Network meta-analysis

a short primer

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Outline

1. Introduction
2. Bayesian statistics
3. Meta-analysis
4. Network meta-analysis
5. Demo in ADDIS
6. References

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After every part, there will be an opportunity to ask questions.

Slides

Slides on `http://drugis.org/`

- under publications

Research Project (Escher 3.2) Goals

Develop a drug information system:

- Effective knowledge access and management
- Answer drug efficacy and safety questions
  - in an efficient, transparent and accountable way
  - within and across compounds
  - for a broad audience (including regulators)
- Improve consistency in regulatory decision making
- Based on systematic review and meta-analysis

$\longrightarrow$

ADDIS: Aggregate Data Drug Information System

Assisted evidence synthesis and benefit-risk assessment

- Based on a database of clinical trials

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For ADDIS I developed the MTC library:

- **Automated network meta-analysis**
- `http://drugis.org/`

Related manuscripts:
2) G. van Valkenhoef, T. Tervonen, T. Zwinkels, B. de Brock, H. Hillege, *ADDIS: a decision support system for evidence-based medicine.* Manuscript under review.
5) G. van Valkenhoef, T. Tervonen, B. de Brock, H. Hillege, *Algorithmic Parameterization of Mixed Treatment Comparisons.* Manuscript under review.
6) G. van Valkenhoef, B. de Brock, H. Hillege, *Automating network meta-analysis.* Initiated (conference paper).

Bayesian Statistics

Network meta-analysis is usually done in a Bayesian framework

- The Bayesian perspective is quite different
  - from the 'usual' frequentist perspective
- Thus, you may see some unfamiliar things
- The next few slides should help put them in perspective

Why Bayesian Statistics?

- Automated inference is ‘easy’ using simulation
  - Markov Chain Monte Carlo (MCMC)
- The models assume uncertainty over parameters
  - Strictly, frequentist statistics does not allow this

Different perspectives...

Frequentist statistics

- Evaluate whether observed samples are likely to arise given an assumed *objective* probability θ
- Assumes long-run, repeated sampling to be possible
- Parameters are fixed unknowns

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Frequentist statistics

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Bayesian statistics

- A framework to support the rational updating of beliefs about the world, expressed as the *subjective* probability of events
- Any observations can contribute to our beliefs
- Parameters are uncertain and described using distributions

Different perspectives... inference

Frequentist statistics

$$
\begin{array}{ccc}
\text{Model: } f(x|\theta) & H_0 : \theta = \theta_0 & \text{Data: } y \\
\searrow & \downarrow & \swarrow \\
 & p = P(x \geq y | f, H_0) & \\
 & \downarrow & \\
 & \text{Reject } H_0 \text{ iff } p \leq \alpha &
\end{array}
$$

Different perspectives... inference

Frequentist statistics

Model: $f(x|\theta)$ $\quad H_0 : \theta = \theta_0 \quad$ Data: y

$$p = P(x \geq y | f, H_0)$$

$\geq$ means 'at least as extreme as'

Reject H_0 iff $p \leq \alpha$

Different perspectives... inference

Frequentist statistics

Model: $f(x|\theta)$ $H_0 : \theta = \theta_0$ Data: y

$$p = P(x \geq y | f, H_0) \longleftarrow \geq \text{ means `at least as extreme as'}$$

Reject H_0 iff $p \leq \alpha$

Central question: given infinitely many samples, what proportion p would give a result x 'at least as extreme as' y, under f and H_0?

Different perspectives... inference

Bayesian statistics

Model: $f(x|\theta)$ Prior: $\pi(\theta)$ Data: y

Posterior: $f(\theta|y) \propto \pi(\theta) f(y|\theta)$

Different perspectives... inference

Bayesian statistics

Model: $f(x|\theta)$ Prior: $\pi(\theta)$ Data: y

Posterior: $f(\theta|y) \propto \pi(\theta) f(y|\theta)$

- $L(\theta) = f(y|\theta)$ is the *likelihood* (for fixed data y)
- The posterior is (proportional to) the prior times the likelihood
- Bayes' theorem, or: law of inverse probability
- Valid (and used) in frequentist statistics

Different perspectives... inference

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Estimation Inference Prediction

Different perspectives... inference

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Estimation Inference Prediction

Does θ_0 lie in the $(1-\alpha)$ HPD region?

Different perspectives... inference

Bayesian statistics

Model: $f(x|\theta)$ Prior: $\pi(\theta)$ Data: y

Posterior: $f(\theta|y) \propto \pi(\theta)f(y|\theta)$

Estimation Inference Prediction

Central question: how should new data change our beliefs about the world?

Different perspectives... summary

- The mathematical foundations are similar
- Perspectives differ:
  - Bayesian statistics:
    what should I reasonably believe about X?
  - Frequentist statistics:
    what repeated sampling properties can I expect under H_0?
- The Bayesian approach has some practical advantages:
  - Can be used if 'repeated sampling' is not reasonable
  - General inference is 'easy' using stochastic simulation
  - Readily supports decision models with uncertainty

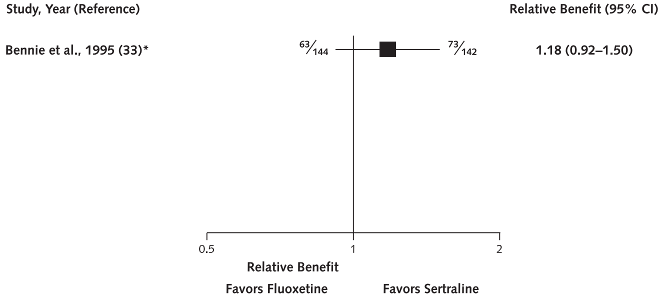
Questions?

Meta-analysis

Study, Year (Reference)	Fluoxetine	Sertraline
Bennie et al., 1995 (33)*	63/144	73/142

Hansen et al. Ann Intern Med 2005;143:415-426

Meta-analysis



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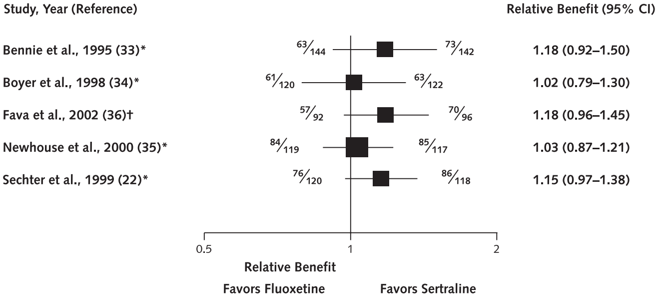

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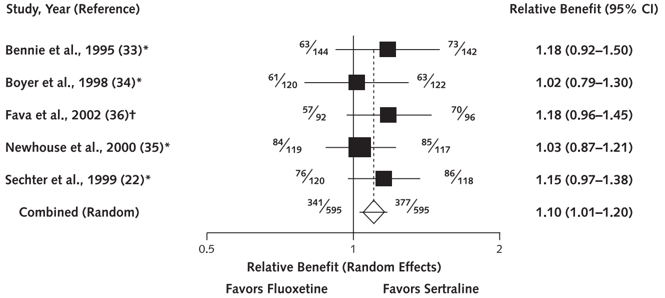

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Bayesian meta-analysis

I will provide a Bayesian version of meta-analysis

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- I will assume a *random effects* model
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In general, the analysis proceeds as follows:

1. Construct a Bayesian Hierarchical Model
2. Use MCMC software (BUGS, JAGS, etc.) to estimate it

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In general, the analysis proceeds as follows:

1. Construct a Bayesian Hierarchical Model
2. Use MCMC software (BUGS, JAGS, etc.) to estimate it

I will only explain (1).

Example

Mortality rates under different PCI strategies:

Study nr.	iPCI	mPCI	sPCI
1	42/354	5/26	12/126
2	0/17	1/52	
3	57/707	11/70	
4	5/149		3/93
5	28/503	36/503	
6	14/259		10/259
...			
16	18/152	24/142	3/85

Example: data to random effects

Study 6: iPCI: 14/259, sPCI: 10/259

$$n_{6,i} = 259;\ r_{6,i} = 14;\ n_{6,s} = 259;\ r_{6,s} = 10$$

The event rates r are generated by a binomial process:

$$r_{6,i} \sim \mathrm{Bin}(p_{6,i}, n_{6,i})$$

Then, taking iPCI as the baseline for study 6:

$$p_{6,i} = \mathrm{ilogit}(\mu_6)$$
$$p_{6,s} = \mathrm{ilogit}(\mu_6 + \delta_{6,i,s})$$

The ilogit link function

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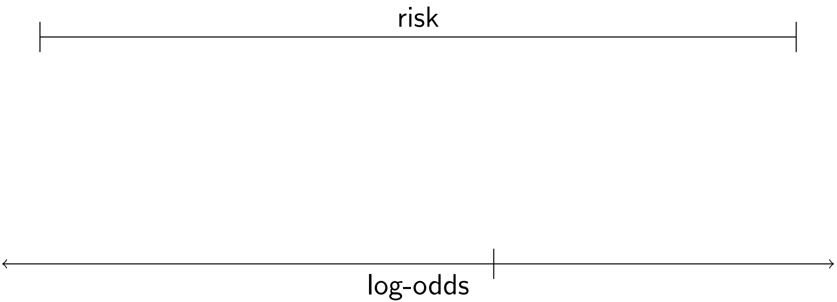
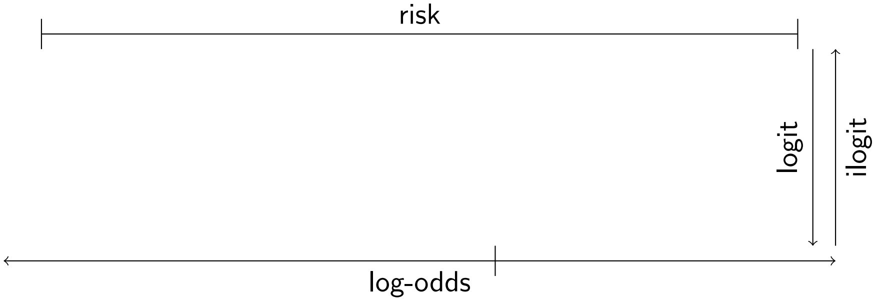
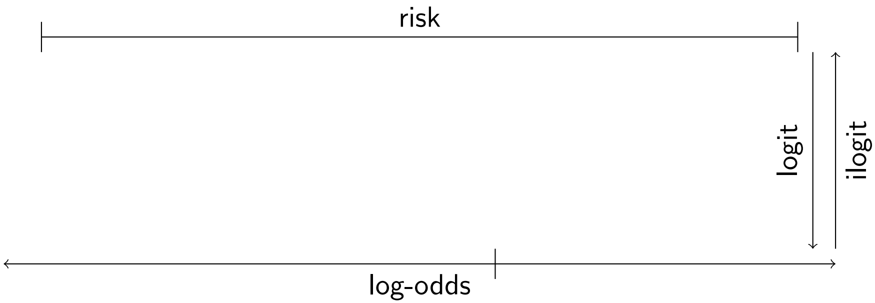


The ilogit link function



The ilogit link function

$p_{6,i} = 0.1$ $p_{6,s} = 0.6$



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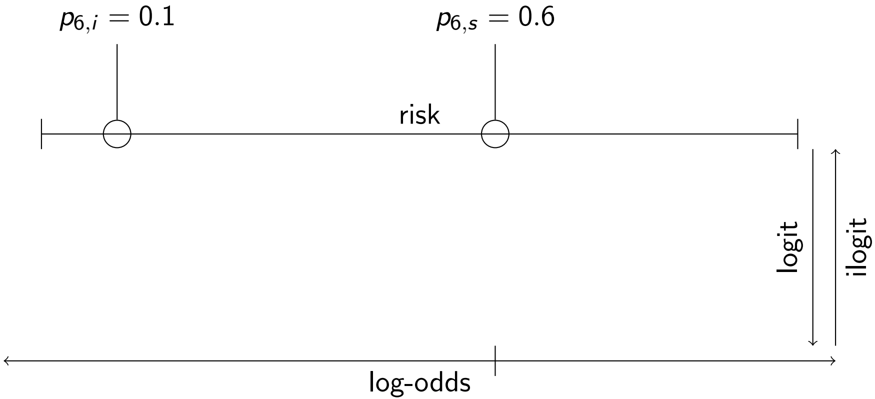

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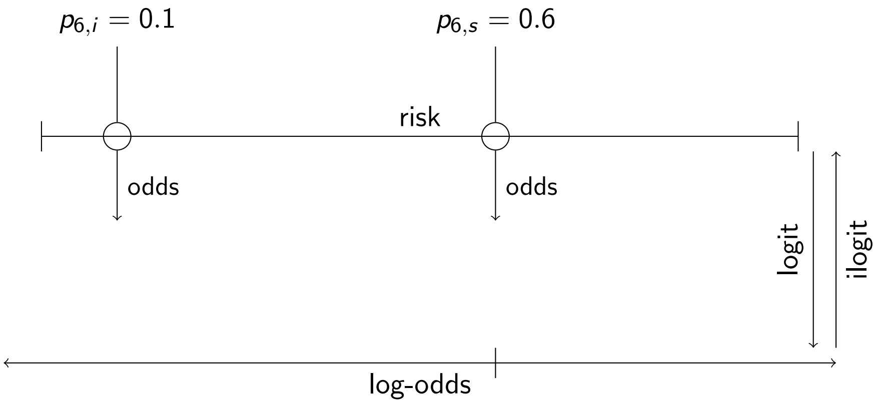

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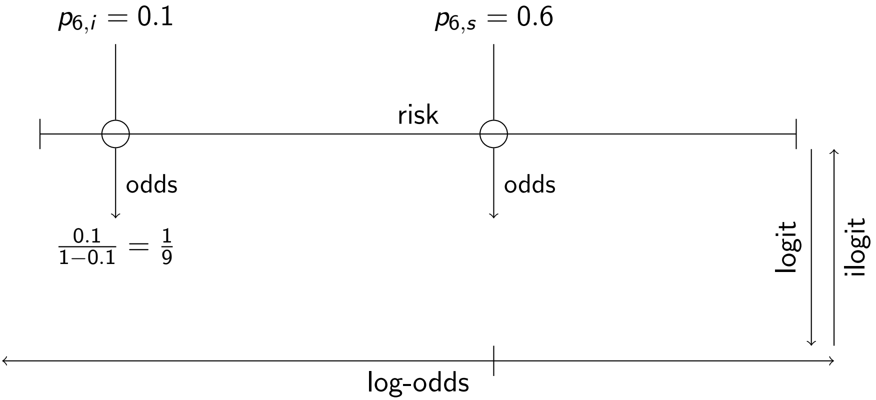

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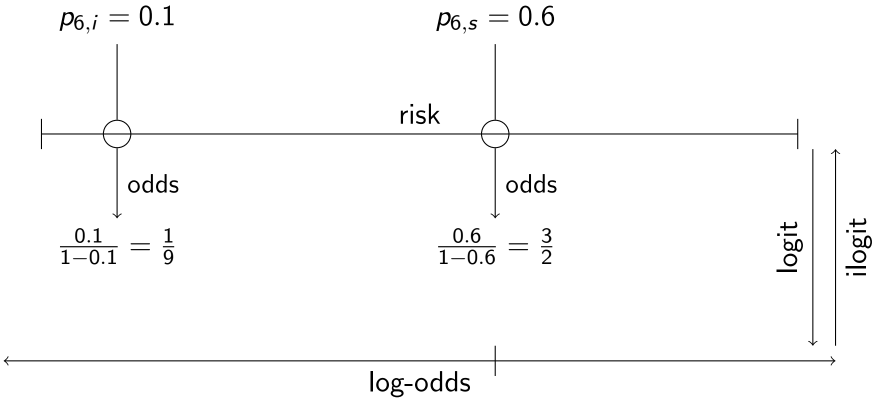

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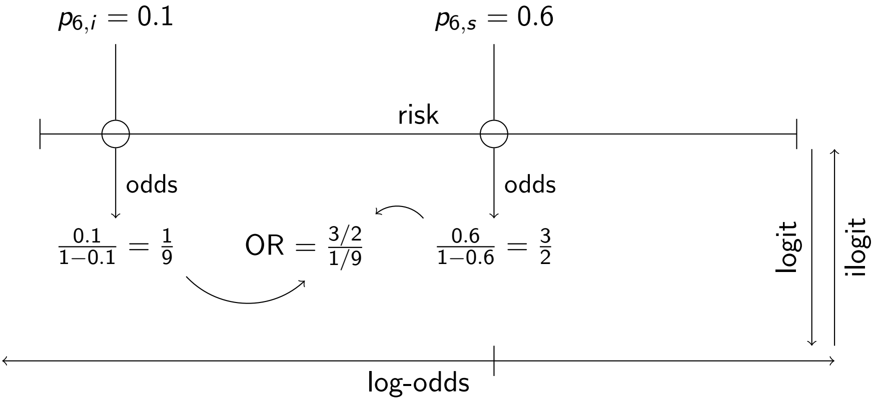

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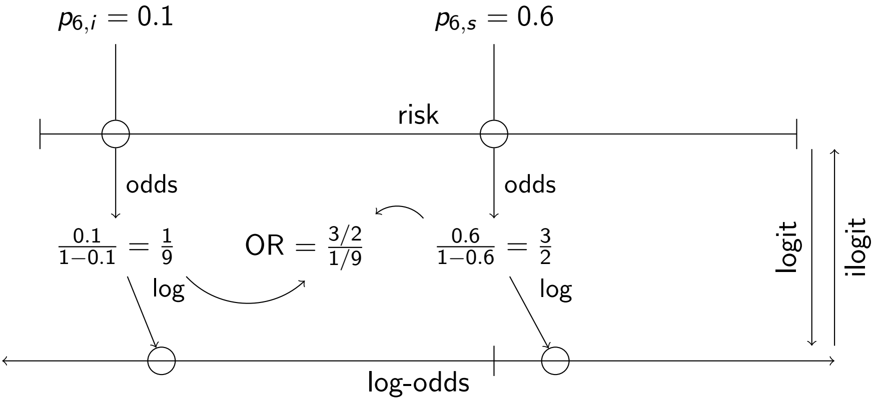

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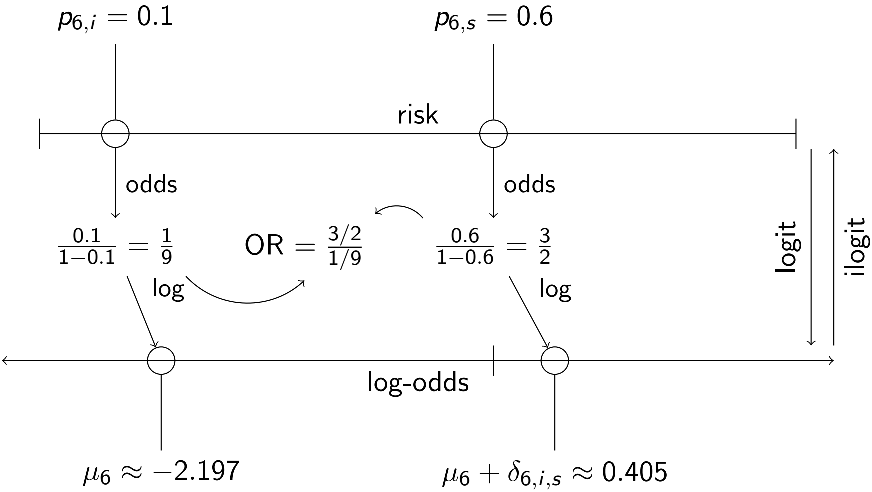

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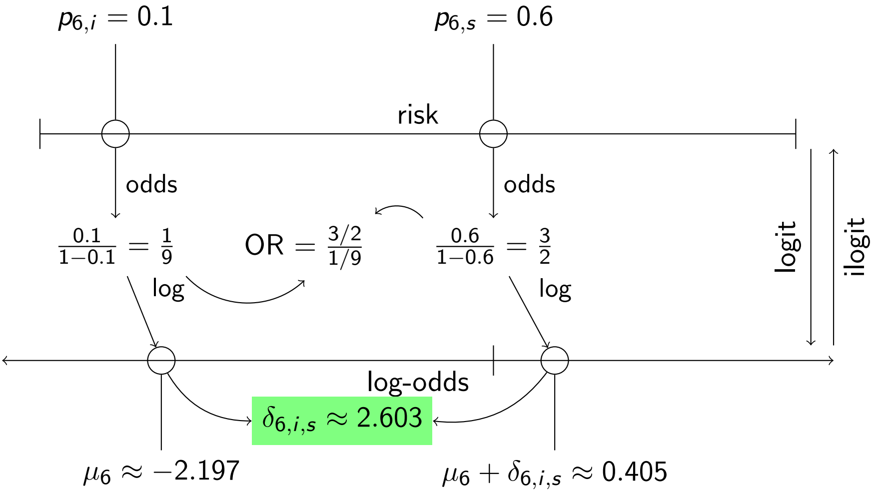

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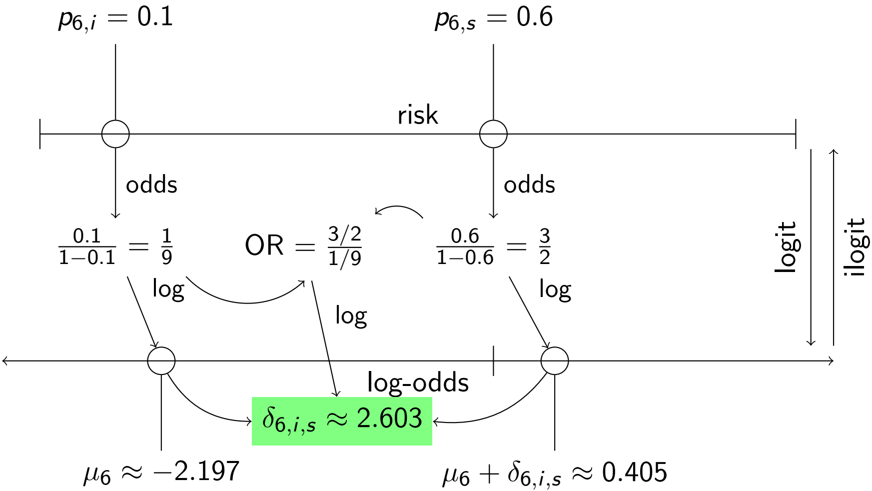

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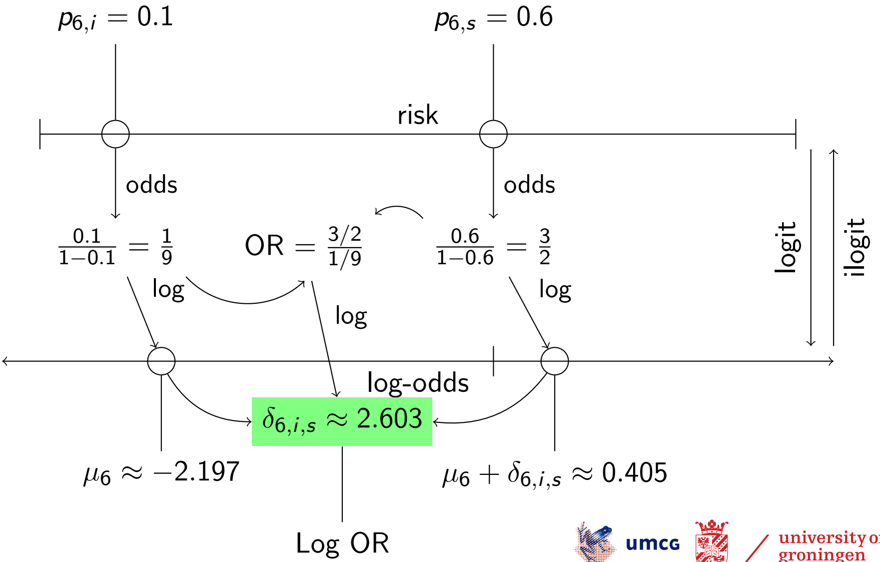

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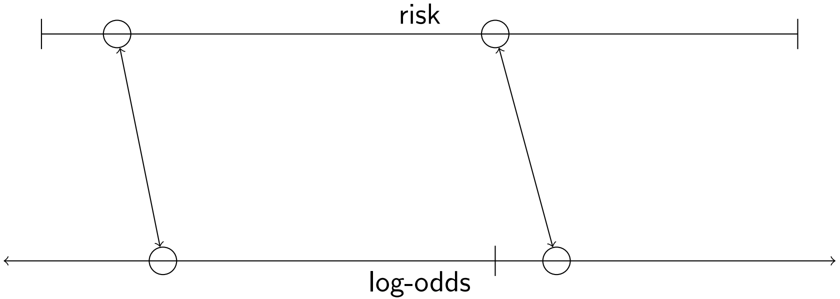

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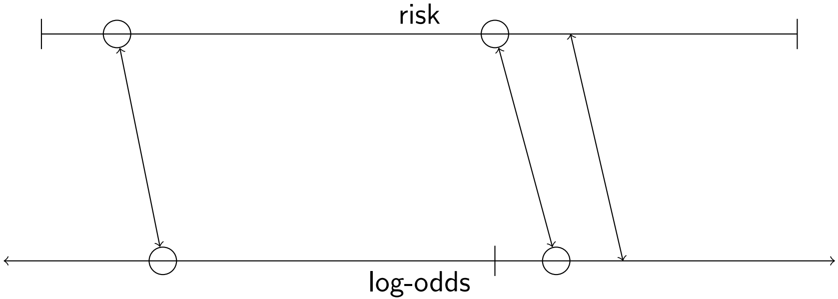

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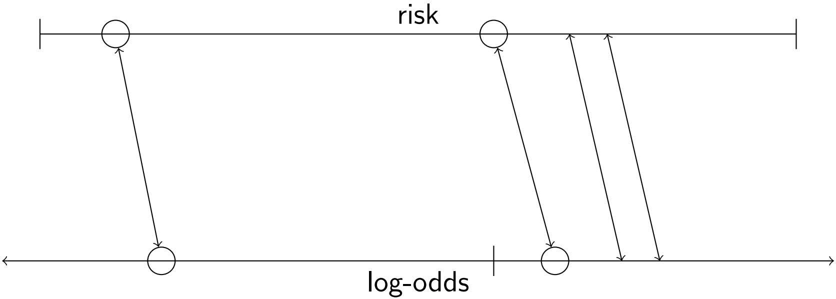

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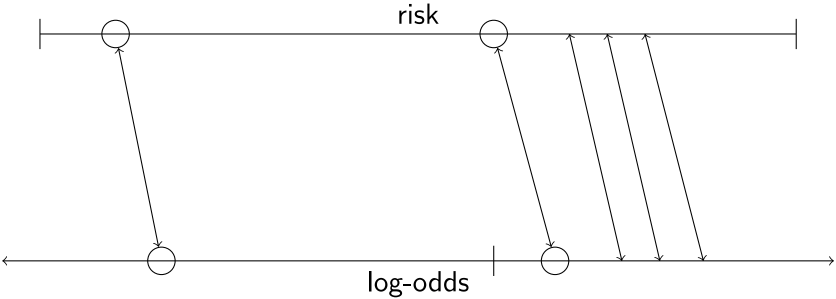

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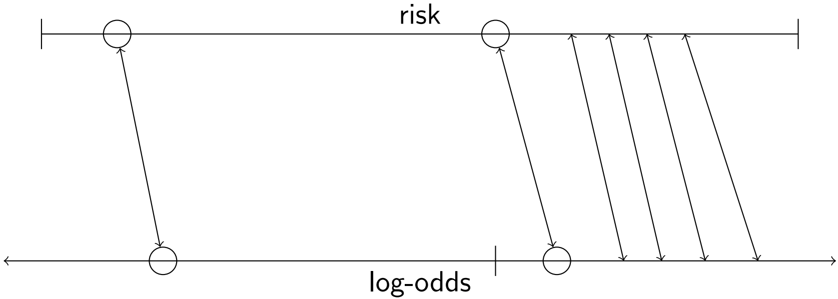

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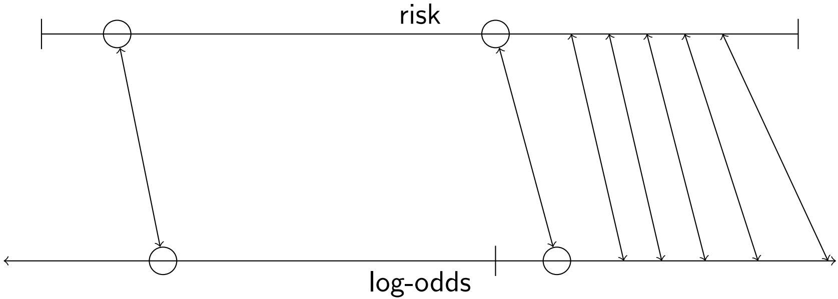


Example: random effects to relative effects

The $\delta_{6,i,s}$ is a random effect parameter (Log OR):

$$p_{6,s} = \mathrm{ilogit}(\mu_6 + \delta_{6,i,s})$$

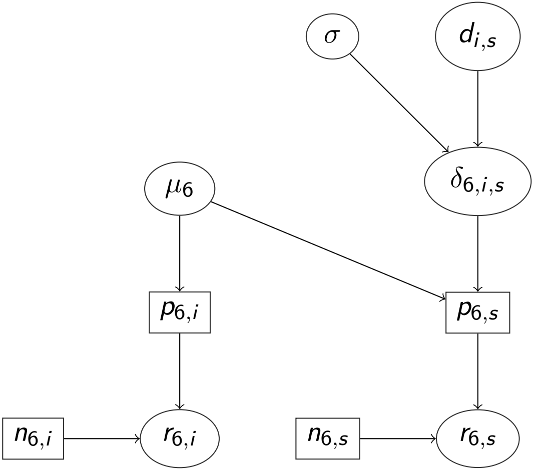
Which is distributed according to:

$$\delta_{6,i,s} \sim \mathcal{N}(d_{i,s}, \sigma)$$

Where

- σ is the *random effects variance*
- $d_{i,s}$ is the *relative effect estimate* of sPCI compared to iPCI

Example: data to relative effects



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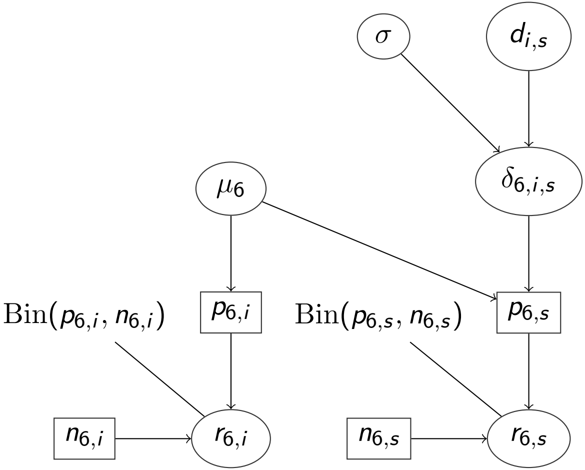

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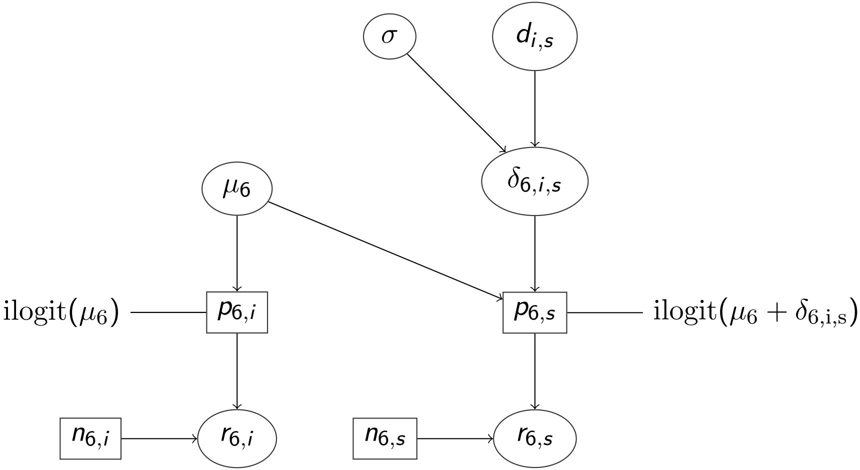

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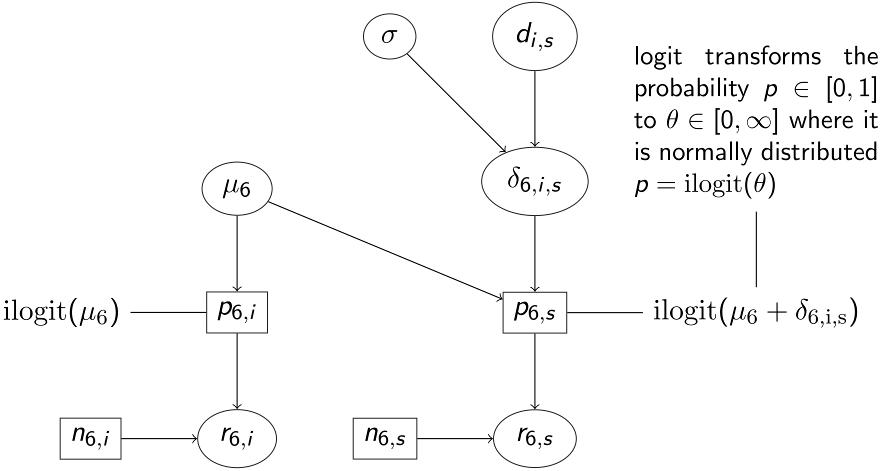

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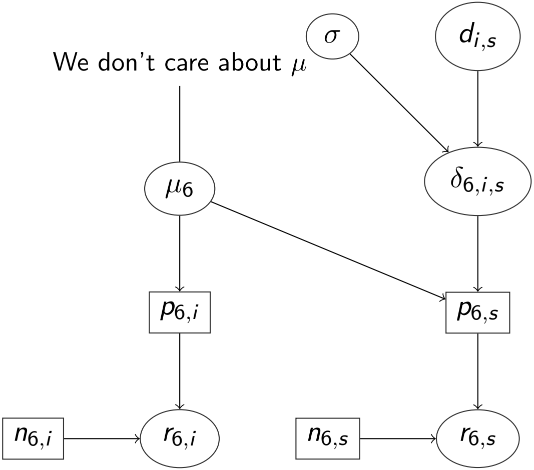

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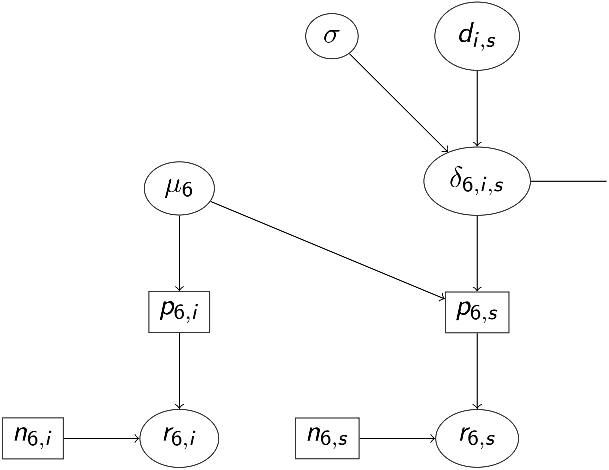
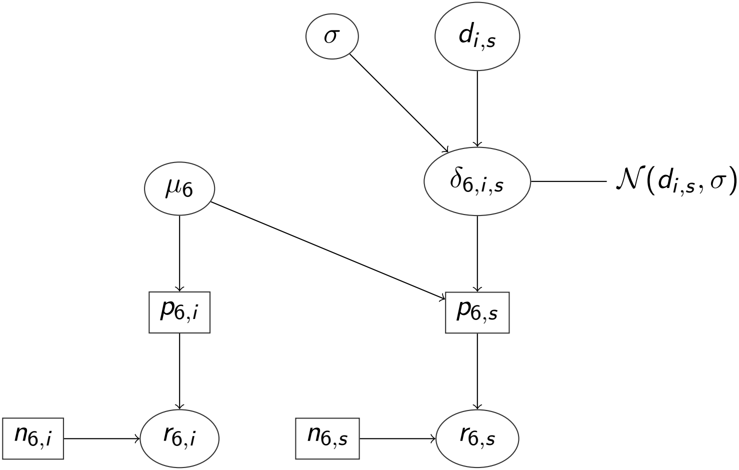


Thus, an n-arm study gives us $n - 1$ δ's of interest

Example: data to relative effects



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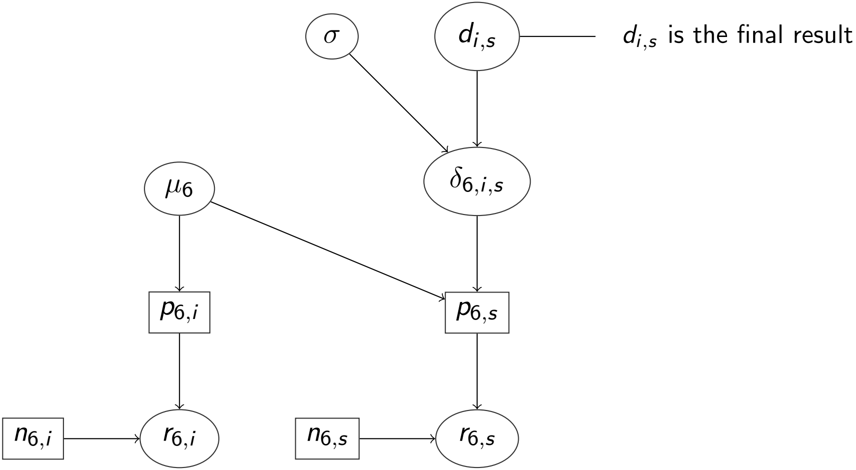

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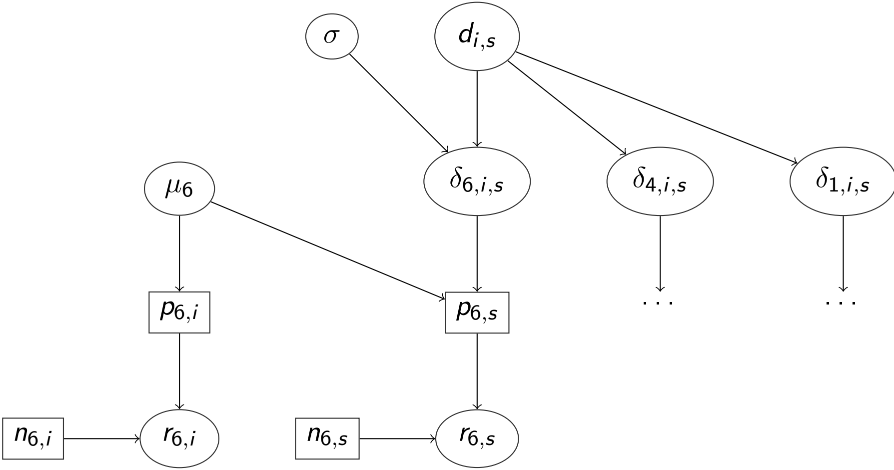

Meta-analysis limits (1)

Hansen et al. (2005) systematic review:

- 46 studies comparing $n = 10$ second-generation AD

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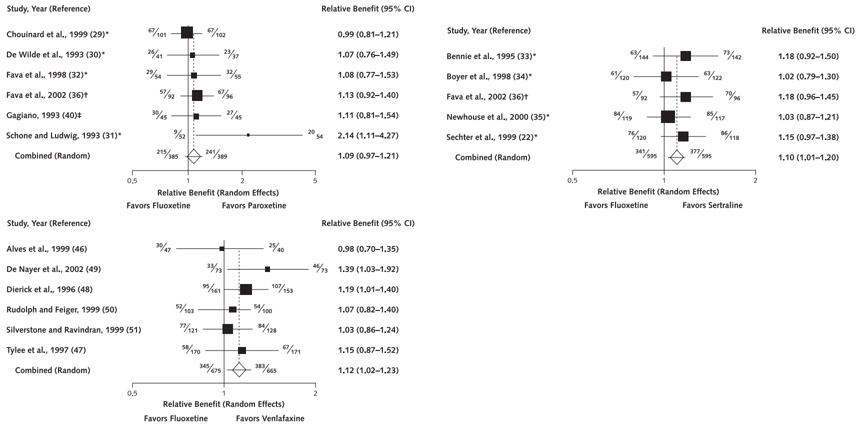

Hansen et al. Ann Intern Med 2005;143:415-426

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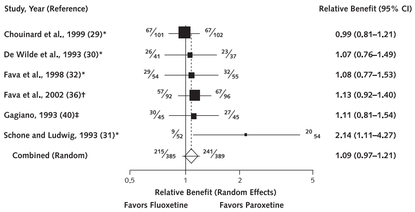

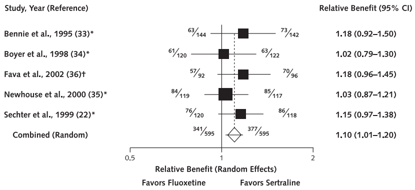

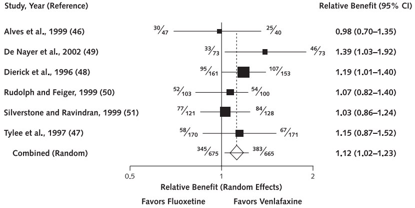

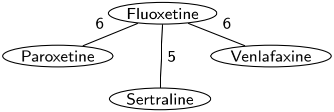

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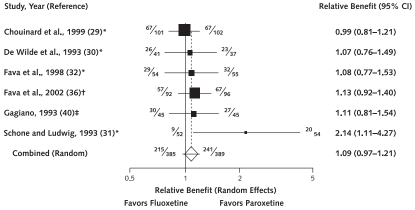

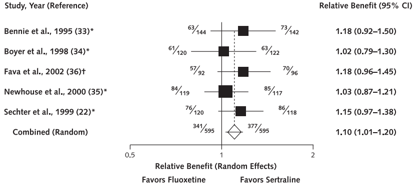

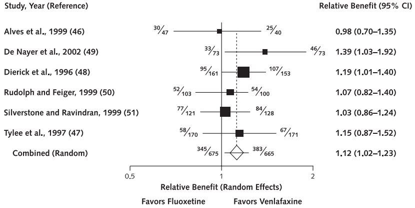

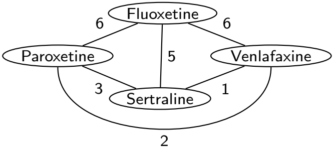

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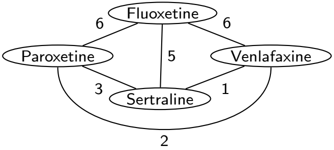
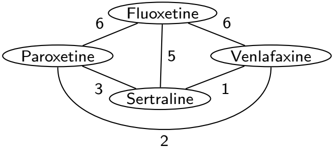
Meta-analysis limits (2)



Hansen et al. (2005) systematic review:

- 46 studies comparing $n = 10$ second-generation AD
- Only **3** meta-analyses, all agains **fluoxetine**

Meta-analysis limits (2)



- How do paroxetine, sertraline and venlafaxine compare?

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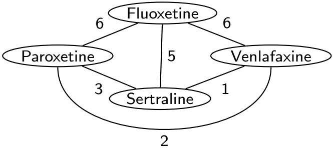

- How do paroxetine, sertraline and venlafaxine compare?
- Can we compare sertraline/venlafaxine?

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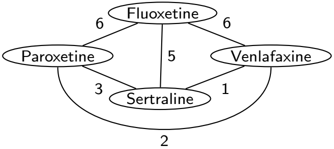

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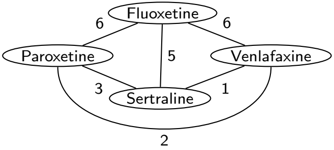

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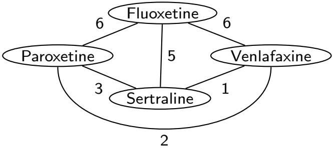

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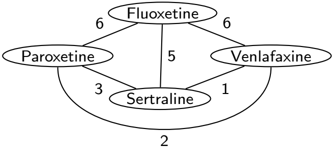
  - Only **one** direct trial
  - Ignoring the **11** trials sertr-fluox-venla
  - Is this justified?
- Ignore 3 parox-sertr trials in fluox/parox, fluox/sertr?

Meta-analysis limits (2)



- How do paroxetine, sertraline and venlafaxine compare?
- Can we compare sertraline/venlafaxine?
  - Only **one** direct trial
  - Ignoring the **11** trials sertr-fluox-venla
  - Is this justified?
- Ignore 3 parox-sertr trials in fluox/parox, fluox/sertr?
- Parox as comparator → same conclusions?

Conclusion

- Meta-analysis is good if we compare *two* drugs
- It is problematic for more
  - Selection bias: choice of common comparator?
  - Are results of different comparisons consistent?
- We need a way to include *all* trials/drugs

Conclusion

- Meta-analysis is good if we compare *two* drugs
- It is problematic for more
  - Selection bias: choice of common comparator?
  - Are results of different comparisons consistent?
- We need a way to include *all* trials/drugs
- A straightforward extension of Bayesian meta-analysis is possible: **network meta-analysis**

Questions?

Network meta-analysis

Network meta-analysis:

- Is an extension of normal meta-analysis
- Allows comparison of ≥ 2 alternatives
  - Integrating direct and indirect evidence
  - While checking for (in-)consistencies
- A.K.A.: Mixed/Multiple Treatment Comparison (MTC)

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- Allows comparison of ≥ 2 alternatives
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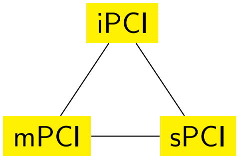
- A.K.A.: Mixed/Multiple Treatment Comparison (MTC)

My research:

- Automated in ADDIS (2, 5, 6)

Related manuscripts:
2) G. van Valkenhoef, T. Tervonen, T. Zwinkels, B. de Brock, H. Hillege, *ADDIS: a decision support system for evidence-based medicine.* Manuscript under review.
5) G. van Valkenhoef, T. Tervonen, B. de Brock, H. Hillege, *Algorithmic Parameterization of Mixed Treatment Comparisons.* Manuscript under review.
6) G. van Valkenhoef, B. de Brock, H. Hillege, *Automating network meta-analysis.* Initiated (conference paper).

Example: relative effects, consistency



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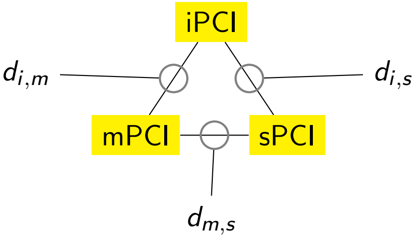
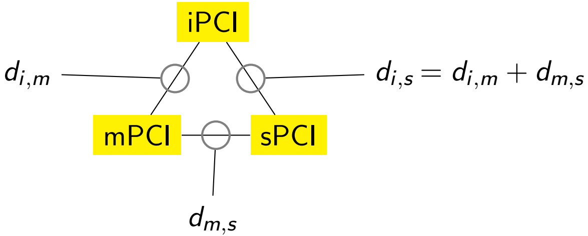
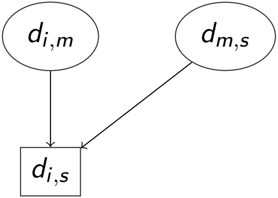


Example: relative effects, consistency

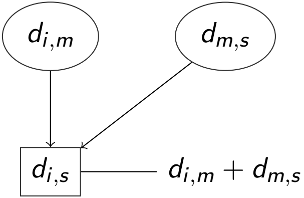


We assume *consistency*: direct and indirect estimates lead to the same conclusions.

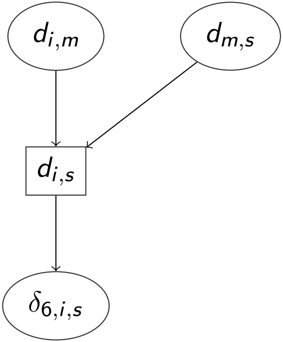
Example: consistency



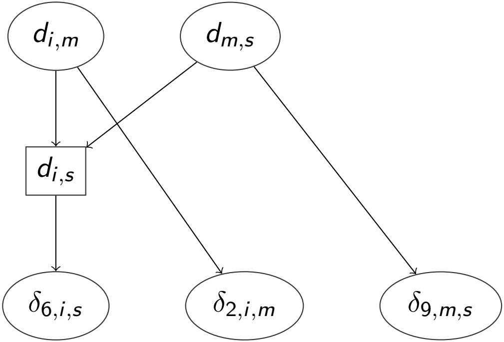
Example: consistency



Example: consistency



Example: consistency



Consistency

We assume *consistency*: direct and indirect estimates lead to the same conclusions.

- Estimate *all* relative effects simultaneously
- Including *all* studies
- Leading to *consistent* conclusions
- Also estimate missing comparisons

Example: results (relative effects)

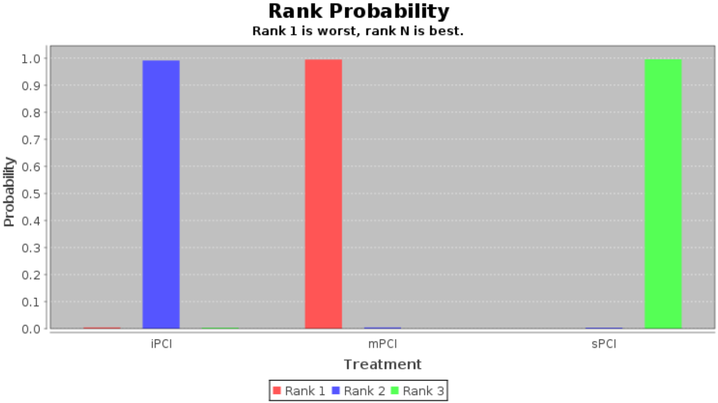
The *relative effect* of x vs y: odds ratio

iPCI	1.62 (1.18, 2.23)	0.55 (0.35, 0.87)
	mPCI	0.34 (0.21, 0.56)
		sPCI

Table: OR (95% CrI) for mortality

Example: results (rank probabilities)

The *rank probability*: how likely is x to be the best treatment?



Rank probability

Rank probabilities

- Based on the posterior distributions
  - Of the relative effects
- Estimate the probability that treatment x has rank i
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- Complements relative effects table

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- Based on the posterior distributions
  - Of the relative effects
- Estimate the probability that treatment x has rank i
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- Provide additional insight with few significant results
- Complements relative effects table

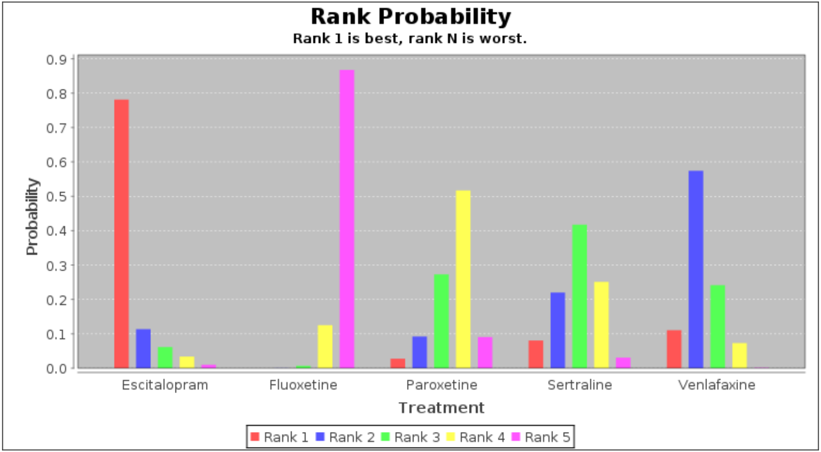
Illustrated in the next example!

Quick example: efficacy of anti-depressants (1/2)

Escit	**0.59 (0.37, 0.94)**	0.69 (0.41, 1.15)	0.74 (0.44, 1.25)	0.81 (0.53, 1.24)
	Fluox	1.18 (0.91, 1.52)	1.27 (0.99, 1.63)	**1.38 (1.10, 1.72)**
		Parox	1.08 (0.77, 1.51)	1.17 (0.86, 1.59)
			Sertr	1.09 (0.80, 1.48)
				Venla

Table: OR (95% CrI) for efficacy (treatment response) defined as improvement of $\geq$ 50% on the HAM-D rating scale

Quick example: efficacy of anti-depressants (2/2)



Obstacles

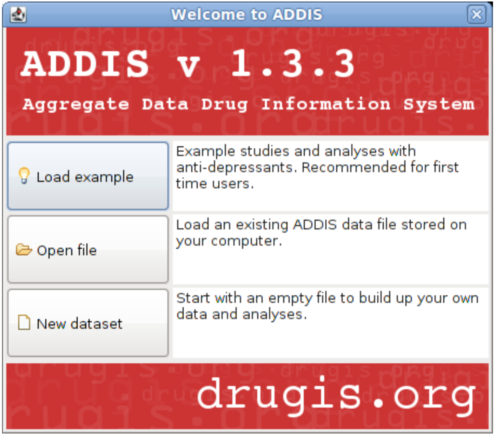
Before the conclusions under consistency can be accepted:

- Possible *inconsistency* should be evaluated:
    - First, by assessing the studies for exchangeability
    - Second, by statistical means (inconsistency/node-split model)
- Assess convergence & run-length of the MCMC simulation
- Reasonable priors have to be specified

The references provide more information on these topics.

Questions?

Time for a live demonstration!



Network meta-analysis (general)

- Cipriani, A., Furukawa, T.A., Salanti, G., Geddes, J.R., Higgins, J.P.T., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I.M., McGuire, H., Tansella, M. and Barbui, C., Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. The Lancet, 373 (9665): 746–758, 2009.
- Salanti, G., Kavvoura, F.K. and Ioannidis, J.P.A., Exploring the Geometry of Treatment Networks. Annals of Internal Medicine, 148 (7): 544–553, 2008.
- Lu, G. and Ades, A.E., Combination of Direct and Indirect Evidence in Mixed Treatment Comparisons. Statistics in Medicine 23 (20): 3105–3124, 2004.

Network meta-analysis (inconsistency models)

- Lu, G. and Ades, A.E., Assessing Evidence Inconsistency in Mixed Treatment Comparisons. Journal of the American Statistical Association 101 (474): 447–459, 2006.
- Salanti, G., Higgins, J.P.T., Ades, A.E. and Ioannidis, J.P.A., Evaluation of Networks of Randomized Trials. Statistical Methods in Medical Research 17 (3): 279–301, 2008.

Network meta-analysis (node-split models)

Another way of analyzing inconsistency.

- Dias, S. Welton, N.J., Caldwell, D.M. and Ades, A.E., Checking Consistency in Mixed Treatment Comparison Meta-Analysis. Statistics in Medicine 29 (7-8, Sp. Iss. SI): 932–944, 2010.

MCMC methods

A gentle introduction:

- Jackman, S., Bayesian Analysis for the Social Sciences. Wiley Series in Probability and Statistics, 2009.

Evaluating convergence:

- Brooks, S.P. and Gelman, A., General Methods for Monitoring Convergence of Iterative Simulations. Journal of Computational and Graphical Statistics 7 (4): 434–455, 1998.