Why & how meta-analysis?

Olaf Dekkers/Sønderborg/2016

Why meta-analysis?

Meta-analysis

	Number of meta-analyses
1985-1989	460
1990-1994	2510
1995-1999	5160
2000-2004	10220
2005-2009	21200
2010-2014	38800

PubMed survey

Meta-analysis: "…"

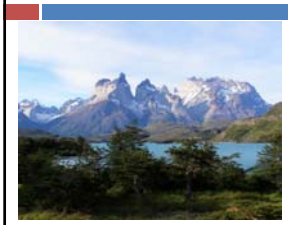
"Meta-analysis = Grade A evidence"

"Lies, damned lies and meta-analysis"

"Meta-analysis = exercise in meta-silliness"

"When you don't know what to do with your life, do a meta-analysis!"

Why meta-analysis?

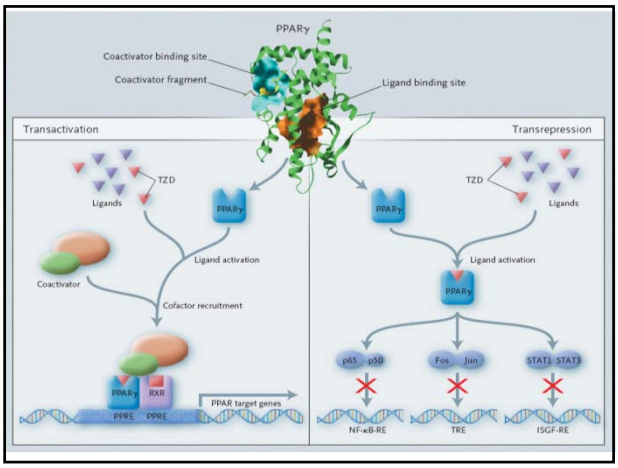


Why meta-analysis I

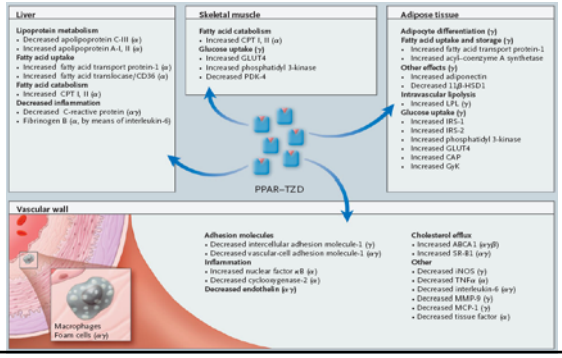
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

NEJM 2007;356;24



Why meta-analysis I



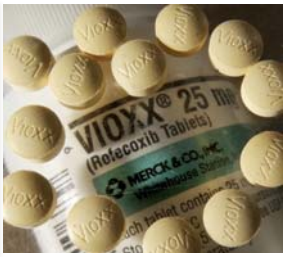
Why meta-analysis I

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

NEJM 2007:356;24

Why meta-analysis II



Why meta-analysis II

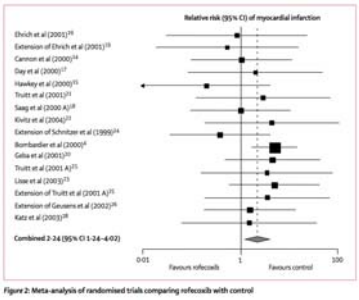


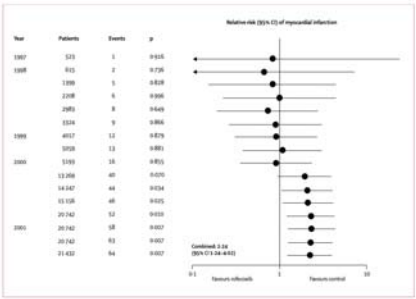
Figure 2: Meta-analysis of randomised trials comparing rofecoxib with control

Lancet 2004;364

Why meta-analysis II

1997

2001



Lancet 2004;364

Why meta-analysis II

Merck was indeed fully aware of Vioxx's potential risks by 2000. Investigations by the Wall Street Journal have revealed e-mails that confirm Merck executives' knowledge of their drug's adverse cardiovascular profile—the risk was "clearly there", according to one senior researcher. Merck's marketing literature included a document intended for its sales representatives which discussed how to respond to questions about Vioxx—it was labelled "Dodge Ball Vioxx".

Lancet editorial, 4-12-2004

Why meta-analysis?

Because it can give a clear and quantitative overview that trumps individual studies

Why meta-analysis III

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death by end of trial	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 high risk patients	1	445	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.20, 0.46]
1.2 low risk patients	1	315	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.23, 1.39]
1.3 all patients	6	6782	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]

Cochrane Database 2007

Why meta-analysis III

Comparison 1. INTERCESSORY PRAYER versus STANDARD CARE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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Cochrane Database 2007

Effect of intercessory prayer

Effects of remote, retroactive intercessory prayer on outcomes in patients with bloodstream infection: randomised controlled trial

Leibovici 2001

Methods	Allocation: Randomised (random number generator to split the two groups and then coin toss to decide allocation). Blindness: double Duration: until discharge.
Participants	Diagnosis: Blood stream infection 1990-1996 N=3,393. Age: mean- 72 years. Sex: 1785M, 1608F History: hospitalised.
Interventions	1. Intercessory prayer : standard medical care + IP (one short daily prayer for entire group) . N=1691. 2. Standard medical care. N=1702.
Outcomes	Death. Leaving the study early. Unable to use Clinical state: duration of fever (no mean, SD). Service use: length of hospital stay (no mean, SD).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Effect of intercessory prayer

In July 2000 a random number generator (Proc Uniform, SAS, Cary, NC, USA) was used to randomise the patients into two groups. A coin was tossed to designate the intervention group. A list of the first names of the patients in the intervention group was given to a person who said a short prayer for the well being and full recovery of the group as a whole. There was no sham intervention.

BMJ 2001;323

Effect of intercessory prayer

The purpose of the present study was to study the effect of prayer on bloodstream infection. As we cannot assume a priori that time is linear, as we perceive it, or that God is limited by a linear time, as we are, the intervention was carried out 4-10 years after the patients' infection and hospitalisation. The hypothesis was that remote, retroactive intercessory prayer reduces mortality and shortens the length of stay in hospital and duration of fever.

BMJ 2001;323

Why meta-analysis IV

Quadriphasic versus monophasic oral contraceptives for contraception (Review)

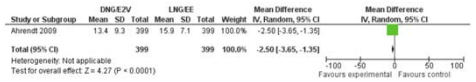
Van Vliet HAAM, Raps M, Lopez LM, Helmerhorst FM

THE COCHRANE COLLABORATION®

Cochrane 2011

Why meta-analysis IV

Figure 3. Forest plot of comparison: 1 3 mg E2V on days 1-2, 2 mg DNG/2 mg E2V on days 3-7, 3 mg DNG/2 mg E2V on days 8-24, 1 mg E2V on days 25-26 and placebo on days 27-28 versus 100 μg LNG/20 μg EE on days 1-21 and placebo on days 22-28, outcome: 1.24 Number of bleeding/spotting days in reference period 2.



Meta-analysis over the edge….

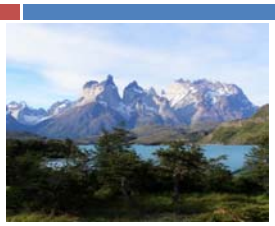
But sometimes meta-analytic methods push data too hard….

The discussion

"From a scientific perspective, the a priori likelihood that prayer could be effective is very small, as it involves three assumptions that are all unlikely to be true. First, the existence of God; second that prayer can somehow travel in space and reach this God, or that it works through another mechanism unknown to science; third that God is responsive to prayer and can influence at a distance what would otherwise have happened."

J Neg Res Biomed 2009;8

Why meta-analysis?



Why meta-analysis

- Transparant way to describe and report evidence
- Prevents selective use of literature
- Increases precision

- Bottomline: as long as you can defend what you do

How meta-analysis?

Meta-analysis

Meta-analysis is a standardized and quantitative approach to review and assess the literature, where the unit of observation is the individual study

Meta-analysis

1. Well defined research question
2. Searching the literature
3. Selection of the literature
4. Risk of bias assessment
5. Data extraction
6. Data synthesis
7. Publication/manuscript

Meta-analysis

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2. Searching the literature
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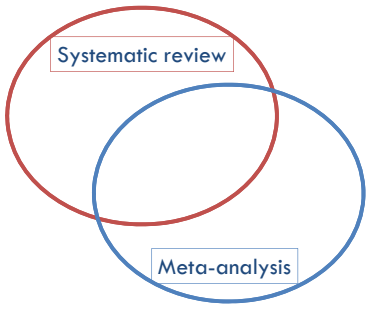
Systematic review

Meta-analysis

Systematic review & meta-analysis



I. Research question

I. Research question

- Definition of
  - Population
  - Intervention/exposure
  - Control group
  - Outcome(s)
  - Study design

I. Research question

Broadly defined etiologic question

Treatment effect in specific population

I. Research question

- If the research question is very specific
  - You may end up with few studies only
- If the research question is not well defined:
  - You may end up with too much articles in your search
  - In- and exclusion criteria will not be well-defined

II. Search strategy

II: Search strategy

- Based on research question
- *In cooperation with trained librarian*
- Check the results of your search strategy
- Document the search to facilitate updates and transparency

- There is no single best search!
- But: search should be defendable

Search string

- ("Adrenal Insufficiency"[Mesh:NoExp] OR "adrenal insufficiency"[all fields] OR "adrenal insufficiencies"[all fields] OR "adrenal insufficient"[all fields] OR "Addison Disease"[Mesh] OR "Addison Disease"[all fields] OR "Addison's Disease"[all fields] OR "Addisons Disease"[all fields] OR (("hypothalamic-pituitary-adrenal axis"[all fields] OR "hypothalamo-pituitary-adrenal axis"[all fields] OR "hypothalamic-pituitary-adrenal axes"[all fields] OR "hypothalamo-pituitary-adrenal axes"[all fields] OR "hpa-axis"[all fields] OR "hpa-axes"[all fields]) AND ("insufficiency"[all fields] OR "suppression"[all fields])) OR "adrenocortical insufficiency"[all fields] OR "adrenal cortex insufficiency"[all fields] OR "adrenal failure"[all fields])

II: Search strategy

- **Sources:**
  - Electronic databases:
    - Cochrane Library
    - Medline, Embase, PsychLit
    - Science Citation Index
  - Hand search/Google
  - Snowballing/Reference lists
  - Registers
  - Personal communication (authors, experts)
  - Companies

Sources of literature: an example

- 42 studies included
  - 5 studies from FDA registers for approval (N=1967)
  - 35 studies from the GSK register, of which 26 unpublished (N=9502)
  - DREAM and ADOPT (N=4091)

NEJM 2007;356;24

II: Why different databases?

Medline

- Produced in US
- 1966 to date
- 52% of journals covered are published in US
- Covers 5300 journals in 40 languages
- MeSH

Embase

- Produced in Europe
- 1980 to date
- 33% of journal covered are from North America
- Covers 3500 journals from 70 countries
- EMTREE

Overlap approx 40% (10-80% depending on topic)

II Search strategy cancer & alcohol

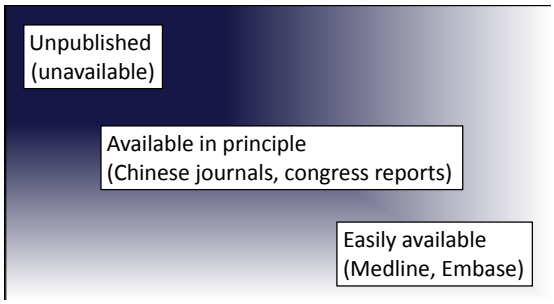
Database	Sensitivity breast cancer	Unique papers breast cancer	Sensitivity colon cancer	Unique papers colon cancer
Biosis	78%	3	66%	4
Embase	81%	2	61%	1
ETOH	72%	0	61%	2
Medline	65%	1	66%	2
Total		11		15

Lemeshow JCE 58;867-873

II: Search strategy

- Restriction:
  - Methods filter?
    - Works well for RCTs
  - Time?
    - Can safe time and effort
  - Full publications? Meeting abstracts?
  - Language?
    - Chinese articles often not included in standard databases

II: Search strategy



II: Search strategy

Potential bias

- **Publication bias:** studies with significant positive results are more likely to get published
- **Time lag bias:** studies with significant results are published more rapidly
- **Language bias:** results from studies in non-English journals may differ from results in English journals
- **Multiple publication bias:** studies with significant results are more likely to be published twice
- **Citation bias:** studies with significant results are more likely to be cited

Language restriction

	German Articles (40)	English Articles (40)
Parallel/cross over	29/11	29/11
Placebo/standard/no treatment	13/23/4	18/19/3
Mean sample size	63	59
Double/single-blind/open label	18/2/13	22/2/14

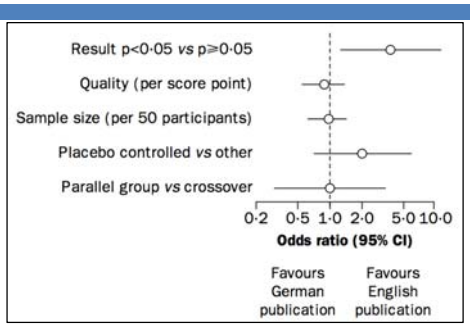
Lancet 1997;350:326-29

Language restriction

	German Articles (40)	English Articles
P>0.05	65%	38%
0.01<p<0.05	20%	38%
P<0.01	15%	24%

Lancet 1997;350:326-29

Language restriction



Lancet 1997;350:326-29

II: Search strategy

- Concluding remarks
  - There is no single best search strategy
  - Perform a search with a trained librarian
  - Be transparant and state your choices
  - Iterate if the ratio noise-eligible articles is too large

III. Literature selection

III: Literature selection

- 'Follows' from inclusion criteria and search
- Track record of excluded studies (with reason)
  - For the final report
  - In case of redefinition of eligibility criteria

Literature selection: flow-chart

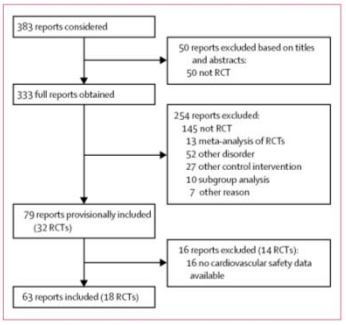


Figure 1: Identification of eligible randomised controlled trials (RCTs)

Literature selection: An example

Background

Tests for thrombophilia are being performed on a large scale in people after venous thromboembolism (VTE) even though the benefits of testing are still subject to debate. The most important benefit would be a reduction in the risk of recurrent VTE due to the use of additional prophylactic measures.

Objectives

The objective of this review was to assess the benefit of testing for thrombophilia after VTE in terms of risk reduction of recurrent VTE.

Search strategy

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Trials Register (last searched 15 October 2008) and CENTRAL (last searched *The Cochrane Library* 2008, Issue 4). We searched MEDLINE, EMBASE, and reference lists.

Selection criteria

Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that compared the rate of recurrent VTE in participants with VTE who were tested for thrombophilia with the rate in participants with VTE who were not tested were eligible.

Cochrane 2009

Literature selection: An example

Main results

No studies were included because no RCTs or CCTs could be identified.

Cochrane 2009

IV. Risk of bias

IV: Risk of bias assessment

- Central for every SR and MA
- Assessment of internal validity
  - Assessment at study level
  - How likely are the results of individual studies biased?
- Does not account for publication bias
- External validity
  - Is about generalizability
  - Discussion section

IV: Risk of bias assessment in RCTs

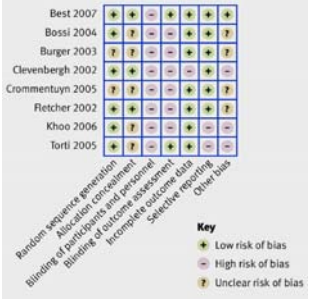
Type of bias	Source of bias
Confounding bias	1. Random sequence generation 2. Concealment of allocation
Performance bias	Blinding of participants and personnel
Detection bias	Blinded outcome assessment
Attrition bias	Incomplete outcome data
Reporting bias	Selective outcome reporting

BMJ 2011;343

IV: Risk of bias assessment in RCTs

- Careful consideration of design elements that could bias effect estimates
  - Noninferiority trials: ITT vs per protocol
  - Side effects: ITT vs per protocol
- Nothing against adding an additional design element

IV: Risk of bias assessment in RCTs



IV: Risk of bias assessment in RCTs

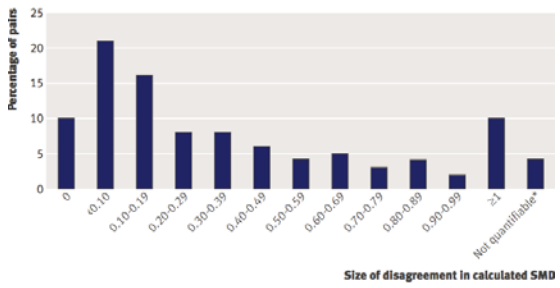
- How to deal with risk of bias?
  - Exclude high risk studies
  - Sensitivity analysis
  - Meta-regression
  - (Aggregate scores)
  - (Scales)

V. Data extraction

V: Data extraction

- Predefined forms
- Pilot
- Data at group level vs subgroup level
- Two data extractors is standard
- Always more difficulties than hoped/expected (for observational studies)

Disagreement between extractors



BMJ 2009;339

Disagreement between extractors

Different choices regarding:	
Groups, pooling, splitting	15
Timing	9
Scales	6
Different calculations or imputations	6
Dropouts	4
Use of change from baseline or values after treatment	4
Individual patient data	1
Exclusion of trials because:	
Did not meet protocol inclusion criteria	14

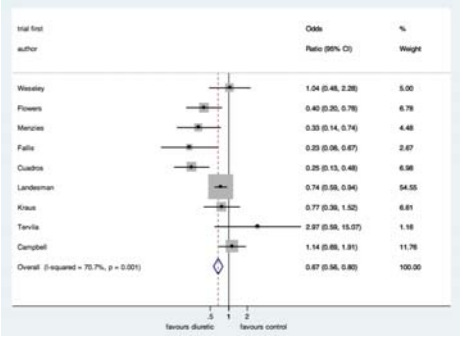
BMJ 2009;339

VI. Data synthesis

VI: Data synthesis

- To pool or not to pool?
  - Clinical heterogeneity
  - Outcome heterogeneity
  - Low quality data
  - Statistical heterogeneity
  - Nothing to pool

Forest plot



Forest plot