## کارگاه آموزشی مقدماتی

# مرور سیستماتیک و متاآنالیز

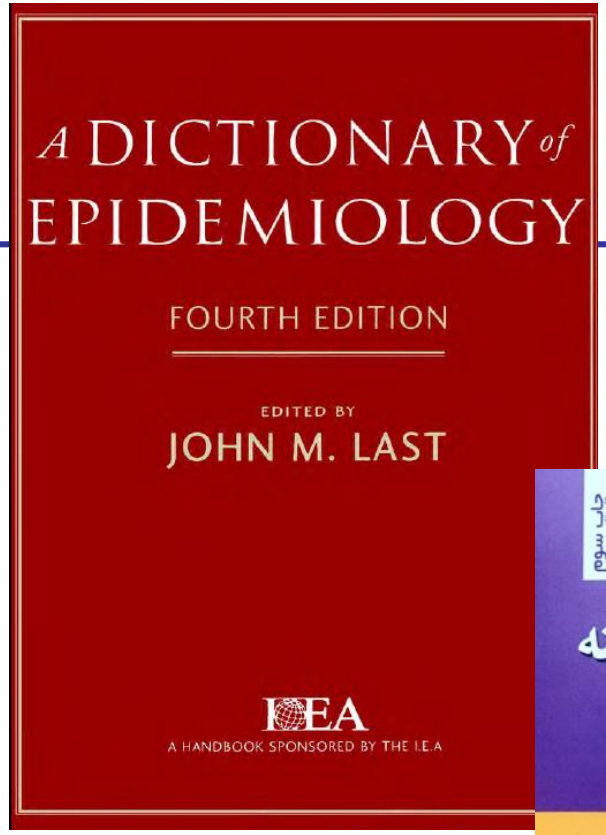
**Systematic Reviews**
**&**
**Meta-Analysis**

۱۳ و ۱۴ آذر ۱۳۹۵

# مباحث پیش رو

- تعاریف و اهمیت مطالعات مروری با تاکید بر مطالعات مرور ساختارمند و متاانالیز

- اجزا و مراحل انجام یک مرورساختارمند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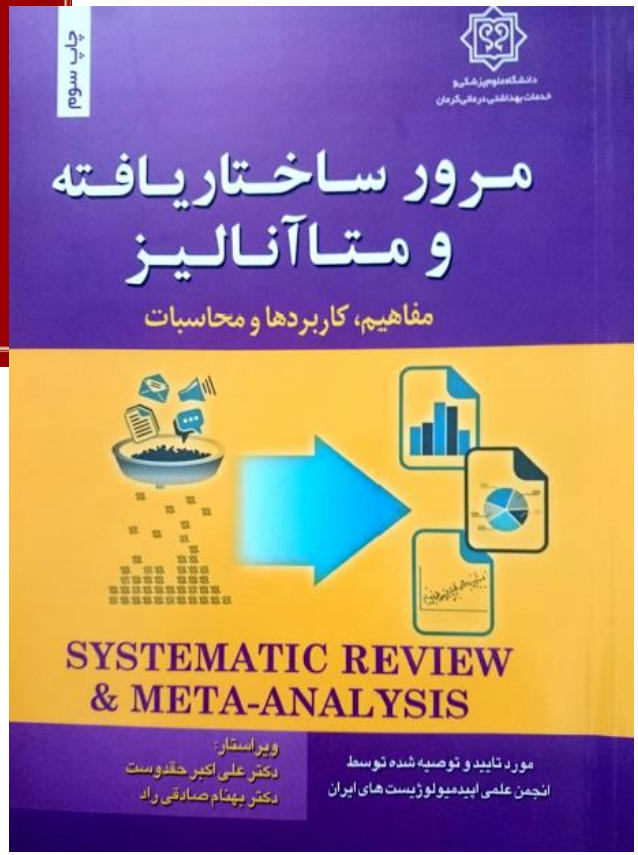
چاپ سوم
مرور ساختاریافته و متاآنالیز
مفاهیم، کاربردها و محاسبات
SYSTEMATIC REVIEW & META-ANALYSIS
ویراستار:
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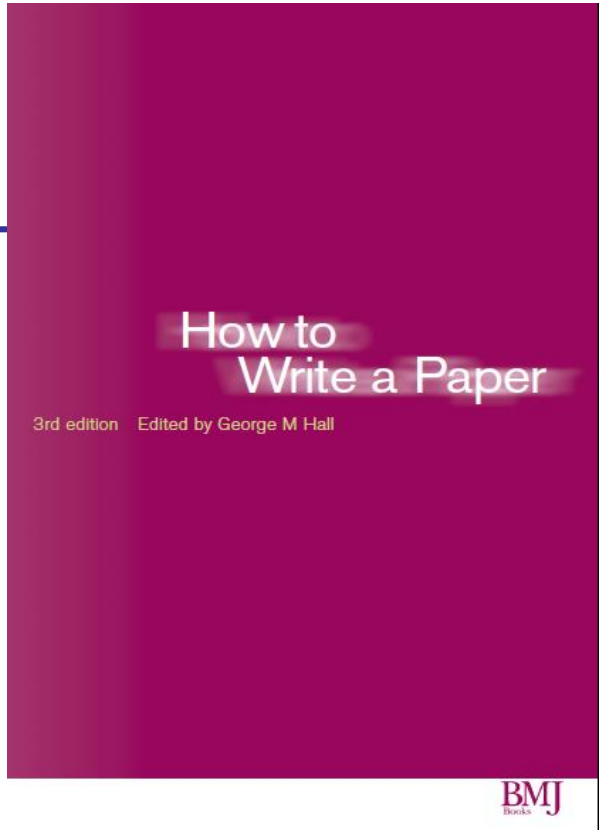
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Cochrane Handbook for Systematic Reviews of Interventions - Windows Internet Explorer

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## Cochrane Handbook for Systematic Reviews of Interventions

THE COCHRANE COLLABORATION®

Version 5.1.0

[updated March 2011]

Editors: Julian PT Higgins and Sally Green

# مطالعه اولیه در مقابل مطالعه ثانویه

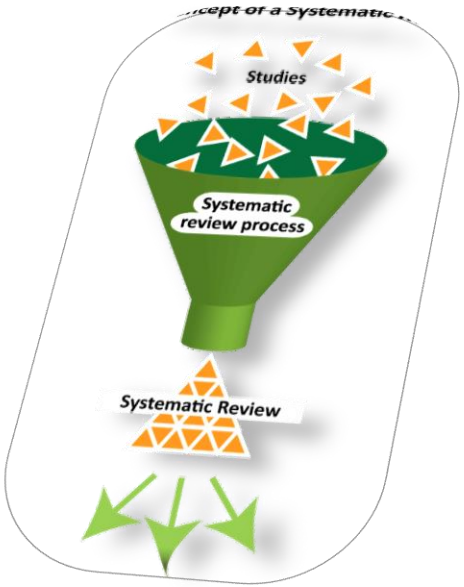
## تفاوت، مربوط به واحد مطالعه است.

در یک مطالعه اولیه، واحد مطالعه، یک فرد (انسان سالم، بیمار، حیوان آزمایشگاهی و ...) است.

در یک مطالعه ثانویه، واحد مطالعه، مطالعه اولیه (یافته های یک مطالعه اولیه) است.

# مطالعات مروری : مهمترین مطالعات ثانویه

- **Narrative (Traditional) Review,**
- **Systematic Review/Meta-analysis**



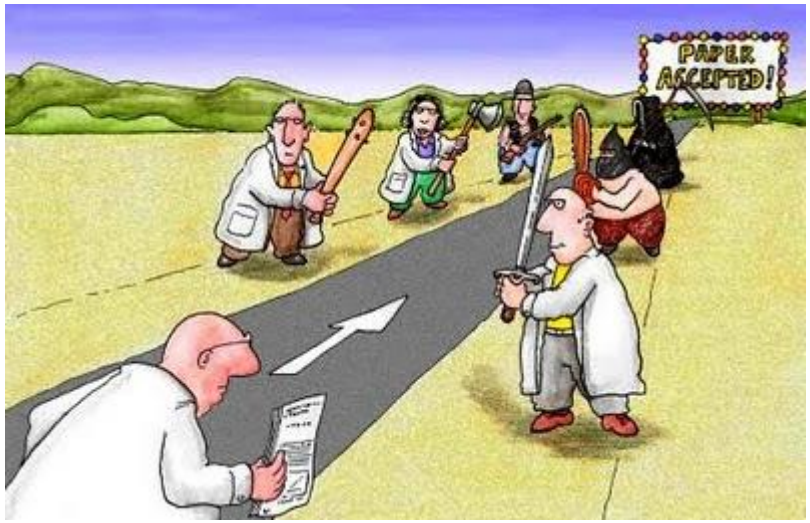
# Review articles

- *Review articles* are in a state of somewhat uncontrolled proliferation.

- Both general and specialist journals have grown to love them.

# Review articles

- Yet, unquestionably the task of writing a review article has become a whole lot tougher in recent years.



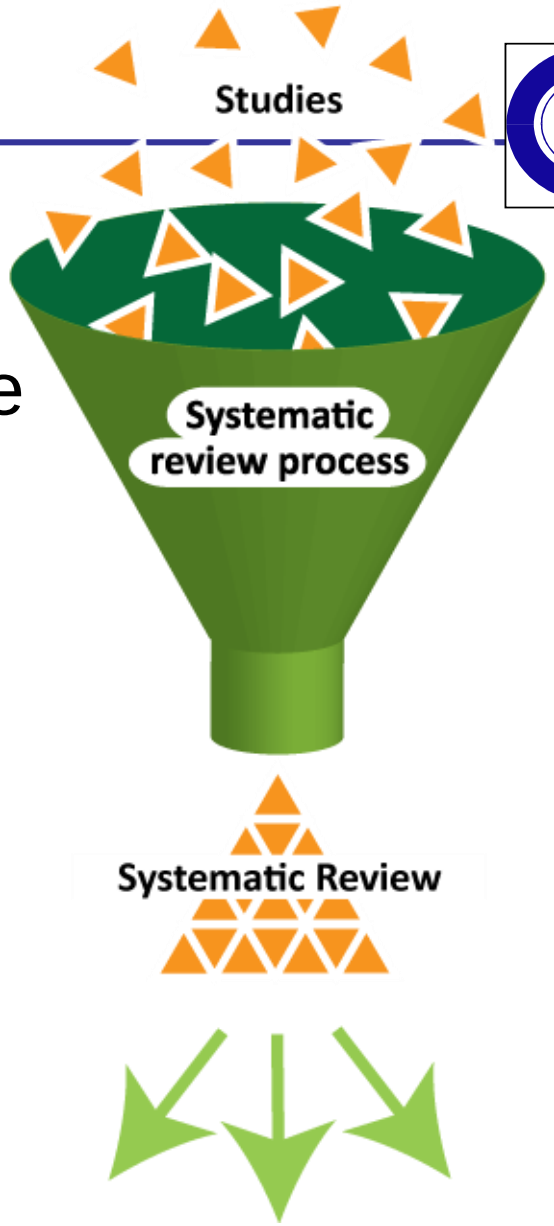
I BELIEVE!!
RESEARCH
SLOW DOWN! THE EVIDENCE ISN'T COMPLETE

# Review articles

- For areas in which a wealth of valuable data exists, the personal perspective has gone out of fashion:

  *systematic review*

- Of course, whole areas where there is a lack of evidence the more traditional or *narrative review* retains its place for these.



# Who needs review articles?

- Journal editors like reviews.
  - The thorough, authoritative review is likely to be widely read and highly cited, and this may increase the journal's **impact factor** (a measure of a journal's success).
  - A good way to attract readers.

# Who needs review articles?

- Expansion of a *paper journal's educational role* is seen as one route to ensure a viable future.

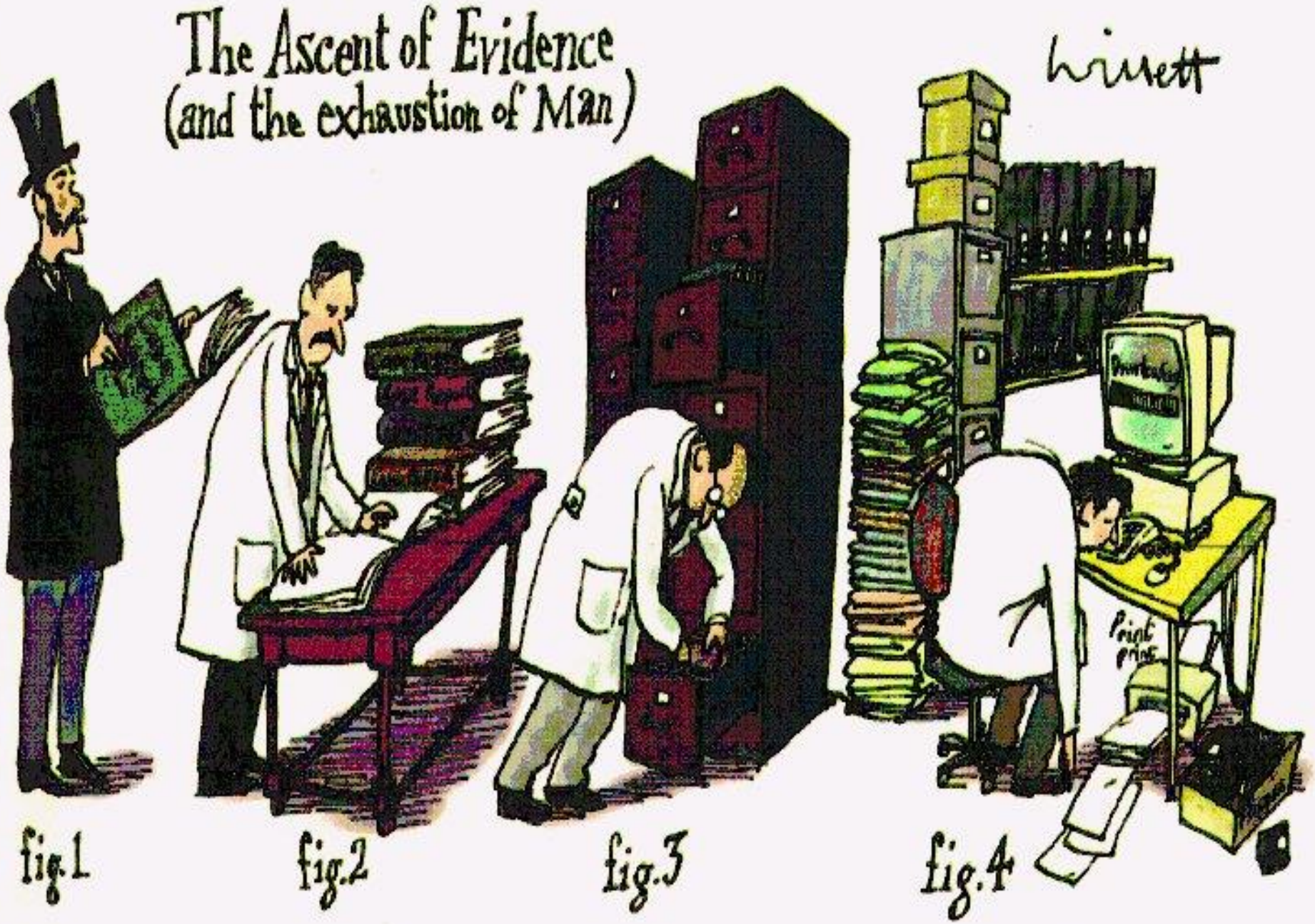

The Ascent of Evidence
(and the exhaustion of Man)
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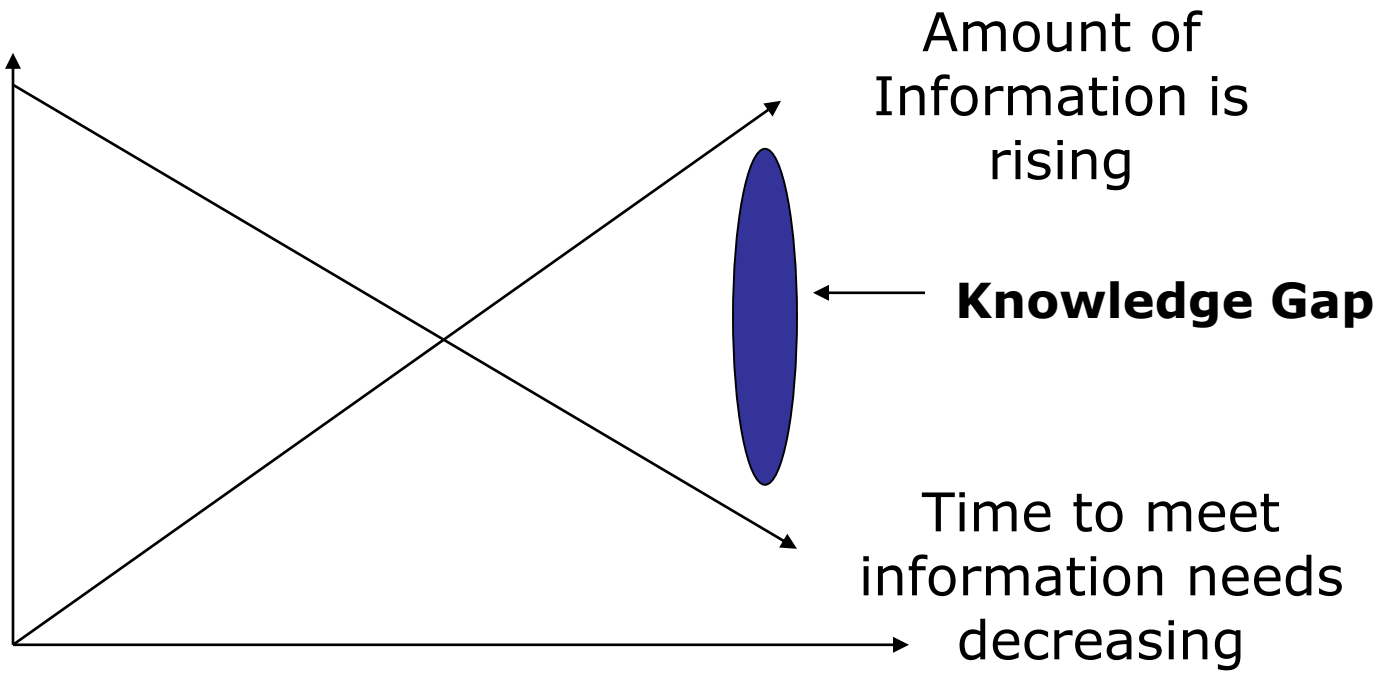
fig.3
fig.4

# The Knowledge gap



# Who should write a review?

- Editors will usually try to persuade someone *"right at the cutting edge of a particular field"* to provide the article.

  - In general, the further the author is from the frontier of knowledge in that particular area, the less well informed is the review.

# What is a Systematic Review?

- A **systematic review** is a literature review focused on a research question that tries to **identify**, **appraise**, **select** and **synthesize** all high quality research evidence relevant to that question.

# Systematic Review; definition

A review of a **clearly formulated question** that uses ***systematic*** and ***explicit*** methods to **identify, select** and **critically appraise** relevant research, and to **collect** and **analyse** data from the studies that are included in the review.

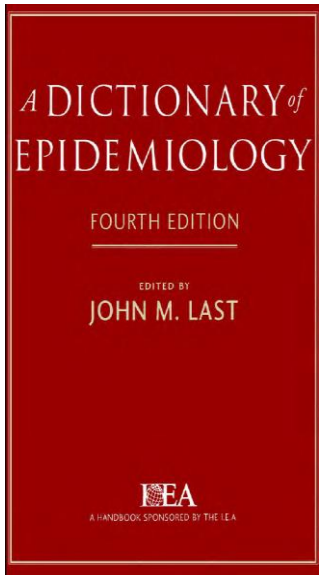
*Cochrane Reviewers' Handbook*

## •SYSTEMATIC REVIEW

✓The application of strategies that limit **bias** in the assembly, **critical appraisal**, and **synthesis** of all relevant studies on a specific topic.

✓Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for **selecting** and **assessing** articles.

✓Meta-analysis may be, but is not necessarily, used as part of this process.



# Why Systematic Review?

I. The conclusions of systematic reviews may be more generalizable than single studies.

II. Combining studies in meta-analyses increases the sample size and generally produces more precise estimates of the effect size.

III. Clinicians rarely have the time or resources to critically evaluate the body of evidence relevant to a particular clinical question.

IV. Systematic reviews minimize bias.

# Bias; definition

- Bias means something that will cause a consistent deviation from the truth.
- This is different from the play of **chance (Random Error).**

# How do systematic reviews minimize bias?

*Inclusion/Exclusion Criteria*

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

# Differences Between Traditional and Systematic Reviews

**Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials.**

Kandula P, Dobre M, Schold JD, Schreiber MJ Jr, Mehrotra R, Navaneethan SD.

Department of Nephrology, Indiana University, Indianapolis, Indiana, USA.

## Abstract

**BACKGROUND AND OBJECTIVES:** Vitamin D deficiency is highly prevalent among patients with chronic kidney disease (CKD). The benefits and harms of vitamin D supplementation (ergocalciferol or cholecalciferol) were assessed in patients with nondialysis-dependent CKD, dialysis-dependent CKD, and renal transplant recipients.

**DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** MEDLINE (1966 to September 2009), SCOPUS (September 2009), and nephrology conference proceedings were searched for relevant observational and randomized controlled trials (RCTs). Treatment effects were summarized as mean differences (MDs) with 95% confidence intervals (CIs) using a random effects model. Separate analyses were conducted for observational studies and RCTs.

**RESULTS:** Twenty-two studies (17 observational and 5 RCTs) were included. There was a significant improvement in 25-hydroxyvitamin D (MD 24.1 ng/ml, 95% CI 19.6 to 28.6) and an associated decline in parathyroid hormone (PTH) levels (MD -41.7 pg/ml, 95% CI -55.8 to -27.7) among observational studies. PTH reduction was higher in dialysis patients. Among RCTs, there was a significant improvement in 25-hydroxyvitamin D (MD 14 ng/ml, 95% CI 5.6 to 22.4) and an associated decline in PTH levels (MD -31.5 pg/ml, 95% CI -57 to -6.1). A low incidence of hypercalcemia and hyperphosphatemia was reported with vitamin D supplementation. Cardiovascular and skeletal effects of vitamin D supplementation have not been studied. Included studies were mostly of low to moderate quality.

**CONCLUSIONS:** Available evidence from low-to-moderate quality observational studies and fewer RCTs suggests that vitamin D supplementation improves biochemical endpoints. However, whether such improvements translate into clinically significant outcomes is yet to be determined.

# Differences Between Traditional and Systematic Reviews

Clin J Am Soc Nephrol. 2012 Feb;7(2):358-65. doi: 10.2215/CJN.04040411. Epub 2011 Dec 22.

**Vitamin D therapy in chronic kidney disease and end stage renal disease.**

Melamed ML, Thadhani RI.

Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461, USA. michalmelamed@yahoo.com

**Abstract**

Vitamin D has garnered much research and debate about supplementation in recent years, not only as it pertain
kidney disease but also to those in the general population. This review discusses observational and available cli
about the effects of both calcitriol and vitamin D analogs (active) and ergocalciferol and cholecalciferol (nutritiona
patients with CKD and ESRD.

# 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

# History of Systematic Review

- The statistical basis of meta-analysis reaches back to the 17th century in astronomy and geodesy.
- In 1976 the psychologist Glass coined the term “meta-analysis”.
- In the 1980s meta-analysis became increasingly popular in medicine.

# History of Systematic Review

- Cochrane Collaboration was held in Oxford in **October 1993**.

  The Collaboration aims to help people make well-informed decision about health care by preparing, maintaining and promoting the accessibility of **systematic review**.

# The Cochrane Collaboration

Preparing, maintaining and disseminating systematic reviews of the effects of health care

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offcampus.tums.ac.ir:2493/view/0/index.html
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Independent high-quality evidence for health care decision making

from The Cochrane Collaboration

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## COCHRANE DATABASE OF SYSTEMATIC REVIEWS

Issue 10 of 12, October 2013

(Updated Daily) | Contents

## BROWSE BY TOPICS

- Anaesthesia & pain control (255)
- Blood disorders (192)

## SPECIAL COLLECTIONS

Hospital-acquired infection

World day for Safety and Health at Work 2013

Tuberculosis

## EDITORIALS

**Cochrane and Wikipedia: the collaborative potential for a quantum leap in the dissemination and uptake of trusted evidence**

Manu Mathew, Anna Joseph, James Heilman & Prathap Tharyan

**Rotator cuff tears and shoulder impingement: a tale of two diagnostic test accuracy reviews**

COCHRANE METHODS

CLICK HERE

# سایر مراکز و سازمانهای فعال

- JBI:Joanna Brigges Institute

1996

- توسعه همکاریهای بین المللی در حوزه بهداشت، درمان و پرستاری و تصمیم گیری مبتنی بر شواهد در پرستاری
- The Center for Reviews & Dissemination

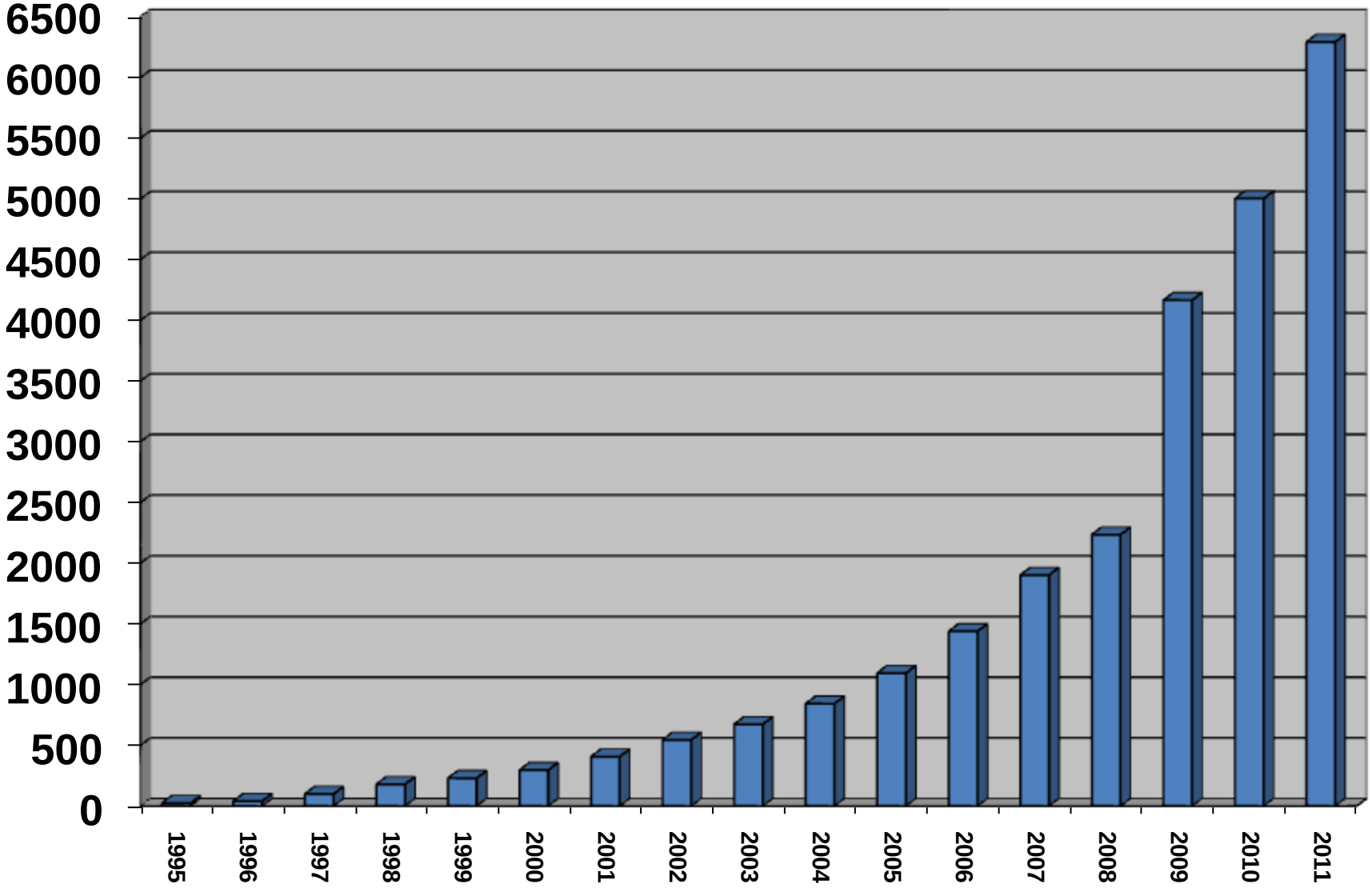
1994

- تولید شواهد در حوزه سلامت
- Campbell collaboration

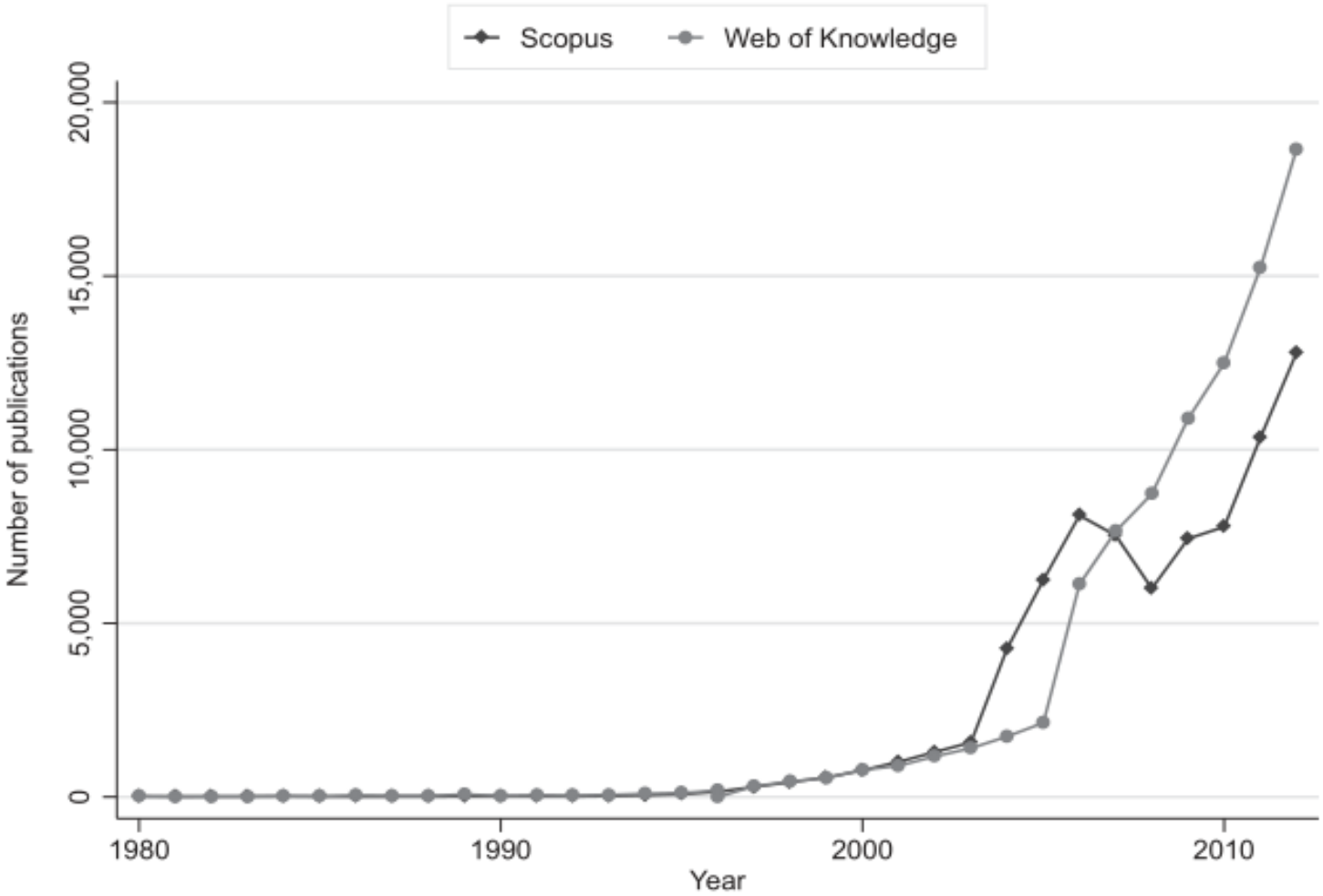
2000

- شبیه کاکرین بیشتر در حوزه های مختلف علوم اجتماعی

# Systematic Review papers in PubMed



# Trend of systematic review papers in SCOPUS and WON




**Hansen, Henrik, and Neda Trifkovic. *Systematic Reviews: Questions, Methods and Usage*. DANIDA, Udenrigsministeriet, 2013.**

# Meta-analysis; definition

- When an systematic review incorporates a specific statistical strategy for assembling the results of several studies into a **single estimate.** (specific OR, Combined OR)

- Statistical combination of results, estimating the **weighted average** of treatment effect.

# چگونه میتوان یک ایده پژوهشی را به یک عنوان مطالعه مرور سیستماتیک تبدیل نمود؟

برای پاسخ به این سوال باید:

الف) جایگاه مطالعات مرور سیستماتیک بشناسیم.

ب) کاربرد آنها در علوم پزشکی و سلامت را بدانیم.

ج) کارکرد آنها را از منظر متدولوژی و آماری بدانیم.

# جایگاه

## قله هرم شواهد

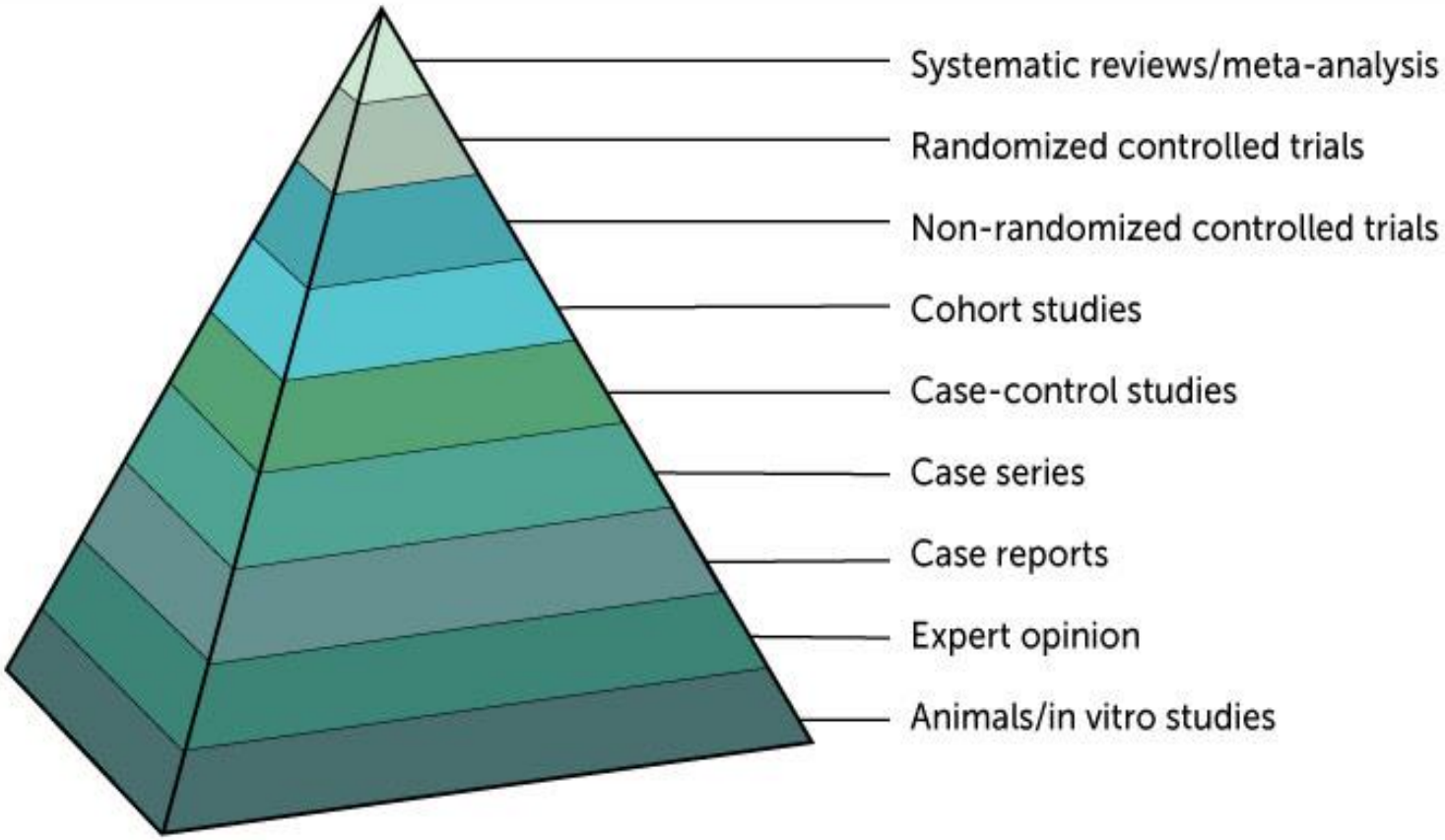



**Figure 1** - Levels of scientific evidence in evidence-based Dentistry.

# کاربرد

| ردیف | نوع مرور سیستماتیک / متاآنالیز | انواع طراحیهای مطالعات اولیه | شاخص آماری اصلی در متاآنالیز |
|---|---|---|---|
| ۱ | مرور سیستماتیک مطالعات شیوع/مقطعی | مقطعی توصیفی | شیوع (فراوانی)<br>میانگین |
| ۲ | مرور سیستماتیک مطالعات مشاهده ای تحلیلی | مقطعی توصیفی-تحلیلی<br>مورد شاهدی<br>کوهورت | بروز(خطر ابتلا)<br>Relative Risk<br>Mean Diff |
| ۳ | مرور سیستماتیک کارآزماییهای بالینی | کارآزمایی بالینی تصادفی<br>کارازمایی بالینی غیرتصادفی | Relative Risk یا Risk Diff<br>Mean Diff |
| ۴ | مرور سیستماتیک مطالعات ارزش تشخیصی | مطالعات ارزش تشخیصی | حساسیت، ویژگی، PPV، NPV |

# کاربرد

| ردیف | نوع مرور سیستماتیک / متاآنالیز | هدف مرور سیستماتیک |
|---|---|---|
| ۱ | مرور سیستماتیک مطالعات موردی | ترکیب یا جمع بندی یافته های مطالعات موردی ارزیابی تفاوتها (بدون متاآنالیز) |
| ۲ | مرور سیستماتیک مطالعات موارد | ترکیب یا جمع بندی یافته های مطالعات موردی ارزیابی تفاوتها (معمولا بدون متاآنالیز) |
| ۳ | مرور سیستماتیک مطالعات تجربی (حیوانی)/ مدل حیوانی | ارزیابی اثر مداخله /مداخلات معین بر روی حیوانات آزمایشگاهی |
| ۴ | مرور سیستماتیک مطالعات in-vitro | تقریبا شبیه مرور سیستماتیک ایتم ۳ است. |
| ۵ | متاآنالیز شبکه ای | نوعی از متاانالیز کارآزمایهای بالینی است که بجای مقایسه دو درمان یا مداخله (درمان جدید، درمان استاندارد)، درمانهای متعدد یا دوزهای متعدد یک درمان، با یکدیگر مقایسه میگردند |
| ۶ | متاآنالیز آینده نگر | معمولا نوعی از متاآنالیز کارازمایهای بالینی است که بجای حالت معمول که مطالعات وارد شده، نسبت به زمان انجام مرور منظم، گذشته نگر محسوب میگردند، کرایتریای ورود مطالعات و ... در زمان حال تدوین میگردد |
| ۷ | مرور سیستماتیک مطالعات مروری Systematic Review of Reviews | همانطور که از نام این گروه مشخص است، این مطالعه مرور سیستماتیک مطالعات مروری (مرور منظم) است. |

# کارکرد

۱. در شرایطی که **خطای تصادفی بالا** باشد.

۲. در شرایطی که **سوگرایی قابل توجهی** وجود داشته باشد.

۳. در شرایطی که **عدم تطبیق** بین نتایج مطالعات وجود داشته باشد.

۴. مطالعه **مرور سیستماتیک مناسبی** وجود نداشته باشد.

# Different or controversial results

L-Jaramillo et al 1997

A randomised, double blind, placebo controlled trial, evaluating calcium supplementation during pregnancy for preventing hypertensive disorders and related problems.

| Group | Pre-eclampsia | N | Risk |
|---|---|---|---|
| Calcium | 4 | 125 | 3.2% |
| Placebo | 21 | 135 | 15.6% |

Relative risk = 0.21 (95% CI: 0.07 to 0.58)

# Different or controversial results

CPEP 1997

A randomised, double blind, placebo controlled trial, evaluating calcium supplementation during pregnancy for preventing hypertensive disorders and related problems.

| Group | Pre-eclampsia | N | Risk |
|---|---|---|---|
| Calcium | 158 | 2163 | 7.3% |
| Placebo | 168 | 2173 | 7.7% |

Relative risk = 0.94 (95% CI: 0.77 to 1.16)

# ارتباط مرور منظم با سایر حیطه ها:

- پزشکی مبتنی بر شواهد Evidence Based Medicine
- سیاستگذاری سلامت مبتنی بر شواهد Evidence Based Health Policy making
- ارزیابی فن آوری سلامت Health Technology Assessment
- ارزشیابی اقتصادی مداخلات سلامت Economic Evaluation

# Two main objectives of Systematic Reviews

1. **Systematic review estimates the more accurate measure(s) by combining study-specific measure that is named "*Summary Measure*" or "*Combined Measure*".**
2. **Systematic review can be used to explore the *heterogeneity* and *its source(s)* and make new hypothesis.**

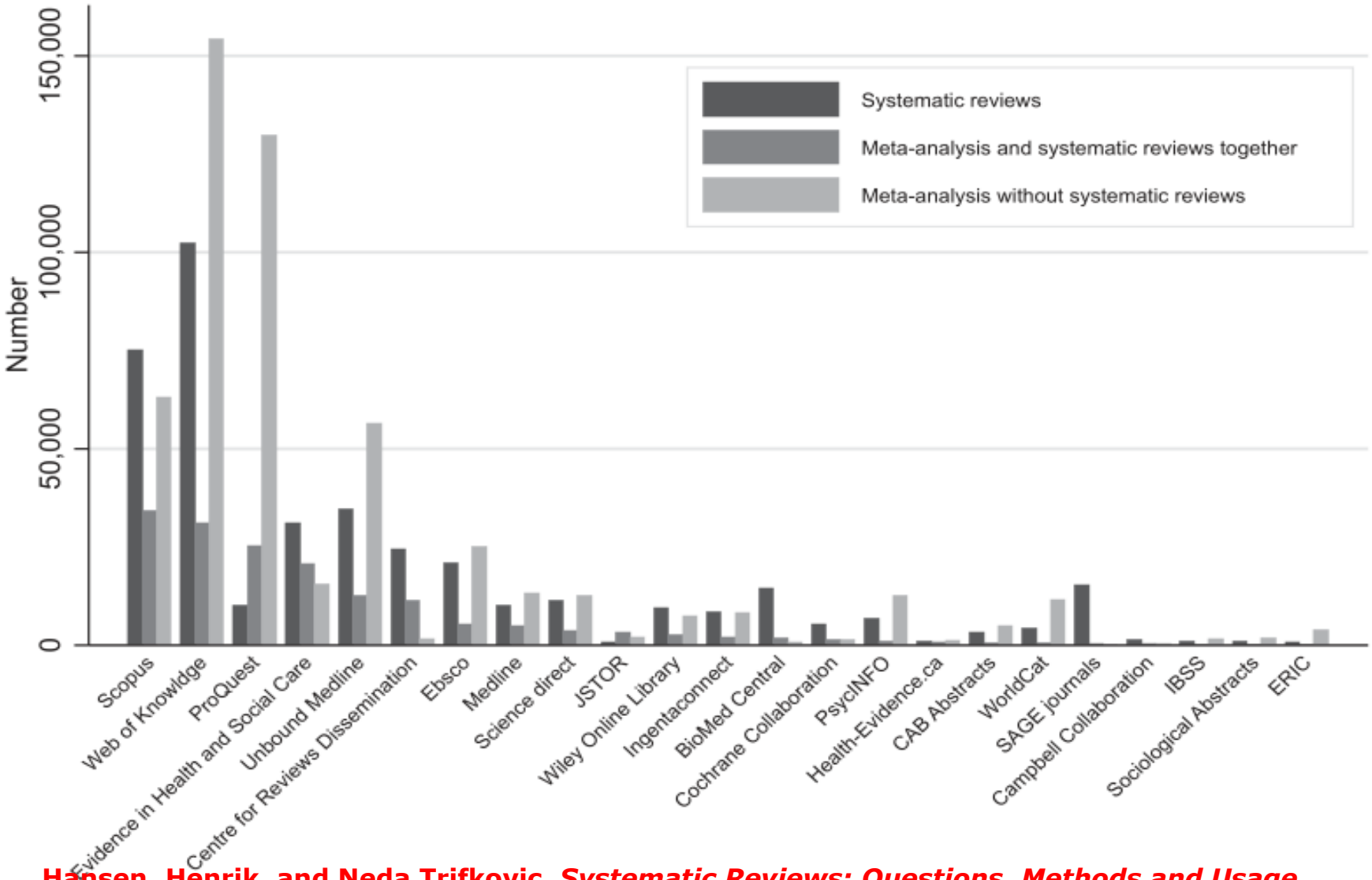
# یک سوال مهم

**آیا مطالعات مرور سیستماتیک همواره با متاآنالیز همراه هستند؟**

**یا**

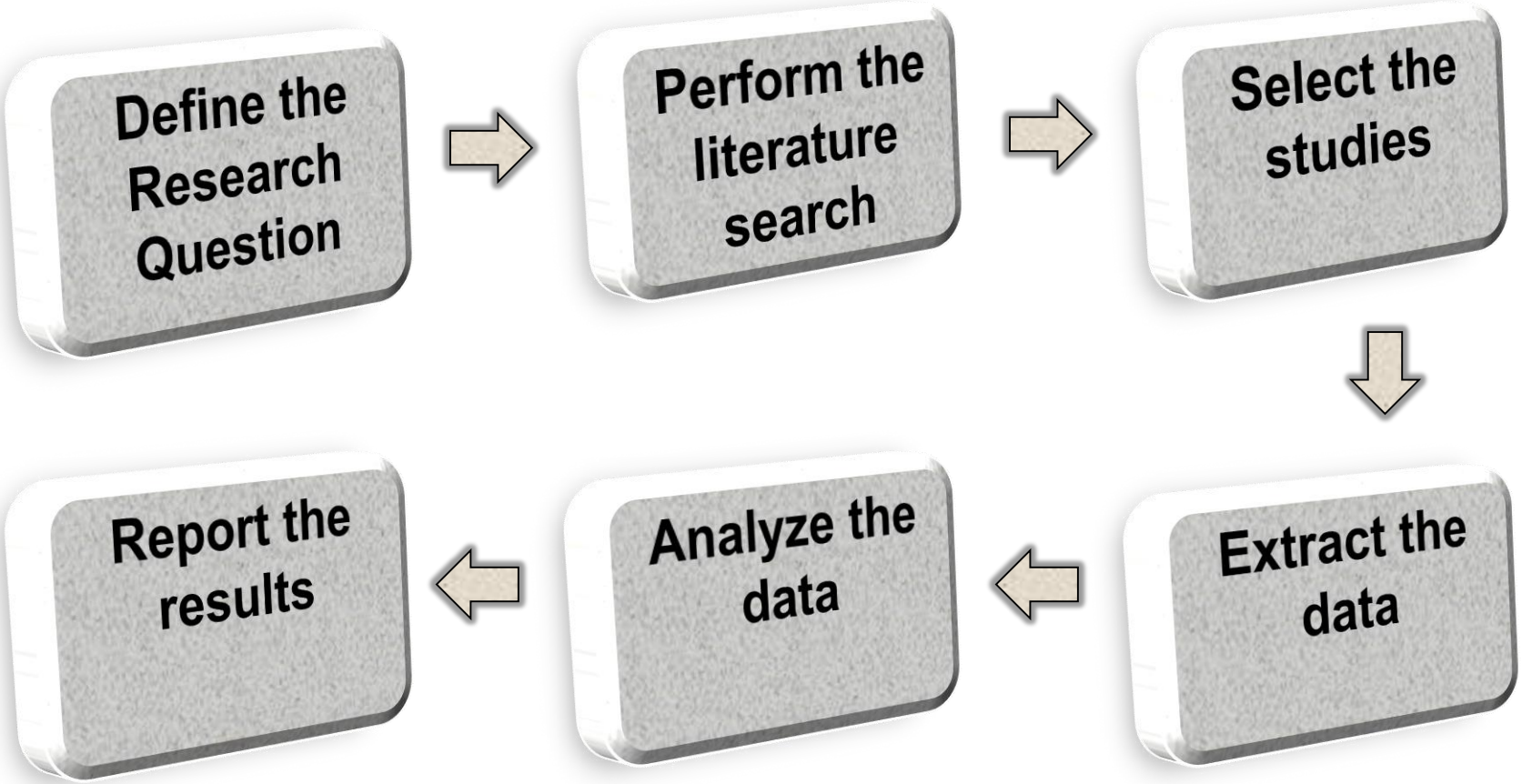
**آیا همواره مطالعات مرور سیستماتیک به متاآنالیز منجر میگردند؟**

# پاسخ سوال:




**Hansen, Henrik, and Neda Trifkovic. *Systematic Reviews: Questions, Methods and Usage*. DANIDA, Udenrigsministeriet, 2013.**

# Steps of Systematic Reviews



# Literature Search

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

# Literature Search Challenges

- **English-language bias** - Occurs when reviewers exclude papers published in languages other than English

- **Citation bias** - Statistically significant studies may be cited more than negative studies on the same topic.

# Literature Search Challenges

**Database Bias** - No single database is likely to contain all published studies on a given subject.

**Publication Bias** - selective publication of articles that show positive treatment of effects and statistical significance. Hence, it is important to search for unpublished studies.

# Meta-Analysis

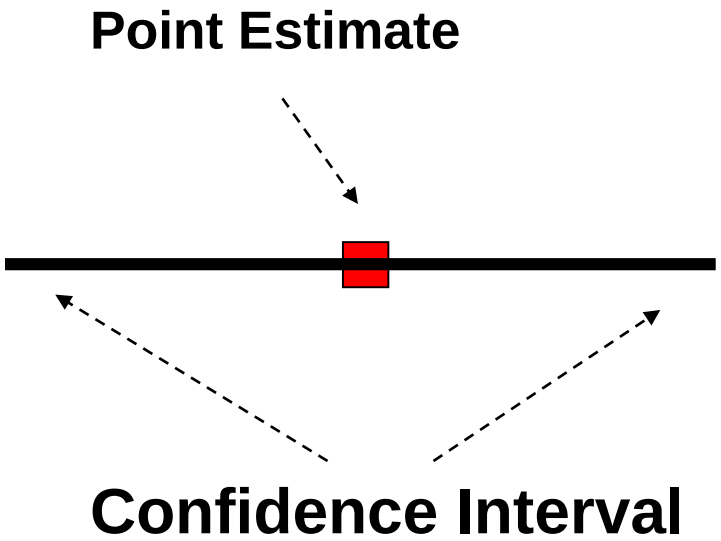
- "Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect."

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

# Data Types and Outcome Measures

| Data Type | Outcome Measures |
|---|---|
| Continuous | Mean |
| Dichotomous (binary) | Odds ratio (OR),<br>Risk ratio (RR),<br>Risk difference (RD) |
| Survival | Hazard ratio (HR) |

# The Precision of Effect Size




$$\overline{X} \mp Z_{1-\alpha/2} SE_{(x)}$$

$$SE(x)=SD(x)/\sqrt{n}$$

# Binary Comparative Outcome: Relative Risk (RR)

$$\text{RR} = \frac{a/(a+b)}{c/(c+d)}$$

| | Success | Failure |
|---|---|---|
| Treatment | a | b |
| Control | c | d |

- RR is also called the Risk Ratio

RR < 1 implies treatment effectiveness (protective)

RR > 1 indicative of treatment inferiority (risk)

# Binary Comparative Outcome: Odds Ratio (OR)

**Odds:** Treatment: a/b , Control: c/d

| | Success | Failure |
|---|---|---|
| Treatment | a | b |
| Control | c | d |

**Odds Ratio** $= \dfrac{a/b}{c/d} = \dfrac{ad}{bc}$

OR < 1 implies treatment effectiveness (protective)

OR > 1 indicative of treatment inferiority (risk)

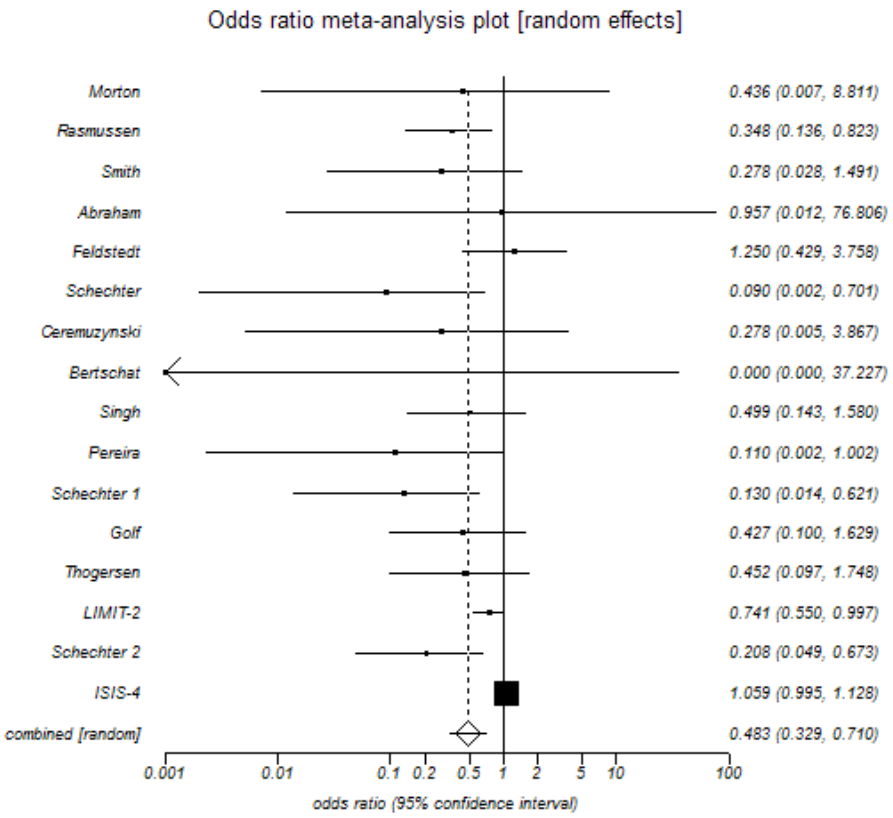
# When can data in a systematic review be synthesized numerically?

- When data are NOT too sparse, or too low quality or too heterogeneous

- When  they are sufficiently simmilar; for example the patients, interventions and outcomes in each of the included studies are sufficiently similar.

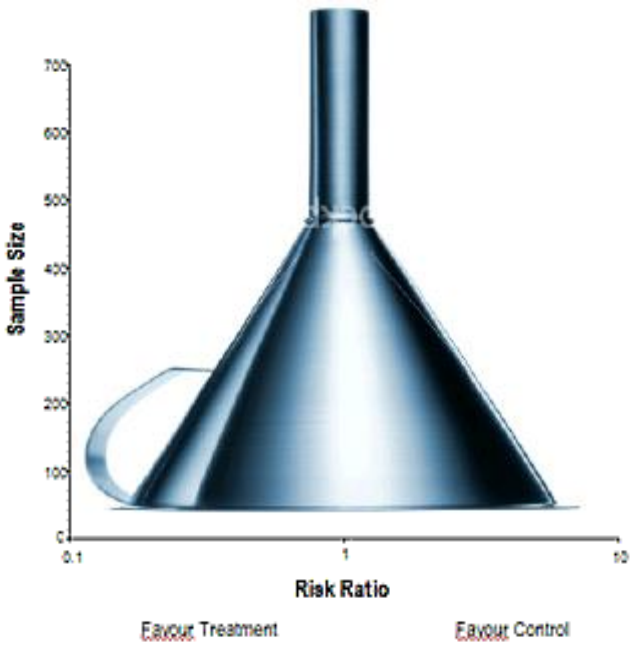
# Forest (meta-analysis) plot

- This plots a series of lines and symbols representing a meta-analysis or overview analysis.



# A Funnel Plot

"A funnel plot is used as a way to assess publication bias in meta-analysis."



# Weaknesses of systematic review

1. Requires a good deal of effort
2. Mechanical aspects don't lend themselves to capturing more qualitative distinctions between studies

3. <u>"Apples and oranges" criticism</u>
4. Most meta-analyses include "blemished" studies (e.g., a randomized design with attrition)
5. <u>Selection bias posses a continual threat</u>
   - ✓ Negative and null finding studies that you were unable to find
   - ✓ Outcomes for which there were negative or null findings that were not reported

# Example of a systematic review & meta-analysis article

CMAJ RESEARCH

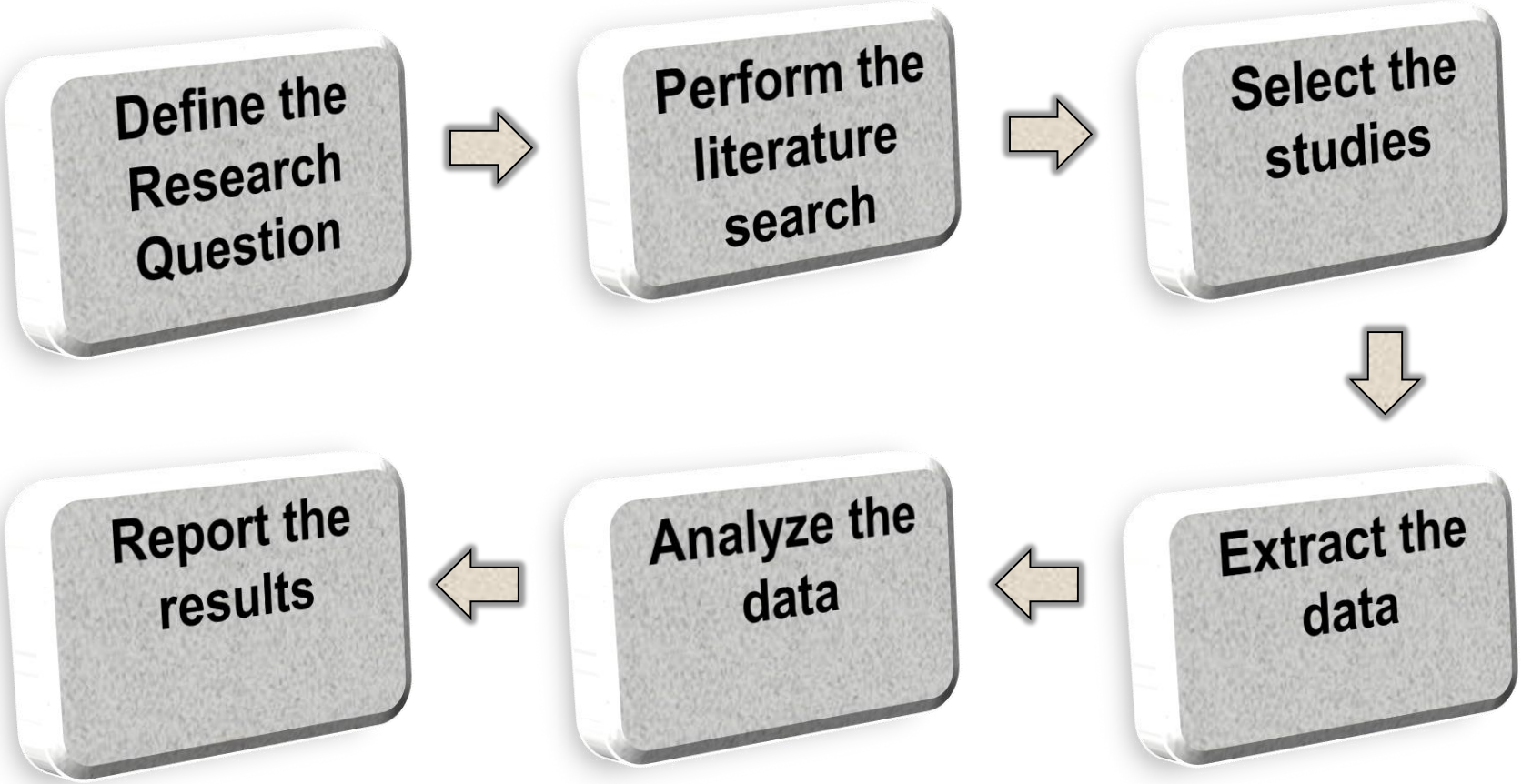
## Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials

George Wells PhD, Ratika Parkash MD MSc, Jeffrey S. Healey MD MSc, Mario Talajic MD, J. Malcolm Arnold MD, Shannon Sullivan MSc, Joan Peterson BA, Elizabeth Yetisir MSc, Patricia Theoret-Patrick BScRN, Marilynn Luce BScRN, Anthony S.L. Tang MD

**Affiliations:** From the University of Ottawa Heart Institute

2011 Canadian Medical Association

# Steps of systematic review



# Background

- Congestive heart failure (CHF) is currently reaching epidemic proportions in Canada, with 500 000 Canadians affected and 50 000 new patients identified each year.

- It accounts for more than 100 000 hospital admissions per year and has a one-year mortality ranging from 15% to 50%, depending on the severity of heart failure.

- By 2050, the number of patients with heart failure is projected to in crease threefold.

# Background…

- Advances in medical therapies have resulted in substantial reductions in mortality associated with CHF.

- The use of devices has recently become an important adjuvant therapy in addition to Optimum Medical Therapy (OMT):

  - Implantable Cardioverter Defibrillator (ICD)
  - Cardiac Resynchronization Therapy (CRT)

# Background…

- CRT has been shown to reduce mortality when compared with OMT alone.
- Until recently, CRT was not shown to reduce mortality among patients who also received an ICD.
- But RAFT trial (2010) showed the superiority of CRT+ICD in reducing mortality.

- The aim of present meta-analysis is to further assess the effect on mortality of CRT with and without an ICD among patients with CHF.

# Methods: PICOD approach for systematic review

- **Population:**

  patients with mildly symptomatic or advanced CHF, with a QRS interval of more than 120 ms.

- **Intervention:**

  CRT with or without an ICD in patients receiving OMT.

- **Comparisons:**

  CRT+ ICD vs ICD

- **Outcome:**

  mortality

- **Design:**

  RCTs with parallel or crossover design evaluating the effects of CRT compared with control in adults with CHF.

# Methods: Literature search

## CRT and ICD in patients with CHF

- **MEDLINE** (1980 to Dec. 31,2010)
- **EMBASE** (1980 to Dec. 31, 2010)
- **Cochrane Library** (1980 to Dec. 31, 2010)
- **Various sources of grey literature**
- **The US Food and Drug Administration website.**
- **Bibliographies of relevant systematic reviews were manually searched.**

# Methods: Data extraction

- Two reviewers independently screened each citation for inclusion.
- Two reviewers independently reviewed the full-text version of relevant articles and extracted the data from the included studies.
- If necessary, discrepancies between the two reviewers were resolved by discussion involving a third independent reviewer to achieve consensus.

# Meta-analysis: Analyzing the Data

- There are 2 statistical models used in a meta-analysis:
  - Fixed effects
  - Random effects

# The Fixed Effects Model

- “The fixed-effects model assumes that the true effect of treatment is the same for every study.”

# The Random Effects Model

- “The random effects model assumes that the true effect estimate for each study vary.”

# Methods: Statistical analysis

- Data were pooled using the random-effects model.
- Treatment effect was expressed as a relative risk.
- Heterogeneity was evaluated.

NCSS 2007/GESS 2006 Data - [E:\Term 4\New Folder\meta5.S0]

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| | Study | Treat_event | Treat_nonevent | Contr_event | Contr_nonevent | C6 | C7 | C8 |
|---|---|---|---|---|---|---|---|---|
| 1 | MUSTIC | 1 | 28 | 2 | 27 | | | |
| 2 | MIRACLE | 12 | 216 | 16 | 209 | | | |
| 3 | COMPANION | 131 | 486 | 77 | 231 | | | |
| 4 | CARE_HF | 101 | 308 | 154 | 250 | | | |
| 5 | VECTOR | 1 | 58 | 1 | 46 | | | |
| 6 | LOZAN | 5 | 104 | 10 | 103 | | | |
| 7 | MIRACLE_ICD | 14 | 173 | 15 | 167 | | | |
| 8 | MIRACLE_ICD2 | 2 | 83 | 2 | 99 | | | |
| 9 | RHYTHM | 6 | 113 | 2 | 58 | | | |
| 10 | REVERSE | 9 | 410 | 3 | 188 | | | |
| 11 | MADIT | 74 | 1015 | 53 | 678 | | | |
| 12 | RAFT_2010 | 186 | 708 | 236 | 668 | | | |

NCSS 2007/GESS 2006 Data - [E:\Term 4\New Folder\meta5.S0]

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| | Study | Treat_event | Treat_nonevent | Contr_event | Contr_nonevent | Group | C7 |
|---|---|---|---|---|---|---|---|
| 1 | MUSTIC | 1 | 28 | 2 | 27 | CRTv.OMT | |
| 2 | MIRACLE | 12 | 216 | 16 | 209 | CRTv.OMT | |
| 3 | COMPANION | 131 | 486 | 77 | 231 | CRTv.OMT | |
| 4 | CARE_HF | 101 | 308 | 154 | 250 | CRTv.OMT | |
| 5 | VECTOR | 1 | 58 | 1 | 46 | CRTv.OMT | |
| 6 | LOZAN | 5 | 104 | 10 | 103 | CRT-ICDv.ICD | |
| 7 | MIRACLE_ICD | 14 | 173 | 15 | 167 | CRT-ICDv.ICD | |
| 8 | MIRACLE_ICD2 | 2 | 83 | 2 | 99 | CRT-ICDv.ICD | |
| 9 | RHYTHM | 6 | 113 | 2 | 58 | CRT-ICDv.ICD | |
| 10 | REVERSE | 9 | 410 | 3 | 188 | CRT-ICDv.ICD | |
| 11 | MADIT | 74 | 1015 | 53 | 678 | CRT-ICDv.ICD | |
| 12 | RAFT_2010 | 186 | 708 | 236 | 668 | CRT-ICDv.ICD | |

# OUTPUT :

## Effect-Equality (Heterogeneity) Test

| Group | Outcome Measure | Cochran's Q | DF | Prob Level |
|---|---|---|---|---|
| CRTv.OMT | Risk Ratio | 2.7029 | 4 | 0.6087 |
| CRT-ICDv.ICD | Risk Ratio | 2.4550 | 6 | 0.8735 |
| Combined | Risk Ratio | 6.6824 | 11 | 0.8242 |

**Note:** This tests the null hypothesis that all effects are equal (homogeneous) versus the alternative that at least one effect had a different effect (heterogeneous).
Sometimes this test is used to choose between the use of a Fixed Effect (homogeneous) model and a Random Effects (heterogeneous) model.

## Risk Ratio Detail Section Using Random Effects Model

| [Group] Study | P1 | P2 | Risk Ratio | 95.0% Lower Confidence Limit | 95.0% Upper Confidence Limit | Percent Random Effects Weight |
|---|---|---|---|---|---|---|
| **[CRTv.OMT]** | | | | | | |
| MUSTIC | 0.0345 | 0.0690 | 0.6000 | 0.0845 | 4.2594 | 0.2875 |
| MIRACLE | 0.0526 | 0.0711 | 0.7477 | 0.3670 | 1.5231 | 2.1808 |
| COMPANION | 0.2123 | 0.2500 | 0.8484 | 0.6639 | 1.0842 | 18.3643 |
| CARE_HF | 0.2469 | 0.3812 | 0.6489 | 0.5263 | 0.8001 | 25.1796 |
| VECTOR | 0.0169 | 0.0213 | 0.8000 | 0.0859 | 7.4482 | 0.2218 |
| Average | | | 0.7270 | 0.6229 | 0.8486 | |
| **[CRT-ICDv.ICD]** | | | | | | |
| LOZAN | 0.0459 | 0.0885 | 0.5429 | 0.2001 | 1.4725 | 1.1091 |
| MIRACLE_ICD | 0.0749 | 0.0824 | 0.9106 | 0.4583 | 1.8092 | 2.3429 |
| MIRACLE_ICD2 | 0.0235 | 0.0198 | 1.1860 | 0.2104 | 6.6861 | 0.3692 |
| RHYTHM | 0.0504 | 0.0333 | 1.3217 | 0.3177 | 5.4991 | 0.5433 |
| REVERSE | 0.0215 | 0.0157 | 1.2408 | 0.3687 | 4.1760 | 0.7498 |
| MADIT | 0.0680 | 0.0725 | 0.9352 | 0.6666 | 1.3119 | 9.6365 |
| RAFT_2010 | 0.2081 | 0.2611 | 0.7974 | 0.6739 | 0.9435 | 39.0153 |
| Average | | | 0.8303 | 0.7194 | 0.9582 | |
| **[Combined]** | | | | | | |
| Average | | | **0.7808** | 0.7030 | 0.8674 | |

Note: This report presents the outcome's value as well as a confidence interval.The 'Average' line presents the combined estimates for the group. The weights let you determine the influence of each study on the combined results.

# The Results Section

- The results section should
  - Include a flow chart of studies included
  - A figure displaying the results from each individual study (forest plot), results of heterogeneity testing, overall summary statistic

# Result

- Of 3071 reports identified, 12 studies were included in our meta- analysis.

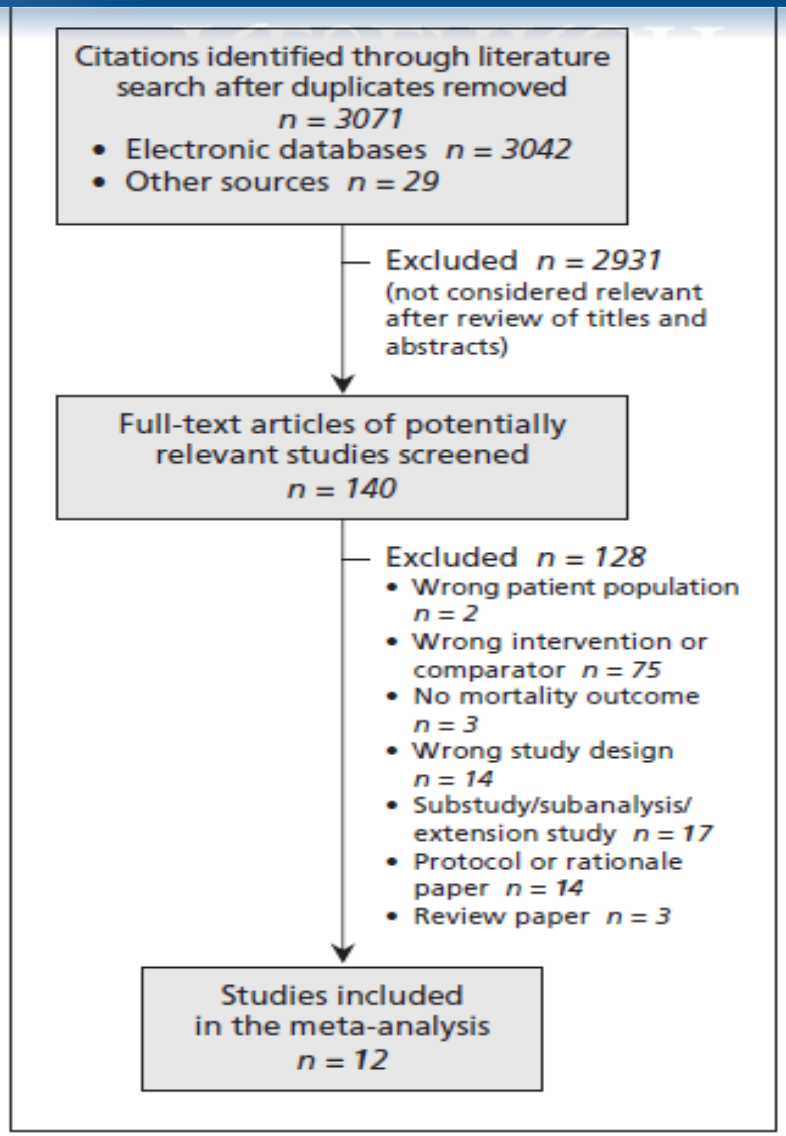


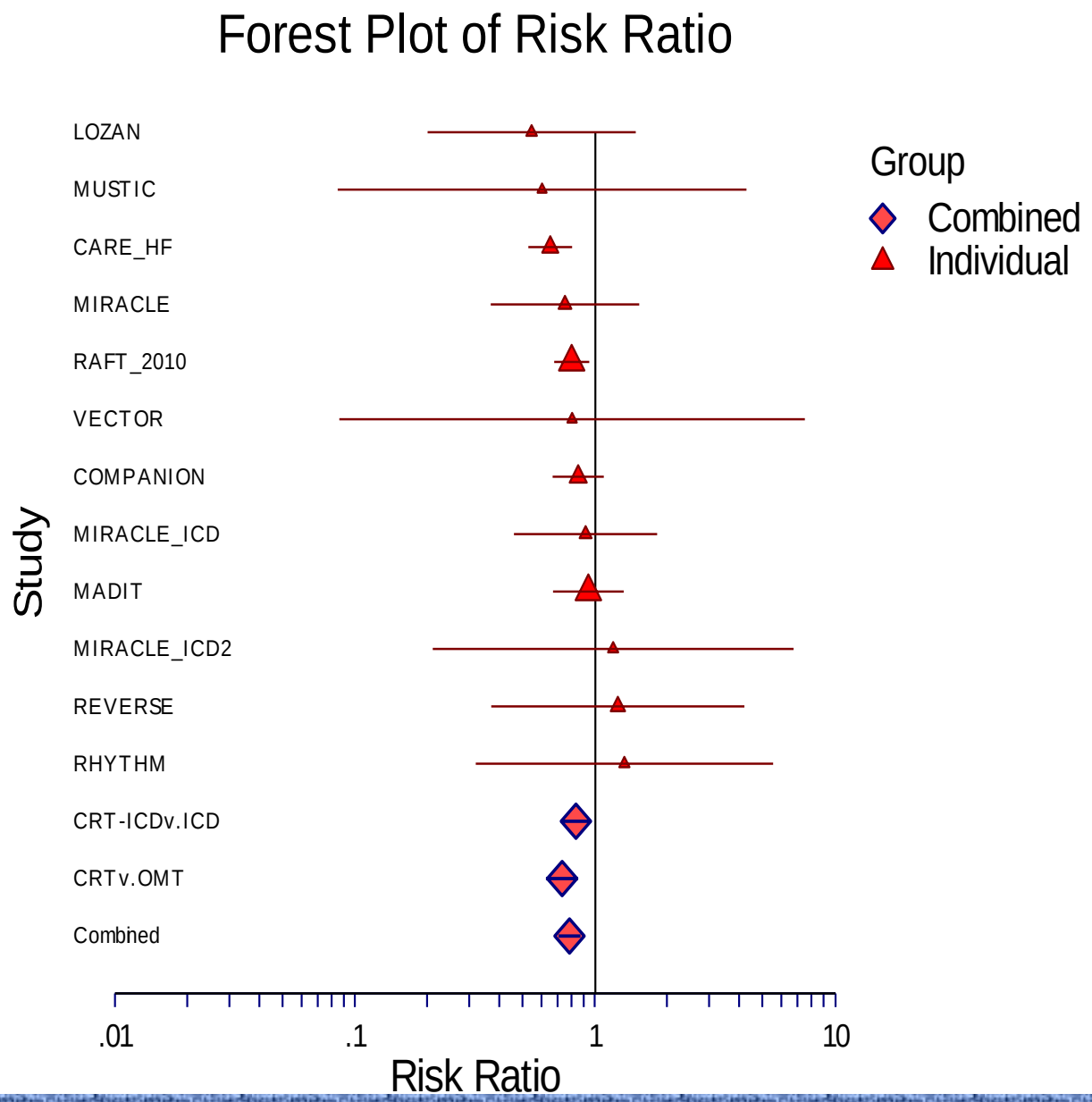

Figure 1: Flow diagram of selection of studies for the meta-analysis.

# Results…

**Table 1:** Characteristics of 12 studies included in the meta-analysis of cardiac resynchronization therapy for congestive heart failure

| Study | No. of patients in intervention/control groups;* study design | Mean length of follow-up, mo | Age, yr, mean (SD) | Male, % | Ischemic cardio-myopathy, % | Mean ejection fraction, % (SD) | QRS interval, ms, mean (SD) | NYHA class, % | AF, % | RBBB, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Lozano et al., 2000[19] | CRT-ICD/ICD (109/113); crossover | 3 | 65 (10) | 83 | 68 | 22 (0.007) | NR | I/II: 35<br>III/IV: 65 | NR | NR |
| MUSTIC, 2001[20] | CRT/OMT (29/29); crossover | 6 | 63 (10) | 75 | NR | NR | 176 (19) | I/II: 100 | NR | NR |
| MIRACLE, 2002[21] | CRT/OMT (228/225); parallel | 6 | 64 (11) | 68 | 54 | 21.7 (6.3) | 166 (20) | III/IV: 100 | 0 | NR |
| MIRACLE ICD, 2003[22] | CRT-ICD/ICD (187/182); parallel | 6 | 67 (10) | 77 | 70 | 24 (6.2) | 163 (22) | III/IV: 100 | 0 | 13 |
| MIRACLE ICD II, 2004[23] | CRT-ICD/ICD (85/101); parallel | 6 | 63 (12) | 89 | 57 | 24.5 (6.7) | 165 (24) | I/II: 100 | NR | 16 |
| COMPANION 2004[24] | CRT-ICD/CRT/OMT (595/617/308); parallel | 14.8–16.5 | 67 | 67 | 55 | 22 | 160 | III/IV: 100 | NR | 10 |
| RHYTHM-ICD, 2004[25] | CRT-ICD/ICD (119/59); parallel | 12.1 | NR | NR | NR | 24.8 (7.7) | 168 | I/II: 8<br>III/IV: 92 | 0 | NR |
| CARE-HF, 2005[26] | CRT/OMT (409/404); parallel | 29.4 | 66 | 74 | 38 | 25 | 160 | III/IV: 100 | 0 | NR |
| VECTOR, 2005[27] | CRT/OMT (59/47); parallel | 19.9 | 67.1 (9.7) | 63 | NR | NR | NR | I/II: 29<br>III/IV: 71 | NR | NR |
| REVERSE, 2008[28] | CRT-ICD/ICD (419/191); parallel | 12 | 62 (11) | 79 | 55 | 27 (7) | 153 (12) | I/II: 100 | 0 | NR |
| MADIT-CRT, 2009[29] | CRT-ICD/ICD (1089/731); parallel | 28.8 | 65 (11) | 75 | 55 | 24 (5) | 65% > 150 | I/II: 100 | 12 | 13 |
| RAFT, 2010[14] | CRT-ICD/ICD (894/904); parallel | 40 | 66 (9) | 83 | 67 | 23 (5) | 158 (24) | I/II: 80<br>III/IV: 20 | 13 | 9 |

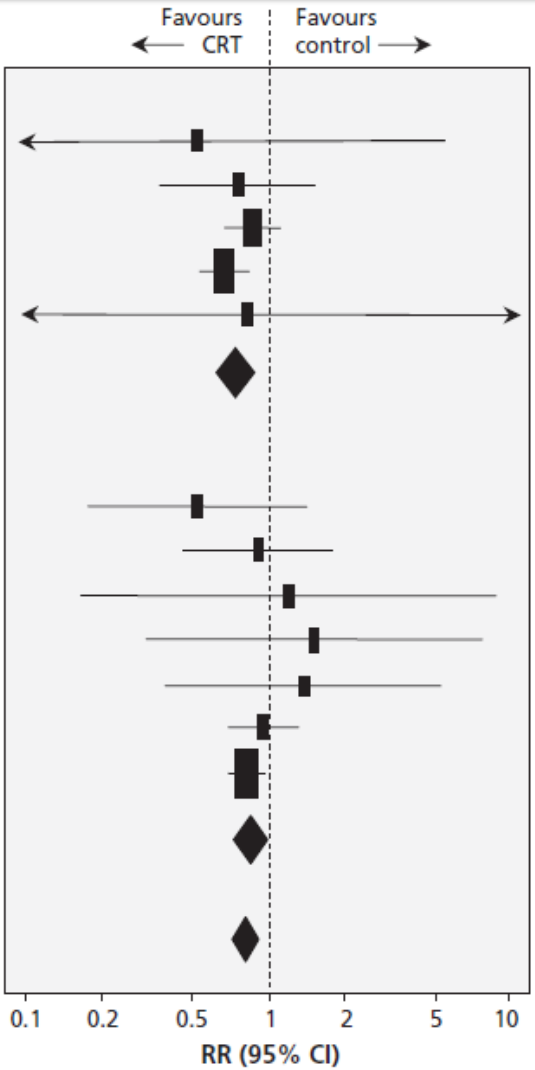
A Forest Plot



## Results..

Compared with an ICD alone, CRT + ICD significantly reduced mortality

| Study | CRT | Control | RR (95% CI) |
|---|---|---|---|
| **CRT v. OMT** | | | |
| MUSTIC, 2001[20] | 1/29 | 2/29 | 0.50 (0.05–5.21) |
| MIRACLE, 2002[21] | 12/228 | 16/225 | 0.74 (0.36–1.53) |
| COMPANION, 2004[24] | 131/617 | 77/308 | 0.85 (0.66–1.09) |
| CARE-HF, 2005[26] | 101/409 | 154/404 | 0.65 (0.53–0.80) |
| VECTOR, 2005[27] | 1/59 | 1/47 | 0.80 (0.05–12.4) |
| Subtotal | 246/1342 | 250/1013 | 0.73 (0.62–0.85) |
| $I^2 = 0$ | | | |
| **CRT-ICD v. ICD** | | | |
| Lozano et al., 2000[19] | 5/109 | 10/113 | 0.52 (0.18–1.47) |
| MIRACLE ICD, 2003[22] | 14/187 | 15/182 | 0.91 (0.45–1.83) |
| MIRACLE ICD II, 2004[23] | 2/85 | 2/101 | 1.19 (0.17–8.26) |
| RHYTHM ICD, 2004[25] | 6/119 | 2/60 | 1.51 (0.31–7.27) |
| REVERSE, 2008[28] | 9/419 | 3/191 | 1.37 (0.37–4.99) |
| MADIT-CRT, 2009[29] | 74/1089 | 53/731 | 0.94 (0.67–1.32) |
| RAFT, 2010[14] | 186/894 | 236/904 | 0.80 (0.67–0.94) |
| Subtotal | 294/2902 | 321/2282 | 0.83 (0.72–0.96) |
| $I^2 = 0$ | | | |
| Overall | 542/4244 | 571/3295 | 0.78 (0.70–0.87) |



# Interpretation

- The cumulative evidence is now conclusive that the addition of cardiac resynchronization to optimal medical therapy or defibrillator therapy significantly reduces mortality among patients with heart failure.

# Questions?

**Science is facts. Just as houses are made of stones, so is science made of facts.**

**But a pile of stones is not a house and a collection of facts is not necessarily science.**

Jules Henri Poincare (1854–1912), French scientist, author. Value of Science, D

Thank you!