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Systematic reviews and meta-analyses

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Learning outcomes

- To understand the need for conducting systematic reviews and meta-analyses.
- To appreciate the potential biases and limitations of systematic reviews and meta-analyses.
- To be able to interpret the findings presented in published systematic reviews and meta-analyses.
- To be able to critically appraise published systematic reviews and meta-analysis.

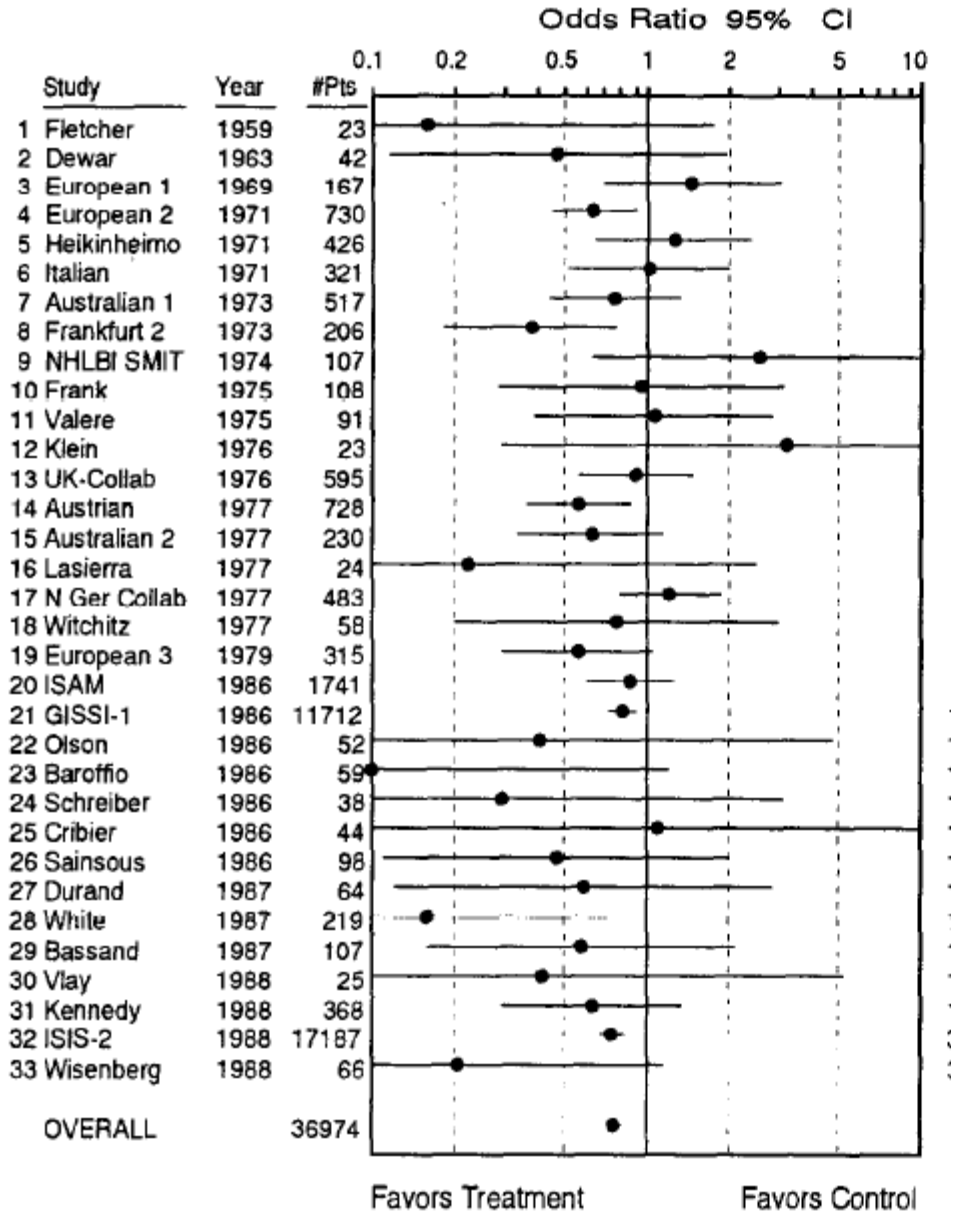
Systematic reviews of all the relevant evidence

Readers of reports of research want answers to four questions:

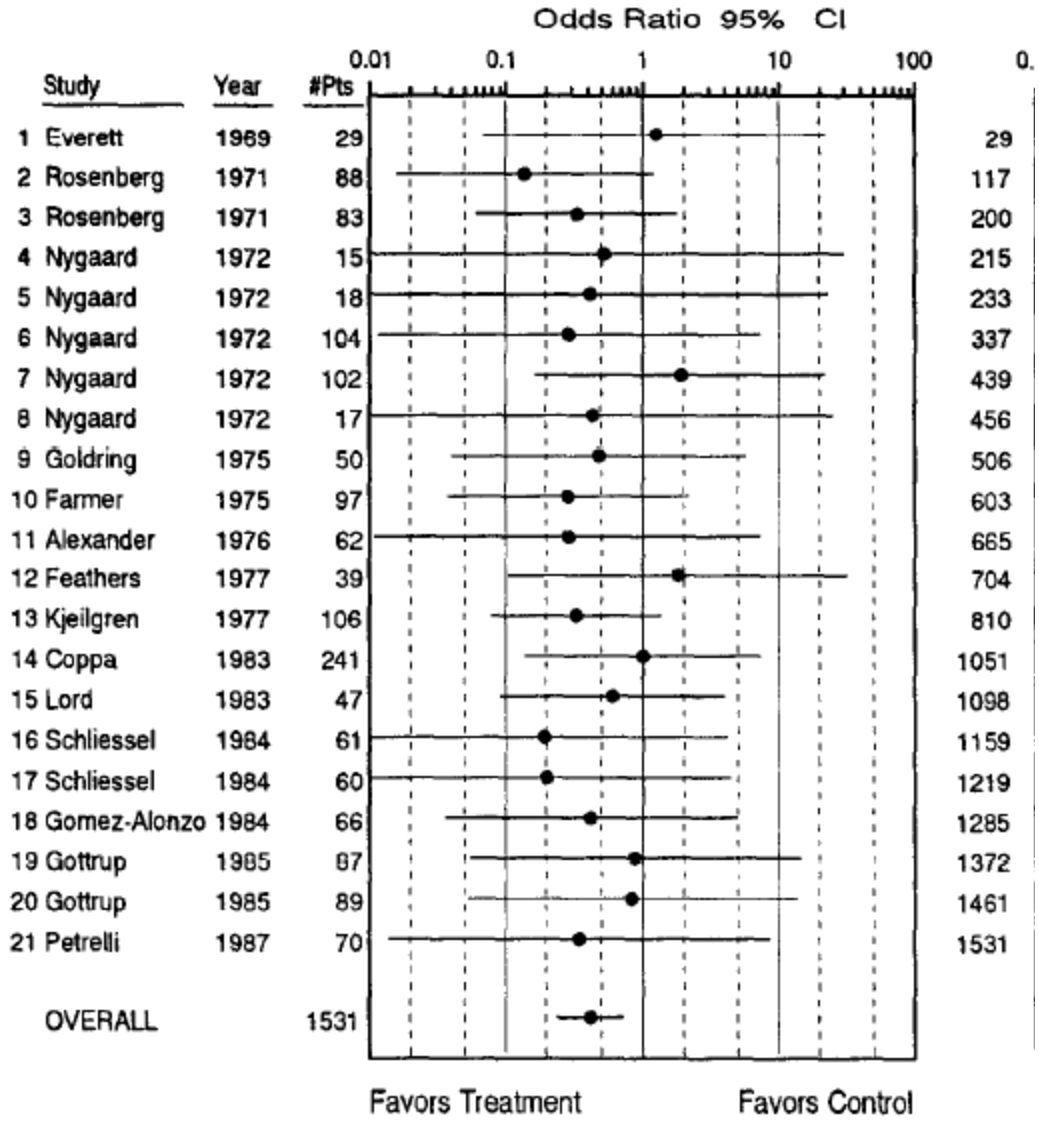
- Why did you start?
- What did you do?
- What did you find?
- What does it mean?

For a reliable answer to the question 'What does it mean?', it is needed to careful assess all the evidence from studies that have addressed the question concerned

Cumulative meta-analysis : Clinical trials of intravenous streptokinase for acute myocardial infarction



Clinical trials of antibiotic prophylaxis for colorectal surgery and perioperative deaths



Systematic Review

‘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 collection glossary (www.cochrane.org)

cochrane

THE COCHRANE COLLABORATION®

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A-Z index | help

- search -

site | reviews

Start planning for the next Cochrane Colloquium!
Dublin, Ireland
23-26 October 2006

What's new

Issue 1, 2006 of *The Cochrane Library* is now online:
[browse free summaries by topic]

[read press releases]
[login for full text reviews]

TamiFlu review featured in *The Lancet*. *[read more]*

Cochrane reviews are now appearing on ISI! *[read more]*

See also:
- *Opportunities page*
- *Calendar*
- *Newsroom*

Evidence Aid: Resources for natural disasters and other healthcare emergencies

The Cochrane Collaboration is an international not-for-profit organisation, providing up-to-date information about the effects of health care. *[learn more]*

Information for *Newcomers*

The Cochrane Library contains regularly updated evidence-based healthcare databases. *[browse systematic reviews]* Now available in a new interface at Wiley InterScience!

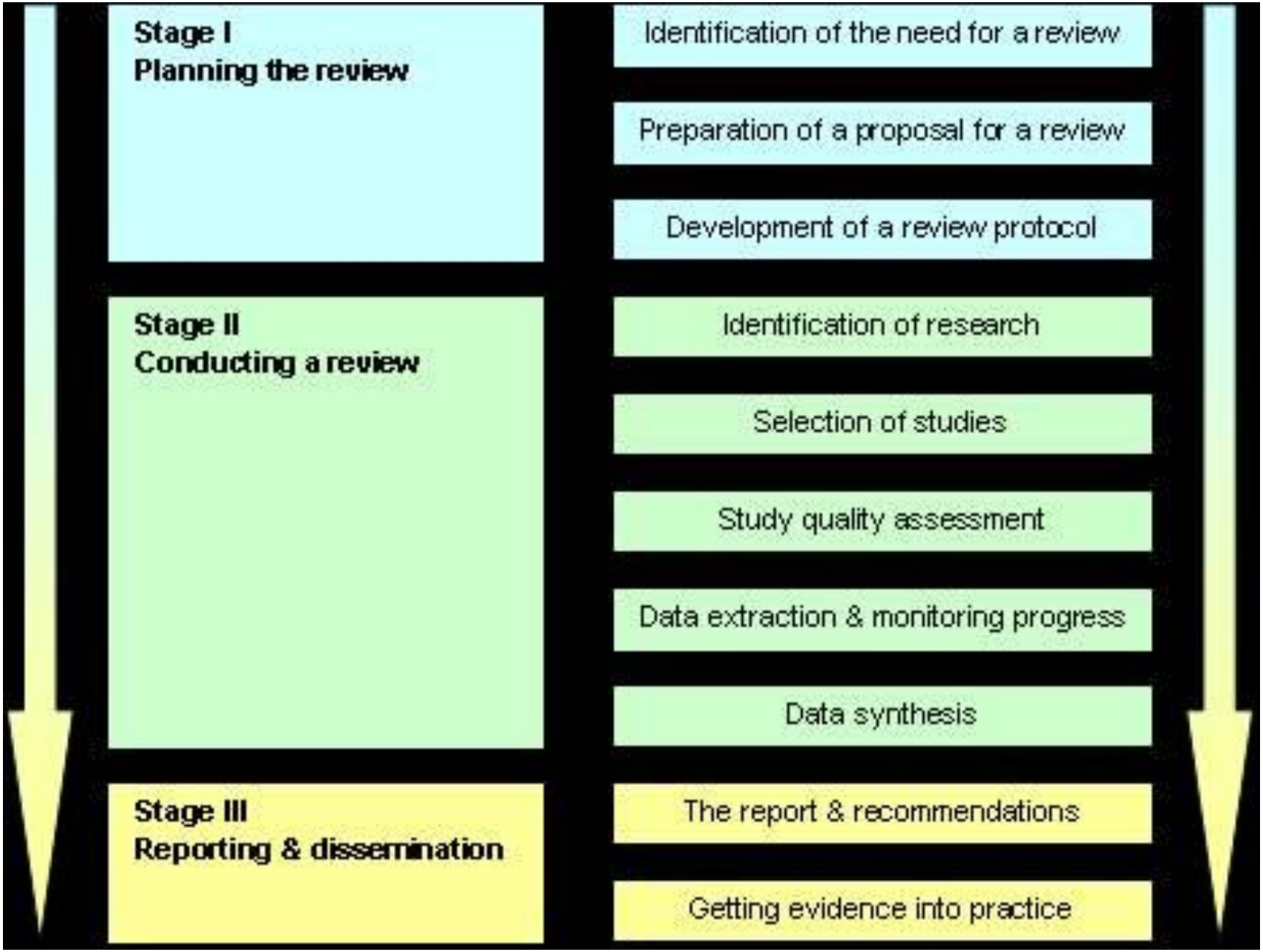
See how we've grown: Cochrane's *publication history*

Administrative resource page - Cochrane internal
(for staff & review authors)

For the media...
(what you need to write the story)

Importance of systematic reviews

- Health care providers, researchers, and policy makers are inundated with unmanageable amounts of information
  - need systematic reviews to efficiently integrate existing information
  - provide data for rational decision making
- Students: exams, dissertation, thesis, mini-projects, other reports



Undertaking Systematic Reviews of Research on Effectiveness

CRD Report Number 4 (2nd Edition), *March 2001*



Interventions for preventing or treating alcohol hangover: systematic review of randomised controlled trials

Pittler et al, BMJ 2005;331;1515-1518

Interventions for alcohol hangover reported on the internet*

Aspirin

Bananas

Barley grass

Berocca containing vitamin B complex, vitamin C, calcium

Blend containing cardamom, amomum, tangerine peel, citrus peel, ginseng, atractylodes, poria, massa fermenata, dried ginger, polyporus

Bloody Mary (that is, alcoholic drinks)

Cabbage

Calcium carbonate

Charcoal tablets

Chaser (that is, alcoholic drinks)

Coffee

Cysteine

Eggs

Exercise

Fresh air

Fruit juice

Ginseng

Glutamine

Green tea

Ibuprofen

Ice pack

Kidney dialysis

Milkshake

Multivitamins

Paracetamol

Pizza

Russia Party

Shower

Sleep

Sob'r-K HangoverStopper

Succinic acid

Vegemite on toast

*Results from the first 20 websites retrieved by Google.com with the search term “hangover cure” (accessed 20 Jan 2005).

Stage I - Planning the review

Need to specify the question to be addressed, usually framed around:

- The population
- The exposure/intervention
- The outcomes
- The study designs

Example: Interventions for preventing or treating alcohol hangover: systematic review of randomised controlled trials

Pittler et al, BMJ 2005;331;1515-1518

Stage I - Planning the review:

- The population : None specified
- The exposure/intervention
  - Any medical intervention for preventing or treating alcohol hangover
- The outcomes: Alcohol induced hangover
- The study designs: Randomised controlled trials that were placebo controlled or controlled against a comparator intervention.

Stage II - Identification of research

- Clearly defined search criteria

  MeSH (Medical Subject headings) and free text words in combination with Boolean operators

- Search the published medical literature

  Electronic databases such as Cochrane Central Register of Trials, Medline, EMBASE

- Search other sources
  - Reference lists/citation searches
  - Conference proceedings/grey literature
  - Contacting established researchers in the field to identify unpublished studies.

Example: Interventions for preventing or treating alcohol hangover: systematic review of randomised controlled trials
Pittler et al, BMJ 2005;331;1515-1518

Stage II - Identification of research

- Search criteria: Hangover OR (Alcohol AND hangover) OR (Hangover cure)
- Searched published literature:
  - Medline/ Embase/ Amed / the Cochrane Library /the National Research Register (UK) /ClincalTrials.gov (USA)
- Other literature
  - Hand searched conference proceedings, bibliographies of all retrieved articles.
  - Contacted six manufacturers of commercial preparations for alcohol hangover and five experts on the subject and asked them to contribute further studies

Stage II - Selection of studies

- Eligibility/Inclusion criteria may be based on*:*
  - Study design
  - Year of study
  - Publication language
  - Sample-size/precision
  - Specific exposure/intervention
  - Specific outcome
  - Completeness of information

Example: Interventions for preventing or treating alcohol hangover: systematic review of randomised controlled trials
Pittler et al, BMJ 2005;331;1515-1518

Stage II - Selection of studies

Eligibility/Inclusion criteria*:*

- Randomised controlled trials that were placebo controlled or controlled against a comparator intervention
- Any year of publication
- Published in any language
- With any medical intervention for preventing or treating alcohol hangover.

Stage II - Study quality assessment

- May be assessed according to recognized or user-defined criteria

  e.g. Cochrane Handbook for Systematic Reviews of Interventions
  http://www.cochrane.dk/cochrane/handbook/hbook.htm

- Quality criteria should assess various biases in study design:
  - Selection bias
  - Measurement bias (in exposure and/or outcome assessment)
  - Attrition bias/loss to follow-up

- Preferably assessed before study results known, and ideally assessed independently by more than one assessor.

Example: Interventions for preventing or treating alcohol hangover: systematic review of randomised controlled trials
Pittler et al, BMJ 2005;331;1515-1518

Stage II - Study quality assessment

Jadad score:

- Is the study randomised?
- Is the study double blinded?
- Is there a description of withdrawals?
- Is the randomization adequately described?
- Is the blindness adequately described?

Stage III - Reporting and dissemination

- Study details tabulated in a meaningful way.
- Should include details of:
  - the populations
  - the interventions/exposure
  - the outcomes
  - the study design
- Often includes a summary of findings.

Stage III - Reporting

Randomised controlled trials of interventions for alcohol hangover

First author	Design; Jadad score	Alcohol challenge	Intervention (brand name)	Dose and regimen	Control; duration	No randomised/No analysed	Main outcome measure	Main result	Adverse events in intervention group (cases)	Control of lifestyle factors
Moesgaard[25]	Parallel, double blind; 3	140-160 ml	γ linolenic acid from *Borago officinalis* (Bio-Glandin 25)	1000 mg before alcohol challenge	Placebo; 1 day	40/18 healthy volunteers	Overall hangover symptom score	Intergroup difference (P<0.01)	Not reported	Participants were recruited at a private party; no restrictions on food and drink reported
Pittler[26]	Crossover, double blind; 5	1.2 g/kg BW	*Cynara scolymus* extract LI120 (Cynara Artichoke)	960 mg before and after alcohol challenge	Placebo; 1 day	15/15 healthy volunteers	Overall hangover symptom score	No intergroup difference (P>0.05)	Redness in the face (1)	A meal was taken before alcohol challenge
Wiese[27]	Crossover, double blind; 4	1.75 g/kg BW	Opuntia ficus-indica (not reported)	1600 IU before alcohol challenge	Placebo; 1 day	64/55 healthy volunteers	Overall hangover symptom score	No intergroup difference (P>0.05)	Not reported	A meal was taken before alcohol challenge
Laas[28]	Parallel, double blind; 3	100 g	Dried yeast (Morning Fit)	750 mg after alcohol challenge	Placebo; 1 day	61/58 healthy volunteers	Hangover symptom scores	Intergroup differences for discomfort, restlessness, impatience (P<0.05)	Not reported	After alcohol challenge soft drinks, water, and a low fat lunch were offered; no caffeine intake
Muhonen[29]	Parallel, double blind; 2	Not reported	Tropisetron (not reported)	5 mg tropisetron and diazepam when patients reached 0% BAC	Placebo; 1 day	11/not reported alcoholics (DSM-III-R)	VAS scores for vomiting, nausea, appetite, headache	No intergroup differences (P>0.05)	Not reported	Participants were patients in hospital for detoxification
Bogin[30]	Crossover, double blind; 4	Not reported; calculated for each patient to estimated BAC levels of 0.1%	Propranolol, long acting (not reported)	160 mg 2 hours before alcohol challenge	Placebo; 1 day	10/10 healthy volunteers	Overall hangover symptom score	No intergroup difference (P>0.05)	Not reported	No analgesics or water were allowed after alcohol challenge

Results…

- Eight randomised controlled trials assessing eight different medical interventions for preventing or treating the symptoms of alcohol hangover were reviewed.

- No compelling evidence exists to suggest that any conventional or complementary intervention is effective for preventing or treating alcohol hangover.

Meta-analysis

‘The use of statistical techniques in a systematic review to integrate the results of included studies’.

Cochrane collection glossary (www.cochrane.org)

NOTE

In a meta-analysis the studies themselves are the primary units of analysis as there is usually no access to raw data from each individual study.

Meta-analysis. History

Many of the groups …. are far to small to allow any definite opinion being formed at all, having regard to the size of the probable error involved

Karl Pearson, 1904

Effectiveness of inoculation against typhoid fever among soldiers

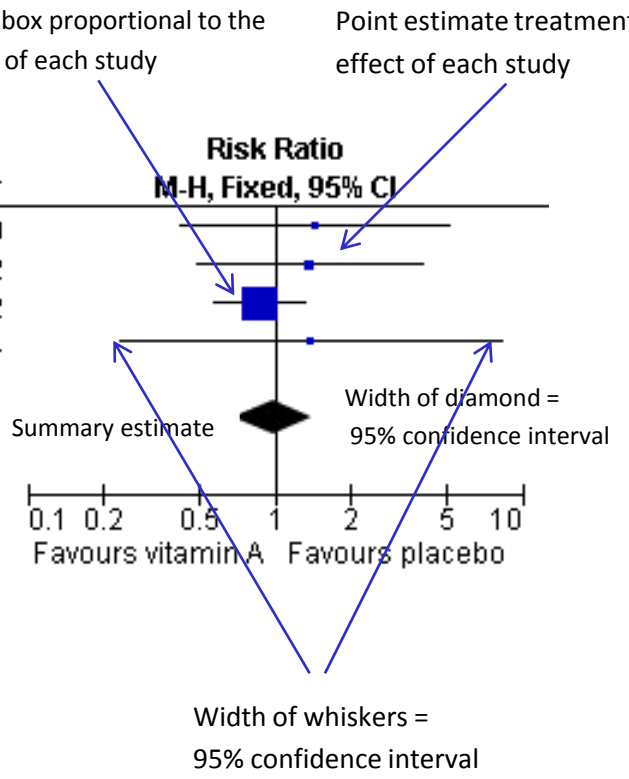
Meta-analysis. Forest plots

Meta-analysis of studies on Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection

	Vitamin A		Placebo			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Coutsoudis 1999	6	341	4	330	7.6%	1.45 [0.41, 5.10]	1999
Semba 2002	8	306	6	317	11.1%	1.38 [0.48, 3.93]	2002
Fawzi 2002	36	521	41	514	77.4%	0.87 [0.56, 1.33]	2002
Friis 2004	3	273	2	253	3.9%	1.39 [0.23, 8.25]	2004
Total (95% CI)		**1441**		**1414**	**100.0%**	**0.99 [0.68, 1.43]**	
Total events	53		53				

Heterogeneity: $Chi^2 = 1.25$, $df = 3$ ($P = 0.74$); $I^2 = 0\%$

Test for overall effect: $Z = 0.06$ ($P = 0.95$)



Wiysonge et al Cochrane Database Syst Rev. 2011 Jan 19;(1):CD003648

What does a meta-analysis involve?

- Effect estimates are abstracted from the selected studies
- To calculate a weighted average of effects across all studies.

$$\hat{\Theta} = \frac{\sum w_i \hat{\Theta}_i}{\sum w_i}$$

where $\hat{\Theta}_i$ are the results of the *i* studies and the weights (w_i) are estimates of the precision of each study

  - Most weight to informative studies (often large studies with precise effect estimates)
  - Least weight to less informative studies (often smaller studies with imprecise effect estimates).

Issues in meta-analysis

- Publication bias
- Inconsistency of results (heterogeneity)

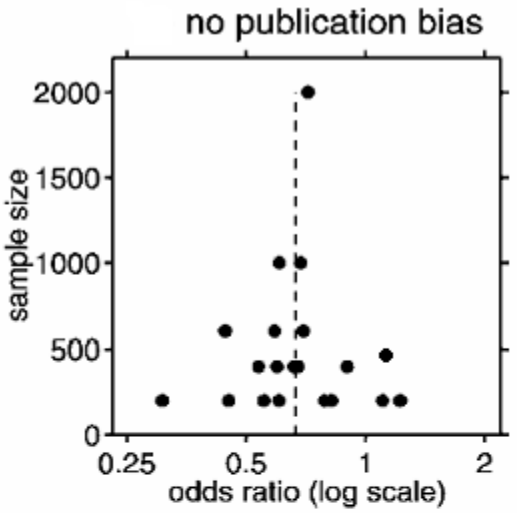
Publication bias:
- only a subset of the relevant data is available

- Failure to include all relevant data in a meta-analysis may mean the effect of an intervention/exposure is over (or under) estimated.

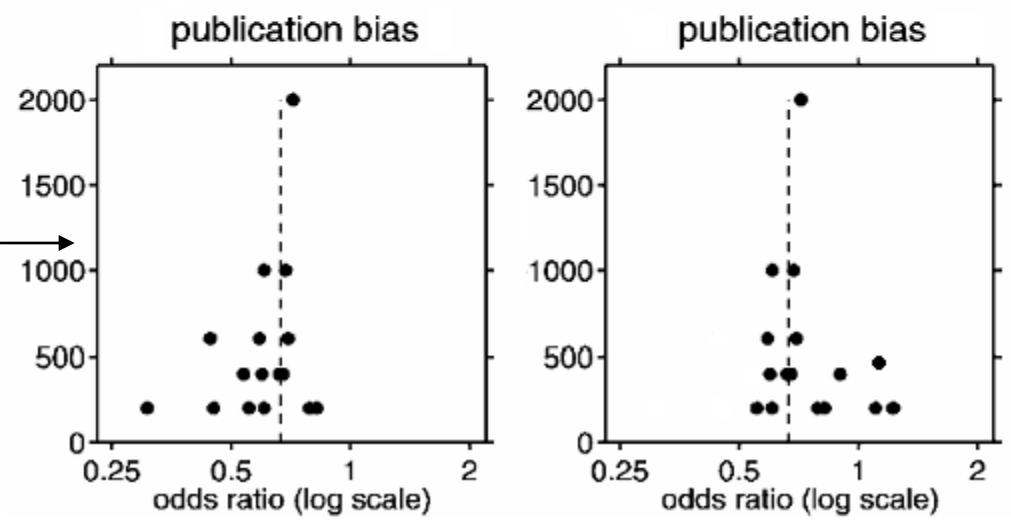
- Null or non significant findings (esp. in small studies) are less likely to be reported/published than statistically significant findings.

Funnel Plot

A funnel plot which is symmetric about the mean effect and shaped like an upside down funnel indicates no publication bias.



A plot with the lower right or left hand corner of the plot missing indicates that publication bias is present.



Inconsistency of study results (heterogeneity)

- Assessment of the between-study **heterogeneity** is an essential component of **meta-analysis**

- Studies differ with respect to:
  - Populations
  - Interventions/exposure
  - Outcomes
  - Study design
  - Clinical differences
  - Methodological differences
  - Unknown study characteristics

Assessing heterogeneity

- **Several methods**

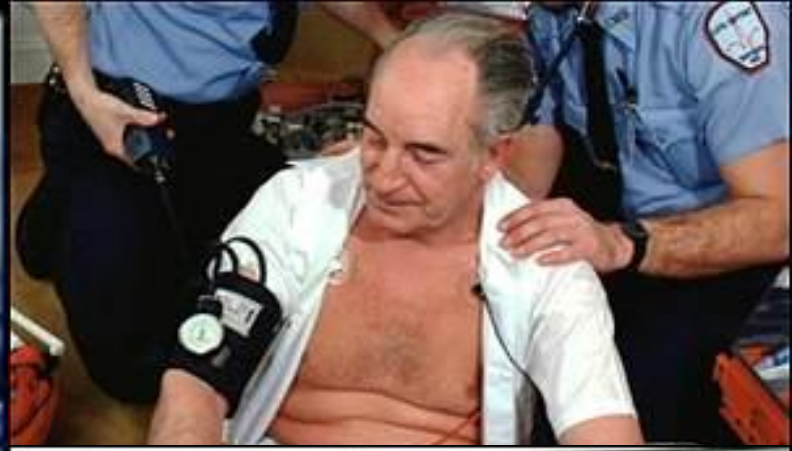
- One method is to analyze different sub-groups and examine whether results differ (e.g. men and women, groups defined by histology, etc.)

Advantages of meta-analyses

- Generate a **pooled overall risk estimate**
- Produce a more **reliable and precise** estimate of effect
- E**xplore differences** (heterogeneity) between published studies.
- Identify whether **publication bias** is occurring.

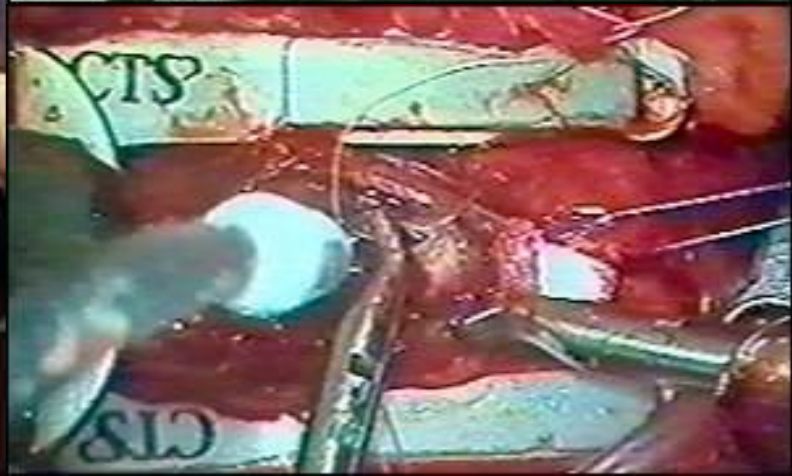
BUT

- If the studies are **too heterogeneous**, it may be inappropriate, even misleading to statistically pool the results from separate studies!




3000
104
180

91


CTS

Example

Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

Huxley et al, BMJ 2006;332:73-78.

- The population
  - Studies in men and women with and without diabetes who died from coronary heart disease.
- The exposure/intervention
  - Studies investigating diabetes.
- The outcomes
  - Studies with fatal coronary heart disease events as outcome
- The study designs
  - Prospective cohort studies.

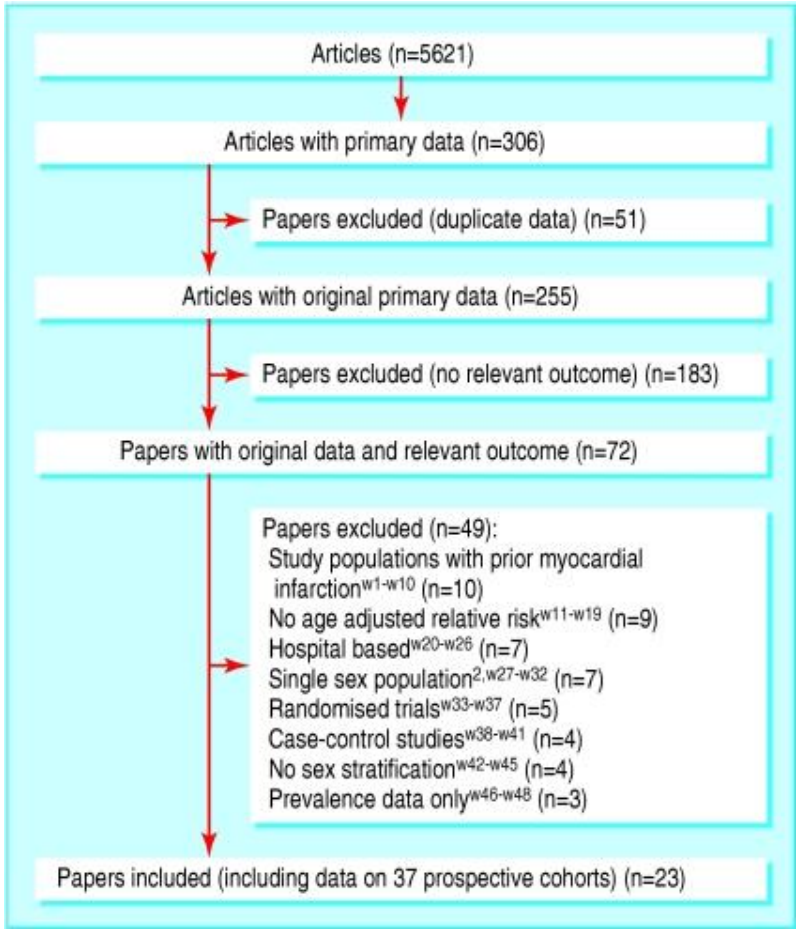
Identification of research

- Search criteria combined text word and MESH heading search strategy of the terms…
  - Diabetes
  - Coronary Heart Disease
- Searched published literature:
  - Medline, Embase
- Other literature
  - Included eligible studies from the three previous reviews
  - Scanned references

Selection of studies

Eligibility/Inclusion criteria:

- Study design
  - Prospective cohort studies
  - Risk estimates with standard errors (or confidence limits)
  - Must have studied both men and women
  - Must have adjusted for age at least
- Year of study
  - Studies published between 1966 and March 2005
- Publication language
  - Any



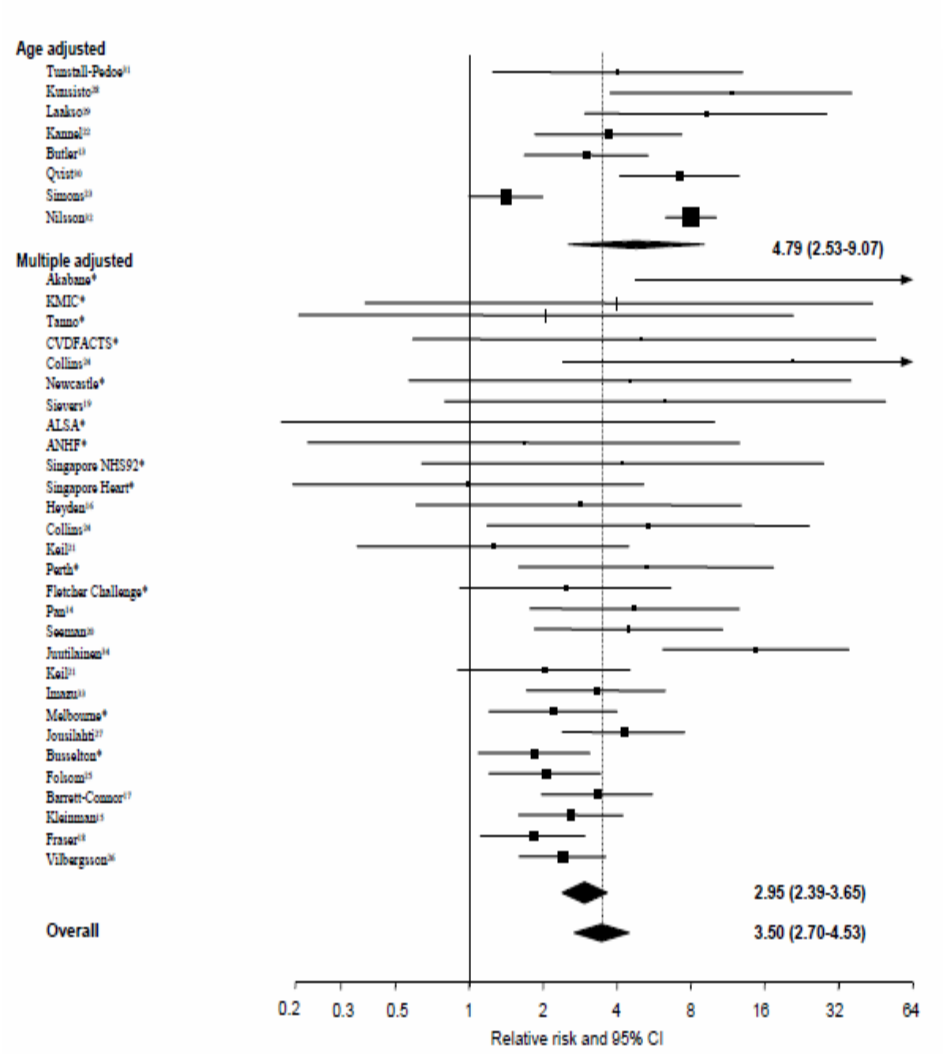
Study quality assessment

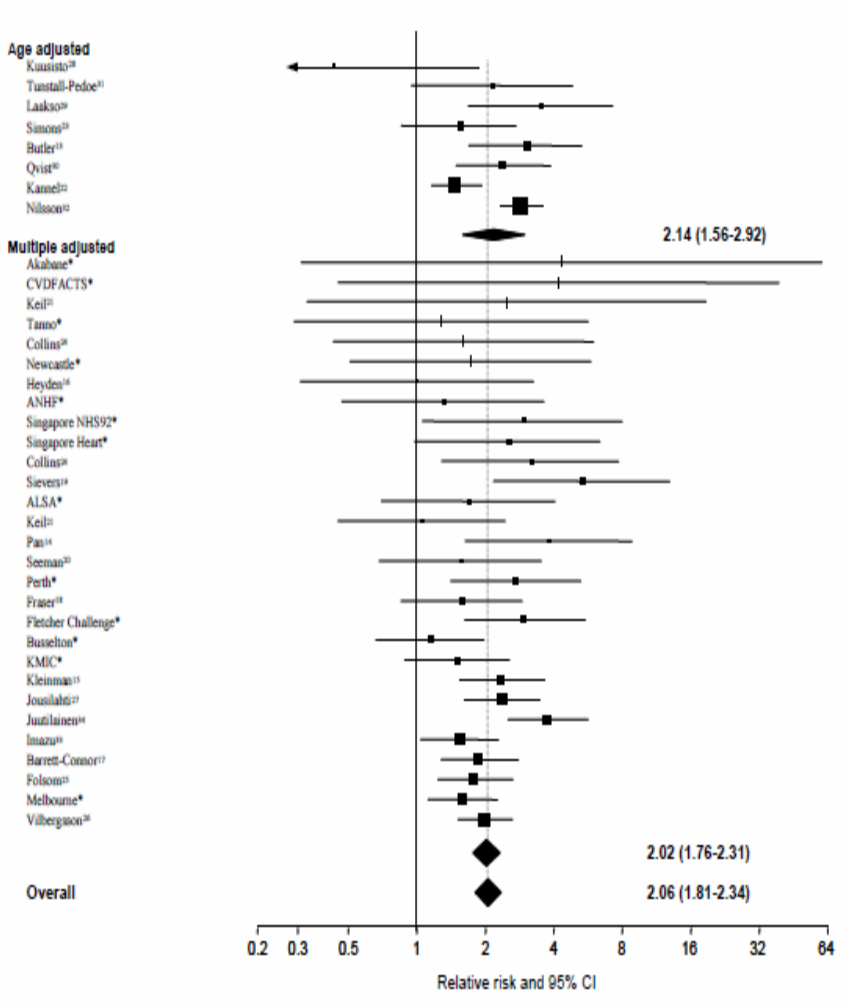
No formal assessment of quality due to the ‘questionable merit of quality scoring in meta-analyses of observational studies’…

Investigated sources of heterogeneity:

- Gender
- method of diabetes diagnosis
- country of origin
- duration of follow-up

Relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes





Women

Men

Results…

- 37 studies, 447 064 patients were included in the analysis.
- The rate of fatal coronary heart disease was higher in patients with diabetes than in those without.
- The relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was significantly greater among women than it was among men
  - Women: pooled relative risks = 2.95 (95% CI 2.39-3.65)
  - Men: pooled relative risk = 2.02 (95% CI 1.76-2.31)
- May be due to
  - more adverse cardiovascular risk profiles among women with diabetes
  - disparities in treatment that favour men.

Reviewing a systematic review

1. Was a clear, unambiguous and predefined question addressed?
   In terms of populations, interventions/exposures, outcomes and study designs?
2. Was a comprehensive search for relevant literature carried out?
   Grey literature; time frame; appropriate inclusion/exclusions; languages; duplicate & independent assessment of literature?
3. Was methodological quality of each study assessed appropriately?
   Quality used as inclusion criteria? Quality measures appropriate? Studies weighted according to quality? Heterogeneity due to quality?
4. Was heterogeneity (consistency of results) explored?
   Heterogeneity due to populations, interventions/exposures, outcomes and study designs?
5. How credible is the evidence?
   Strengths and weaknesses of evidence? Evidence from high quality studies? Impact on clinical practice?

Reviewing a meta-analysis

See points on reviewing systematic reviews, also…

1. Was heterogeneity explored?
   Sub group analyses with respect to sub groups of populations, interventions/exposures, outcomes, study designs, study quality.
2. Was publication bias an issue?
   Evidence for ‘missing’ studies? What impact might this have had on the pooled estimate?
3. Was it appropriate to pool the studies?
   Were studies sufficiently homogeneous for to be pooled?
4. Was the appropriate model used to pool effect estimates?
   Fixed versus random effects model.
5. Did different sub groups of studies give similar results?
   Were results consistent across sub-groups? How generalizable are the findings, are there new hypotheses that should be explored?

Guidelines for reporting meta-analysis

MOOSE (observational studies). JAMA. 2000 Apr 19;283(15):2008-12

QUOROM (randomized controlled trials) Lancet. 1999 Nov 27;354(9193):1896-900

STREGA, STROBE, STARD, SQUIRE, MOOSE, PRISMA, GNOSIS, TREND, ORION, COREQ, QUOROM, REMARK... and CONSORT: for whom does the guideline toll? J Clin Epidemiol. 2009 Jun;62(6):594-6.

Conclusions

- Single studies rarely provide a conclusive, universal answer to a question.
- Systematic reviews can provide an overview of evidence on a particular topic.
- Meta-analyses can provide:
  - A single, more precise, estimate of intervention/exposure effect.
  - A greater understanding of similarities/differences among studies.
  - An assessment of likely publication bias.
- Inconsistencies in results across studies can be identified and new hypotheses generated about particular subgroups.
- Systematic reviews/meta-analyses can provide an evidence-base for clinical decisions.

References

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