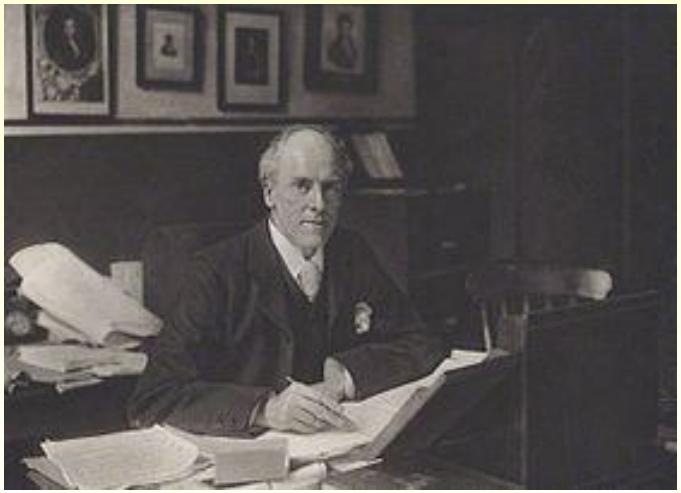
Principles of meta-analysis



The British Medical Journal Nov. 5, 1904. pp. 1243-46.

REPORT ON CERTAIN ENTERIC FEVER INOCULATION STATISTICS.

PROVIDED BY LIEUTENANT-COLONEL R. J. S. SIMPSON, C.M.G., R.A.M.C.

BY KARL PEARSON, F.R.S.,
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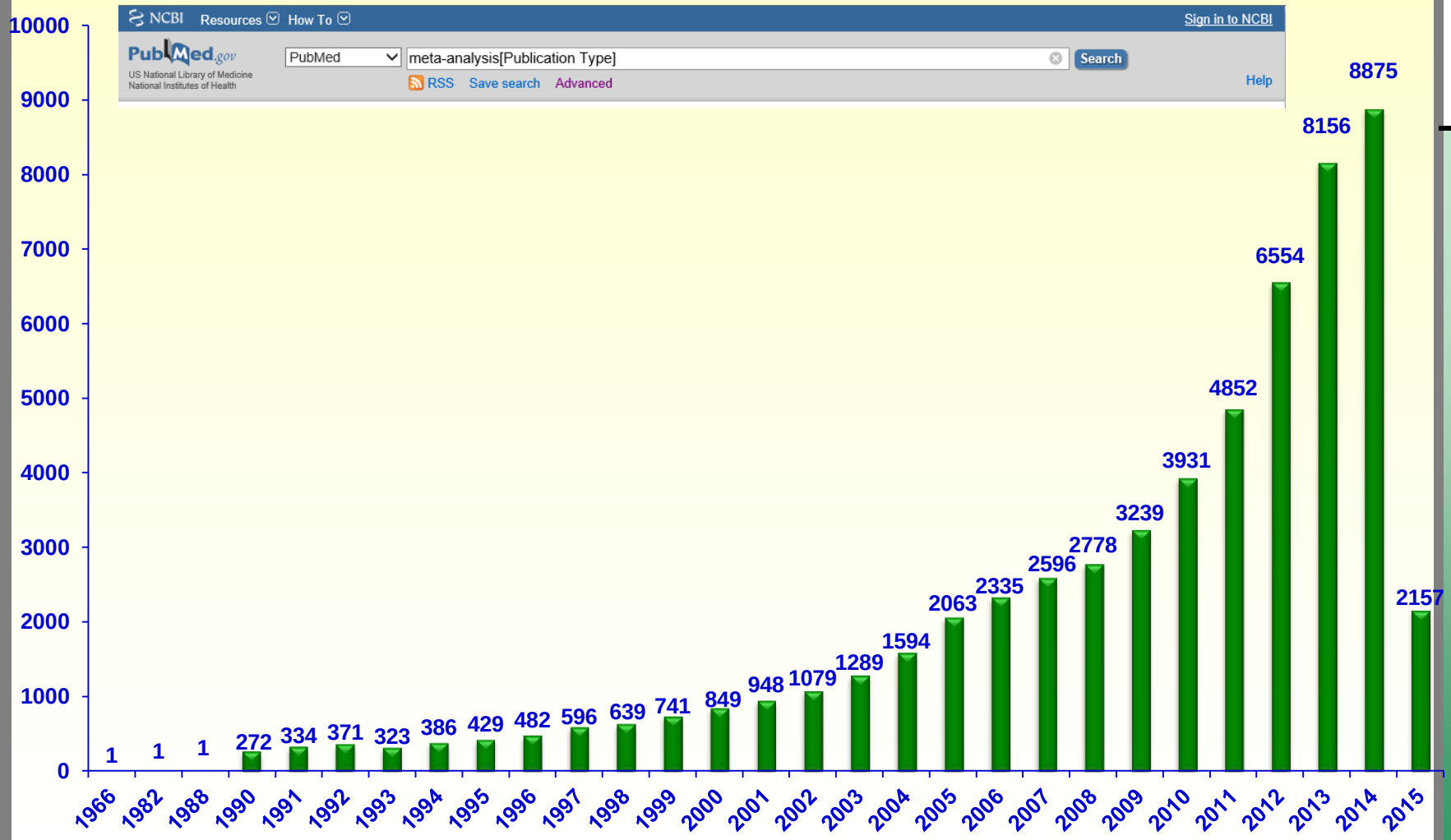
THE statistics in question were of two classes: (A) Incidence (B) Mortality Statistics. Under each of these headings the data belonged to two groups: (i) Indian experience; (ii) South African War experience. These two experiences were of a somewhat different character. That for India covered apparently the European army, of whatever branch and wherever distributed; that for South Africa was given partly by locality, partly by column, and partly by special hospital. Thus the Indian and South African experiences seem hardly comparable. Many of the groups in the South African experience are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved. Accordingly, it was needful to group them into larger series. Even thus the material appears to be so heterogeneous, and the results so irregular, that it must be doubtful how much weight is to be attributed to the different results.

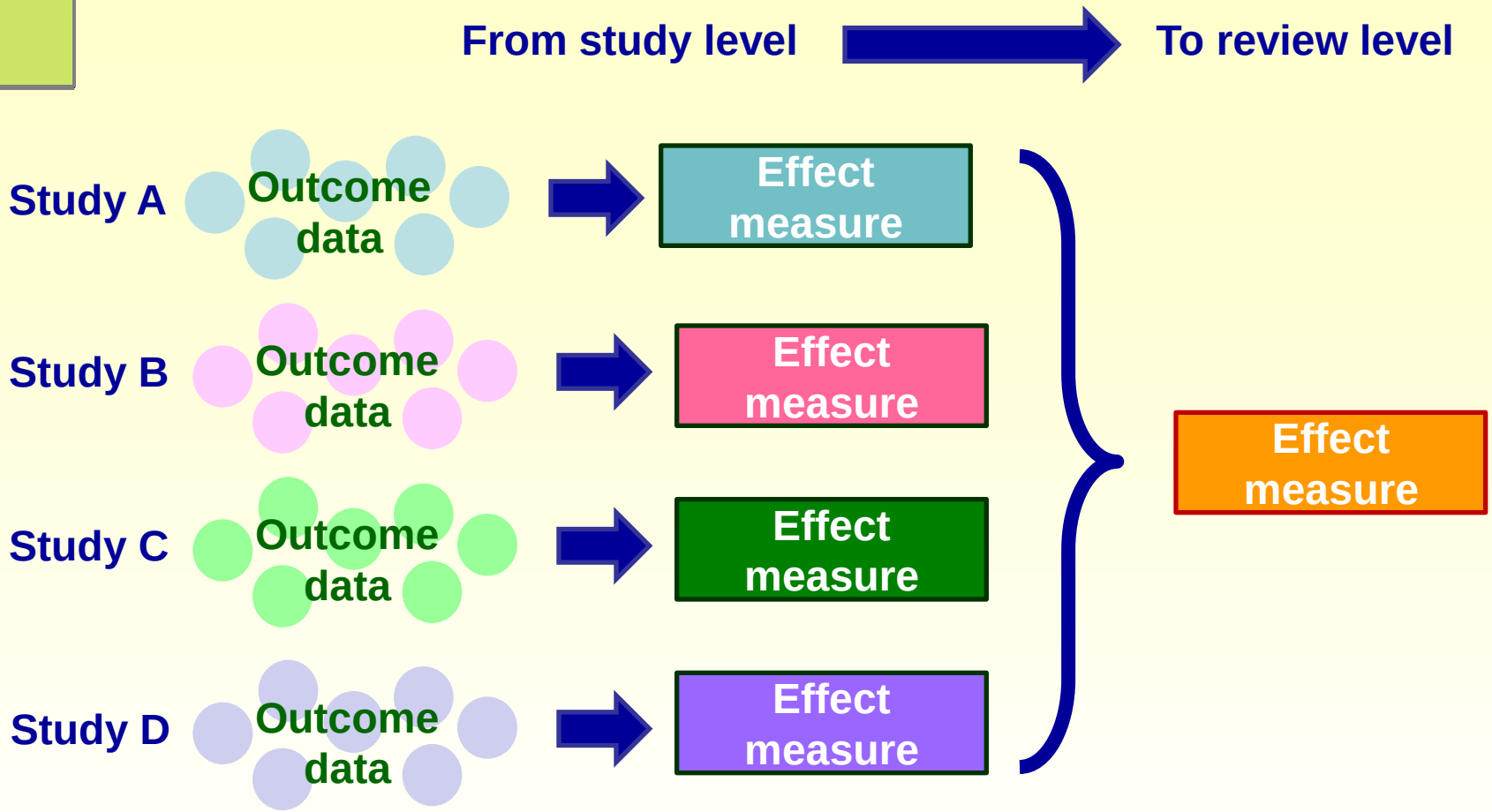
The popularity of meta-analyses

Search on 22 October 2015



Main topics

- What is meta-analysis
- Steps in a meta-analysis
- How results are presented



Meta-analysis is a way to bring together the results of several collections of data belonging to different studies

“Meta-analysis refers to the analysis of analyses…the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating findings. It connotes a rigorous alternative to the casual, narrative discussions of research studies which typify our attempts to make sense of the rapidly expanding literature…”

Glass, 1976

Narrative Review

Strengths

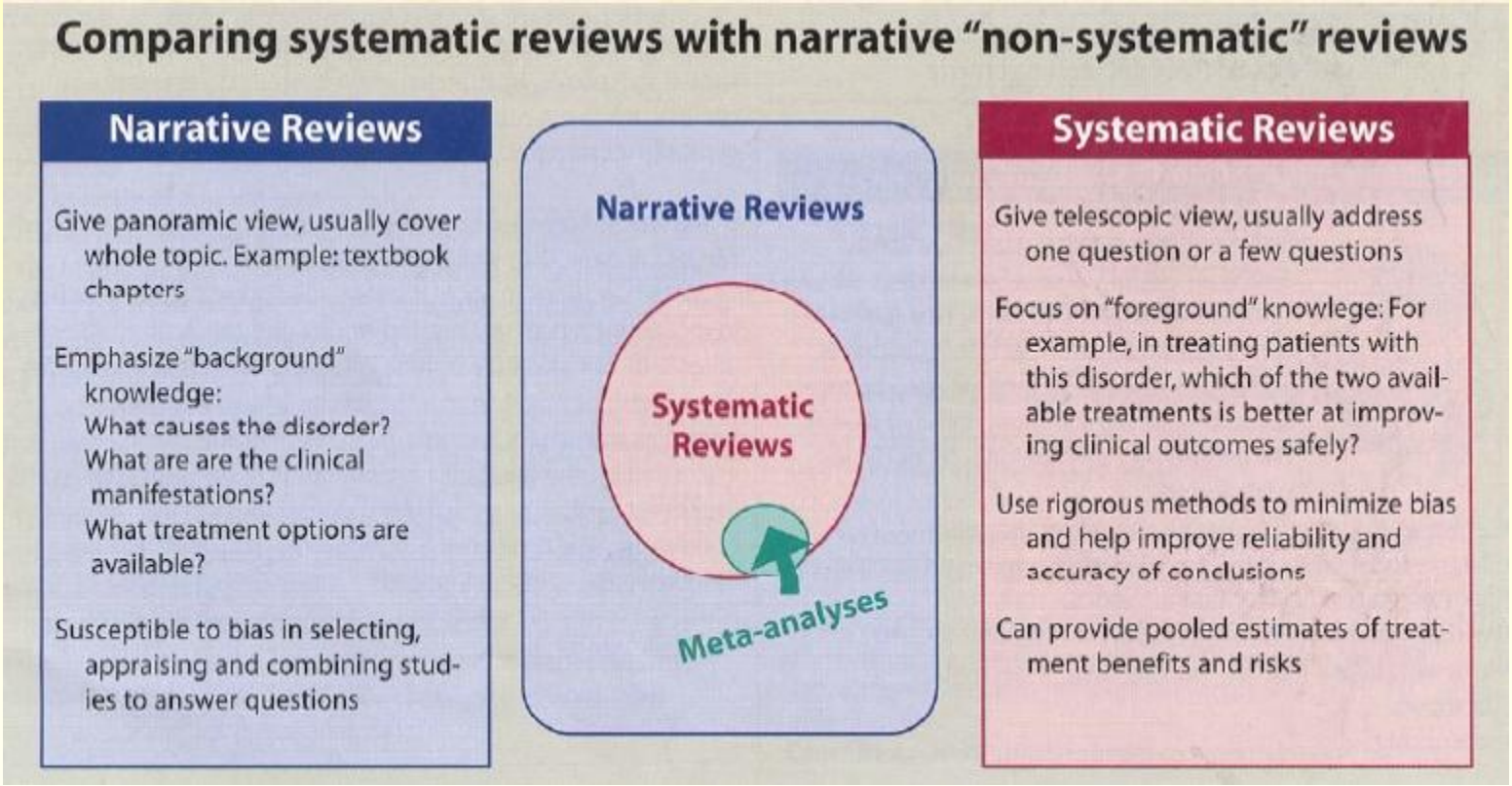
- Short timeframe
- Inexpensive

Limitations

- Provide qualitative summary only → frequently tabulate results
- Subjective
- Selective inclusion of studies
- May be influenced by publication bias

Features of narrative reviews and systematic reviews

	Narrative	Systematic
Question	Broad	Focused
Sources	Usually unspecified	Comprehensive
Search	Possibly biased	Explicit
Selection	Unspecified (biased?)	Criterion based uniformly applied
Appraisal	Variable	Rigorous
Synthesis	Usually qualitative	Quantitative



The meta-analysis differs from traditional literature reviews for:

1. The systematic and exhaustive search of the available evidence (published and unpublished)

2. The clarification of the criteria for inclusion of studies considered

3. Statistical analysis of the results of studies

What is a meta-analysis?

The terms "systematic review" and "meta-analysis" are often used interchangeably, but they are not the same.

Meta-analysis is the term used for

- **the statistical method of combining the results from two or more studies**
- **permitting to estimate the "average" or "common" effect across those studies**
- **It can be optional part of a systematic review**

Why perform a meta-analysis?

- Summarize published literature
- Quantify treatment effects (***how effective a treatment is?***) → we are uncertain about the results of different single studies so by combining samples ***we increase our power to detect differences***, and ***increase the precision of our answer.***
- If individual studies are conflicting, a meta-analysis may settle the controversy by giving an overall answer.
- Increase statistical power.
- Generate new hypotheses to be tested by future studies.

When NOT do a meta-analysis

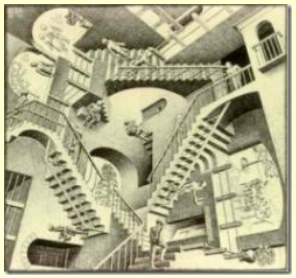
- *mixing apples with oranges*

→ **when the studies are too different from each other, and it would not make sense to combine their results**

- **each included study must address same question**

Answer may be meaningless and genuine effects may be obscured if studies are too diverse

When NOT do a meta-analysis



- **combining a broad mix of studies**

→ when the studies consider different and particular aspects of the same issue

If your objective is to investigate the impact of exercise programs compared to no exercise, then you might be happy to combine studies using many different kinds of exercise programs, and you would get a broad answer about their effectiveness.

When NOT do a meta-analysis

On the other hand, this would not answer questions about the difference between swimming and jogging, or between self-managed exercise versus exercise with a physiotherapist, or between short and long exercise programs, and …….

If that's what you want to do, you might decide to break up your review into several separate meta-analyses.

When NOT do a meta-analysis

- *garbage in – garbage out*

→ when the studies are too unreliable (their risk of bias is too high to be confident that they are telling us the truth)

- a meta-analysis is only as good as the studies in it
- if included studies are biased:
  - meta-analysis result will also be incorrect
  - it will give more credibility, increasing people's confidence in the results
- if serious reporting biases are present:
  - unrepresentative set of studies may give misleading result

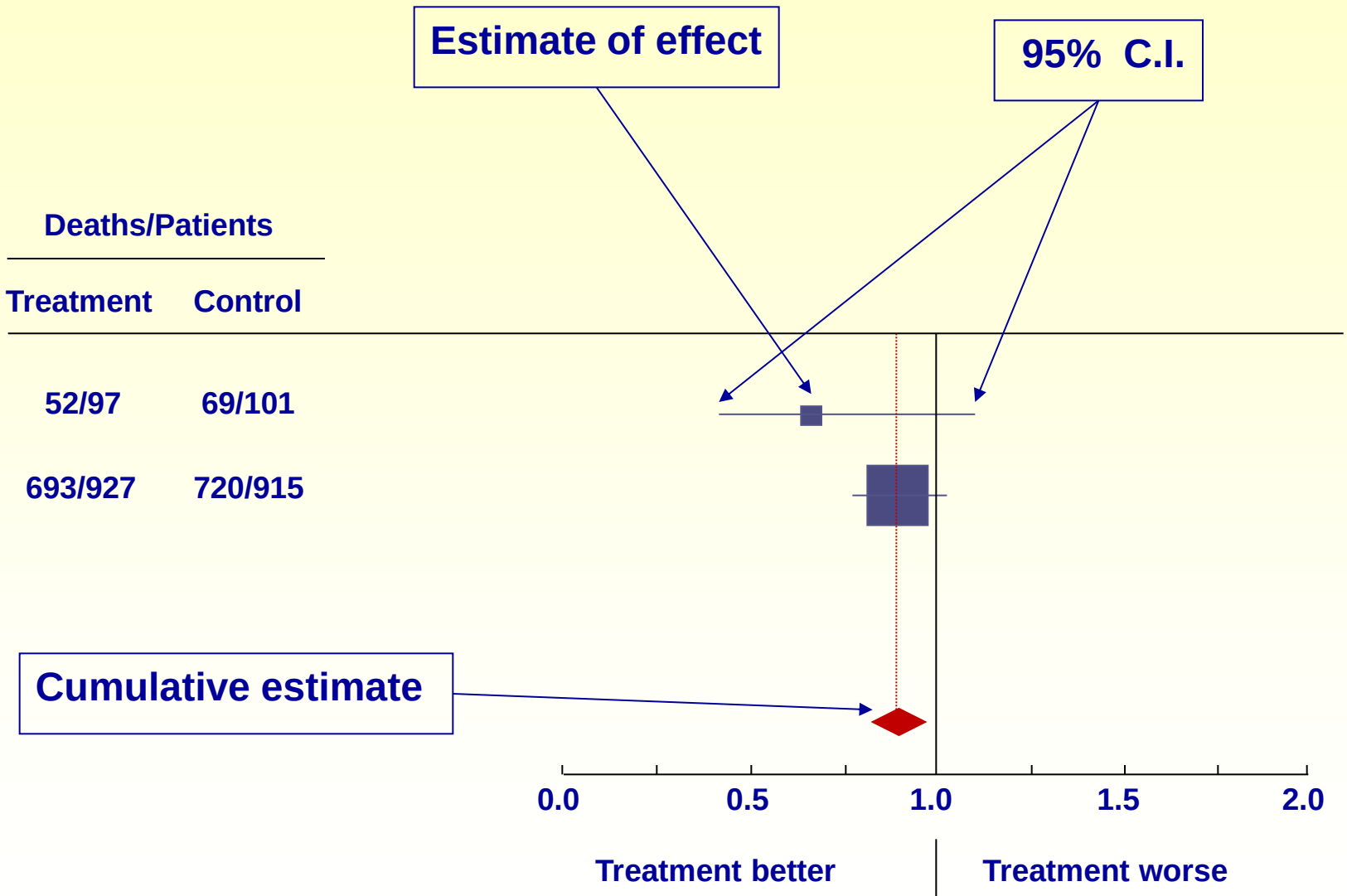
When CAN you do a meta-analysis?

- the studies are sufficiently similar to produce a meaningful and useful result (participants/interventions/outcomes)
- more than one study has measured an effect
- the outcome has been measured in similar way
- data are available in a format we can use

  e.g. for binary outcomes the number of events and the number of people in each group, and for continuous outcomes the mean, SD and number of people in each group are available

Principles of meta-analysis

- Each trials is summarised by a measure of effect
- Those summaries are combined into a summary estimate of effect, taking into account the amount of information available in each study
  - Bigger studies get more weight
- The overall measure of effect is a weighted average of the results of individual trials
- Important to consider uncertainty of resulting estimate
  - Confidence Interval


Estimate of effect
95% C.I.
Deaths/Patients
Treatment Control
52/97 69/101
693/927 720/915
Cumulative estimate
0.0
0.5
1.0
1.5
2.0
Treatment better
Treatment worse

Methodological steps

1. Formulation of the clinical query
2. Research all studies related to the clinical query
3. Systematic selection based on specific inclusion criteria for relevant eligible studies
4. Data extraction
5. Assessment of methodological quality of the studies
6. Quantitative synthesis (meta-analysis): increase statistical power of the comparison
   a. Sensitivity analysis and subgroup analysis, if appropriate
   b. Study of heterogeneity
7. Review report

1. Formulation of the clinical query

- Aim of the study
  - To validate the results in a large population
  - To kick off to new studies

- Ask this question in biological and clinical terms, specifying operational definitions
  - Population
  - Intervention/ Exposure
  - Comparisons
  - Outcomes (in terms of both risks and benefits)
  - Types of studies

2. Research all studies related to the clinical query

- Search with the help of an expert in literature review
- Specify restrictions of language (it would be desirable to have no restrictions)

Since all studies on a similar topic will not be listed in just one database, it's important to search multiple databases in order to minimize your chances of omitting studies that may meet your inclusion criteria.

It's also important to check the bibliographies of retrieved studies and review articles in order to identify other studies that may meet your inclusion criteria. Furthermore, if time and resources are available, one should hand search appropriate journals for studies!!

Study Sources

- Published literature
- Citation indexes
- Bibliographic databases (PubMed, EMBASE, ...)
- Reference lists
- Conference abstracts and proceedings
- Dissertations
- Contact with authors
- Unpublished literature
- Research reports
- Trial registries
- Journal handsearching

3. Systematic selection based on specific inclusion criteria for relevant eligible studies

- Studies identified as eligible are selected according to predefined inclusion and exclusion criteria

- Data are extracted **independently by at least two evaluators** who do not know the name of the authors, their institutions and the journal of publication

4. Data extraction

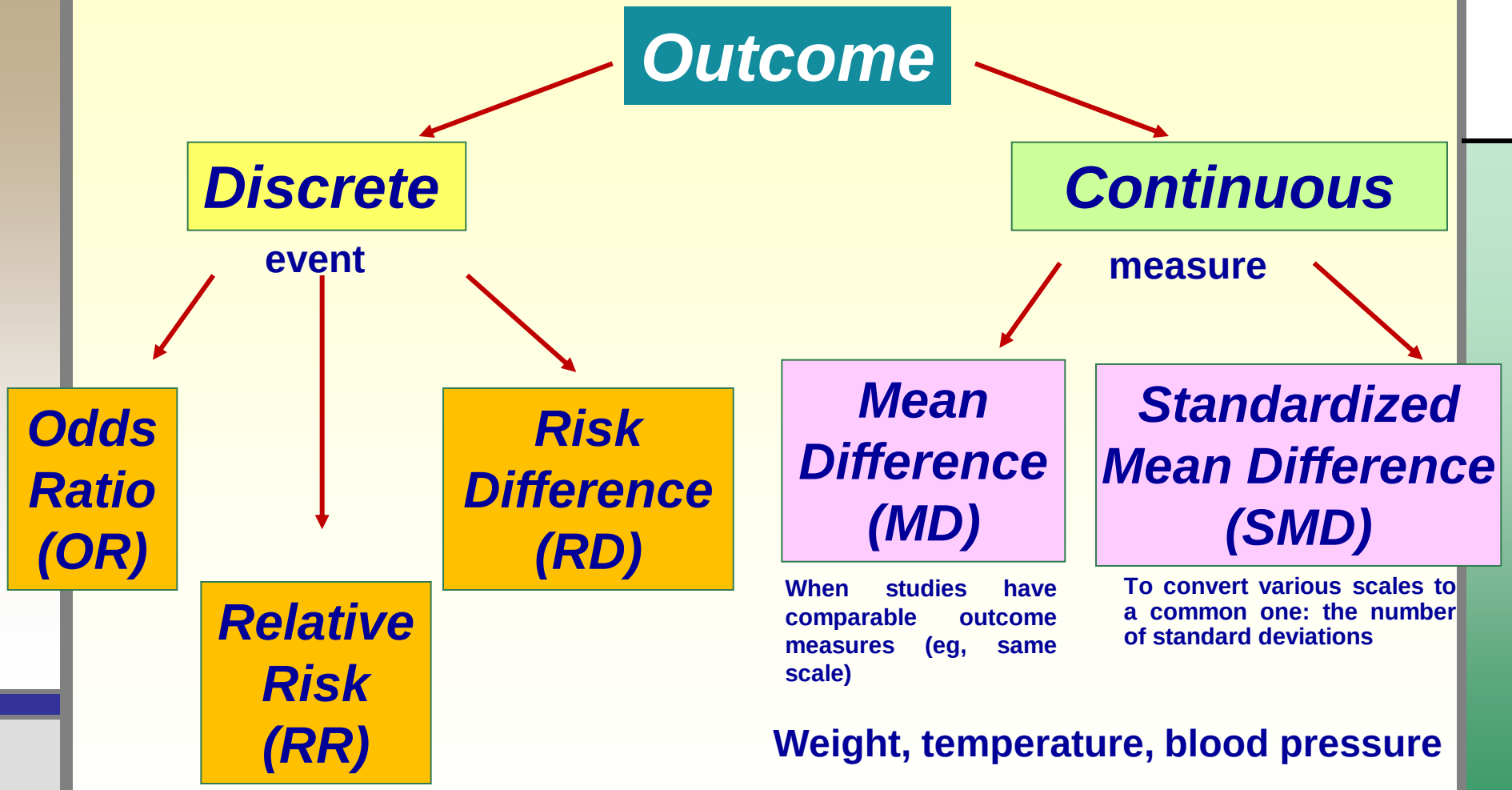
- Data are extracted from multiple reviewers through the use of predetermined form and compared

a.name of the study
b.name of the author, year published
c.geographical setting
d.number of participants who received intervention
e.number of participants who were in control arm
f.number of participants who developed outcomes in intervention
g.number of participants who develop outcomes in control arm
h.assessment procedures
i.risk estimates and variance

5. Assessment of methodological quality of studies

- The methodological quality of the studies is evaluated and discussed among the reviewers (quality of data, design, statistical analysis)
- Criteria developed by the reviewers should be stated
- It is necessary to eliminate low-quality studies
- Weigh studies

Selecting outcomes



Discrete data

P1 = event rate in experimental group

P2 = event rate in control group

- **RD = Risk difference = P2 - P1**
- **RR = Relative risk = P1 / P2**
- **RRR = Relative risk reduction = (P2-P1)/P2**
- **OR = Odds ratio = P1/(1-P1)/[P2/(1-P2)]**
- **NNT = No. needed to treat = 1 / (P2-P1)**

	Disease+	Disease -	
Exp +	a	b	a + b
Exp -	c	d	c + d
	a + c	b + d	N

$$(OR) = \frac{ad}{bc}$$

6. Quantitative synthesis and results presentation

- Combine the results to obtain the summary of effect
- Explore differences between the studies
- Interpret the results and describe it in a review

Selecting comparisons

***Each review may have one or many comparisons*:**

For example, we may have a collection of studies comparing ordinary coffee with decaffeinated coffee, but our review includes any studies of caffeine, so we may have other comparisons as well. We might have some studies comparing coffee vs. tea, or tea vs. placebo, or drinks vs. coffee. We might also decide that the effect of caffeine in children should be treated as a separate comparison to the effect in adults. Although our review is interested in all those things, we need to break them down and look at them systematically, two at a time.

***Break your topic down into pair-wise comparisons*:**

e.g. intervention vs. placebo, intervention A vs. intervention B → we can compare the two results each other and test which intervention is most effective

Calculating the summary result

- collect a summary statistic from each contributing study: starting with the first outcome in our first comparison, we need to combine the results from our set of studies together
- how do we bring them together?

- treat as one big study → add intervention & control data and then compare the groups as if they were part of one big study is NOT CORRECT we are comparing the intervention data from one study with the control data from other studies, which is not a randomised comparison.
- simple average → NOT CORRECT some studies are contributing more information than others (closer to the truth).
- weighted average → CORRECT

Results from different studies are pooled in a quantitative manner and weighed

- **Quantitative combination is not equivalent to the arithmetic sum → the results observed in the patients included in a study are not simply added together with those of another study**
- **The treatment effect is measured within individual studies and used as a function of the variability of the observed effect, expressed as function of the number of patients studied.**
- **It gives a different weight to different studies, depending on the size of the sample studied → the larger study is, the more it will affect the overall result of the meta-analysis.**

Weighting studies

It is important to give the *most weight* to the studies that give the *most information* about the effect that means *the most precise estimate of the difference between the two groups*.

Most weight if:

- **Studies have more participants**
- **Studies have more events of interest for binary data**
- **Studies have more precise estimates of the mean for continuous data**

Narrower confidence interval

Heterogeneity

The heterogeneity occurs when there is variability among the included studies.

- **Homogeneity of the effect refers to the hypothesis that unknown effect on which we make inference is identical in all studies. Each study produces a measure (affected by sampling error) of the same amount.**
- **Heterogeneity of the effect refers to that hypothesis that the effect is going to be measured is not the same in all studies. Variability between studies is a source of additional variability.**

It may be due to several factors:

- **Characteristics of the population**
- **Study design (selection procedures, sources of information, data collection)**
- **Different statistical methods, and use of different adjustment variables**

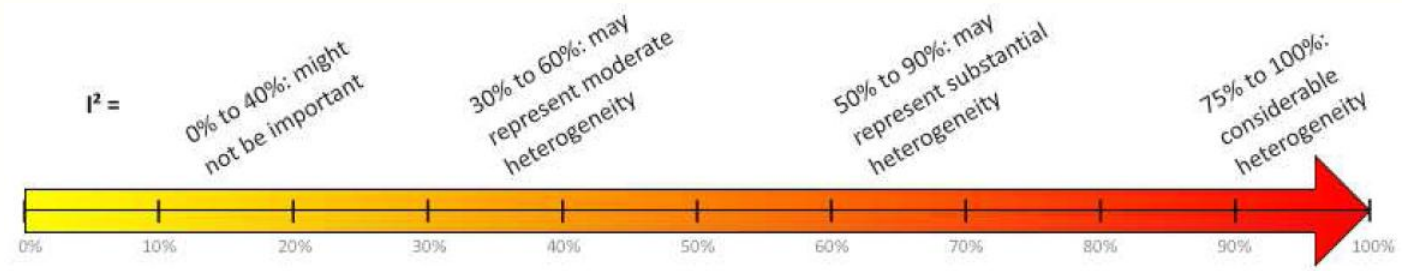
To verify the presence of heterogeneity, it is necessary to examine statistically the degree of similarity of the outcomes of the different studies.

The test measures whether the differences between the results of individual studies are larger than those that would be expected if all studies had measured the same effect and whether the observed differences were due to chance alone.

More significant is the heterogeneity test, the lower is the probability that the differences observed are due to chance alone, indicating that other factors (for example, the design of the study, the patients) are responsible for the differences in treatment effect between studies.

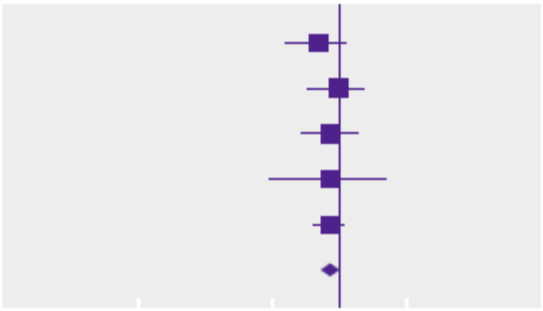
There is the possibility of heterogeneity when

- **Observation of forest plot** → **CI of the various studies do not overlap**
- **Chi-square** → **Chi square > df (n-1)**
- **p value** → **If p> 0.05 there is no heterogeneity (random difference) if <0.05 there is heterogeneity (real difference)**
- **I^2 → inconsistency describes the percentage of variability of the estimate that is attributable to heterogeneity rather than chance (sampling variability)**



Heterogeneity is not present

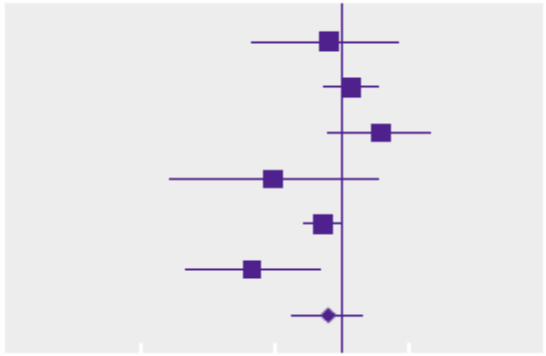
	No of events/No in group		Relative risk (95% CI)	Relative risk (95% CI)
	Aspirin	Control or placebo		
Major cardiovascular events				
JPAD[10]	68/1262	86/1277		0.80 (0.59 to 1.09)
POPADAD[9]	105/638	108/638		0.97 (0.76 to 1.24)
WHS[8]	58/514	62/513		0.90 (0.63 to 1.29)
PPP[22]	20/519	22/512		0.90 (0.50 to 1.62)
ETDRS[21]	350/1856	379/1855		0.90 (0.78 to 1.04)
Total	601/4789	657/4795		0.90 (0.81 to 1.00)



$p=0.92$; $I^2=0\%$

Heterogeneity is present

Myocardial infarction			
JPAD[10]	12/1262	14/1277	0.87 (0.40 to 1.87)
POPADAD[9]	90/638	82/638	1.10 (0.83 to 1.45)
WHS[8]	36/514	24/513	1.48 (0.88 to 2.49)
PPP[22]	5/519	10/512	0.49 (0.17 to 1.43)
ETDRS[21]	241/1856	283/1855	0.82 (0.69 to 0.98)
PHS[17]	11/275	26/258	0.40 (0.20 to 0.79)
Total	395/5064	439/5053	0.86 (0.61 to 1.21)

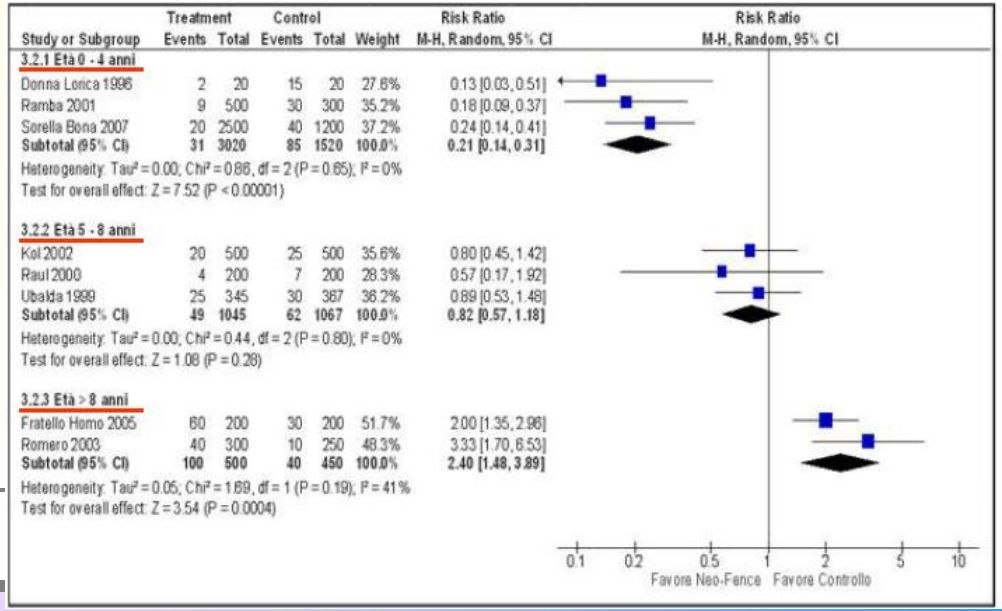


$p=0.02$; $I^2=62.2\%$

How to deal with the heterogeneity

1. Avoid performing meta-analysis
2. Ignore heterogeneity: use the fixed effects model
3. Incorporate heterogeneity: use the random effects model
4. Exploring the heterogeneity
   - Analysis of subgroups
   - Stratification

Repeated analysis taking into account that the studies differed mainly for the age of the patients.



Fixed Effect Model

- It assumes that the true effect of treatment is the same for every study
- Variability only from sampling of people within each study
- Precision depends mainly on study size

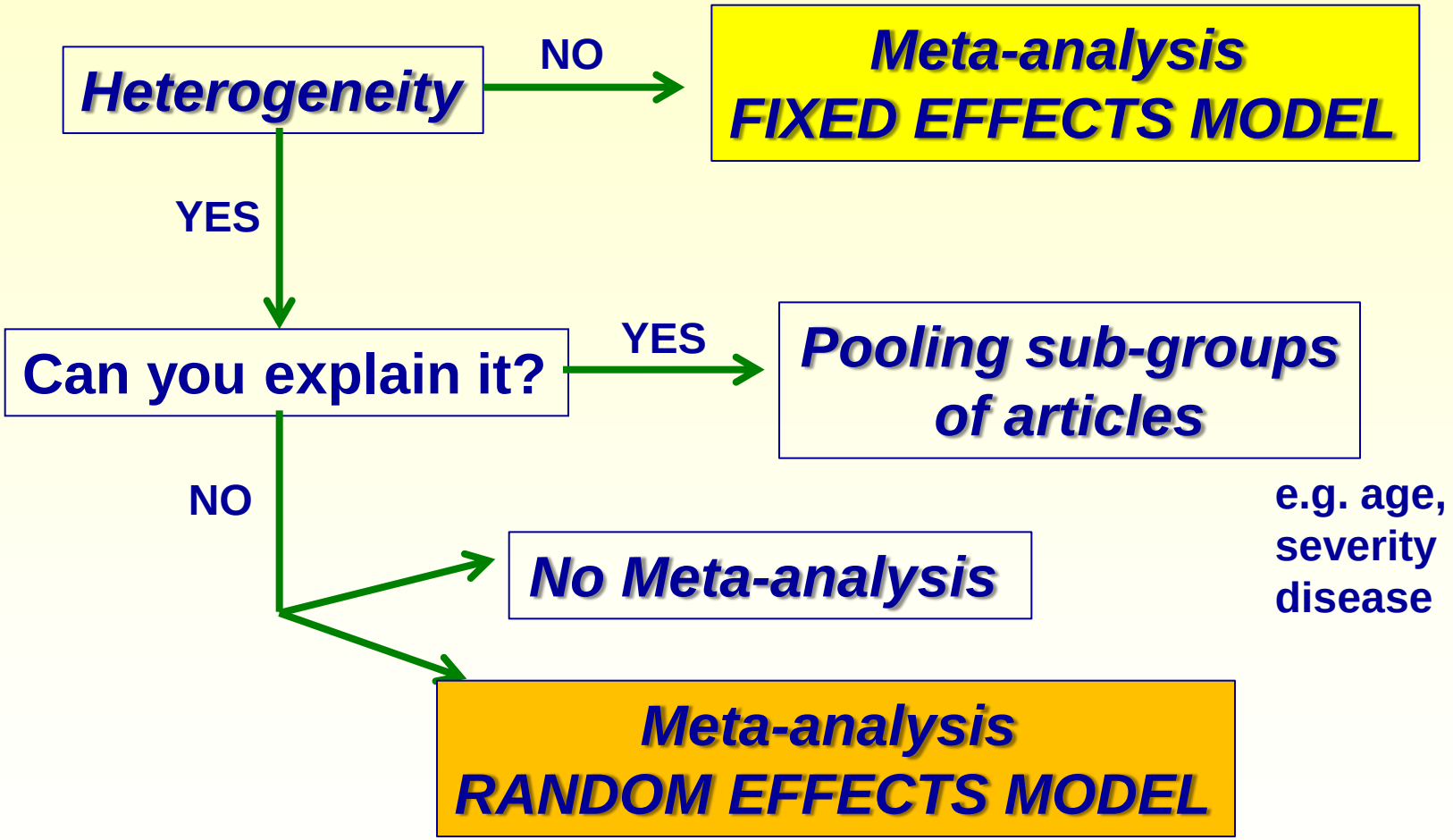
Random Effect Model

- It assumes that the true effect estimate for each study vary
- It allows variation between studies as well as within studies

Sources of Between Study Heterogeneity

- Different study designs
- Different incidence rates among unexposed
- Different length of follow-up
- Different distributions of effect modifiers
- Different statistical methods/models used
- Different sources of bias
- Study quality

In presence of heterogeneity



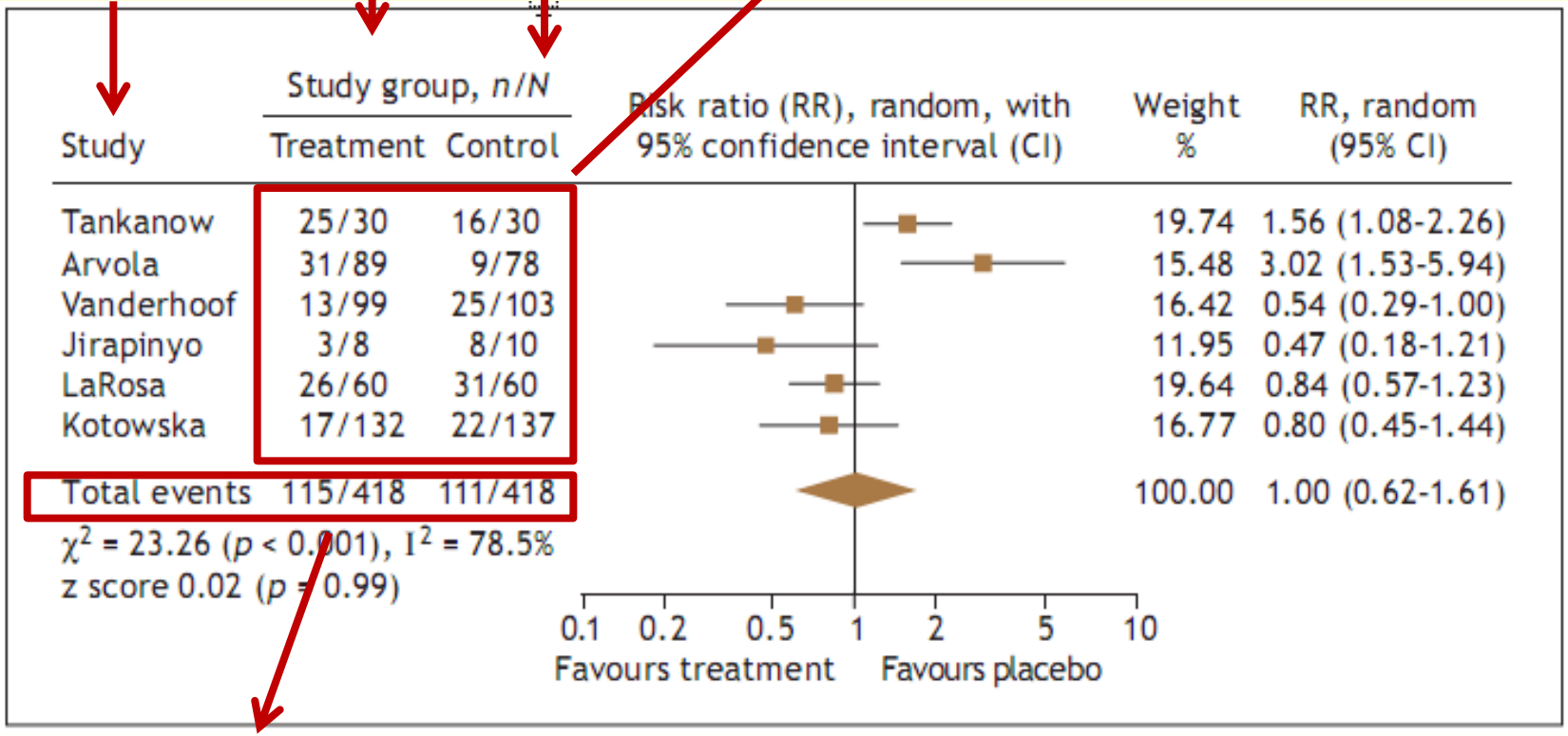
Forest plots

List of included studies

Intervention

Control

Raw data for each study

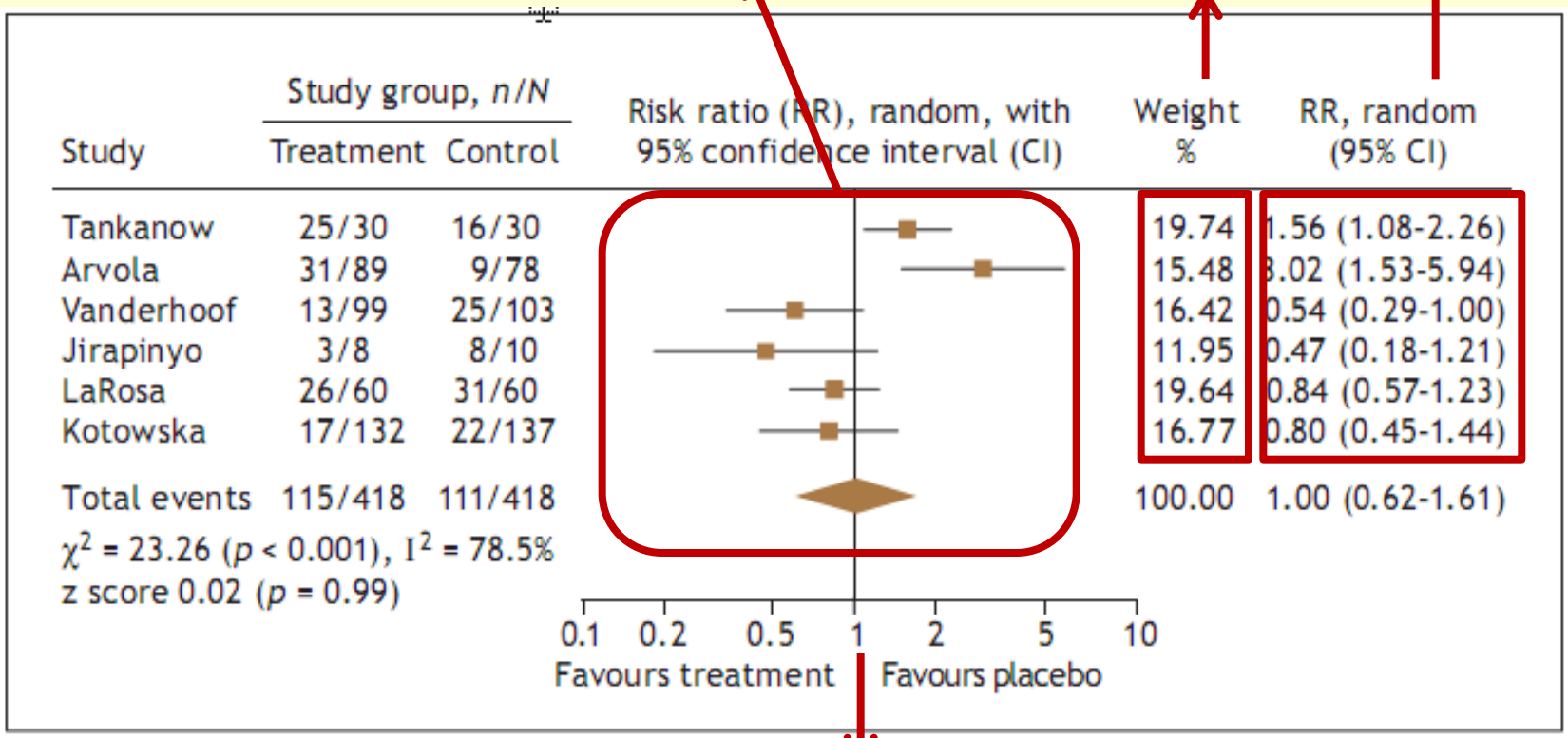


Total data for all the included studies: the total number of events and participants in the intervention groups and control groups.

The individual study results are also presented graphically. The coloured square shows the effect estimate and the size of the square corresponds to the weight given to the study in the meta-analysis. The horizontal line shows the confidence interval.

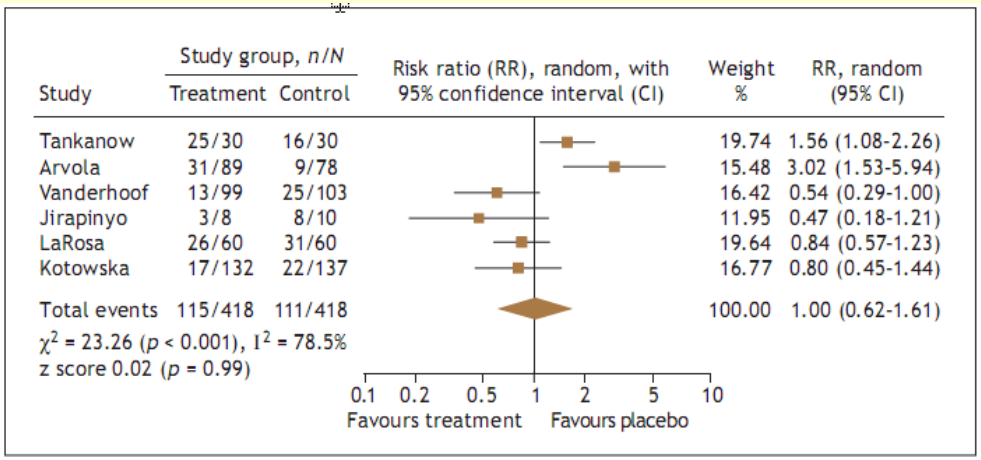
Effect estimate for each study with 95% CI

Weight assigned to each study

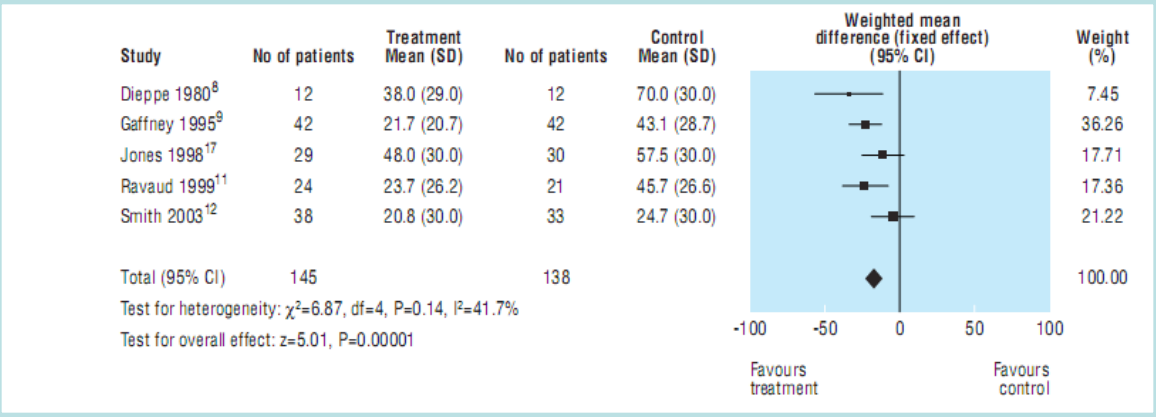


The vertical line down the middle indicates the line of no effect (in this case, for a ratio, at 1)

The vertical line down the middle indicates the line of no effect



For a ratio, as OR or RR, fixed at 1



For MD fixed at 0

Relative risks and confidence intervals

- ***RR is a ratio***
  - Values "significantly" >1 indicate increase in risk with increased exposure
  - Values "significantly" <1 indicate protective effect of exposure
  - Values "close" to 1 indicate no significant effect

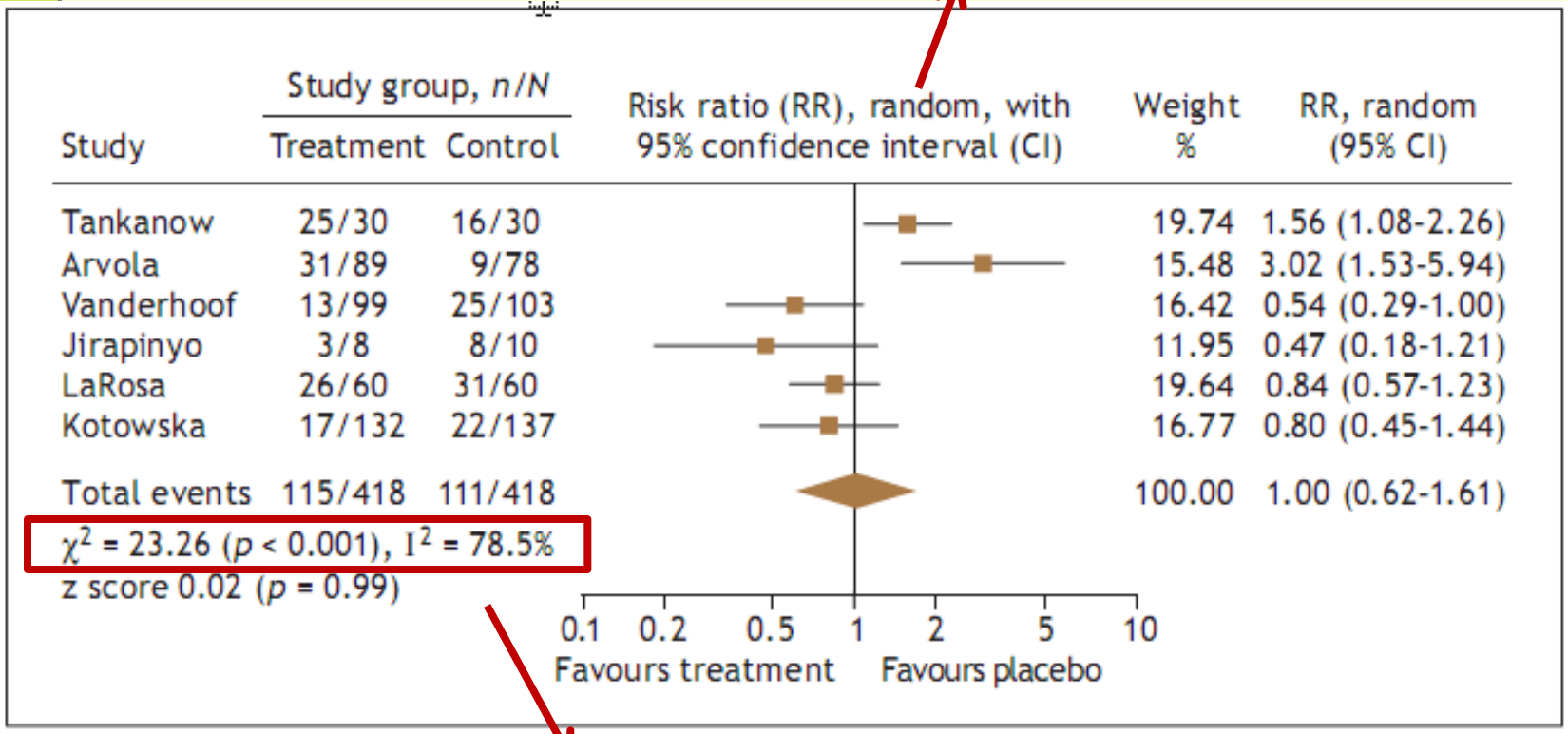
- ***95% confidence interval***
  - Gives a range of values within which we are "confident" the true relative risk lies

Interpreting confidence intervals

- Always present estimate with a confidence interval
- **Precision**
- CI expresses uncertainty – range of values we can be reasonably sure includes the true effect (CI represents the range of values we can be reasonably sure includes the true value of the effect – for a 95% CI, if we repeated the study indefinitely, the CI would include the true effect 95% of the time)
- **Significance**
- if the CI includes the null value (the result is not statistically significant at that level, e.g. a 95% CI corresponds to a P value of 0.05, a 90% CI corresponds to a P value of 0.1)
- rarely means "evidence of no effect" better "no evidence of effect"

A non-significant result may mean that we don't have enough information to be certain that the intervention works, but if we had more studies our precision might increase. Alternatively, if we have lots of studies, and a very precise result sitting right on the line of no effect, then perhaps we can be certain that the intervention has no effect.

Random effects model

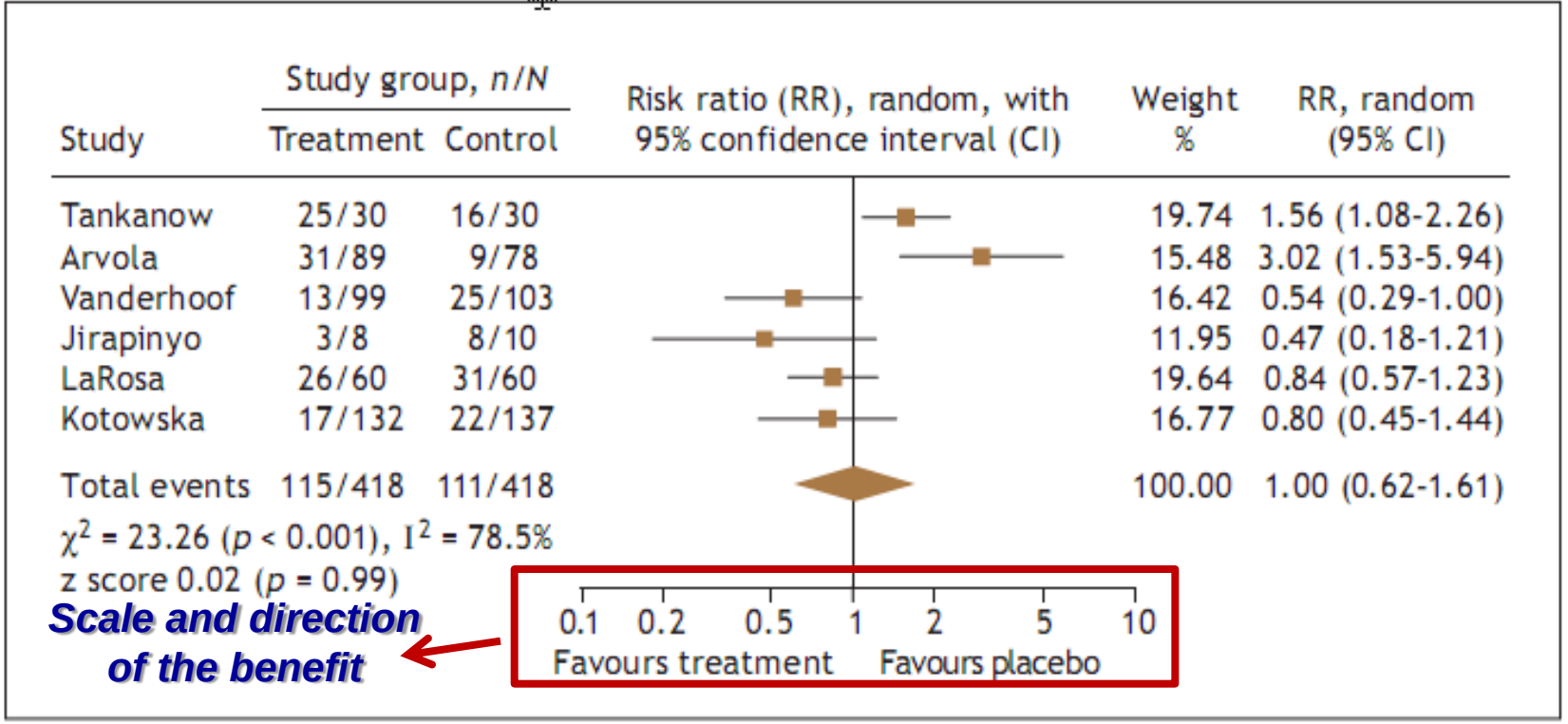


Test for heterogeneity

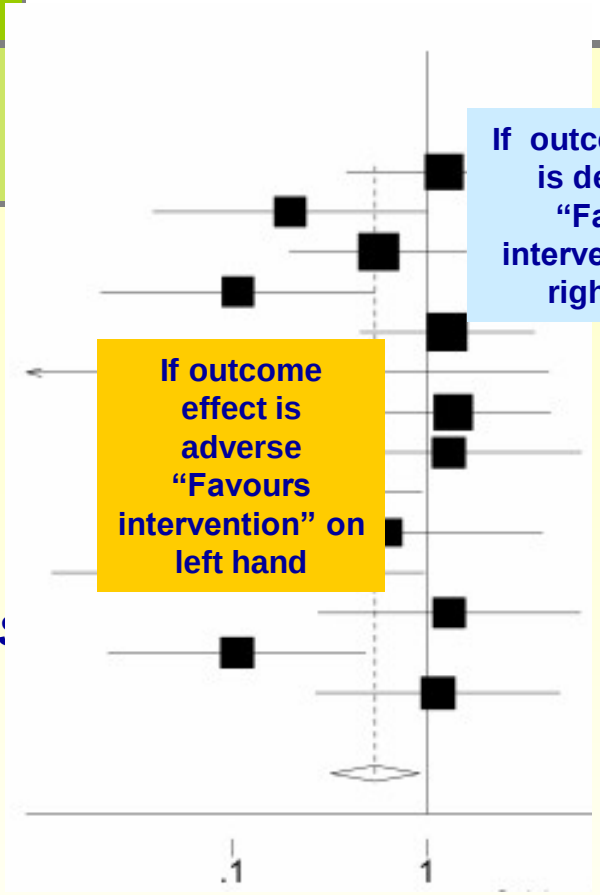
I^2 test (heterogeneity)

0 to 40%: Might not be important
30 to 60%: May be moderate
50 to 90%: May be substantial
75 to 100%: May be considerable

the "whiskers" of the IC do not overlap = high heterogeneity



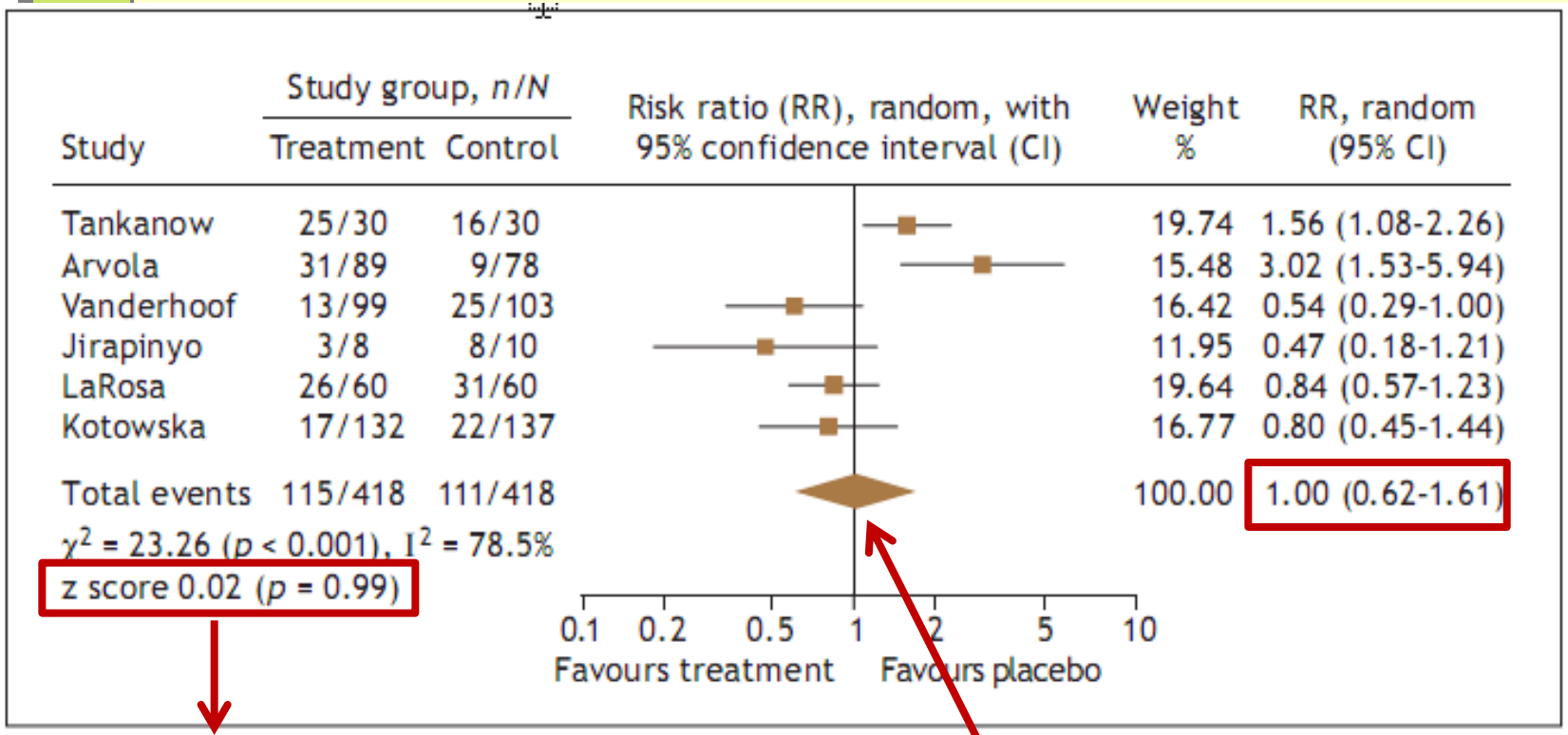
Note that for *ratios* the scale is a *log scale*. Value of 1 represents no effect. For an absolute effect, the scale is symmetrical, showing positive and negative values around 0 as the point of no effect. Below the scale is an indication of which side of the plot favours the intervention. Differences with a negative sign (left of the vertical equivalence) indicate a higher incidence of events in the controls and therefore a therapeutic benefit of the experimental treatment.



If you're measuring something good, such as recovery or quality of life, then a result on the right side will be a good outcome for the intervention, because you want an increase in your outcome.

If you're measuring something bad, such as pain, then a result on the left side of the scale will indicate a favourable result for your intervention, because you wanted to reduce the outcome. A result on the right side will be bad for the intervention, because it indicates an increase in the negative outcome, and so results on the right side favour the control.

Pooled result for all studies combined is presented at the bottom, both in numbers and graphically.



Test for overall effect

Overall effect
Trivial: 0.0 < 0.2
Small: 0.2 < 0.5
Moderate :0.5 < 0.8
Large: > 0.8

The result is shown graphically as a diamond. The width of the diamond represents the confidence interval.

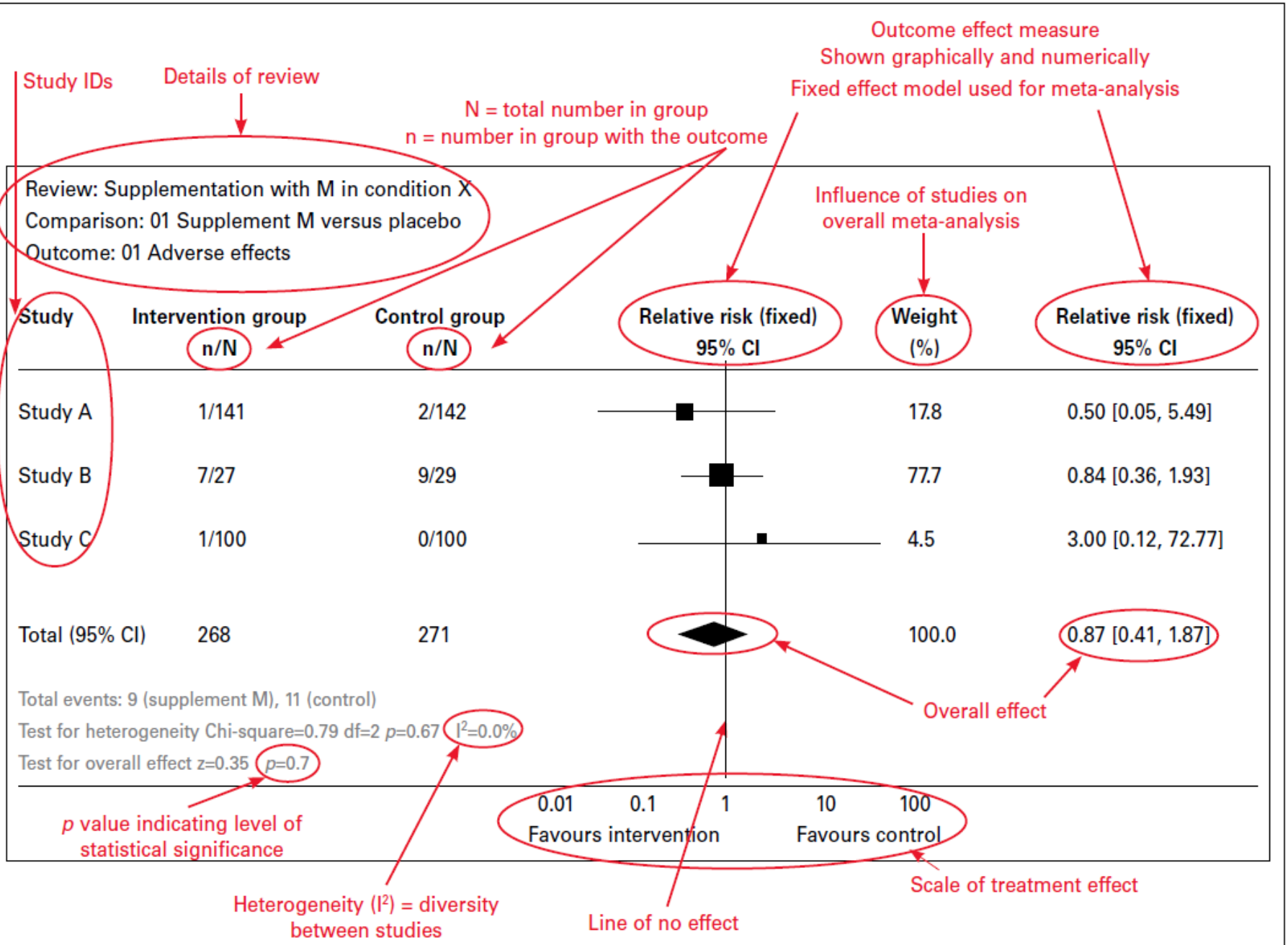


Figure 1. Meta-analysis of binary outcome measure

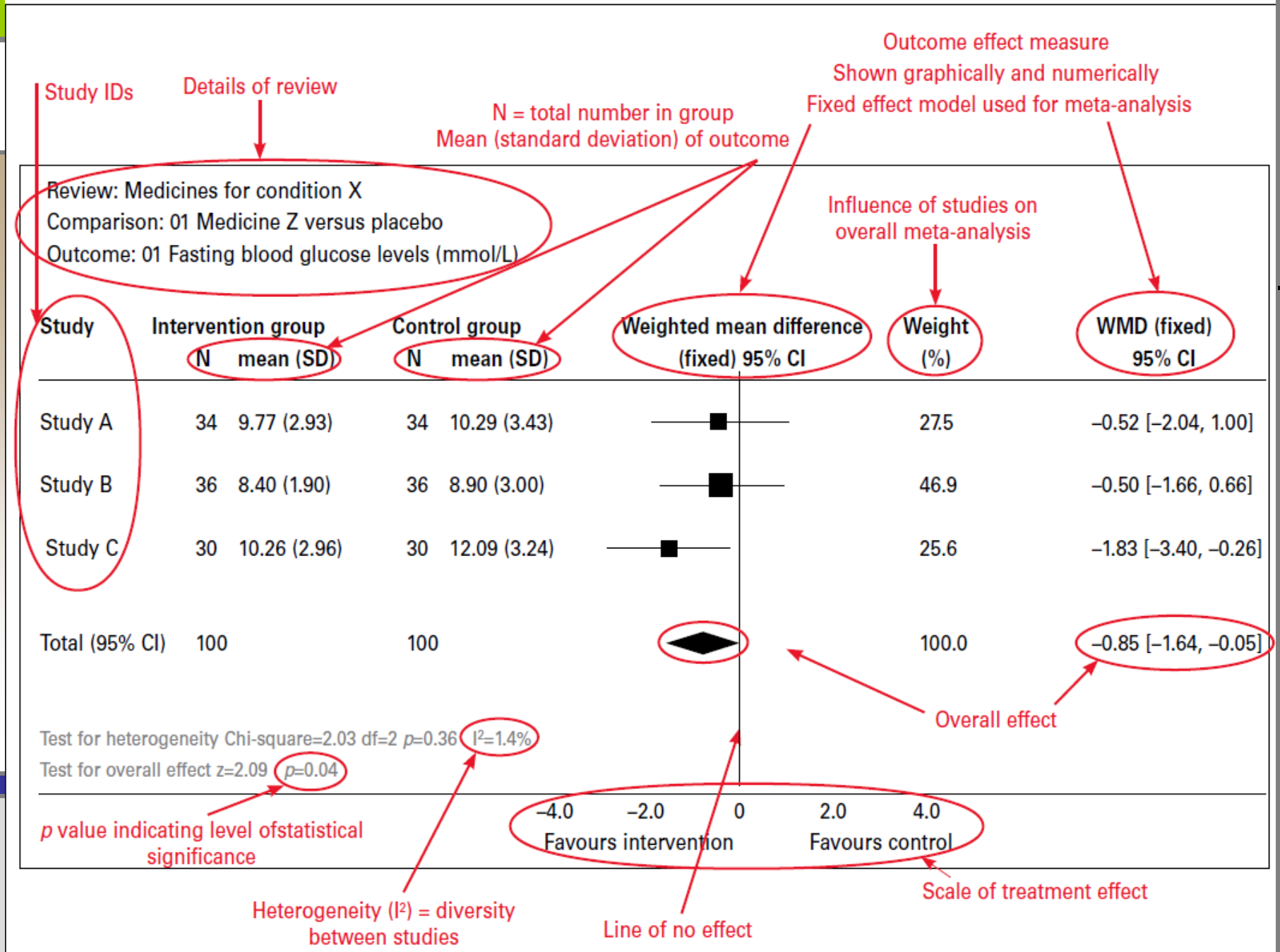


Figure 2. Meta-analysis of continuous outcome measures

Publication bias

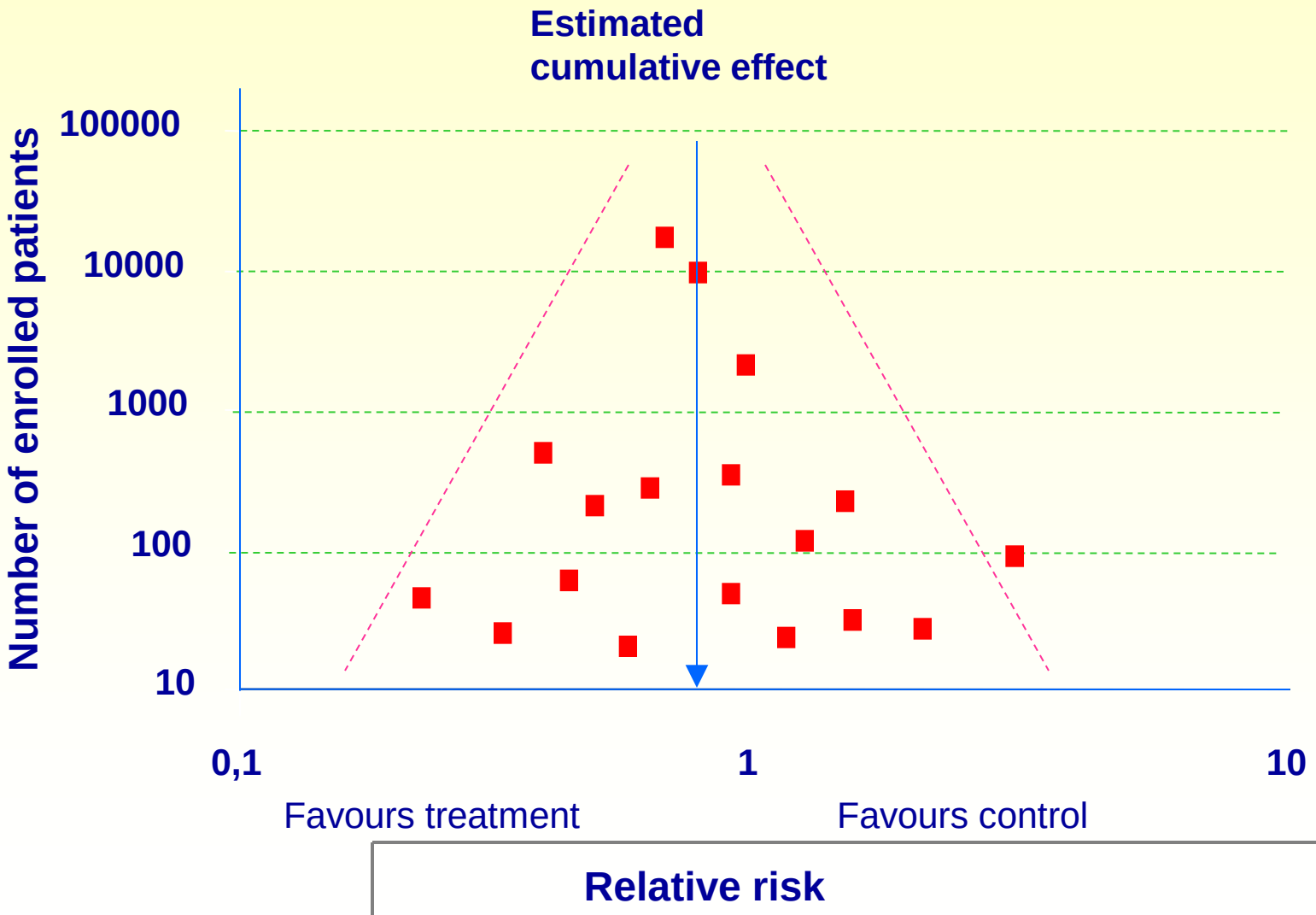
- Positive and statistically significant studies are more likely to be published.
- Negative studies, especially if small, tend to be not published.

To estimate the extent of publication bias we can use the method of inverted funnel, based on the fact that the measures of the effect should be distributed randomly around the average effect with less variation in the studies more numerous than in small ones.

Publication bias occur when:

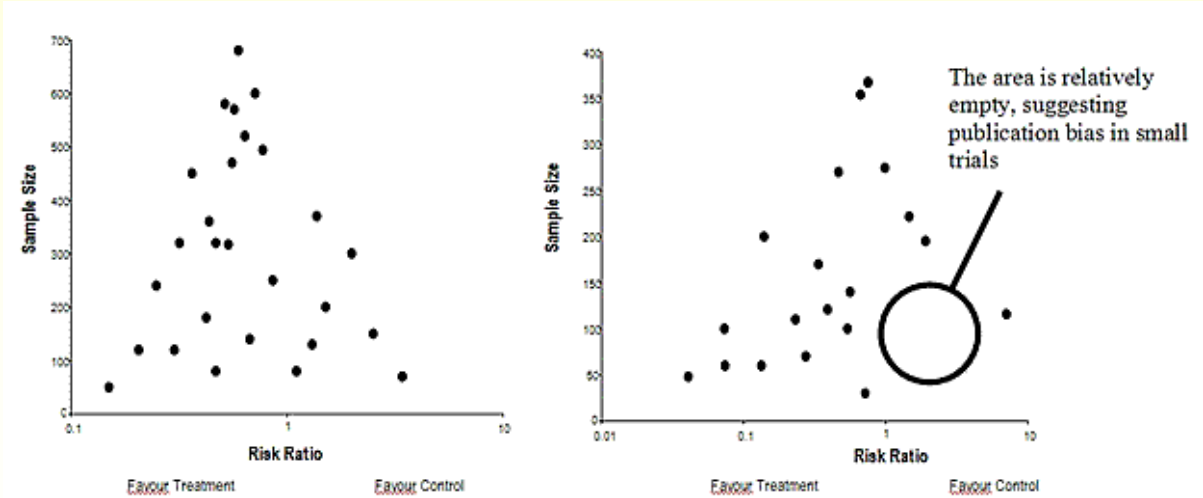
- Project dropped when preliminary analyses suggest results are negative
- Authors do not submit negative study
- Results reported in small, non-indexed journal
- Editor rejects manuscript
- Reviewers reject manuscript
- Author does not resubmit rejected manuscript
- Journal delays publication of negative study

Funnel Plot

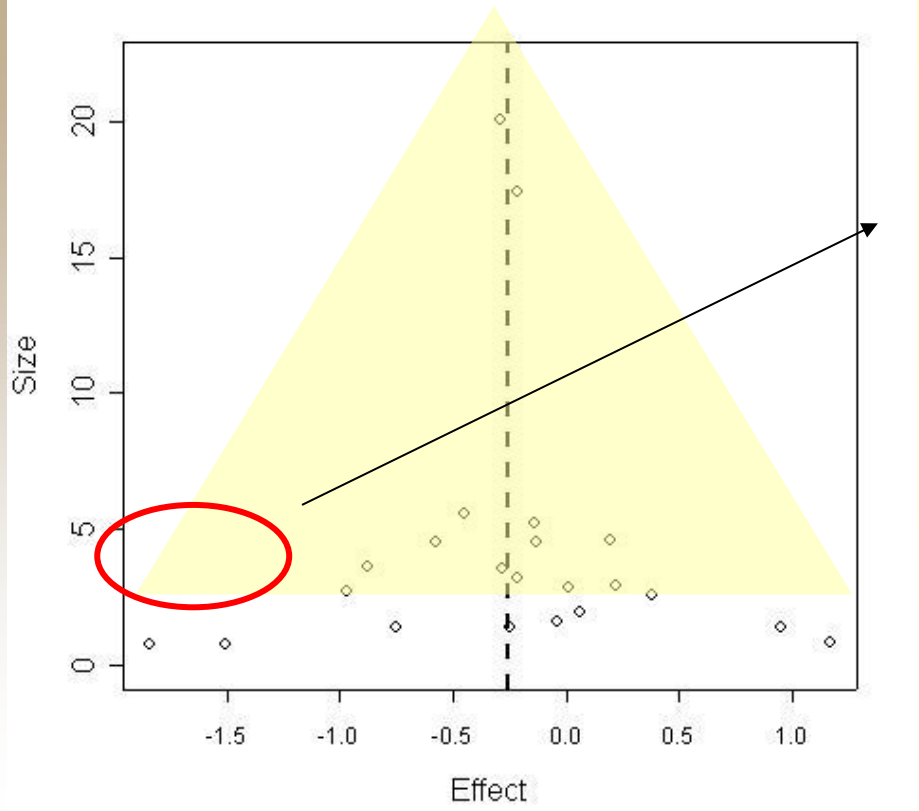

Estimated
cumulative effect
Number of enrolled patients
100000
10000
1000
100
10
0,1
1
10
Favours treatment
Favours control
Relative risk

Funnel Plot

Drawing in a graph the measurement of effect on the abscissa and the size of the study on the ordinate, the various points, each corresponding to one study, should draw a sort of inverted funnel. The publication bias means that are more or less rare points from a bottom side, e.g. those corresponding to smaller studies and results with the most unfavorable result for the treatment of interest.

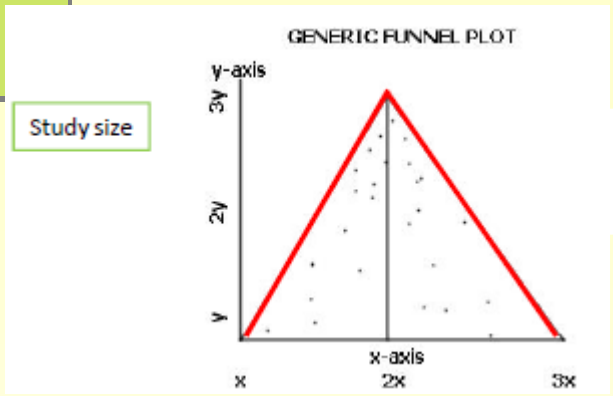


Funnel Plot



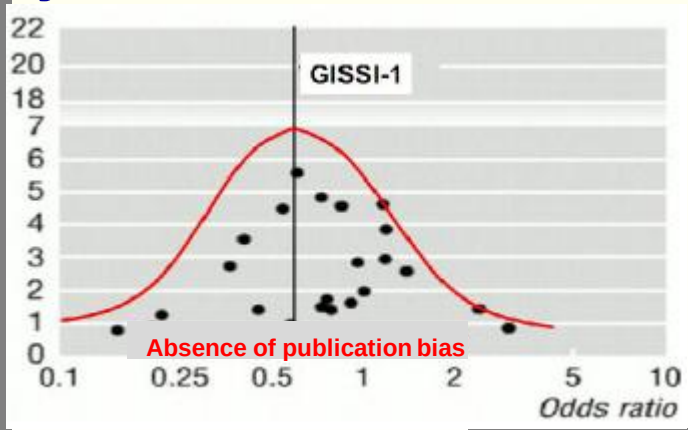
To study a funnel plot, look at its lower left corner, that's where negative or null studies are located → if empty, this indicates "PUBLICATION BIAS"

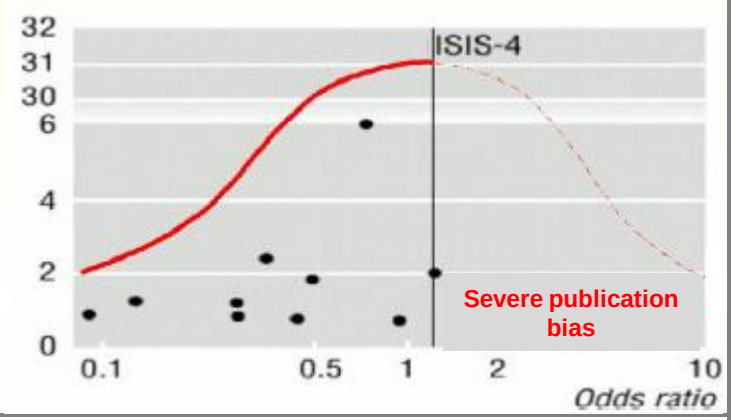
Note that here, the plot fits in a funnel, and that the left corner is not all that empty, but we cannot rule out publication bias



An image similar to an inverted funnel, symmetrical, evidences the presence of a good "data set", with absence of publication bias

If graphical representation shows heterogeneity from the results of individual studies, meta-analysis is not justified





Sponsorship bias

- **Published trials with industrial sponsor have a greater chance to have positive results than those with non profit sponsorship.**

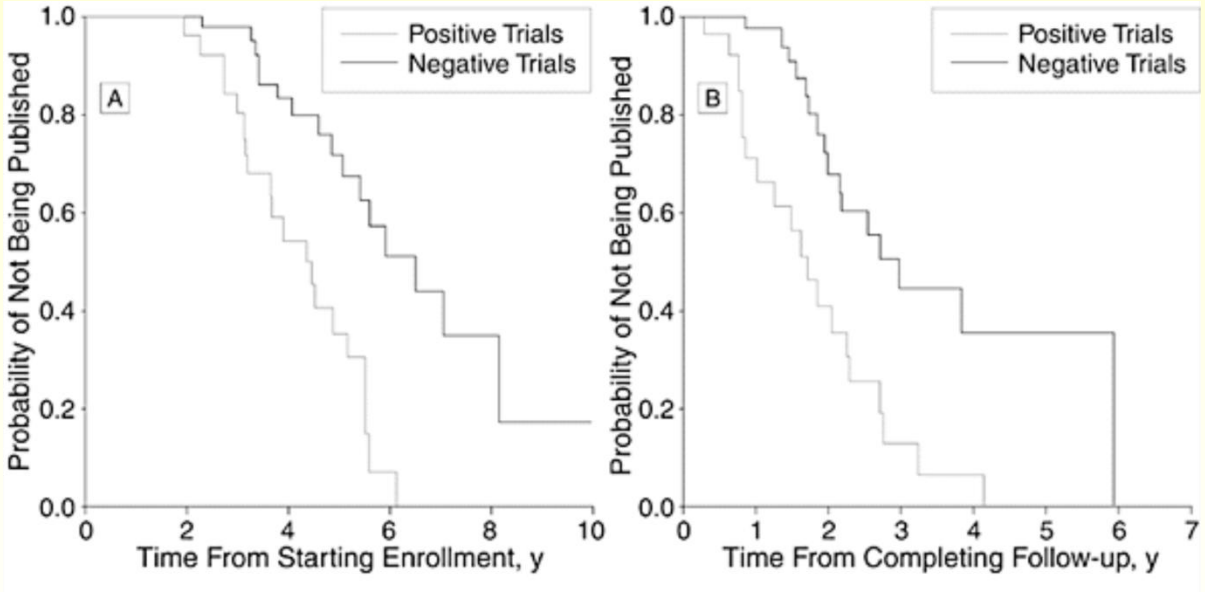
Table 2. Relation Between Industry Sponsorship and Study Conclusion and Study Design

Source	Study Design	Study Sample	No. of Studies*	Definition of Industry Sponsorship	Study Outcome Defined*	Blinded Review†	Findings: No. (%) With Pro-industry Conclusion: Industry	Findings: No. (%) With Pro-industry Conclusion: Nonindustry	*P* Value‡
Industry Sponsorship vs Study Conclusion									
Davidson,[38] 1986	Systematic review	RCTs published in 5 general medical journals	107	A, B	Yes	Yes	33 of 37 (89)	43 of 70 (61)	.002
Djulbegovic et al,[40] 2000	Systematic review	RCTs involving multiple myeloma	136	A, C	Yes	Yes	26 of 35 (74)	50 of 95 (53)	.03
Yaphe et al,[39] 2001	Systematic review	RCTs published in 5 general medical journals	314	A, C, D, H	Yes	No	181 of 209 (87)	62 of 96 (65)	<.001
Kjaergard and Als-Nielsen,[48] 2002	Systematic review	RCTs published in *BMJ*	159	§	Yes	Yes	25 of 27 (93)	71 of 105 (68)	.009‖
Friedberg et al,[43] 1999	Systematic review	Economic analysis of oncology drugs	44	A	Yes	No	12 of 20 (60)	10 of 24 (42)	.23¶
Cho and Bero,[41] 1996	Systematic review	Original clinical drug articles	152	A, C, D	Yes	Yes	39 of 40 (98)	89 of 112 (79)	.01
Turner and Spilich,[42] 1997	Systematic review	Articles investigating nicotine and cognitive performance	91	A, D	Yes	No	27 of 35 (77)	29 of 56 (52)	.02
Swaen and Meijers,[44] 1988	Systematic review	Retrospective cohort studies	179	D	Yes	No	34 of 72 (47)	28 of 107 (26)	.001
Rochon et al,[45] 1994	Systematic review	RCTs of NSAIDs	61	A, C, D, E	Yes	Yes	15 of 52 (29)	No studies reported	NA
Stelfox et al,[46] 1998	Systematic review and survey	Authors of articles on calcium channel blockers	69	A, D, F	Yes	Yes	24 of 47 (51)	0 of 22 (0)	<.001
Barnes and Bero,[47] 1998	Systematic review and secondary data analysis	Review articles on the health effects of passive smoking	106	A, E, G	Yes	Yes	29 of 31 (94)	10 of 75 (13)	<.001

Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003 Jan 22-29;289(4):454-65.

Publication lag

- **Trials with negative results tend to be published with greater delay than those with positive results.**



Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA. 1998 Jan 28;279(4):281-6.

Possible sources of systematic error in a meta-analysis

- Selection bias
  - Inclusion criteria
  - Size of the studies: less quality in little studies
  - Quality of the studies (randomization, double blind, follow-up time)
- Heterogeneity of the studies
- Publication bias
  - Studies with positive results are more readily published
  - Exclusion of articles not published in English
  - Citation bias (more likely to be cited by others)
  - Multiple citation bias (more likely to be published more than once)

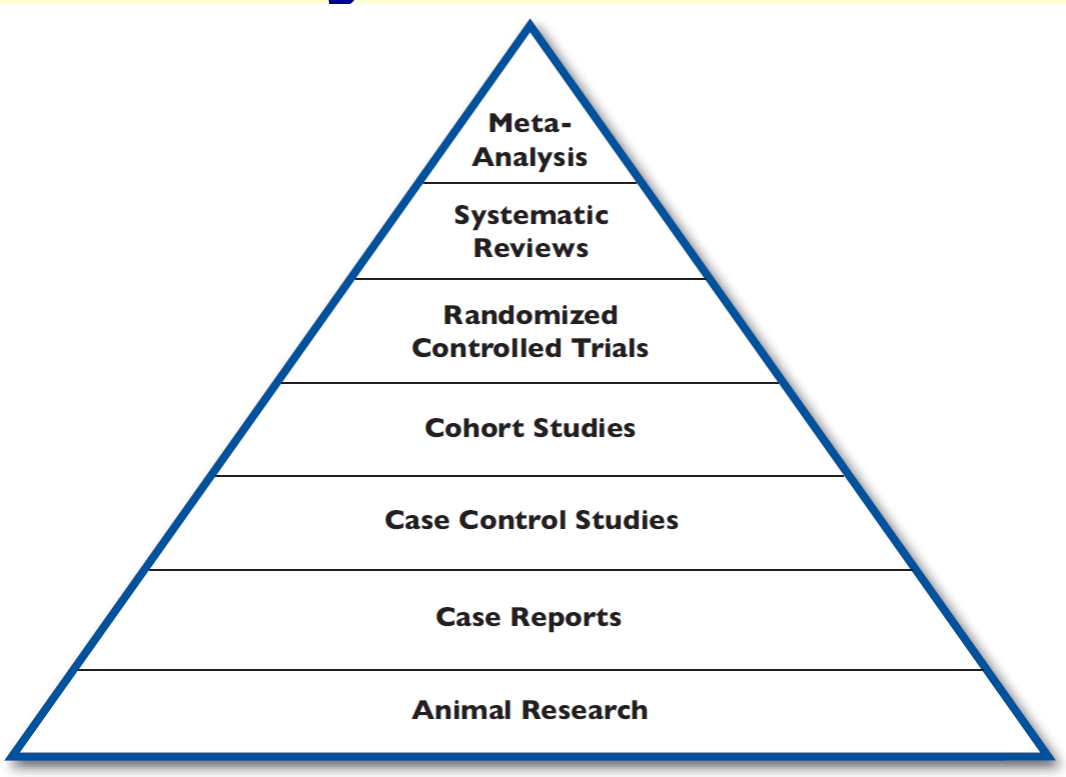
Advantages of meta-analysis

- They are the only way, even if imperfect, to synthesize the scientific evidence produced in a specific aspect of interest
- They constitute an objective and reproducible measure and thus avoid the problems of conflicts of interest and authoritative opinions (“ipse dixit”)
- They give an overall estimate of the effect that exceeds the limits of size of the individual studies, in particular for studies with small sample
- They allow analysis of subgroups
- They are relatively quick and inexpensive

Limits of meta-analysis

- The quality of the meta-analysis depends on the quality of the studies
- They can provide different results depending on the weight assigned to the various studies and methods of analysis
- They should take into account the quality of the studies, but to date there is no standardized criteria for evaluating the quality of scientific papers
- The lower probability of publication of trials with negative results amplifies the weight of the trials with positive results
- A meta-analysis can detect but not correct publication bias or methodological errors in study conduction
- It requires the same methodological rigor of “primary” studies and can be equally affected by systematic errors

Meta-analysis….. what else?



In vitro research

EVIDENCE BASED MEDICINE

CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines

Clinical practice guidelines are recommendations for clinicians about optimal and appropriate care for specific situations.

- **Basis for most clinical decisions**
- **Foundation of clinical teaching**
- **Mental short-cuts and memory aids for common or complex problems**
- **Primary method to evaluate care patterns and monitor standards of care**

Evidence Based Medicine

Evidence based medicine is the *conscientious*, *explicit*, and *judicious use* of *current best evidence* in making decisions about the *care of individual patients*.

Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312: 71-2

- **EBM specifically advocates for individualized application of evidence to patient care, not forcing patient care to conform to generalized evidence**

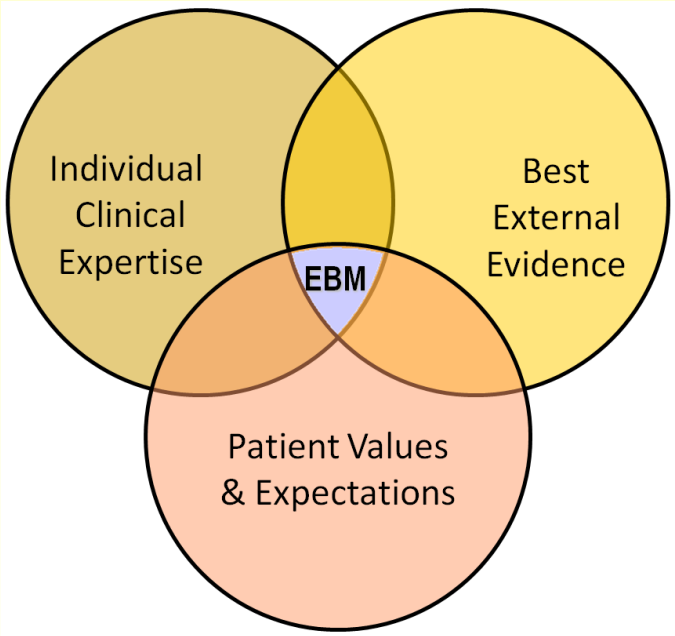
- **EBM is intended to guide practitioners to provide the best, not necessarily the cheapest, care**

- **EBM is not intended to be only concerned with randomized controlled trials, but with the best relevant evidence applicable to the situation in question**

Evidence Based Medicine

- The revised and improved definition of evidence-based medicine is

> **"the integration of the best research evidence with clinical expertise and patient values"**



- It reflects a systematic approach to clinical problem solving

Sackett DL, Strauss SE, Richardson WS, et al. Evidence-based medicine: how to practice and teach EBM. 2nd Ed. London: Churchill-Livingstone, 2000

Cochrane Library

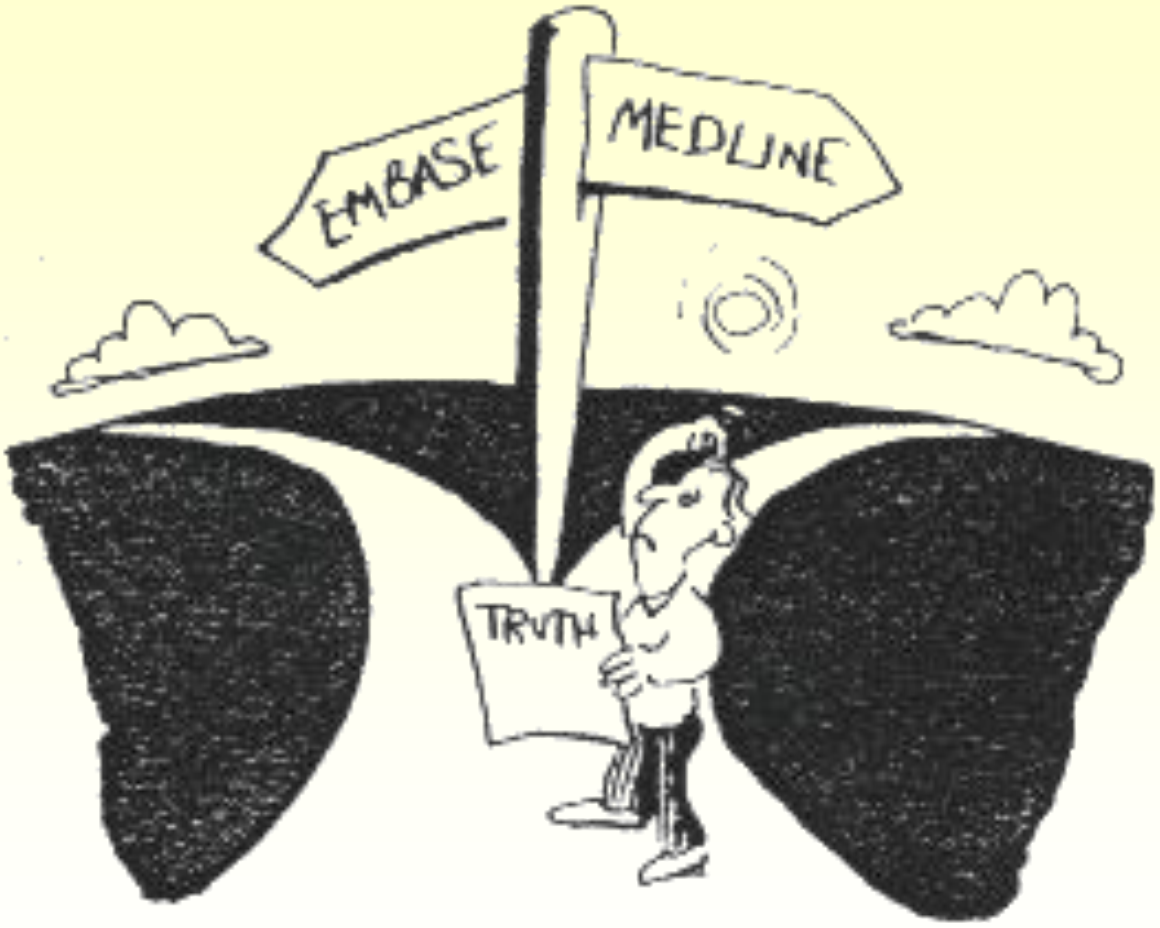
- It is an international non-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.
- The major product of the Collaboration is the Cochrane Database of Systematic Reviews which is published quarterly as part of The Cochrane Library.
- Those who prepare the reviews are mostly health care professionals who voluntarily work in one of the many Collaborative Review Groups, with editorial teams overseeing the preparation and maintenance of the reviews, as well as application of the rigorous quality standards for which Cochrane Reviews have become well known.

ACP Journal Club

- About 140 internal medicine journals systematically surveyed
- Highest-validity articles abstracted
- Structured abstracts to guide critical appraisal
- Clinical commentary
- Web site acpjc.org
- Also published in Annals of IM

In Italy?

http://www.gimbe.org


EMBASE
MEDLINE
TRUTH