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Addressing multiple treatments II: introduction to network meta-analysis

Madrid, October 2011

University of BRISTOL

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Workshop outline

- **The Basics: indirect comparisons**
  - What are indirect comparisons & why are they necessary
  - Exercise: how to do an indirect comparison (calculator)
- **Slightly more advanced:**
  - Checking assumptions for IC (and NMA) with exercise
  - Checking consistency
  - What does an NMA look like?
- **Advantages and examples of NMA**
  - Meta-regression approach
  - Methodological challenges

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Multiple treatment decision-making

- For many clinical indications there will often be several possible interventions.
- The Cochrane Database of Systematic Reviews
  - 22 interventions for adult smoking cessation
  - >12 interventions for chronic asthma in adults
- Health care decisions should be based on 'best available' evidence from systematic reviews & meta-analysis of RCTs

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Problem…

- Systematic reviews focus on direct, head-to-head comparisons of interventions.
  - e.g. NRT vs placebo; Olanzapine vs placebo
  - A vs B; A vs C.
- The evidence base consists of a set of pair-wise comparisons of interventions
  - Placebo comparisons of limited use to the practitioner or policy-maker who wants to know the 'best' treatment to recommend/ prescribe.

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Problem... (2)

- 'Best available' evidence is not always available or sufficient
  - Placebo controlled trials sufficient for regulatory approval of new drugs
  - Even when active comparisons have been made such direct evidence is often limited.
- Therefore, evidence base may not contain treatment comparisons of relevance for clinician or policy maker.

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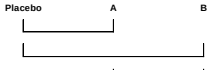
Example evidence structure #1

- Common situation is to have multiple competing treatments (often within class) each studied in placebo-controlled RCTs but none compared directly to each other.



- How do we know which treatment to use?

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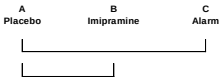
Case study: childhood nocturnal enuresis *

Evidence base: 3 treatment options; 2 comparisons



Summary of results from 2 separate enuresis meta-analyses

Comparison	n/ N active	n/ N no.treat	Relative Risk	CIs
Alarm vs no treatment	107/ 316	250/ 260	0.39	(0.33 to 0.46)
Imipramine vs no treatment	314/ 400	391/ 403	0.95	(0.87 to 0.99)

Outcome: failure to achieve 14 days consecutive dry nights

*Source: Russell and Kiddoo (2006)

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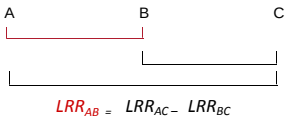
Indirect comparisons

- In absence of direct evidence for treatments A vs B, an *indirect* estimate of log risk ratio lrr_{AB} can be obtained from RCTs comparing A vs C and B vs C:



$$LRR_{AB} = LRR_{AC} - LRR_{BC}$$

*Bucher HC, et al.(1997); Glenny et al (2005)

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Indirect comparisons

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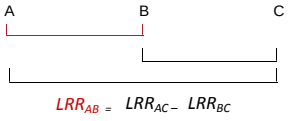

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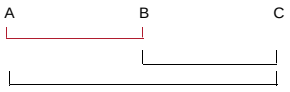

Consistency equation*

10 *Lu et al (2007) Journal of the American Statistical Association

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3 treatment network

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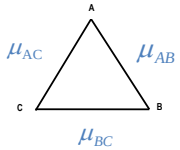

Three possible indirect comparisons, all equivalent:

$\mu_{AB}^{Indirect} = \mu_{AC} - \mu_{BC}$;

$\mu_{AC}^{Indirect} = \mu_{BC} - \mu_{AB}$;

$\mu_{BC}^{Indirect} = \mu_{AC} - \mu_{AB}$

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Simple exercise

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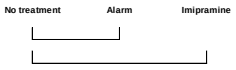

Comparison	RR	CIs
No treatment vs Imipramine	0.95	(0.87 to 0.99)
No treatment vs Alarm	0.39	(0.33 to 0.46)

Outcome: failure to achieve 14 days consecutive dry nights

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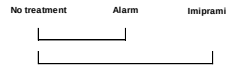
Simple exercise



Comparison		RR	CIs
No treatment vs Imipramine	AB	0.95	(0.87 to 0.99)
No treatment vs Alarm	AC	0.39	(0.33 to 0.46)

A vs B is the effect of B relative to A: imipramine relative to placebo (or treated over control)

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Pen and paper exercise.

$LRR_{BC} = LRR_{AC} - LRR_{AB}$

lrr_{AB} = -0.06

lrr_{AC} = -0.93

$lrr_{BC} = lrr_{AC} - lrr_{AB}$=

Indirect $RR_{BC} = \exp(lrr_{BC})$ =

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Pen and paper exercise.

$LRR_{BC} = LRR_{AC} - LRR_{AB}$

lrr_{AB} = -0.06

lrr_{AC} = -0.93

$lrr_{BC} = lrr_{AC} - lrr_{AB}$= -0.93 – (-0.06) = -0.87

Indirect $RR_{BC} = \exp(lrr_{BC})$ = **0.42**

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Confidence intervals and p-value

$Var(\hat{LRR}_{BC}^{Indirect}) = Var(\hat{LRR}_{AC}^{Direct}) + Var(\hat{LRR}_{AB}^{Direct})$ = 0.007 + 0.001 = 0.008

$SE(\hat{LRR}_{BC}^{Indirect}) = \sqrt{var(\hat{LRR}_{BC}^{Indirect})} =$ $\sqrt{0.008} =$ **0.09**

95% CI= LRR ±1.96*SE = 0.35 to 0.50 p= <0.0001 (z = -9.66)

Note: $Var(\hat{LRR}_{BC}^{Indirect}) = Var(\hat{LRR}_{AB}^{Direct}) + Var(\hat{LRR}_{AC}^{Direct})$

Therefore, all things being equal (trials all of same size, equal variance and assuming a common treatment effect) 1 directly randomised trial is as precise as an indirect comparison based on 4 randomised trials (see Glenny, 2005 for more detail)

Online calculator:
http://www.cadth.ca/en/resources/itc-user-guide

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When is an indirect comparison sensible…

- Validity relies on the AB & AC RCTs being **similar** across factors which may affect the outcome (modify treatment effect).
- A clinical/ epidemiological judgement:
  - No treatment by comparison interaction
  - Assuming inclusion/ exclusion criteria same across comparisons
  - Patients, trial protocols, doses, administration etc are similar in ways which might modify treatment effect.

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"Between-trial comparisons [Indirect Comparisons] are unreliable. Patient populations may differ in their responsiveness to treatment. Therefore an apparently more effective treatment may have been tested in a more responsive population"

Cranney, Guyatt et al. *End Rev* 2002, 23; 570-8

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"Placebo controlled trials lacking an active control give little useful information about comparative effectiveness. Such information cannot reliably be obtained from cross-study comparisons, as the conditions of the studies may have been quite different"

International Council of Harmonisation E10 2.7.1.4

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"Indirect comparisons are observational studies across trials, and may suffer the biases of observational studies, for example confounding"

Cochrane Handbook for systematic reviews of interventions 4.2.5. Cochrane Library Issue 3

(Watch this space for CMIMG update…)

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Checking assumptions

Exercise:

- Using the forest plots and study characteristics tables provided, work with a neighbour/ in small groups to discuss whether the AB and AC trials are similar enough across factors which may modify treatment effect.
- Suggested time: 10 minutes

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Handout: trial characteristics

Alarm vs placebo characteristics of studies

	Age	Boys(%)	Exclusion	Previous treatment	Dropouts	Baseline wetting (SD)	Recruitment/setting
Bennet	8.5 (5-12)	63%	Gross psychopathology	Exc. If previous behavioural	32/40	2.7 in 14 nights	GP referral
Bollard(a)	9.6	71%	No details	No details	3/45	4.97 per week	No details
Bollard(b)	8.9	82%	No details	No details	12/100	5.56 mean wet nights	No details
Houts	5-13	63%	No details	No details	7/56	5.41(1.63) mean wet nights/week	Media/ consultant referral
Jehu	9.3 (4.8-14.6)	64%	No details	Exc. If previous alarm	1/39	4 mean wet nights/week	childrens home
Lynch	5-12	Not clear	Daytime wetting	No details	6/60	11.33 in 14 nights	School/ consultant referral
Moffatt	8-14	Not clear	No details	No details	5/121	64% wet nights	Hospital clinic
Nawaz	7-12	50%	Psychiatric pathology	No details	0/36	5.67 per week	GPs
Ronen	10 (SD 2.28)	48%	Developmental problems <5years	No details	23/77	19.1 days in 3 weeks	Mental health clinic
Sacks	5.5-14	Not clear	Severe psychosis	No details	Not clear	No details	No details
Sloop	12.5(7-18)	52%	Severe behavioural probs. tranquilisers	No previous treatment	Not clear	3.99 Not clear	Residential setting for learning disabled
Wagner	7.9(5-14)	51%	IQ<70	No conditioning treatment	0/39	84% wet nights per week	No details
Wagner(b)	6-16	82%	Daytime wetting	Drugs/alarm in prev. yr	13/49	72% 3x week	Media/consultant referral/school/GP
Werry	9.99 (SD 2.25)	66%	Dry >3months	No details	10/70	Min 1x per week	Hospital clinic

Imipramine vs placebo characteristics of studies

	Age	Boys(%)	Exclusion	Previous treatment	Dropouts	Baseline wetting (SD)	Recruitment/setting
Argawala	6-12	52%	Mental disability	Some patients had imipramine	29	No details	No details
Forsythe	4-15	64%	No UTI	No details	51/298	>6xper week/ for 1yr	Children's hospital
Hodes	5-15	Not clear	No details	No details	No details	No details	GP
Khorana	8.2 (5-15)	74%	Severe mental disability	No details	24/100	No details	Psychiatric inpatients (India)
Manhas	5-15	43%	No details	No details	No details	No details	No details
Poussaint	5-16	77%	No details	3 had psychotherapy	7/47	5.6 per week	No details
Schroder	3.5-10	No details	Organic causes	Resistant to previous therapy	34/62	No details	No details
Smellie	5-13	81%	Organic causes	No details	4/80	1.4 Dry nights	No details
Tahmaz	6-14	100%	Organic causes Daytime wetting	Fluid reduction/ night waking	11/30	No details	Military hospital (Turkey)
Wagner	6-16	82%	Daytime wetting	Drugs/alarm in prev. yr	13/49	72% 3x week	Media/consultant referral/school/GP

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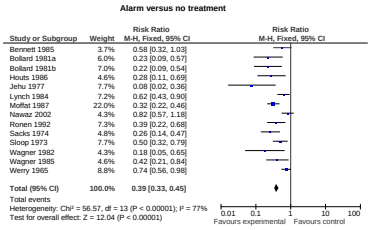
Forest plot for AvB



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Forest plot for AvC

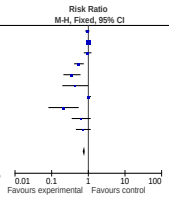
Imipramine versus no treatment

Study or Subgroup	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwala 1965	10.1%	0.93 [0.83, 1.05]
Forsythe 1969	28.3%	0.99 [0.95, 1.02]
Hodes 1973	10.6%	0.96 [0.77, 1.18]
Khorana 1972	13.0%	0.55 [0.42, 0.73]
Manhas 1967	9.2%	0.36 [0.22, 0.59]
Poussaint 1965	3.3%	0.44 [0.20, 0.96]
Schroder 1971	10.2%	1.04 [0.95, 1.15]
Smellie 1976	7.0%	0.21 [0.08, 0.53]
Tahmaz 2000	4.7%	0.64 [0.36, 1.13]
Wagner 1982b	3.8%	0.73 [0.47, 1.12]
Total (95% CI)	**100.0%**	**0.77 [0.72, 0.83]**

Total events

Heterogeneity: Chi² = 269.99, df = 9 (P < 0.00001); I² = 97%

Test for overall effect: Z = 6.97 (P < 0.00001)



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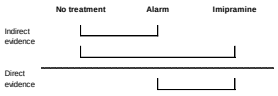
Example evidence structure #2

- Another common evidence structure is where we have **some** direct evidence on the relevant treatment comparisons (active vs active) but on its own its insufficient.



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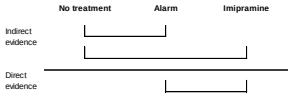
Evidence base: 3 treatment options; 3 comparisons



Summary of results from 3 enuresis meta-analyses

Comparison	Relative Risk	CIs
Alarm vs no treatment	0.39	(0.33 to 0.46)
Imipramine vs no treatment	0.95	(0.87 to 0.99)
Alarm vs imipramine	0.77	(0.64 to 0.93)

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Network meta-analysis

Combines direct and indirect evidence. Also known as:

1) Mixed treatment comparison
2) Multiple treatment meta-analysis

ALL 3 mean the same thing – **simultaneous** comparison of multiple competing treatments using direct & indirect evidence (usually from RCTs) in a single analysis.

SAME assumption as made for indirect comparison alone: the consistency assumption.

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Combining direct and indirect evidence

Simple approach to pooling direct and indirect evidence on lrr_{BC}

1. lrr_{BC}^{direct}
2. $lrr_{BC}^{indirect}$
3. $$lrr_{BC}^{NMA} = \frac{(w^{direct}\, lrr_{BC}^{direct}) + (w^{indirect}\, lrr_{BC}^{indirect})}{(w^{direct} + w^{indirect})}$$

$$w = 1/se(BC_i)^2$$

Indirect evidence given less weight than direct evidence

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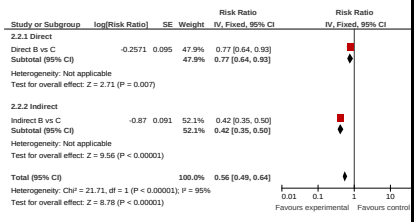
Using GIV to combine in RevMan



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NMA: The **big** assumption

IC and NMA assume that the "Direct" and "Indirect" evidence estimate the same parameter, i.e. are CONSISTENT.

That the Treatment effect μ_{BC} estimated by the BC trials, would be the same as the treatment effect estimated by the AC and AB trials (if they had included B and C arms).

Nearly all the doubts about IC and NMA are doubts about this assumption.

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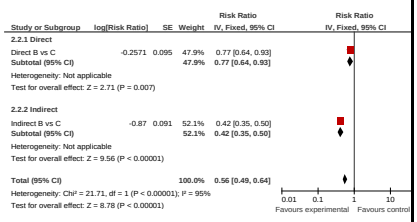
Discussion of indirect and direct estimates



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Bucher approach to checking consistency

The difference ω between direct LRR_{BC} and indirect LRR_{BC}

$\hat{\omega}$ = -0.257 - -0.87 = 0.61

To calculate the standard error of the difference we sum the SE from the direct and indirect log risk ratios

$$SE(\Delta) = \sqrt{SE(LLR^{Direct})^2 + SE(LRR^{Indirect})^2}$$

$$= \sqrt{0.095^2 + 0.091^2} \quad = 0.13$$

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Bucher approach to checking consistency

Calculate confidence intervals & p-values for : $\hat{\omega}$

95% CI = $\hat{\omega}$ ±(1.96*SE) = exp [0.36] to exp [0.86]

= 1.43 to 2.37

z-score = $\frac{\hat{\omega}}{SE(\hat{\omega})}$ = 4.64 p-value = <0.000002

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Limitations of simple approach

Straightforward & conceptually intuitive
- Extension of pairwise meta-analysis
- Checking consistency of evidence

BUT it is very LIMITED:
- Pool separately for each treatment comparison (separate meta-analyses)

What happens when

Treatments	4	5	6	7	8	9	10	11
Pairwise	6	10	15	21	28	36	45	55
Indirect	12	30	60	105	168	252	360	495

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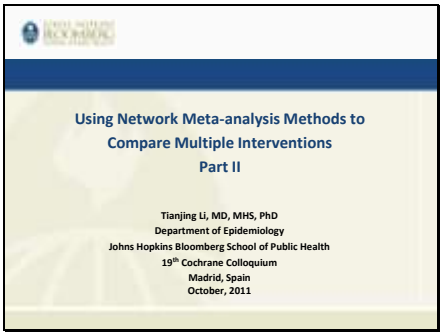

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Key Messages

- Network meta-analysis is an extension of standard, pair-wise meta-analysis; meta-regression, generalized linear model, and Bayesian approaches could be used.
- To ensure validity of findings from meta-analyses, the systematic review, whether it involves a standard, pair-wise meta-analysis or a network meta-analysis, must be designed rigorously and conducted carefully.

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An Overview of Meta-regression

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An Overview of Meta-regression

- In primary studies we use regression to examine the relationship between one or more covariates and a dependent variable.
- The same approach can be used with meta-analysis, except that
  - ***Unit of analysis***, each observation in the regression model, ***is usually a study***;
  - ***Dependent variable is the summary estimate in each primary study*** rather than outcomes measured in individual participants;
  - ***Covariates*** are ***at level of the study*** rather than the level of the participant.

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Why do a Meta-regression?

- Examine the relationship between study-level characteristics and intervention effect
  - ***Study potential effect modification:***
    Does the intervention effect (association) vary with different population or study characteristics?
- Explore and explain between study variation

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Bacillus Calmette-Guérin (BCG) Vaccine to Prevent Tuberculosis Dataset

		Vaccinated		Control				
ID	Study	TB	No TB	TB	No TB	RR[1]	SE(lnRR)	Latitude[2]
1	Ferguson_1949	6	300	29	274	0.205	0.441	55
2	Hart_1977	62	13536	248	12619	0.237	0.141	52
3	Aronson_1948	4	119	11	128	0.411	0.571	44
3	Stein_1953	180	1361	372	1079	0.456	0.083	44
4	Rosenthal_1961	17	1699	65	1600	0.254	0.270	42
4	Rosenthal_1960	3	228	11	209	0.260	0.644	42
5	Comstock_1976	27	16886	29	17825	0.983	0.267	33
5	Comstock_1969	5	2493	3	2338	1.562	0.730	33
6	Coetzz_1968	29	7470	45	7232	0.625	0.238	27
7	Vandiviere_1973	8	2537	10	619	0.198	0.472	19
8	Comstock_1974	186	50448	141	27197	0.712	0.111	18
9	Frimodt_1973	33	5036	47	5761	0.804	0.226	13
9	TB Preventiaon Trial_1980	505	87886	499	87892	1.012	0.063	13

1. RR <1.0 indicates the vaccine decreased the risk of TB.
2. The higher the latitude the farther away the study location was from the equator (used as surrogate for climates).

Colditz, et al. JAMA 1994;271:698-702; Borenstein, et al. Introduction to Meta-analysis. Chapter 20.

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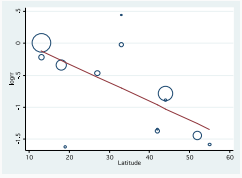
Meta-regression Model Specification

$$\ln(RR)_i = a + b * latitude_i + \eta_i + e_i$$

$$\eta_i \sim N(0, (se(\ln RR)_i)^2)$$

$$e_i \sim N(0, t^2)$$

- Parameters to estimate:
  a – intercept, ln(RR) at latitude=0 (equator)
  b – slope, the average change in ln(RR) for every unit change in latitude
  τ^2 – between study variance



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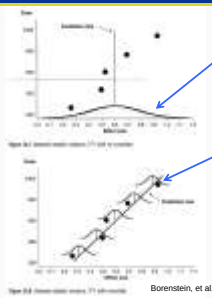
Variance(Heterogeneity) Explained by a Covariate



The spread of this distribution reflects the amount of between study variance (tau^2) without any covariate.

The spread of this distribution reflects the amount of between study variance with a covariate; assumed to be the same at each level of covariate.

The decrease in spread from the top to the bottom pane illustrates how a covariate explains some of the between-studies variance.

Borenstein, et al. Introduction to Meta-analysis. Chapter 20. 42

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Network Meta-analysis using
Meta-regression and Other Approaches

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What is a Network Meta-analysis?

Network (multiple treatments comparison) meta-analysis:

Meta-analysis, in the context of a systematic review, in which three or more treatments have been compared using both direct and indirect evidence from several studies.

Bucher 1997; Caldwell 2005; Glenny 2005; Song 2003; Li 2011

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Meta-regression Formulation

- We observe y_i in each study (e.g. the log(OR))
- Network meta-analysis and indirect comparison could be conducted under the meta-regression framework where treatments are treated as "covariates" in the model

Slides 11-16 were adapted from workshop given previously by Georgia Salanati

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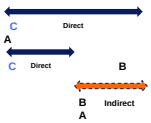
Meta-regression Parameterization

AC, AB, BC studies, chose C as *reference,* then

$y_i = \theta_i^{AC} \times (treat_i=A) + \theta_i^{BC} \times (treat_i=B)$

Coding for indicator variables ($treat_i=A$, $treat_i=B$)

- AC studies (1, 0)
- BC studies (0, 1)
- AB studies (1, -1)



$$q_{direct}^{AC} * 1 + q_{direct}^{BC} * 0$$

$$q_{direct}^{AC} * 0 + q_{direct}^{BC} * 1$$

$$q_{indirect}^{AB} = q_{direct}^{AC} * 1 + q_{direct}^{BC} * (-1) = q_{direct}^{AC} - q_{direct}^{BC}$$

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Bucher 1997; Song 2003; Glenny 2005

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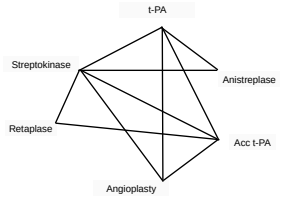
Parameterization of the Network



Choose basic parameters

Write all other contrasts as linear functions of the basic parameters to built the design matrix

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ln(OR) for Death in Treatments for MI

$y_i = \mu^A$ t-PA + μ^B Anistreplase$_i$ + μ^C Accelerated t-PA$_i$ + μ^D Angioplasty$_i$ + μ^E Reteplase$_i$

Use as 'covariates'

No. studies	Streptokinase	t-PA	Anistreplase	Acc t-PA	Angioplasty	Reteplase
3	-1	1	0	0	0	0
1	-1	0	1	0	0	0
1	-1	0	0	1	0	0
3	-1	0	0	0	1	0
1	-1	0	0	0	0	1
1		-1	1	0	0	0
2		-1	0	0	1	0
2		0	0	-1	1	0
2		0	0	-1	0	1

Lumley 2002, Stat Med

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ln(OR) for Death in Treatments for MI

$y_i = \mu^A$ t-PA + μ^B Anistreplase$_i$ + μ^C Accelerated t-PA$_i$ + μ^D Angioplasty$_i$ + μ^E Reteplase$_i$

$$Y = (\mu^A, \mu^B, \mu^C, \mu^D, \mu^E) \times X + \Delta$$

- Y: Matrix of all observations
- $(\mu^A, \mu^B, \mu^C, \mu^D, \mu^E)$: Vector of LogOR
- X: Design matrix
- Δ: Random effects matrix

$$Y \sim N(\boldsymbol{\mu} X, V)$$

Variance-covariance matrix (for the observed LOR)

$$\Delta \sim N(\mathbf{0}, diag(\tau^2))$$

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ln(OR) compared to Streptokinase (RE Model)

$$Y = (\mu^A, \mu^B, \mu^C, \mu^D, \mu^E) \times X + \Delta$$

Treatment	LOR(SE)
t-PA	–0.02 (0.03)
Anistreplase	–0.00 (0.03)
Accelerated t-PA	– 0.15 (0.05)
Angioplasty	– 0.43 (0.20)
Reteplase	– 0.11 (0.06)

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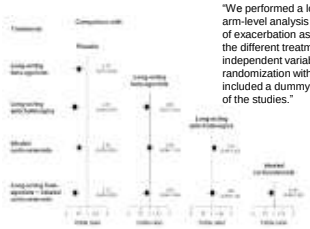
Generalized Linear Model for Network Meta-analysis

Example: Inhaled Drugs to Reduce Exacerbations in Patients with COPD



"We performed a logistic regression arm-level analysis with the presence of exacerbation as dependent and the different treatment options as independent variables… To preserve randomization within each trial, we included a dummy variable for each of the studies."

Puhan M, BMC Med. 2009,14;7:2.

Slide 52

Methodologic Challenges and Research Opportunities for Network Meta-analysis

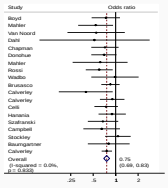
Slide 53

Challenge of Considering Risk of Bias and Quality of Evidence

With particular thanks to Dr. Milo Puhan for the next 3 slides – drawing on his ideas

Slide 54

Conventional meta-analysis: Entire evidence for 1 estimate



X trials inform

1 point estimate

Quality of evidence

- Risk of bias (Cochrane)
- Summary of quality items
- ●●●○ (GRADE)
- scores (Jadad, etc)

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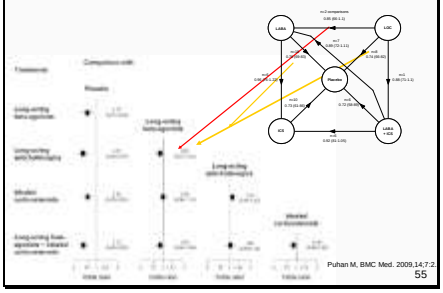
Network meta-analysis: Trials contribute to different estimates



Puhan M, BMC Med. 2009,14;7:2.

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Quality of evidence likely to be heterogeneous across network

Within and across comparisons

Low risk for bias

High risk for bias

Moderate risk for bias

High risk for bias

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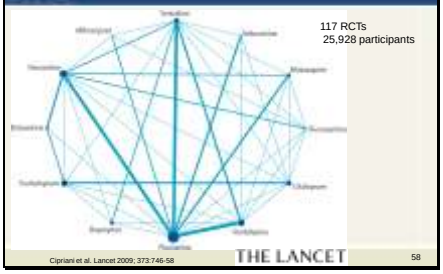
Slide 57

Challenge of Reporting Bias

Slide 58

Evidence Network of Comparative Efficacy and Acceptability of 12 New Generation Antidepressants



Cipriani et al. Lancet 2009; 373:746-58 THE LANCET 58

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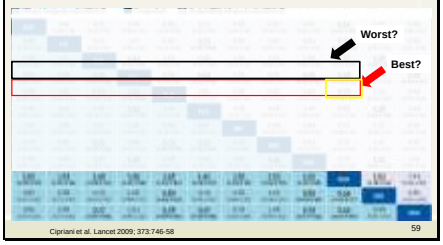
Efficacy and Acceptability of 12 New-generation Antidepressants

ORs < 1 favor the row-defining treatment



Cipriani et al. Lancet 2009; 373:746-58 59

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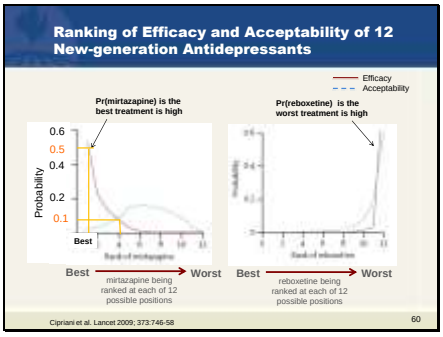

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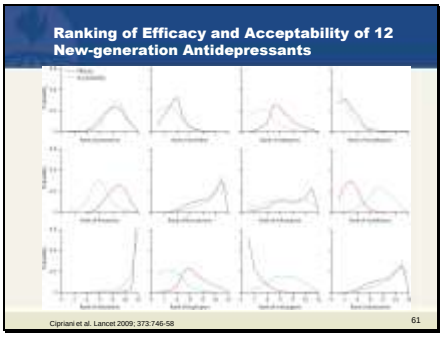

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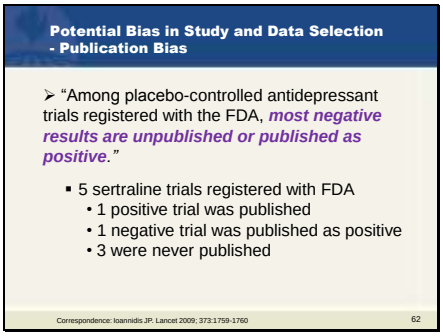
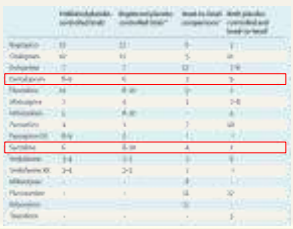


Slide 63

Potential Bias in Study and Data Selection - Publication Bias (cont'd)

Discrepant Rankings of Effect Sizes for Effectiveness of Antidepressants



Correspondence: Ioannidis JP. Lancet 2009; 373:1759-1760

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Methodologic considerations in doing a conventional systematic review	Challenges and areas of research for indirect comparison and network meta-analysis
Define the review question and eligibility criteria	• Define "network" • Inclusion of observational studies for harms?
Search for and select studies	• Rely on studies included in published systematic reviews vs. a new comprehensive literature search? • Different sources of data?
Assess risk of bias, collect data	• Quality of indirect and combined evidence? • Efficiency • Workforce
Synthesize evidence qualitatively	• Extremely important but often overlooked
Synthesize evidence quantitatively	• Heterogeneity, inconsistency • Subgroup analysis, meta-regression, sensitivity analysis • Individual patient data network meta-analysis • Rare events, missing data • More/less bias? Adjustment of bias • Implementation and user friendly software
Interpret results and draw conclusions	• Interpretability and recommendations
Report findings	• Reporting standards, peer-review

Li et al. Network meta-analysis - highly attractive but more methodological research is needed. BMC Med. 2011 Jun 27;9(1):79.

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Key Messages

- Network meta-analysis is an extension of standard, pair-wise meta-analysis; meta-regression, generalized linear model, and Bayesian approaches could be used.
- To ensure validity of findings from meta-analyses, the systematic review, whether it involves a standard, pair-wise meta-analysis or a network meta-analysis, must be designed rigorously and conducted carefully.