Evidence-Based Decision Making In Healthcare

Systematic Reviews and Meta-Analysis

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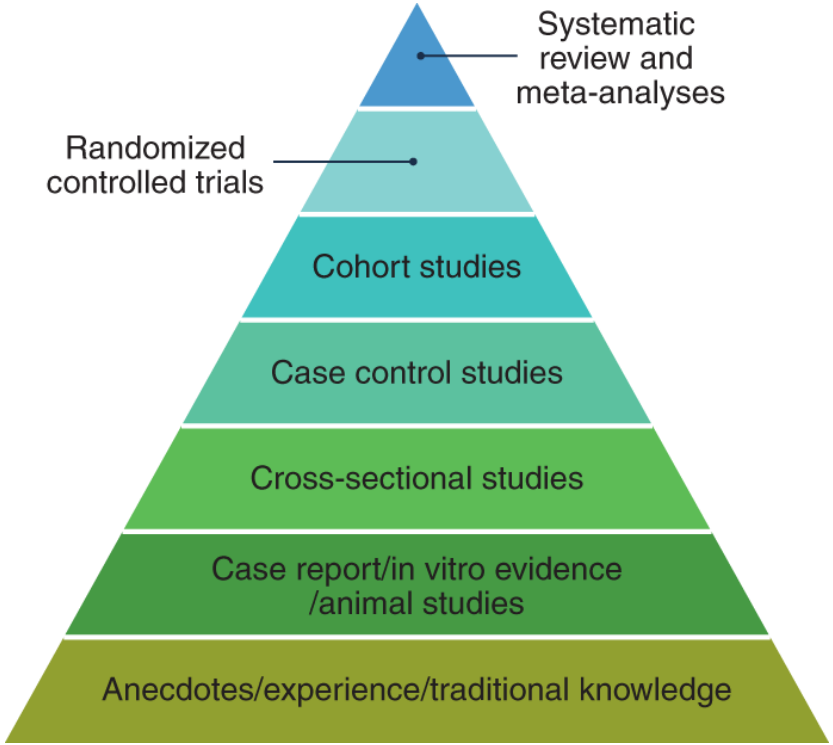
Hierarchy of Evidence



https://www.nature.com/articles/s43016-021-00388-5/figures/1

Definitions

- Systematic Review: Use of explicit, standardized methods to identify, select, and critically appraise research, and to collect and analyze data from the studies identified by the review
- Meta-analysis: Use of statistical methods to integrate results of studies identified by the systematic review to make a quantitative assessment of a test, treatment, or other health intervention

Definitions

- You can do a systematic review without doing a meta-analysis
  - Insufficient data
  - Insufficient quality of data or quality studies
  - Not relevant to the question
- You should not do a meta-analysis without doing a systematic review
- Tools for synthesizing knowledge to improve policy or practice

Example of Why These Are Important

- On Sept 30, 2004, Merck announced withdrawal of rofecoxib (Vioxx) because of increased cardiovascular risk in patients taking drug for >18 months
- Decision based on 3-year results of an (unpublished) RCT of rofecoxib for preventing colorectal polyps
- By 2004, rofecoxib had been taken by ~ 80 million people and generated ~$2.5 billion in sales

Meta-Analysis > Lancet. 2004 Dec;364(9450):2021-9. doi: 10.1016/S0140-6736(04)17514-4.

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

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Affiliations + expand

PMID: 15582059 DOI: 10.1016/S0140-6736(04)17514-4

Abstract

Background: The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods: We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

Findings: We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20742 patients) the relative risk from randomised controlled trials was 2.30 (95% CI 1.22-4.33, p=0.010), and 1 year later (64 events, 21432 patients) it was 2.24 (1.24-4.02, p=0.007). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; p=0.41) or trial duration (p=0.82). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0.86 [95% CI 0.75-0.99]) and could not have explained the findings of the VIGOR trial.

Interpretation: Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

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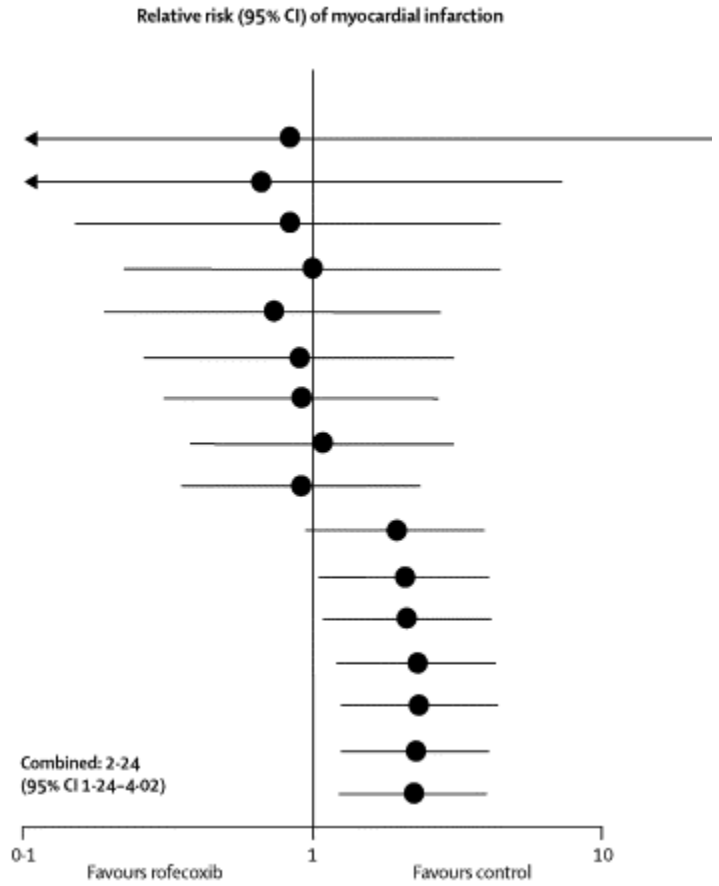
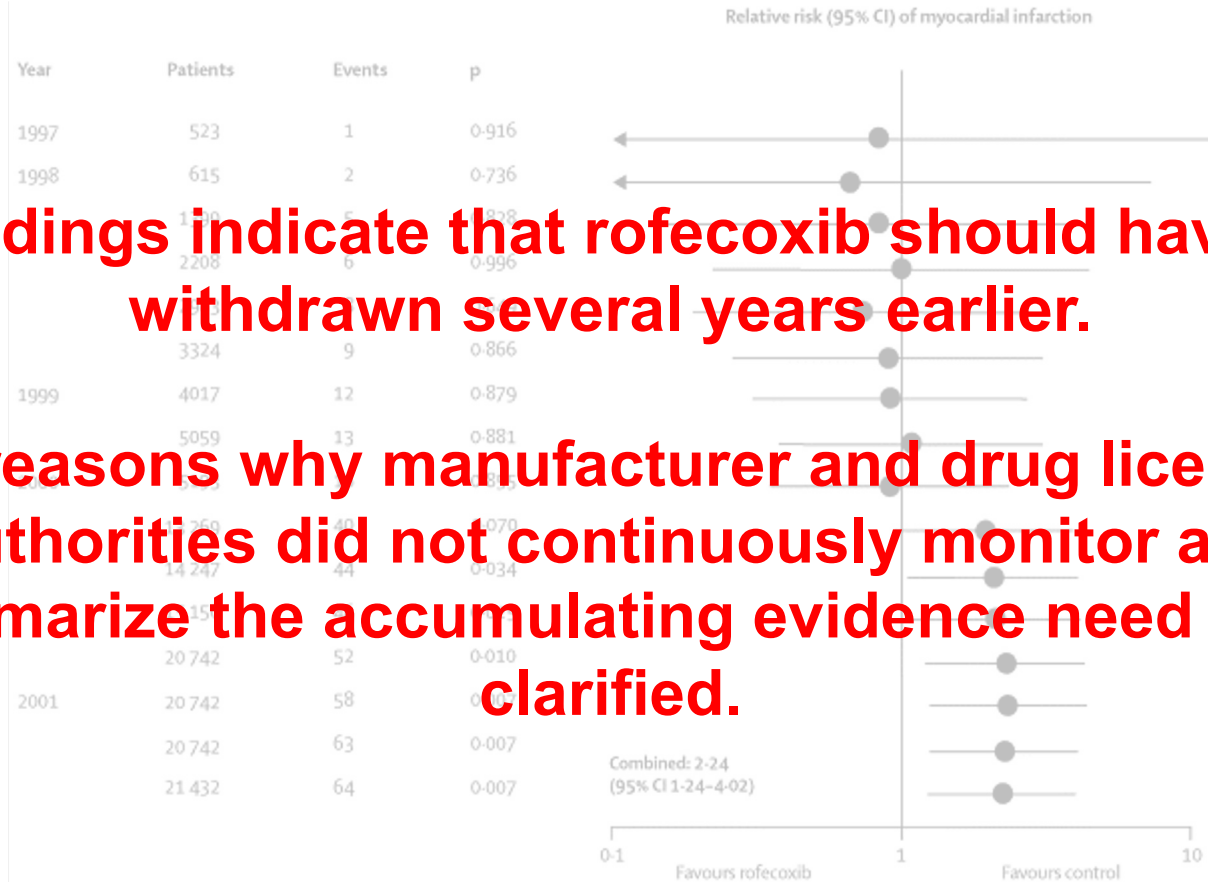
Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007





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SYSTEMATIC REVIEWS

Optimum Review

- Well-defined research question
- Standardized approach, i.e., strict protocol
- Comprehensive literature search
- Free of bias (publication bias, language bias)
- Documentation of all methods for searching and deciding what to include
- Up-to-date as possible

Define Your Research Question Well

- Population: the population to whom recommendation applies
- Intervention: the medication, vaccine, test, or action you will perform on the population
- Comparison: the alternative interventions, including doing nothing
- Outcome: beneficial outcomes (e.g., survival) and harmful outcomes

Electronic Databases: PubMed/Medline

- Includes millions of citations and abstracts from more than 4000 journals back to 1948
- Updated weekly
- Biased toward US journals

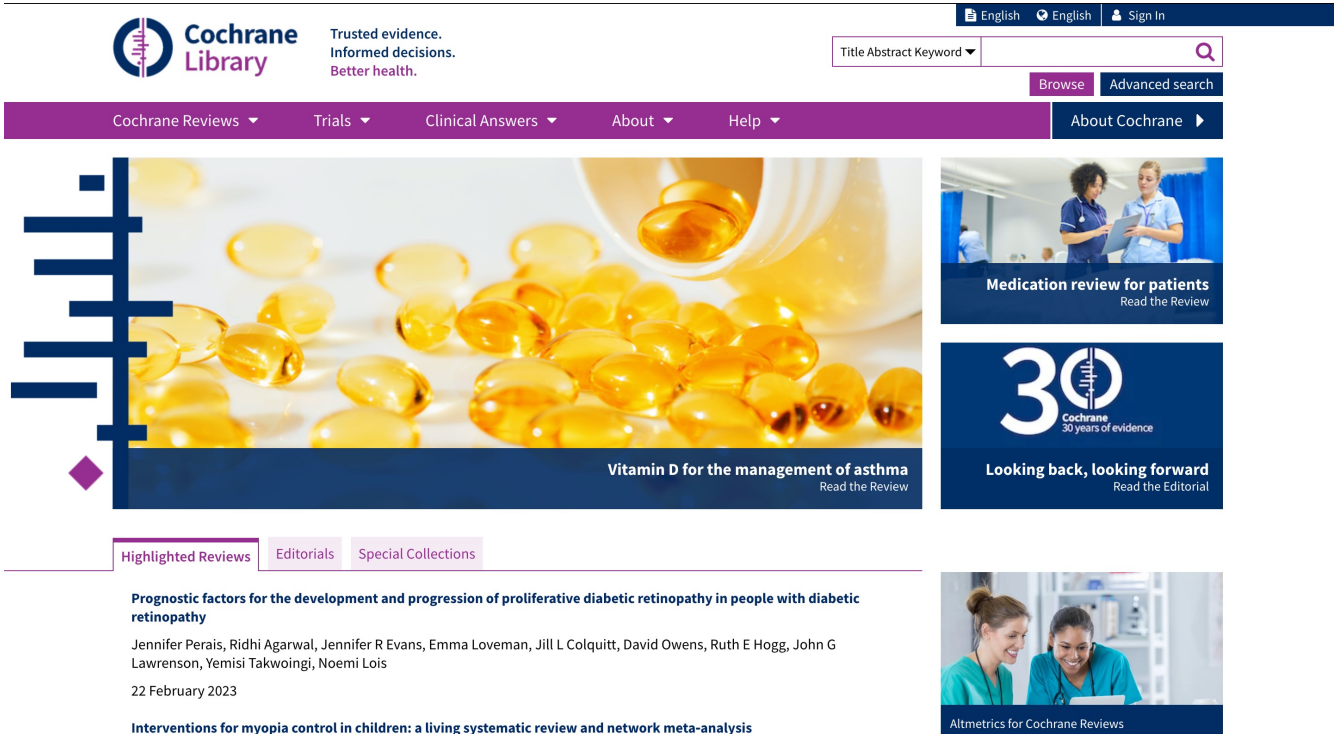
Electronic Databases: Embase

- Biomedical and pharmacological database
- >20 million records, >7000 journals, back to 1947
- Strong coverage of drug literature
- Overlap with Medline averages 34% but can vary
- More global coverage than PubMed/Medline

Electronic Databases: Cochrane Review

- Cochrane Database of Systematic Reviews
- Contains more than 4000 systematic reviews and more than 1900 protocols
- Founded in 1993 and named in honor of Archie Cochrane, who wrote in 1979, "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials”

Electronic Databases: Cochrane Review



Expand to Include Other Data Sources

- Reference lists of included studies
- References lists of earlier reviews, commentaries
- CDSR, DARE, PubMed search with filters for systematic reviews
- Personal communication with experts and authors
- Contacting drug/device companies

Expand to Include Other Data Sources

- Handsearching of key, high-yield journals
- Grey literature
- Dissertation abstracts, reports, conference proceedings, etc.
- Sources of ongoing trials
- Trial registers, drug companies, contacting experts

A suggested COSI strategy…

PubMed

Embase

Cochrane CENTRAL

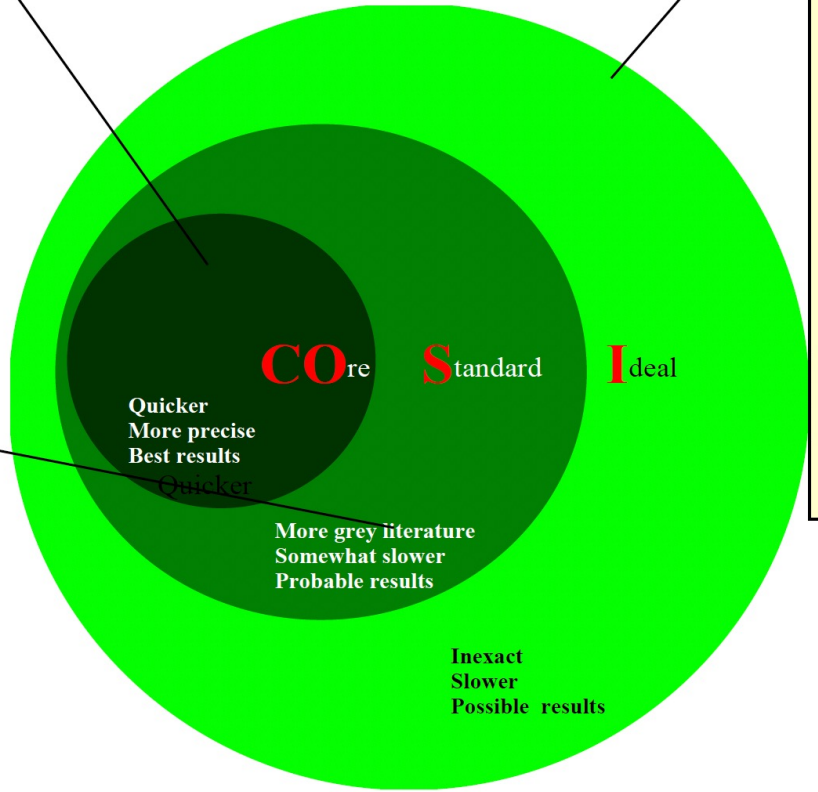
Bibliography of included studies and relevant reviews

Write to experts

Handsearch key journals

Other general databases

Subject-specific databases



Conference proceedings

Grey literature

Unpublished literature

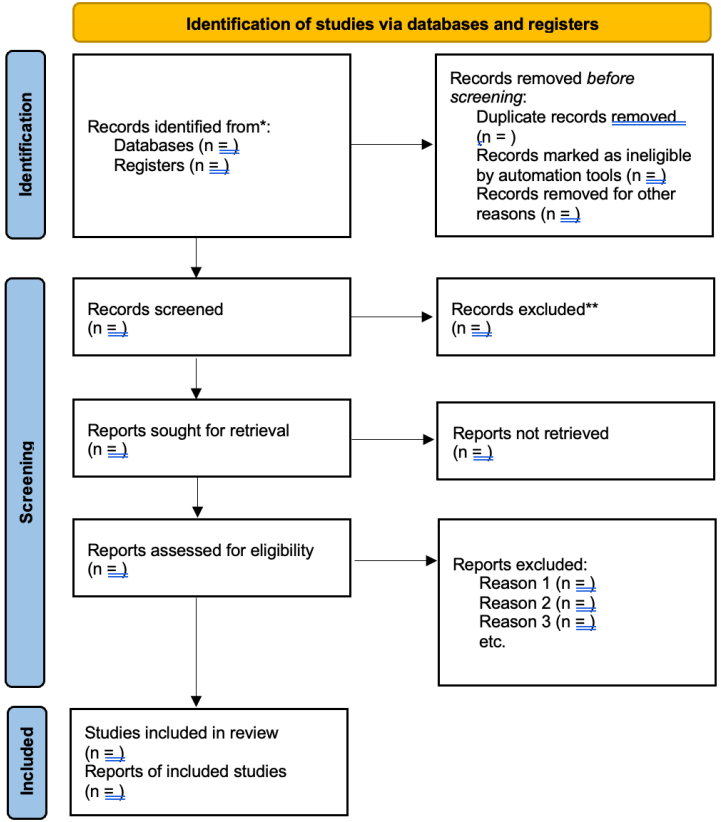
Contact companies

Ongoing trials

Figure courtesy of Madhu Pai, PhD

Managing and Documenting Search

- Use reference software
  - Reference Manager, EndNote, Zotero
- Document all articles you found, where you found them, whether you excluded them and why
- Involve a librarian!



Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Overview

- Develop a focused research question
- Define inclusion/exclusion criteria
- Select the outcomes for your review
- Find the studies
- Abstract the data
- Assess quality of the data

Overview

- Synthesize the data descriptively and inferentially via meta-analysis if appropriate
- Summarize the findings

META-ANALYSIS

Methods – The Bare Basics

- Statistical combination of results from ≥ 2 studies
- Most meta-analyses use a weighted average of the effect estimates from the different studies
- Many judgements made about what outcome to choose, how to manage missing data, how to manage differences in study designs
- Sensitivity analyses often performed to ensure results are valid

Methods – Stage 1

- Pick an outcome that applies to every study in your systematic review (e.g., death, blood pressure)
- Calculate the “effect estimate” for that outcome for each study in your systematic review
  - Called “summary statistic”

Methods – Stage 2

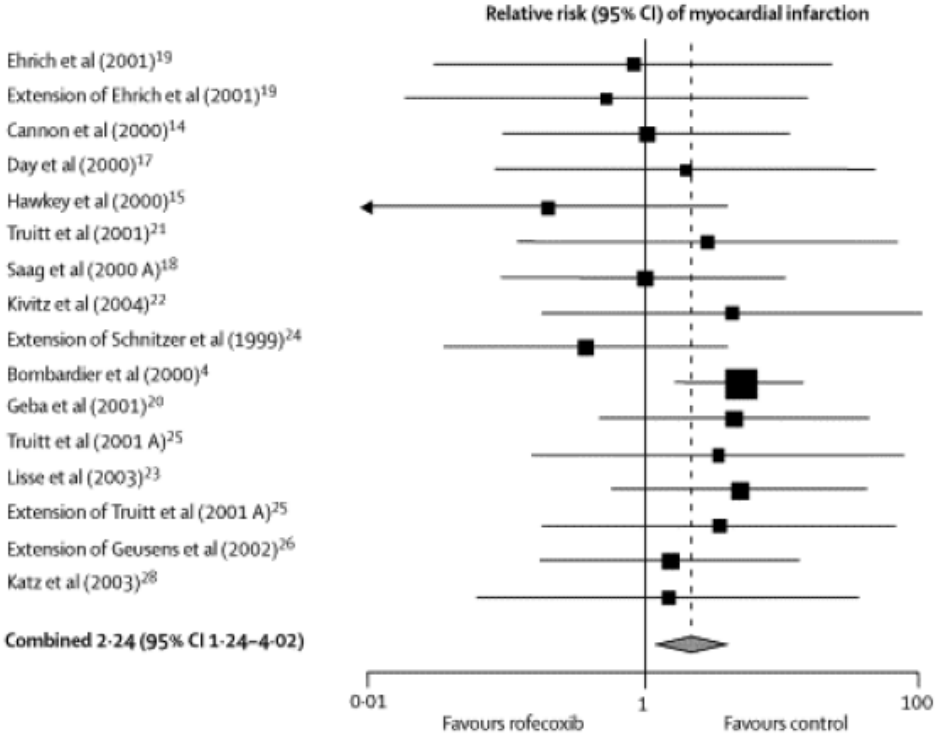
- Calculate a summary (combined) effect estimate
- A weighted average of the intervention effects estimated in the individual studies
  - Each study given a different “weight” depending on size, quality, or other factors

Methods – Stage 2

- Statistical methods to account for differences in studies (“heterogeneity”)
- “random effects model” = each study estimates the outcome differently because of differences in methods, population, or some other issue
- “fixed effects model” = each study estimates the exact same quantity/outcome in a similar way

Forest Plot

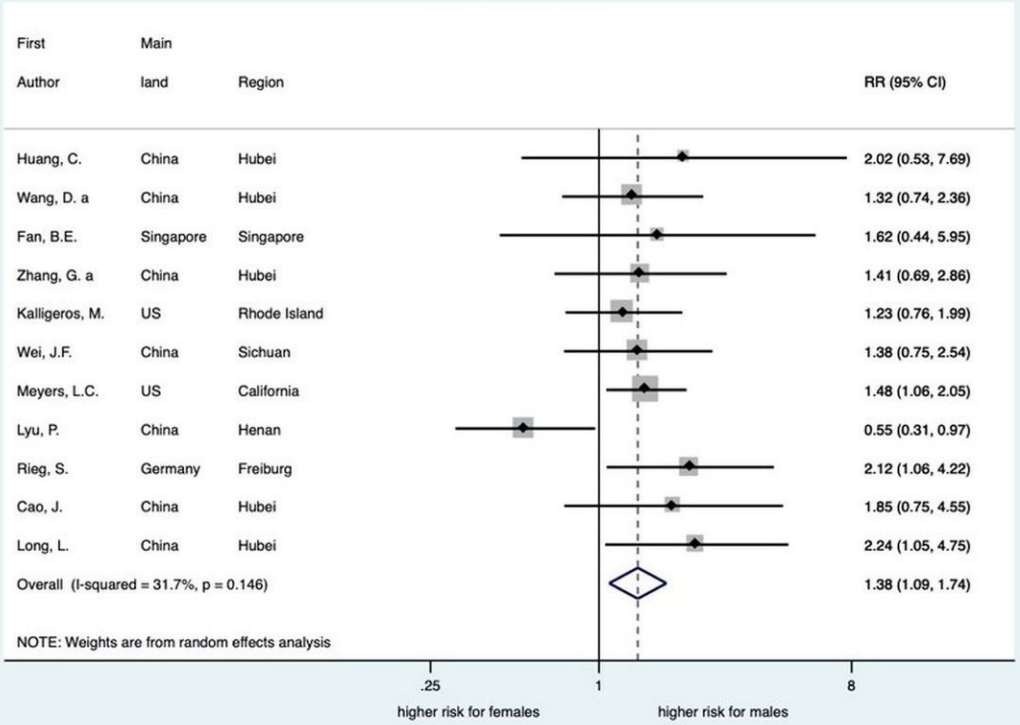
- A way to show the results of the analysis
- Show an effect estimate and confidence interval for each study and for all studies combined
- Each study represented by a block along a line
- The size of the block is bigger for studies with larger sample sizes (more weight), drawing the eye to those studies that have the biggest impact on the final meta-analysis results



Juni et al. Lancet 2004 Dec 4-10;364(9450):2021-9

Relative risk of admission to ICU in COVID-19 patients

male vs female



Pijls, et. al, http://dx.doi.org/10.1136/bmjopen-2020-044640

Challenge of “Heterogeneity”

- Variation in results between studies
- Could be due to random chance if all studies conducted identically
- More often due to differences in study population, design, or analysis methods

Challenge of “Heterogeneity”

- Forest plot
  - Do confidence intervals for studies NOT overlap?
- Calculate I^2 (“I squared”)
  - Ranges ranging from 0-100%,
  - Greater the I^2 = more heterogeneity.
  - $I^2 < 40\%$ likely studies similar
  - $I^2 > 75\%$ studies very dissimilar (heterogeneous)

A Meta-Analysis May Mislead

- Review not systematic, eg, missing important studies
- Review includes low quality studies, eg, those that are small and inconclusive
- Review does not adjust for study quality
- Methods of combining results flawed
- Publication bias (to be discussed in future lecture)