Systematic reviews- a clinical perspective

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Hierarchy of evidence table: (Oxford CEBM)

1A	**Systematic reviews of RCTs**
1B	Individual RCTs (with narrow CI)
1C	All other RCTs
2A	***Systematic reviews of cohort studies***
2B	Cohort study
2C	"Outcomes" Research; Ecological studies
3A	***Systematic review of case-control studies***
3B	Case-control study
4	**Case-series**
5	**Expert opinion** *without explicit critical appraisal*

Systematic review and meta analysis

- **Systematic review:** When literature is the subject of research
- **Meta analysis**: Results of several studies are combined mathematically to provide a summary estimate

- SR with/without meta analysis: Quantitative/Qualitative
- SR could be for RCTs, non-RCTs, diagnostic studies etc.

Note: Today's focus is on systematic reviews of RCTs

Advantages of systematic reviews

- High volume of publications; most RCTs are small

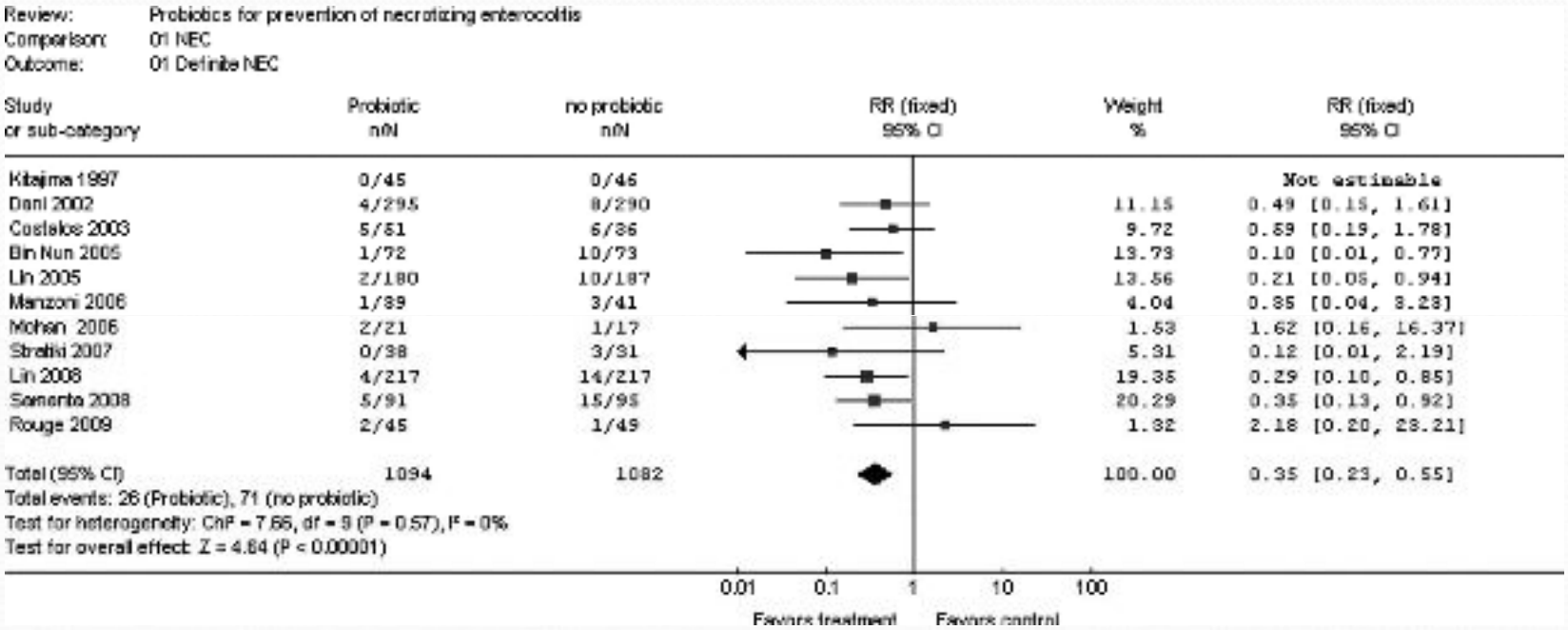
- SRs increase power and precision of effect size, provide summary of evidence
- Help DMCs in deciding whether to continue an RCT
- Help individual units to decide whether it is ethical to continue recruiting patients into a trial
- Can challenge existing practice, identify research priorities

- SRs are prerequisites for future trial design

Iain Chalmers. BMJ Books 2001

Probiotics reduce the risk of NEC in preterm infants

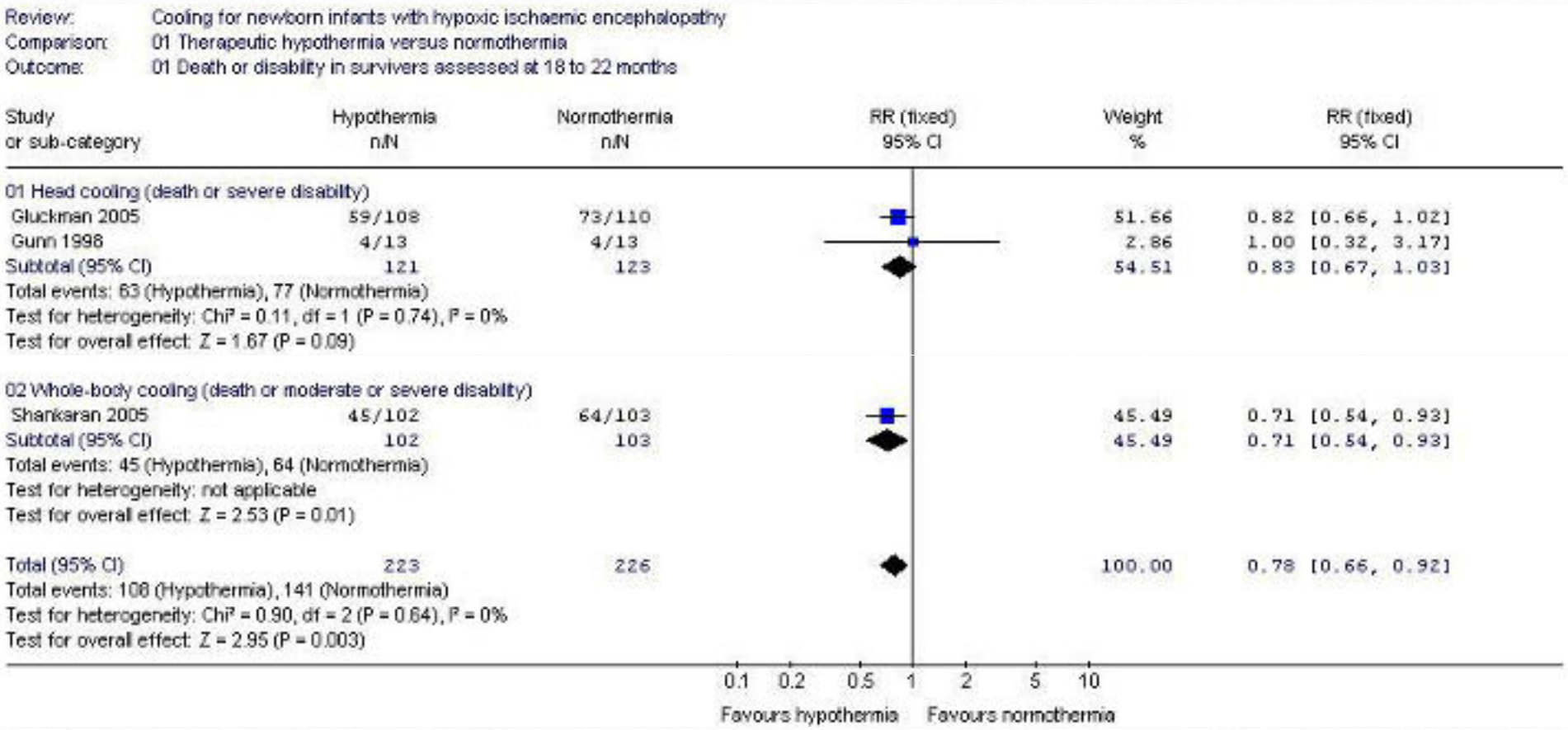
Deshpande et al Pediatrics 2010



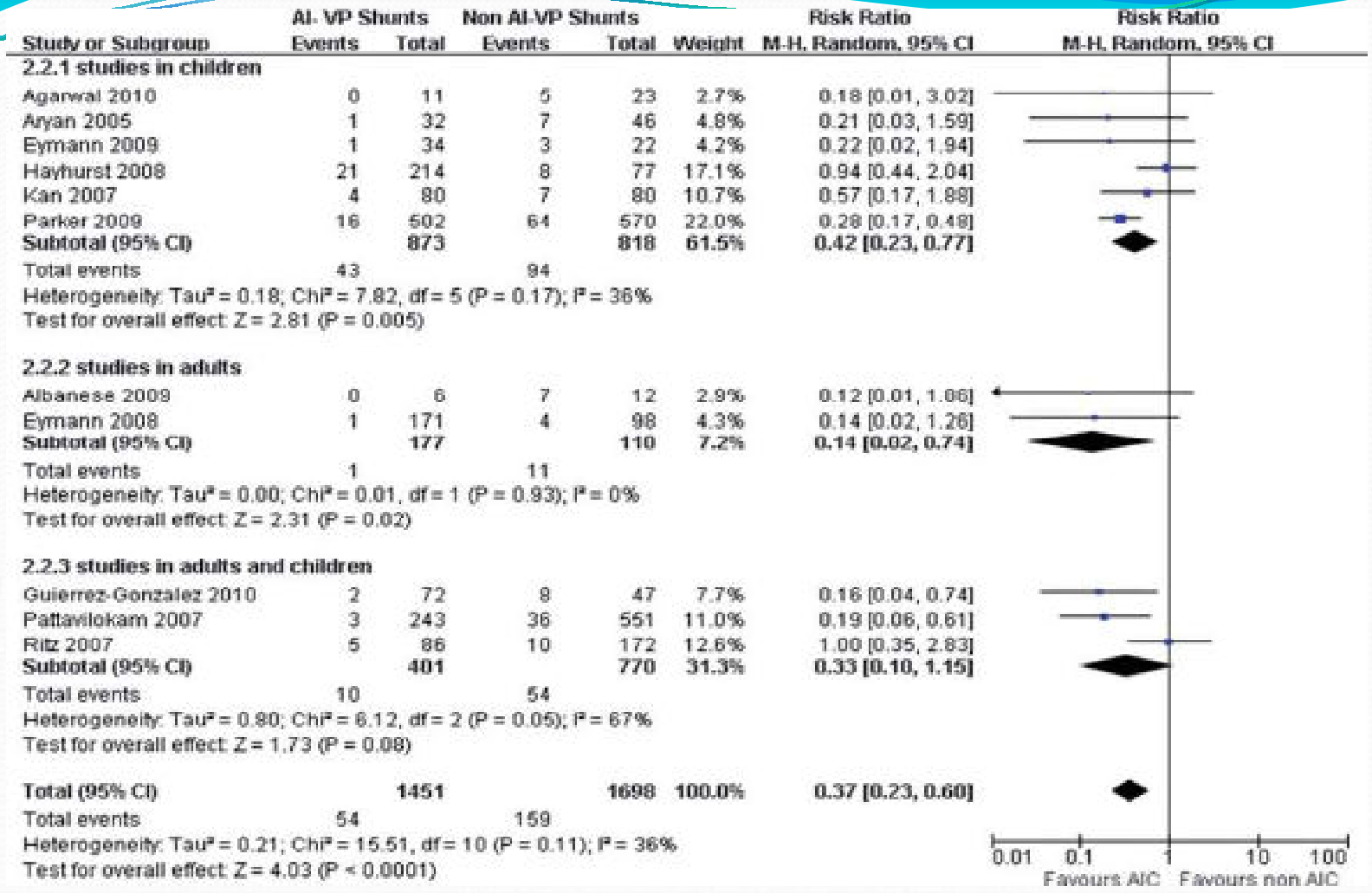
Note: Majority of Australian neonatal units now use probiotics

Cooling for hypoxic ischemic encephalopathy

Schulzke et al. BMC Pediatrics 2007



We decided to continue participation in the ICE trial considering the small sample size (n=449) in this systematic review



AI-VP shunt catheters may decrease shunt infections

Thomas et al. B J Neurosurgery 2011

How to conduct a systematic review

Clinical question must be clearly defined and should include

- **Population of interest (P)**
- **Intervention (I)**
- **Comparator (C)**
- **Outcome (O)**
- **Study design (S)**
- **Time (T)**

Register title, write protocol, receive feedback, start work

Key areas covered in the protocol

- Why?
- Which studies? (Inclusion - Exclusion criteria)
- Search strategy (What, where, how, who etc.)
- Study selection
- Method of data extraction
- Assessment of risk of bias
- Statistical methods used to combine data
- How the results will be disseminated

Literature search

- PubMed: Available free on internet.
- **Medline and Embase**: OVID platform from library
- 70% of the citations in Embase are not on PubMed
- **CINAHL**: EbscoHost platform
- Cochrane register of controlled trials (**CENTRAL**)
- **Grey literature and experts**

Bias vs. Error

- **Bias:** *Systematic deviations* from the true underlying effect (False positive or negative results)
- **Reasons:** Poor study design--conduct--analysis--interpretation, or issues with publication and review
- **Risk of bias:** Classified as Low/High/Unclear
- **Error:** This is a *mistake* (i.e. wrong entry of numbers)

Risk of bias (ROB)

- It is not necessary to exclude studies with high ROB
- Cochrane collaboration allows for quasi-random studies
- ROB could be used for sensitivity analyses
- Studies with lowest ROB are analysed together
- The results compared to the analysis of all studies

Assessing ROB in RCTs

Generation of random sequence

Low risk: Using computer generated random numbers

High risk: Sequence generated by

- Odd or even date of birth
- Day of admission
- Clinician or patient's preference
- Availability of intervention

Allocation concealment

Intervention to be allocated to a participant can not be known in advance

- **Low risk:** Central tel./computer-based randomisation
- **High risk:** Envelopes

Blinding

Carers and patients should not know what intervention they are receiving

- **Low risk:** Placebo **High risk:** No placebo
- Blinding may not be feasible in some RCTs

Blinding of outcome assessors

- Important for subjective outcome measures (e.g. pain)
- Less important for measures such as mortality

Incomplete outcome data

- Some patients drop out from RCTs
- Need to detail the number of drop outs and reasons

Selective reporting

- **High ROB:** Not all pre-specified outcomes reported

Data synthesis

Qualitative: Summaries and Tables

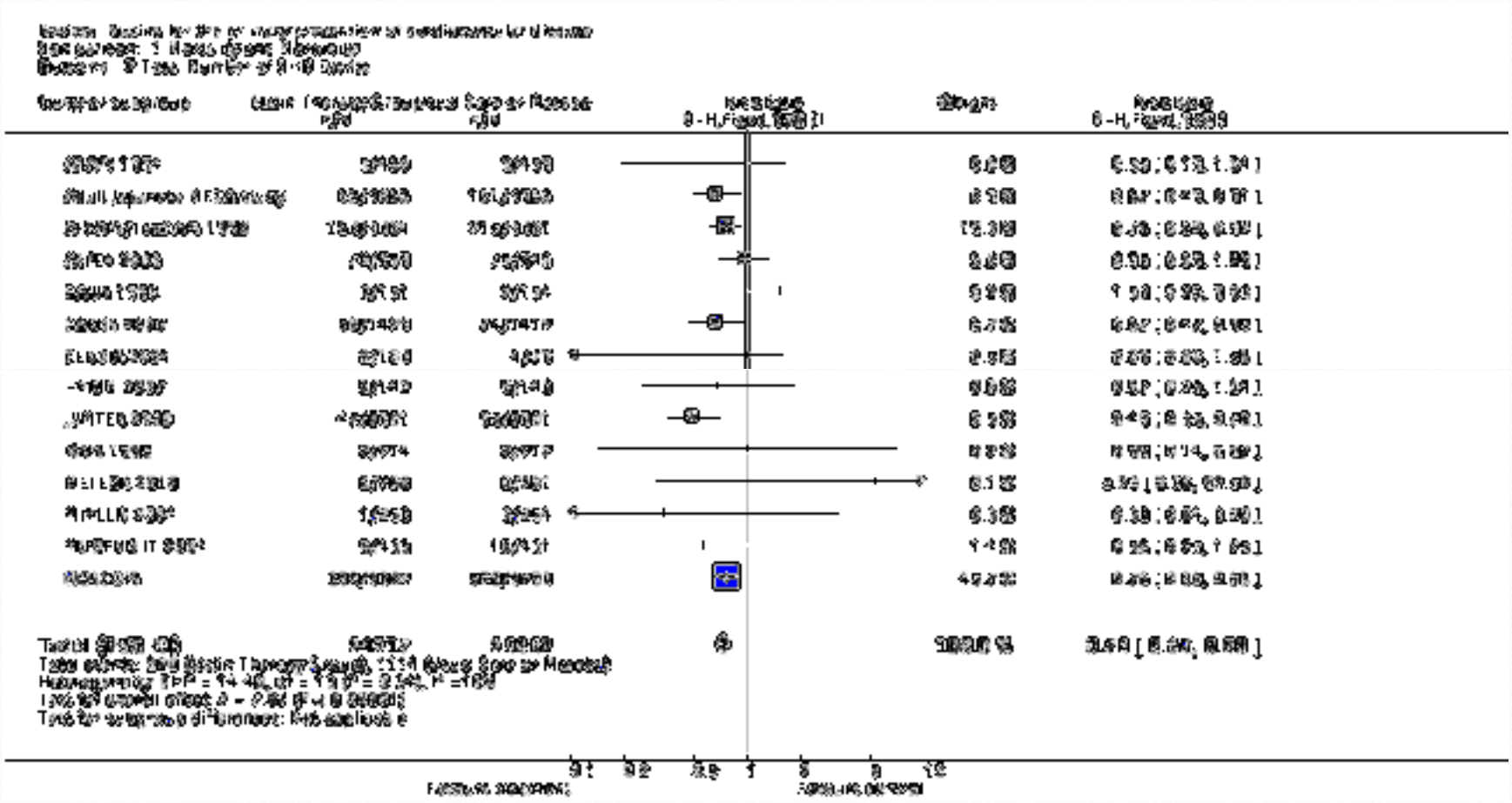
Quantitative: Meta analysis

Meta analysis

- Mathematical pooling of data (RevMan or other softwares)
- Gives an effect size estimate/meta estimate
- **Produces a "Forest plot"**

Statins for preventing cardiovascular disease

Taylor et al. Cochrane library 2013



Cardiovascular events are less with statins: RR: 0.73 (0.67, 0.80)

Forest plot

- Studies listed in chronological order, alphabetically or by study weight.
- Each study's estimated effect size is represented by a square, with the line representing the corresponding 95% confidence interval.
- Size of a study's square indicates its weight toward overall summary effect
- Weight is determined by sample size, baseline risk etc.

Forest plot

- The summary estimate is represented by a diamond
- Centre of the diamond: Point estimate
- Tips of the diamond: 95% Confidence interval

Analytical models for meta analysis

Fixed effects model

- Assumes that intervention is equally effective across all studies. (*Confident* assumption) Ignores "*Between study*" variation
- ***What is the best estimate of the effect?***

Random effects model

- Allows for '*within*' as well as '*between-study*' variability in effectiveness. (*Conservative* assumption)
- Being less confident, it usually has wider CIs and gives adequate emphasis on smaller studies.
- ***What is the average effect?***

Note: Neonatal Cochrane group recommends FEM

Exploring heterogeneity

- Heterogeneity (differences in results) could be due to differences in study design, characteristics (PICO), and conduct

- If heterogeneity exists in a meta analysis, one must explore it.

Conceptual (clinical) heterogeneity

- Studies of clinically diverse treatments, populations, setting, design etc.
- Don't pool data if significant clinical heterogeneity is present
- The results of studies should be combined only when the studies are homogenous (i.e. similar PICO and design)

Note: Don't forget Apples vs. Oranges, different types of apples

Statistical heterogeneity

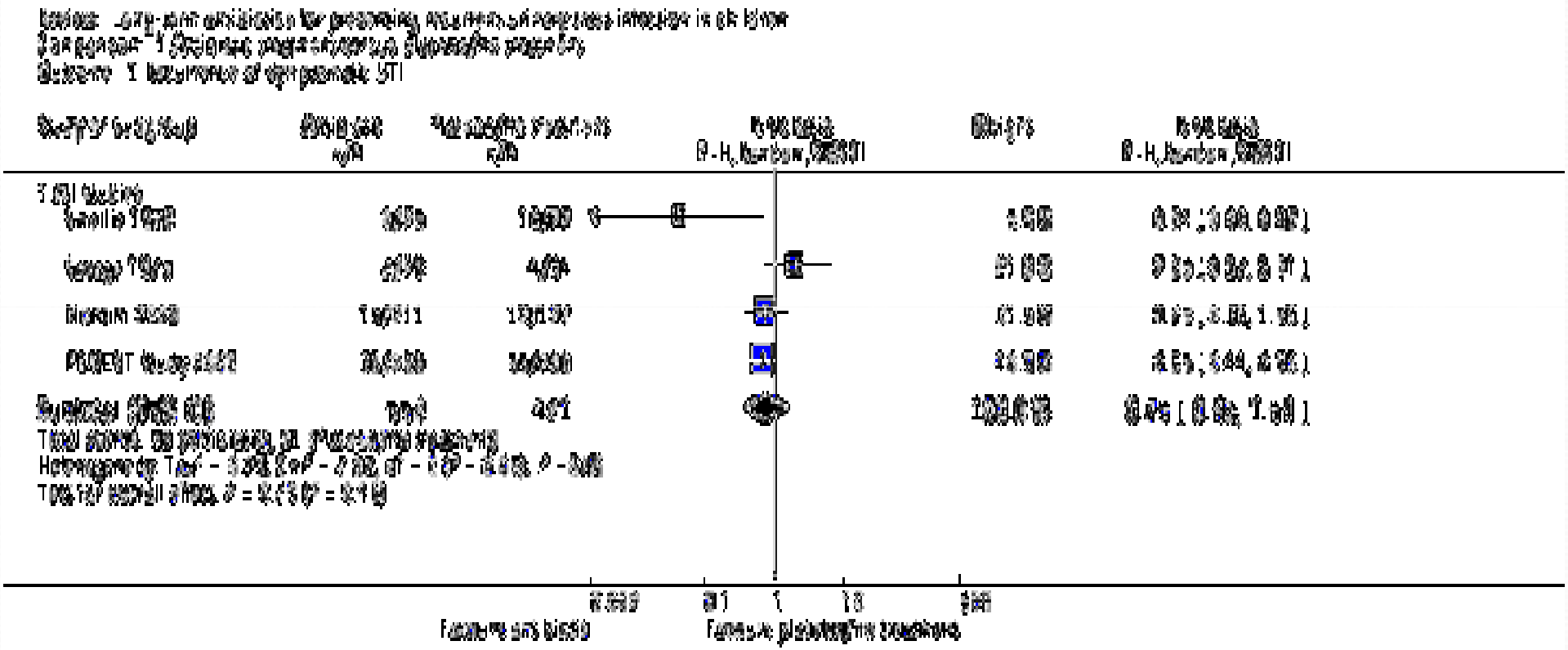
Chi squared test (Q): Is statistical heterogeneity present?

I squared test: Is the observed variability of effects greater than that expected by chance alone?

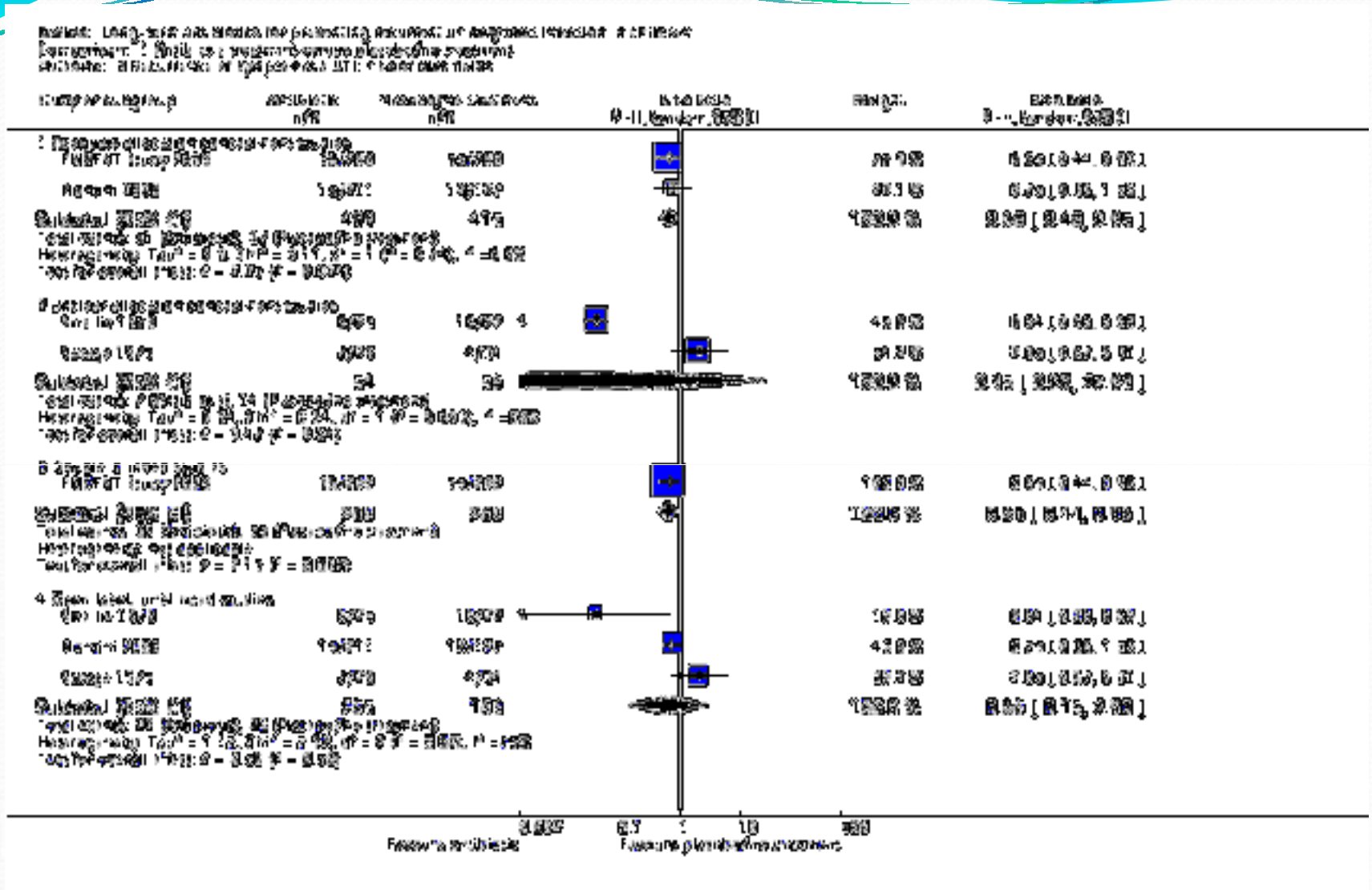
I squared >50%: Significant statistical heterogeneity, so results need to be interpreted cautiously

Long term antibiotics for prevention of recurrent symptomatic UTI

Williams and Craig, Cochrane review 2011



I squared statistic: 62%: Significant statistical heterogeneity was explored with sensitivity analysis



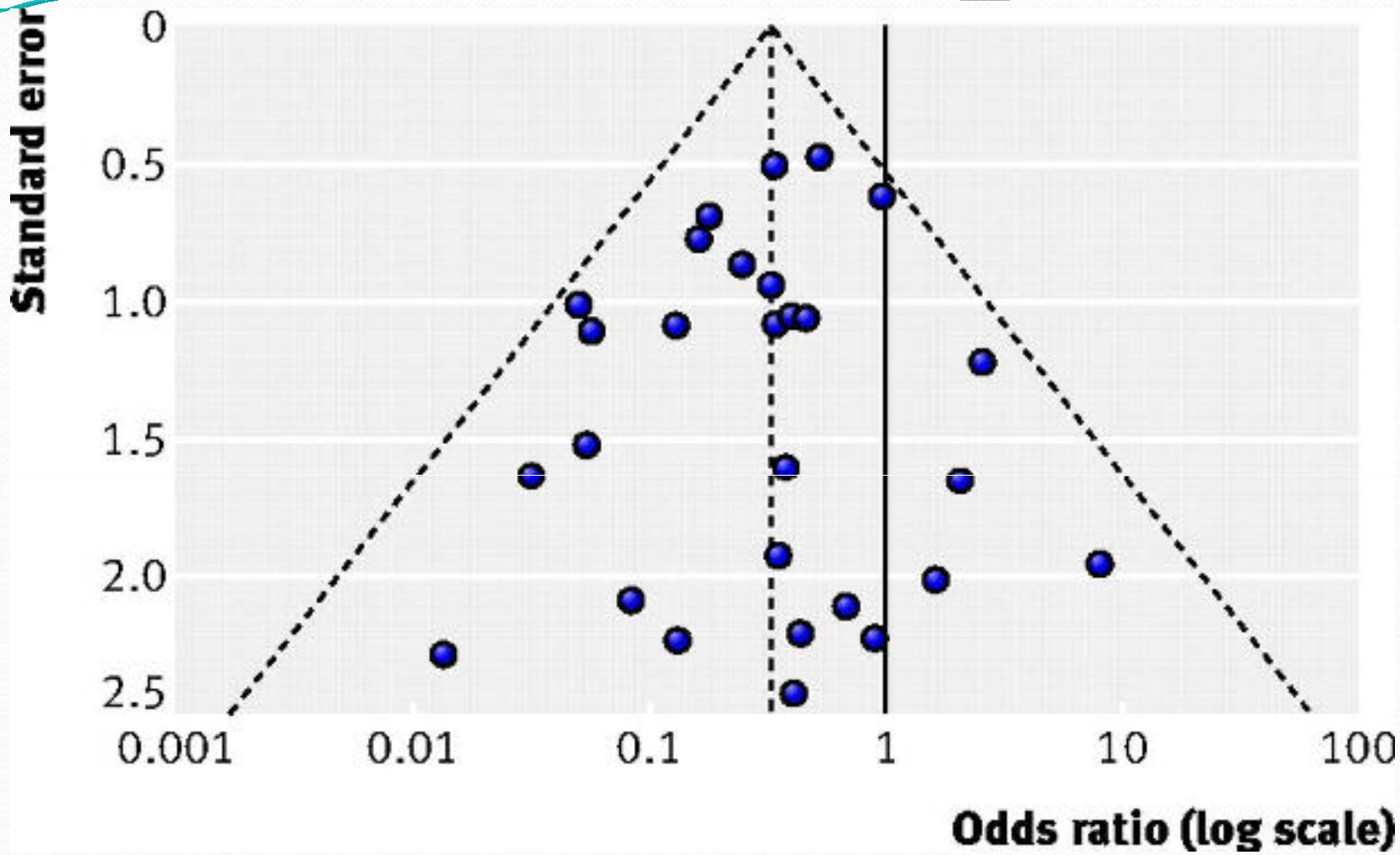
When only studies with low ROB were combined, there was no heterogeneity

Funnel plot: Assessing publication bias

- Scatter plot (X axis: Effect size, Y axis: Study precision)
- Study precision: Standard error (SE) of the effect size

- Effect sizes from smaller studies have larger SE, so will be located lower on the Y axis
- Effect estimates from smaller RCTs will scatter more widely at the bottom of the graph, with the spread narrowing among larger studies.

Note: In absence of bias and between study heterogeneity, the plot resembles a symmetrical inverted funnel.



Symmetrical funnel plot: The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in.

Sterne JAC et al. BMJ 2011

Funnel plot asymmetry

If there is a genuine asymmetry, the pooled effect estimate in a meta-analysis will overestimate the treatment effect. *Egger 1997*

Statistical tests for funnel plot asymmetry

- Do not use if less than 10 studies
- Power is too low to differentiate chance from real asymmetry
- Not routinely recommended

Sterne et al, BMJ 2011

Reporting a systematic review and meta analysis

Preferred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta analyses (PRISMA statement)

Moher et al J Clin Epidemiol 2009

Pitfalls in systematic reviews

Pitfalls in conducting

- Single author
- Not searching all relevant databases
- Not including non-English studies
- Deviating from the protocol depending on the results

Influence of ROB on effect size estimates

- *Unpublished trials underestimate effect size by ~10%*

- Trials published in languages other than English will overestimate by 10%
- Trials not indexed in Medline will overestimate by 5%,

- Trials with inadequate or unclear concealment of allocation will overestimate by 30%

- Trials not double blinded will overestimate by 15%

Egger et al Int J Epidemiol 2002

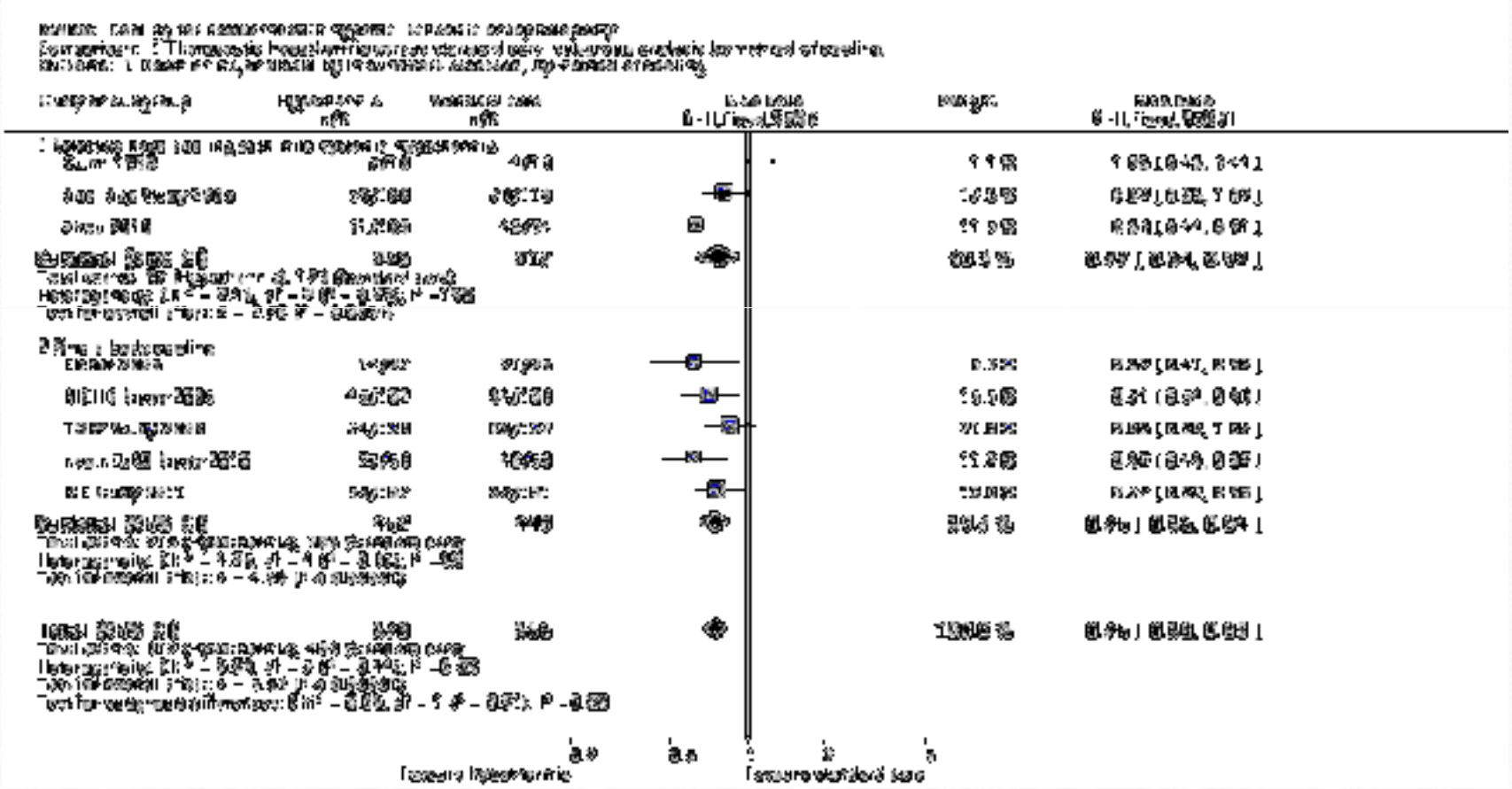
Odds ratio vs. Risk ratio

- **Risk ratio:** 0.82, a 18% decrease in *risk* of infection.
- **Odds ratio:** 0.41, a 59% decrease in *odds* of infection.
- Clinicians can misinterpret OR as RR and overestimate the efficacy of protective intervention

Note: Neonatal Cochrane group recommends relative risk

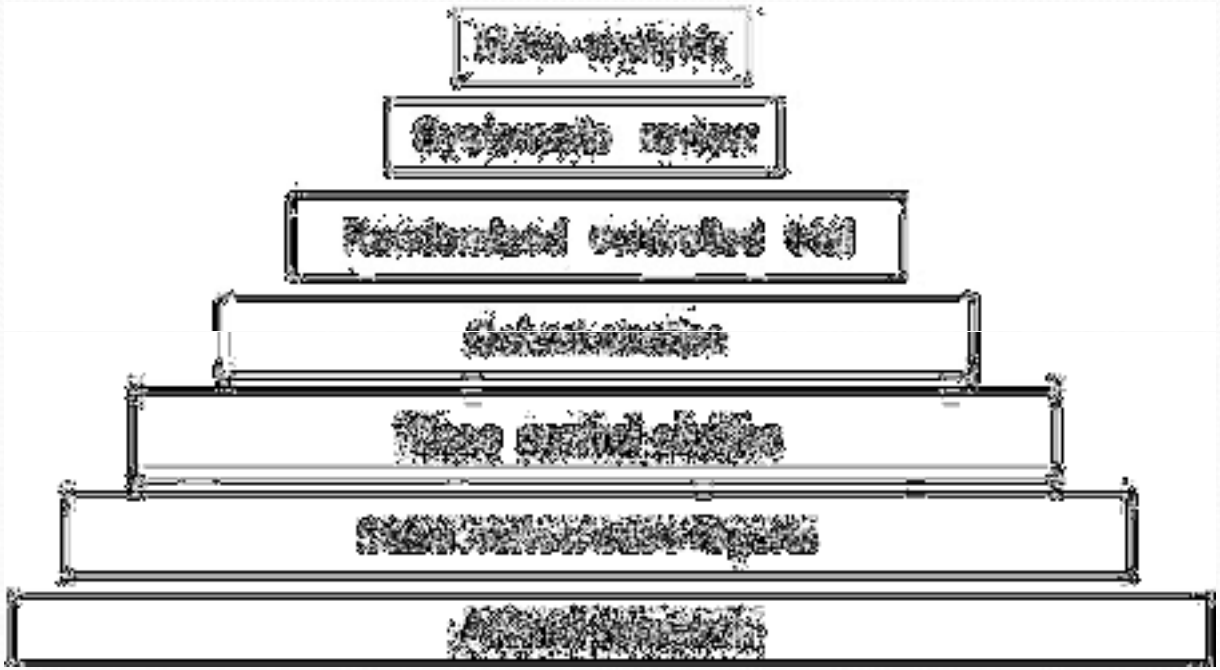
Effect of cooling on death or major disability among survivors

Jacobs et al Cochrane 2013



RR: 0.75 vs. OR: 0.53

Controversies



A well conducted systematic review with meta analysis can represent the pinnacle of evidence based evaluation

Meta analysis vs. Mega RCT

ISIS-4: International study of infarct survival (N=58050)

- No difference in mortality in MgSo4 vs. Control group
- 2216/29011 (7.6%) vs. 2103/29039 (7.2%)

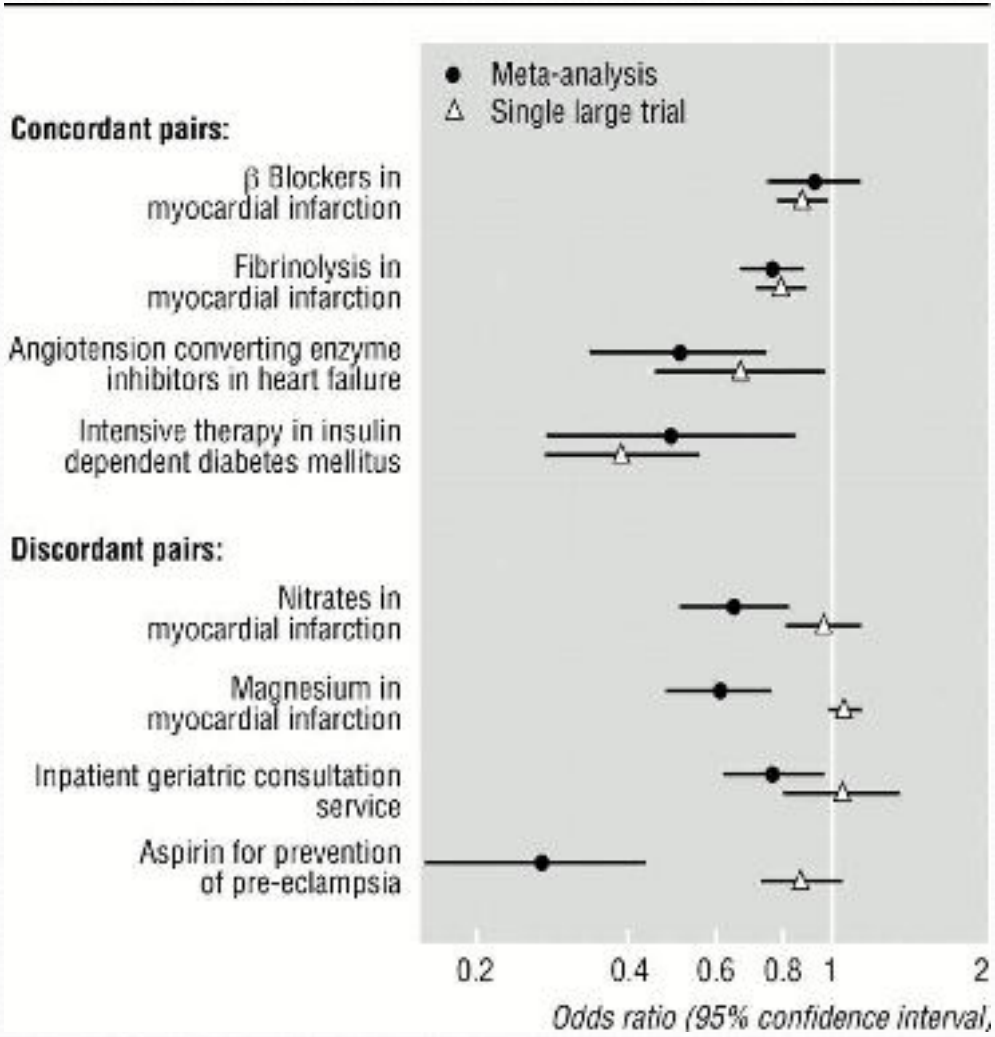
Lancet 1995

- These results overruled previous meta analysis that showed benefit (7 RCTs, N=1300, OR: 0.45, p<0.001).

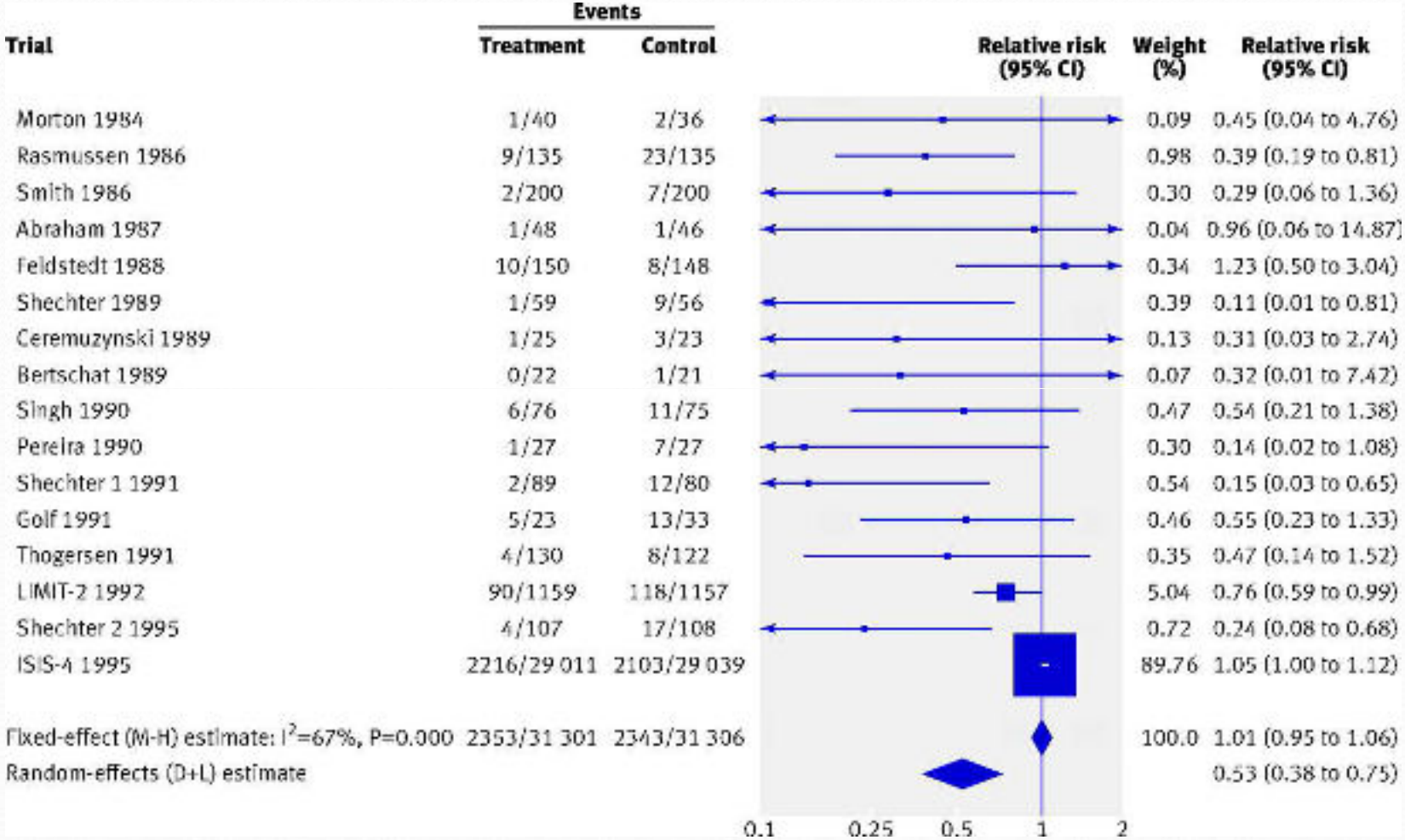
Note: Clinicians have to treat patients using the best possible current evidence (systematic review) rather than waiting for a future RCT

Results from four concordant and four discordant pairs of meta-analysis and large scale RCT

Egger M et al. BMJ 1997



FEM and REM estimates: Effect of IV Magnesium on mortality after MI



Trial	Events: Treatment	Events: Control	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Morton 1984	1/40	2/36		0.09	0.45 (0.04 to 4.76)
Rasmussen 1986	9/135	23/135		0.98	0.39 (0.19 to 0.81)
Smith 1986	2/200	7/200		0.30	0.29 (0.06 to 1.36)
Abraham 1987	1/48	1/46		0.04	0.96 (0.06 to 14.87)
Feldstedt 1988	10/150	8/148		0.34	1.23 (0.50 to 3.04)
Shechter 1989	1/59	9/56		0.39	0.11 (0.01 to 0.81)
Ceremuzynski 1989	1/25	3/23		0.13	0.31 (0.03 to 2.74)
Bertschat 1989	0/22	1/21		0.07	0.32 (0.01 to 7.42)
Singh 1990	6/76	11/75		0.47	0.54 (0.21 to 1.38)
Pereira 1990	1/27	7/27		0.30	0.14 (0.02 to 1.08)
Shechter 1 1991	2/89	12/80		0.54	0.15 (0.03 to 0.65)
Golf 1991	5/23	13/33		0.46	0.55 (0.23 to 1.33)
Thogersen 1991	4/130	8/122		0.35	0.47 (0.14 to 1.52)
LIMIT-2 1992	90/1159	118/1157		5.04	0.76 (0.59 to 0.99)
Shechter 2 1995	4/107	17/108		0.72	0.24 (0.08 to 0.68)
ISIS-4 1995	2216/29 011	2103/29 039		89.76	1.05 (1.00 to 1.12)
Fixed-effect (M-H) estimate: I^2=67%, P=0.000	2353/31 301	2343/31 306		100.0	1.01 (0.95 to 1.06)
Random-effects (D+L) estimate					0.53 (0.38 to 0.75)

FEM showed no difference, because it gave 90% weight to the ISIS-4 trial.

REM showed beneficial effect because smaller studies received adequate weight

- It is better to compare the FEM and REM estimates of the treatment effect.

- If REM estimate appears more beneficial, treatment was more effective in smaller studies because weight given to each study by REM is less influenced by sample size.

- If there is no evidence of heterogeneity between studies, the FEM and REM estimates will be identical.

Checklist for systematic review

- **Methodology:** Robust, Comprehensive, Transparent, and Reproducible?
- **Type of studies** (RCTs, Non-RCTs)
- **Risk of bias** in included studies, Publication bias
- **Time span**

Checklist for forest plots: 10 points

- Number and type of studies, sample sizes, and total sample size
- Number of events and denominators in intervention vs control group
- Confidence intervals and their overlap
- Tests for heterogeneity: Chi^2 (Q statistics) and its P value, I^2: (%)
- Pooled effect (Z) size, P value, and statistical vs. clinical significance
- Risk vs. Odds, RR, AR, ARD
- Model/s used for analysis, Concordance/Discordance of results
- Weightage to different studies? Any study driving the results? Outliers?
- Type of outcome: Primary vs. Secondary
- Labelling of intervention and comparison groups and plotted results

Other clinically important issues

- Benefits vs. Risks (short and long-term)
- NNT, NNH
- Translational potential

Thank you