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

Review: Comparison: Outcome:	Probiotics for prevention of necrotizing en 01 NEC 01 Definite NEC	terocolitis			
Study or sub-category	Probiatic n/N	no probiotic n/N	RR (fixed) 95% Ci	Weight %	RR (fixed) 95% Cl
Kitajima 1997 Doni 2002 Costalos 2003 Bin Nun 2005 Lin 2005 Manzoni 2006 Stratisi 2007	0/45 4/295 5/51 1/72 2/180 1/89 2/21 0/38	0/46 8/290 6/86 10/73 - 10/187 3/41 1/17 3/31 +		11.15 9.72 13.73 13.56 4.04 1.53 5.31	<pre>Mot estimable 0.49 (0.15, 1.61) 0.59 (0.19, 1.78) 0.10 (0.01, 0.77) 0.21 (0.05, 0.94) 0.85 (0.04, 8.28) 1.62 (0.16, 16.37) 0.12 (0.01, 2.19)</pre>
Lin 2008 Somente 2008 Rouge 2009	4/217 5/91 2/45	14/217 15/95 1/49	-	19.35 20.29 - 1.32	0.29 (0.10, 0.85) 0.35 (0.13, 0.92) 2.18 (0.20, 28.21)
Test for heterog	1094 (Probiotic), 71 (no probiotic) enetty: ChP = 7.65, df = 9 (P = 0.57), P = 09 effect: Z = 4.64 (P < 0.00001)	1082	•	100.00	0.35 [0.23, 0.55]
		ەم 1	0.1 1 10 Favors treatment - Favors con	100 Irol	

Note: Majority of Australian neonatal units now use probiotics

Cooling for hypoxic ischemic encephalopathy

Schulzke et al. BMC Pediatrics 2007

Review:	Cooling for newborn infants with hypoxic ischaemic encephalopathy
Comparison	01 Therapeutic hypothermia versus normothermia
Outcome:	01 Death or disability in survivers assessed at 18 to 22 months

Study ar sub-category	Hypothermia n/N	Normothermia n/N	RR (fixed) 95% Cl) VVeight %	RR (fixed) 95% Cl
01 Head cooling (death or se	vere disability)				
Gluckman 2005	59/108	73/110		51.66	0.82 [0.66, 1.02]
Gunn 1998	4/13	4/13		Z.86	1.00 [0.32, 3.17]
Subtotal (95% CI)	121	123	+	54.51	0.83 [0.67, 1.03]
Total events: 63 (Hypothermi	a), 77 (Normothermia)		(A)		
Test for heterogeneity: Chi ² =	0.11, df = 1 (P = 0.74), P = 05	6			
Test for overall effect: Z = 1.	67 (P = 0.09)				
02 Whole-body cooling (deat	h or moderate or severe disab	dty)			
Shankaran 2005	45/102	64/103		45.49	0.71 [0.54, 0.93]
Subtotal (95% CI)	102	103	-	45.49	0.71 [0.54, 0.93]
Total events: 45 (Hypothermi	a), 64 (Normothermia)				
Test for heterogeneity: not a	pplicable				
Test for overall effect: Z = 2.					
Total (95% CI)	223	226		100.00	0.78 [0.66, 0.92]
Total events: 108 (Hypothern	nia), 141 (Normothermia)	ALC: NO.	1000		Constraint States of States
THE REPORT OF A REPORT OF A REPORT OF A REPORT OF A	0.90, df = 2 (P = 0.64), P = 09	6			
Test for overall effect: Z = 2.					
	24517460au 767795210873		0.1 0.2 0.5 1	2 5 10	
			Favours hypothermia Far	yours normathermia	

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

	AL VP SI	unts	Non AI-VP	Shunts		Risk Ratio	Risk
idy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random,
2.1 studies in children	7.4					sectors and reserves	
arwal 2010	0	11	5	23	2.7%	0.18 [0.01, 3.02]	
ran 2005	1	32	7	46	4.8%	0.21 [0.03, 1.59]	
mann 2009	1	34	3	22	4.2%	0.22 [0.02, 1.94]	
yhurst 2008	21	214	8	77	17.1%	0.94 [0.44, 2.04]	
n 2007	4	80	7	80	10.7%	0.57 [0.17, 1.88]	
rker 2009	16	502	64	570	22.0%	0.28 [0.17, 0.48]	
btotal (95% CI)		873		818	61.5%	0.42 [0.23, 0.77]	•
tal events	43		94				
terogeneity: Tau ^a = 0.18; st for overall effect: Z = 2.			5 (P = 0.17);	1"= 36%			
2.2 studies in adults	Ţ						
anese 2009	0	6	7	12	2.9%	0.12 [0.01, 1.86]	•
mann 2008	ĩ	171	4	98	4.3%	0.14 [0.02, 1.26]	
btotal (95% CI)	204	177	0.40	110	7.2%	0.14 [0.02, 0.74]	
tal events	1		11				
terogeneity: Tau ^a = 0.00;	$Chi^{a} = 0.0$	01, df = 1	1 (P = 0.93);	$l^2 = 0.\%$			
st for overall effect $Z = 2$.	31 (P = 0	02)	1464 - LUCEN (* 19				
2.3 studies in adults and	children						
ierrez-Gonzalez 2010	2	72	8	47	7.7%	0.16 [0.04, 0.74]	
ttavilokarn 2007	3	243	36	551	11.0%	0.19 [0.06, 0.61]	
z 2007	5	86	10	172	12.6%	1.00 [0.35, 2.83]	
btotal (95% CI)		401		770	31.3%	0.33 [0.10, 1.15]	-
tal events	10		54				
terogeneity: Tau ² = 0.80; st for overall effect Z = 1.			2 (P = 0.05);	I ² = 67%			
tal (95% CI)		1451		1698	100.0%	0.37 [0.23, 0.60]	•
tal events	54		159				

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

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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?

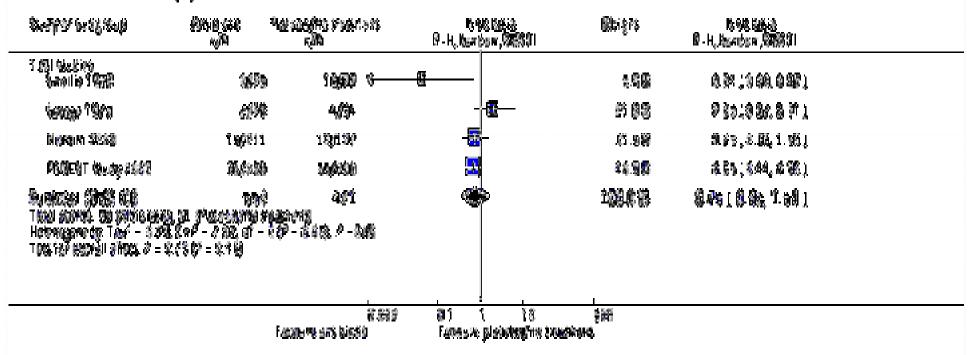
I squared test: Is the observed variability of effects greater than that expected by chance alone?

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

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

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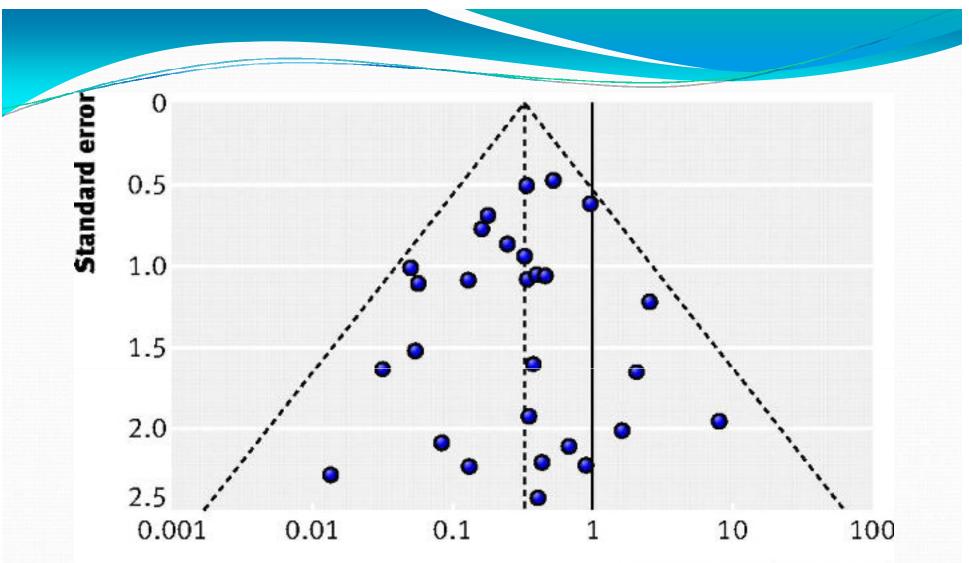
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When only studies with low ROB were combined, there was no heterogeneity

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.



Odds ratio (log scale)

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 Reporting Items for Systematic Reviews and Meta 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

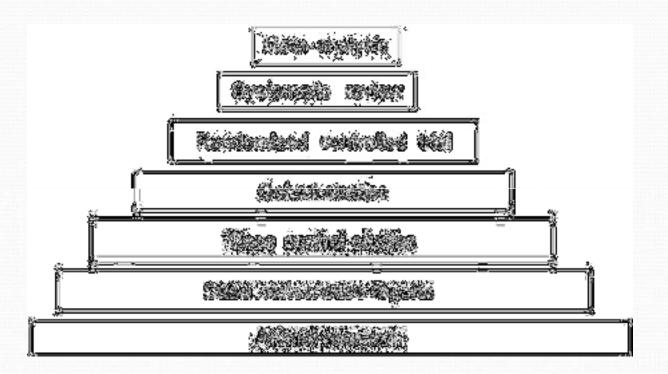
Effect of cooling on death or major disability among survivors

Jacobs et al Cochrane 2013

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		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)

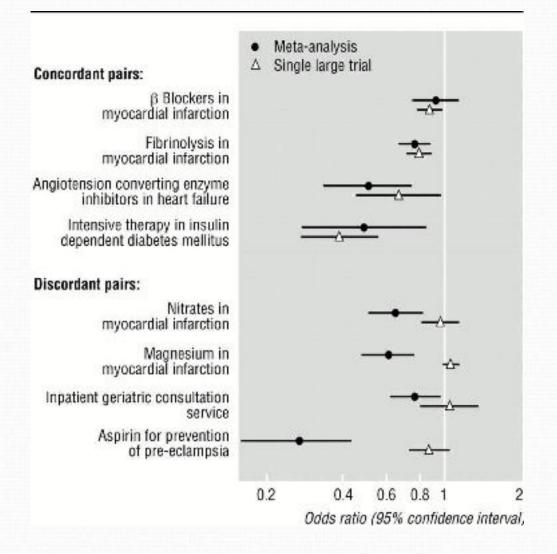
- No difference in mortality in MgSo4 vs. Control group
- 2216/29011 (7.6%) vs. 2103/29039 (7.2%)

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-analysisand large scale RCTEgger M et al. BMJ 1997



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

	Eve	ents				
Trial	Treatment	Control		Relative risk (95% Cl)	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	4		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	4		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	100 0-0-0	-	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		1.00	89.76	1.05 (1.00 to 1.12)
Fixed-effect (M-H) estimate: 12=674	%, 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)
			0.1 0.25 0	0.5 1 3	2	

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: Chi² (Q statistics) and its P value, I²: (%)
- 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

