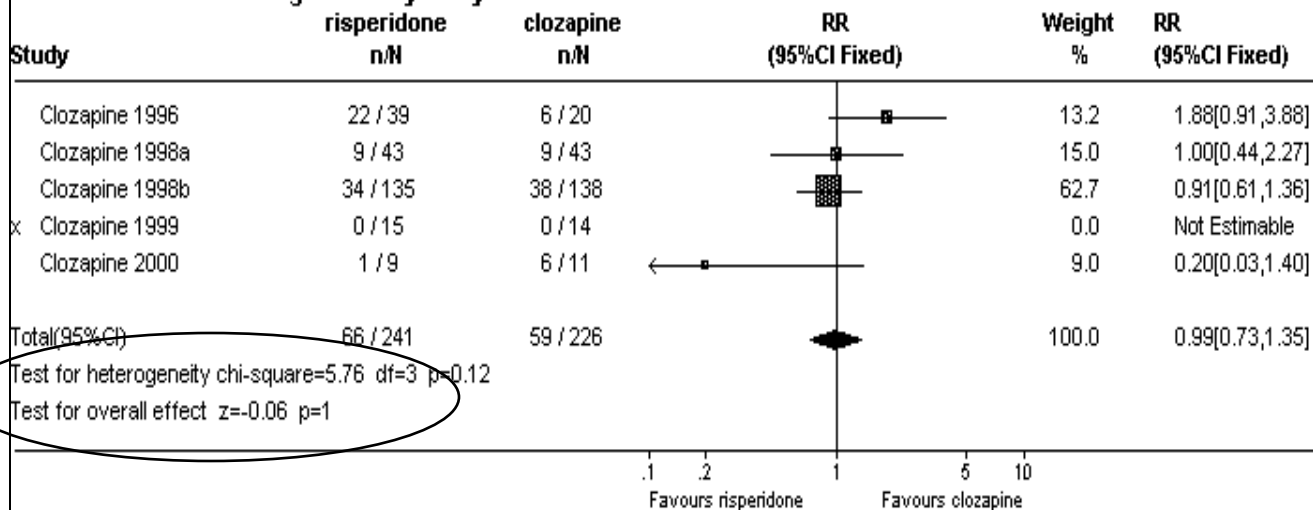
Outcome: 02 Leaving the study early



# Forest plot

Comparison: 01 RISPERIDONE versus CLOZAPINE

Outcome: 02 Leaving the study early



اگر میل داشتید Email بزنید !

[kabiri@tums.ac.ir](mailto:kabiri@tums.ac.ir)