Network meta-analysis using integrated nested Laplace approximations (INLA)

Burak Kürsad Günhan [1] Tim Friede [1] Leonhard Held [2]

[1]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

[2]Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Zürich, Switzerland

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InSPiRe
Innovative methodology for small populations research

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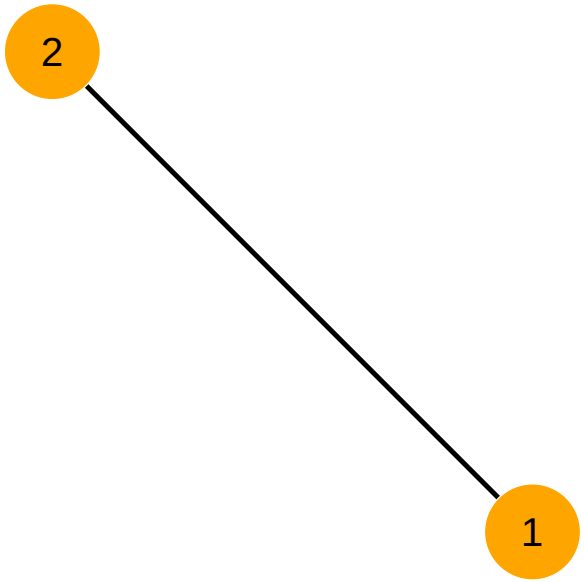
Systematic review

- Review of evidences from different studies
- On a specific question, methods to identify, select, appraise and summarize similar but separate studies
- **Study selection**: inclusion and exclusion criteria

Meta-analysis (The analysis of analyses)

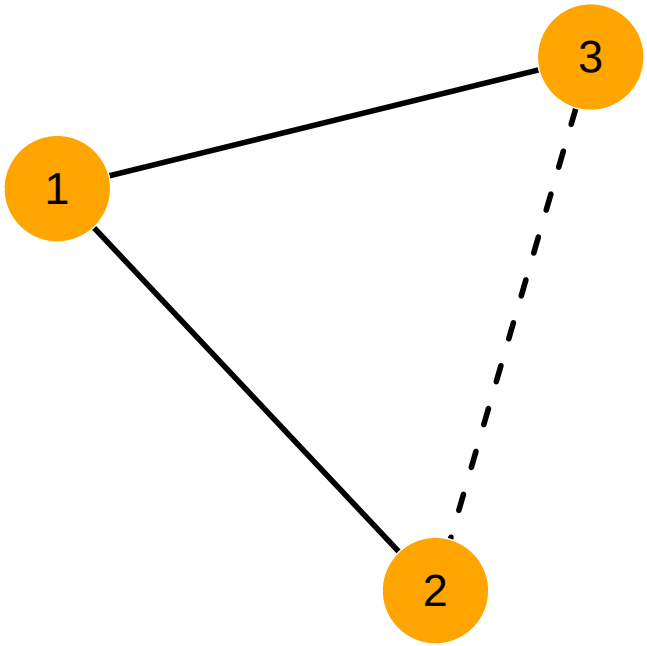
- Quantitative part of systematic review
- SR may or may not include a meta-analysis
- Using statistical methods to combine results from different studies

Conventional meta-analysis



- Only two treatments are compared
- Trt 1 vs Trt 2 can be estimated ($d_{1,2}$)
- **Direct estimate**
- **Heterogeneity** between trials
- Pairwise meta-analysis
- Meta-regression

More than two treatments?



- Increasing number of treatments
- Solid lines indicate comparisons are available
- A generalization of pairwise meta-analysis
- **Indirect estimate** of 2 vs 3

$$d_{2,3}^{Ind} = d_{1,2}^{Dir} - d_{1,3}^{Dir}$$

Terminology in NMA (Salanti, 2012)

- If both direct and indirect estimates are available for $d_{1,2}$
- **Consistency**: No discrepancy between indirect and direct estimates

$$d_{1,2}^{Dir} = d_{1,2}^{Ind}$$

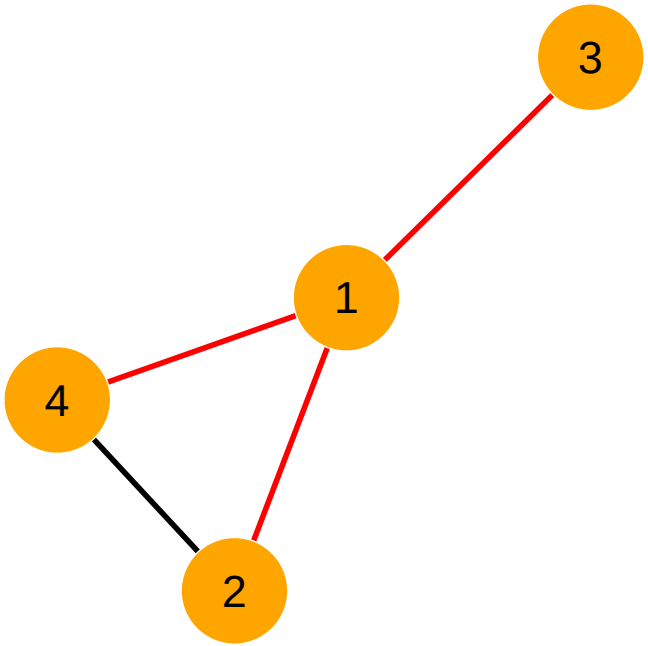
- Consistency relation

$$d_{1,2}^{Dir} = d_{1,3}^{Dir} - d_{2,3}^{Dir}$$

- Trials of different comparisons were undertaken in different periods
- Right-hand side parameters are **basic parameters** ($\mathbf{d}_b$)
  $\Rightarrow$ Parametrization of the network
- Others are **functional parameters** ($\mathbf{d}_f$)

Terminology in NMA

- From Graph theory: vertex, edge, cycle, spanning tree
- **Design**: set of treatments included in a trial; 1-2 design, 1-2-3 design



- Example
  $\mathbf{d}_b = \{d_{12}, d_{13}, d_{14}\}$ (red lines)
  $\Rightarrow d_f = d_{24} = d_{12} - d_{14}$
  Consistency relation
  $\Rightarrow$ 3-cycle

Statistical models for NMA

- **Arm-based** instead of **contrast-based** models
  $\Rightarrow$ Advantage: one-stage approach, exact likelihood
- Bayesian hierarchical models, more specifically generalized linear mixed models (GLMMs)
- Datasets with different endpoints (binomial, continuous, survival) can be modelled
- Basic model is same, but **likelihood** and **link function** can change

Consistency models (Dias et al., 2011)

- For convenience, consider data with binomial endpoints
- In trial i; j, k is treatment pair where j baseline treatment, k remaining treatment
- Number of events, $y_{ik} \sim \text{Bin}(\pi_{ik}, n_{ik})$ and $y_{ij} \sim \text{Bin}(\pi_{ij}, n_{ij})$
- Logit link, model equations:

$$\begin{aligned} \text{logit}(\pi_{ij}) &= \mu_i \\ \text{logit}(\pi_{ik}) &= \mu_i + d_{jk} + \gamma_{ijk} \end{aligned}$$

  where μ_i nuisance parameter and d_{jk} basic parameters

- Heterogeneity random effects: $\gamma_{ijk} \sim \mathcal{N}(0, \tau^2)$

Consistency models (Dias et al., 2011) (cont.)

- But, for a multi-arm trial: dependency within trial!
- Example: A three-arm trial i with the design 1-2-3
  - $\boldsymbol{\gamma}_i = (\gamma_{i12}, \gamma_{i13})^T \sim \mathcal{N}_2(\mathbf{0}, \boldsymbol{\Sigma}_\gamma)$
  - A simple but a convenient structure is as follows (Higgins and Whitehead, 1996):

$$\boldsymbol{\Sigma}_\gamma = \begin{bmatrix} \tau^2 & \tau^2/2 \\ \tau^2/2 & \tau^2 \end{bmatrix}$$

Some comments

- Basic parameters can be any $T-1$ treatment comparisons
- For continuous endpoints, normal likelihood and identity link
- Consistency is assumed in the network!
- Models are needed to account for **inconsistency** in the network

Lu-Ades Model (Lu and Ades, 2006)

- Uses cycle-inconsistency approach
- Assumption: inconsistency **only** occurs from 3-cycles
- Basic parameters should form a spanning tree
- Cycle-specific inconsistency random effects: $\omega_{jkl} \sim \mathcal{N}(0, \kappa^2)$
- Multi-arm trials are inherently consistent
- Number of inconsistency random effects: ICDF $= \#\mathbf{d}_f - S$ where S is the number of cycles only formed by a multi-arm trial
- Algorithm for ICDF (van Valkenhoef et al., 2012), but not efficient
- In the presence of multi-arm trials, **results depend on treatment ordering!**

Jackson Model (Jackson et al., 2014)

- Uses design-inconsistency approach (Higgins et al., 2012)
- **Design inconsistency**: occurs between trials involving different designs
- 1,2,3 trials can be inconsistent with 1,2 trials
- Adding more inconsistency parameters to the model
- Inconsistency parameters as random effects

$$\text{logit}(\pi_{ik}) = a_{ij} + d_{jk} + \gamma_{ijk} + \omega_{jk}^{D}$$

$\boldsymbol{\omega}^{D} = (\omega_{jk_1}, \omega_{jk_2}, \dots) \sim \mathcal{N}_c(\mathbf{0}, \boldsymbol{\Sigma}_{\omega})$ such that $\boldsymbol{\Sigma}_{\omega}$ has diagonal entries κ^2 and all others are $\kappa^2/2$

- NMA-regression: incorporating trial-specific covariates to the model in order to explain sources of inconsistency

Fully-Bayesian inference for NMA models

Markov Chain Monte Carlo (MCMC)

- A simulation-based technique and the most popular
- Popular MCMC-tools: WinBUGS, JAGS or Stan

Integrated Nested Laplace Approximations (INLA)

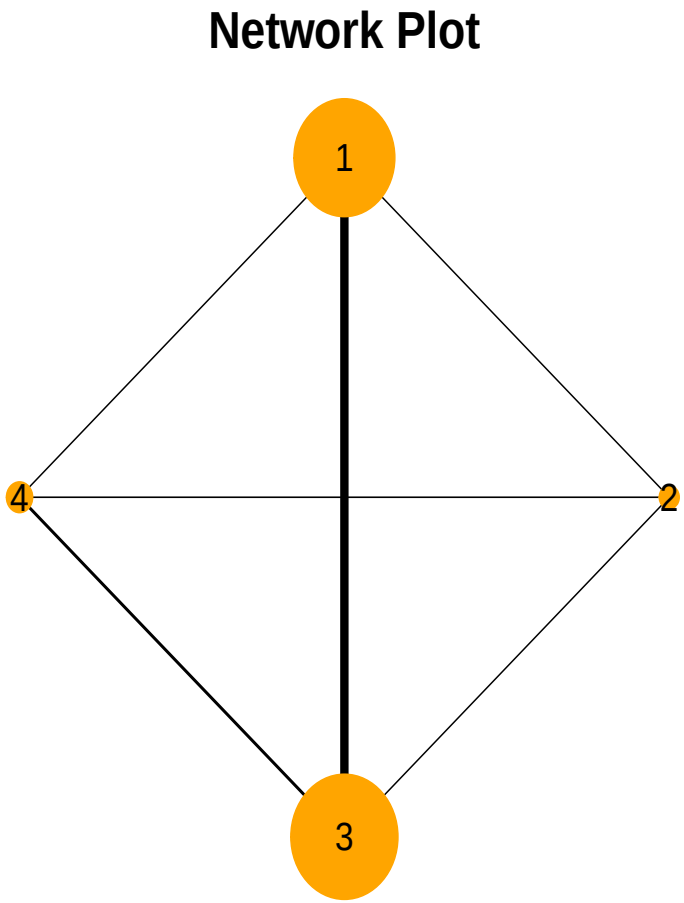
- An approximate Bayesian method (Rue et al., 2009) for latent Gaussian models (LGMs)
- Fast and accurate alternative to MCMC
- How INLA works (Rue et al., 2016)? **Laplace approximations** & **numerical integration**
- Implemented in `R-INLA` (http://www.r-inla.org/)

INLA for NMA models

- By Sauter and Held (2015), INLA can be used for many NMA models
- My goal: Extend INLA implementation to different NMA models (Jackson model, NMA-regression) and also automation
- How NMA models are LGMs? Three stages:
  1. Observational model: $p(\boldsymbol{y}|\boldsymbol{\alpha})$ where $\boldsymbol{\alpha} = (\boldsymbol{\mu}, \boldsymbol{d_b}, \boldsymbol{x}, \boldsymbol{\gamma}, \boldsymbol{\omega})$
  2. Latent Gaussian field: $p(\boldsymbol{\alpha}|\boldsymbol{\theta})$
  3. Hyperparameters: $\boldsymbol{\theta} = (\tau^2, \kappa^2)$

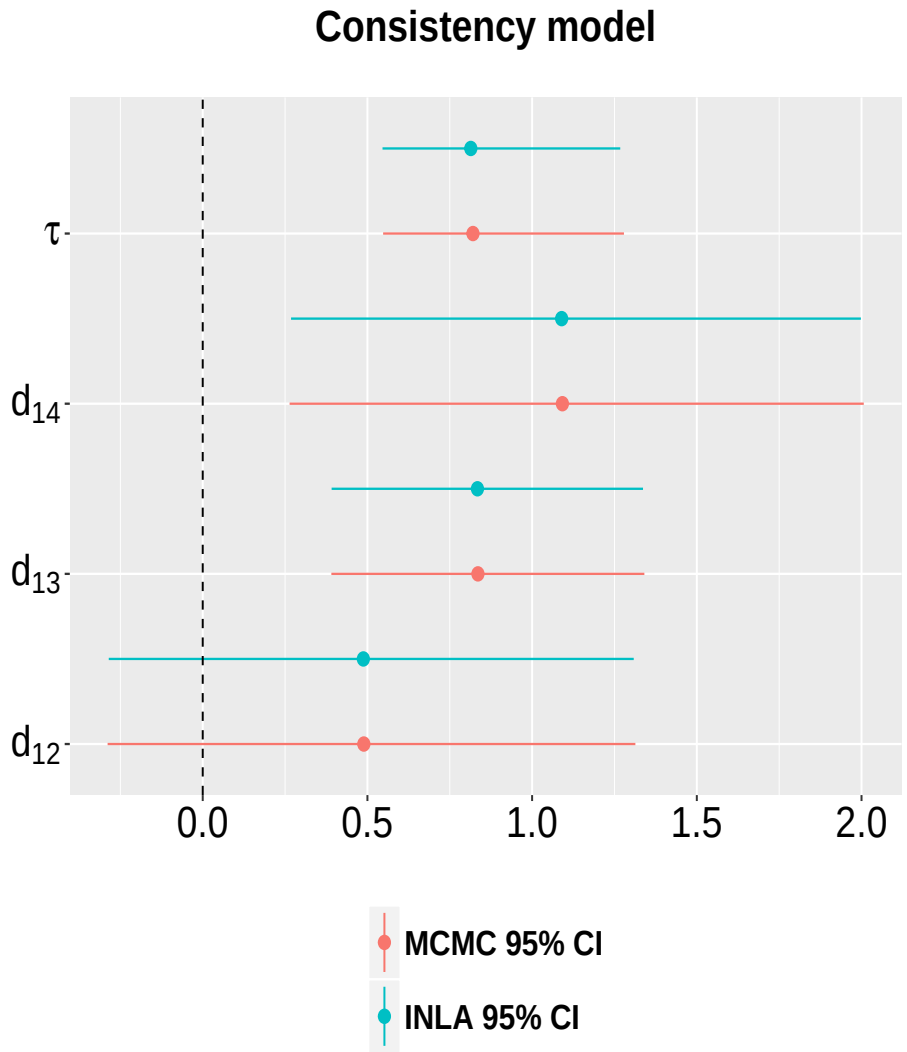
Smoking dataset (Hasselblad, 1998)

- 24 trials investigating four interventions to aid smoking cessation
- Coding; 1: no contact, 2: self-help, 3: individual counseling and 4: group counseling
- Area of circle: participants; width of line: trials
- 8 designs, 1-3-4 and 2-3-4 three arm trials

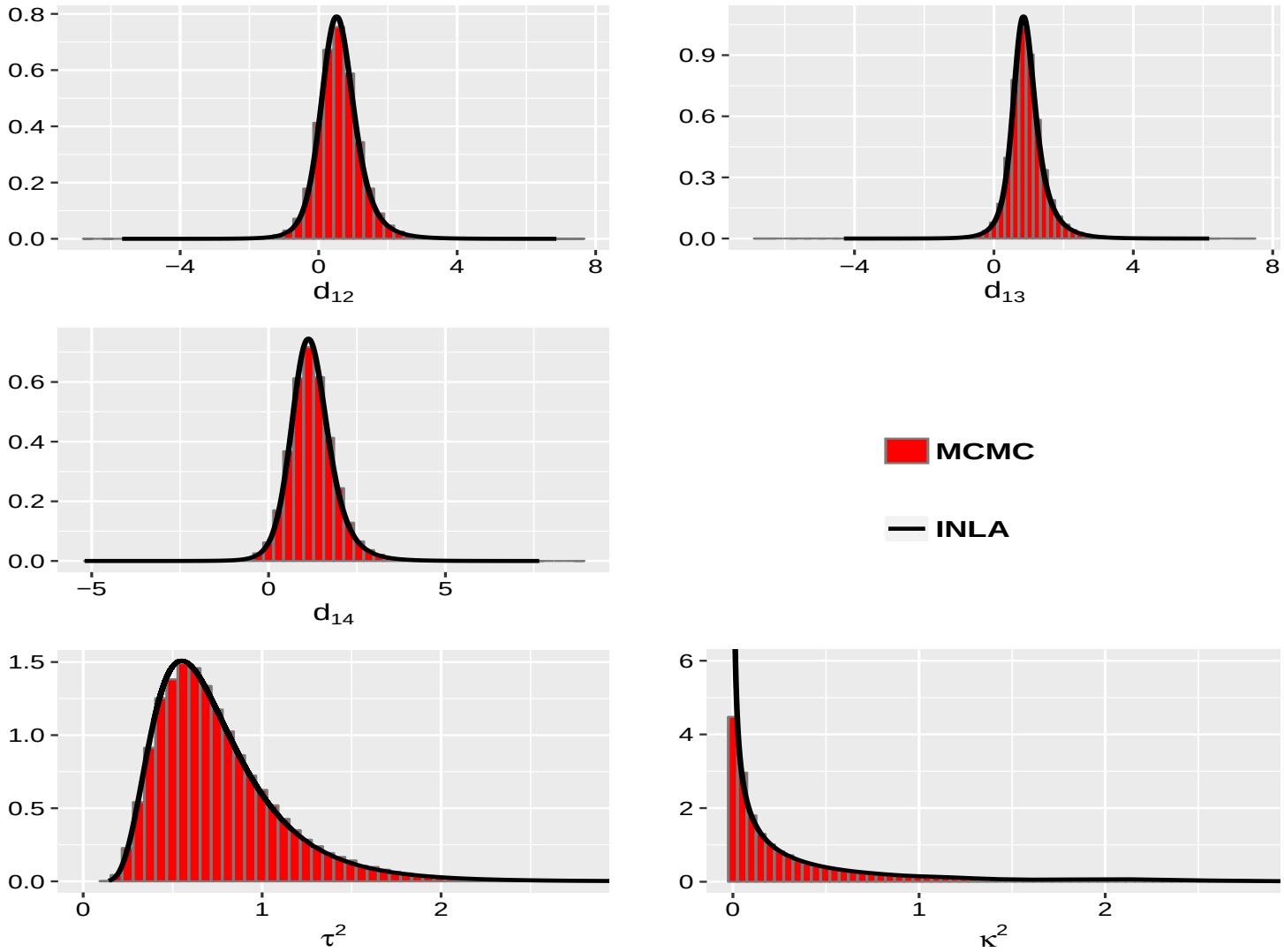


MCMC vs INLA

- $\mathbf{d}_b = \{d_{12}, d_{13}, d_{14}\}$
- Priors:
  $d_{1x} \sim \mathcal{N}(0, 1000)$,
  $\tau \sim \mathcal{U}(0, 5)$,
  $\kappa \sim \mathcal{U}(0, 5)$.
- MCMC using JAGS
- JAGS code (Jackson et al., 2014)
- Convergence diagnostics



Jackson model



Jackson vs Lu-Ades model using INLA

- 4 interventions, $4! = 24$ possibilities of coding
- Lu-Ades model substantially depend on treatment ordering!
- Confirmation of Higgins et al. (2012)

	ICDF	κ	τ
Consistency	0	0.00	0.81
Jackson	10	0.39	0.82
Lu-ades			
1234, 1243	3	0.52	0.84
1324, 1423	3	0.60	0.83
1342, 1432	3	0.55	0.84
2314, 3214	3	1.39	0.79
3412, 4213	3	1.40	0.79

nmainla R package

Installation via devtools(Wickham and Chang, 2016) R package

```
devtools::install_github('gunhanb/nmainla')
```

Data preparation

```
SmokdatINLA <- create_INLA_dat(dat = Smokdat, # one-study-per-row dataset
                               armVars = c('treatment' = 't',
                                           'responders' = 'r',
                                           'sampleSize' = 'n'),
                               nArmsVar = 'na',
                               design = 'des')
```

Fitting a Jackson model

```
nma_inla(SmokdatINLA, likelihood = 'binomial', fixed.par = c(0, 1000),
         type = 'jackson', tau.prior = 'uniform', tau.par = c(0, 5),
         kappa.prior = 'uniform', kappa.par = c(0, 5))
```

Discussion

- No analytical expression for approximation error of INLA
- INLA may be less accurate for binomial data, for example (quasi) complete separation (Sauter and Held, 2016)
- We have encountered (little) inaccuracy for one application (binomial endpoints), can be addressed with more informative priors

Conclusions

- Common framework for arm-based NMA models to analyze dataset with different endpoints
- Faster, no need to check convergence diagnostics
- `nmainla` extracts features needed for NMA
- Reassurance that MCMC estimates are reliable

Outlook

- CRAN submission of `nmainla`
- NMA-regression with baseline risk as covariate: a generalized **nonlinear** mixed model
- Usage of **penalized complexity** (PC) priors (Simpson et al., 2014) which are implemented in `R-INLA`
- Sensitivity analysis for prior specifications

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Acknowledgements

- Dr. Rafael Sauter

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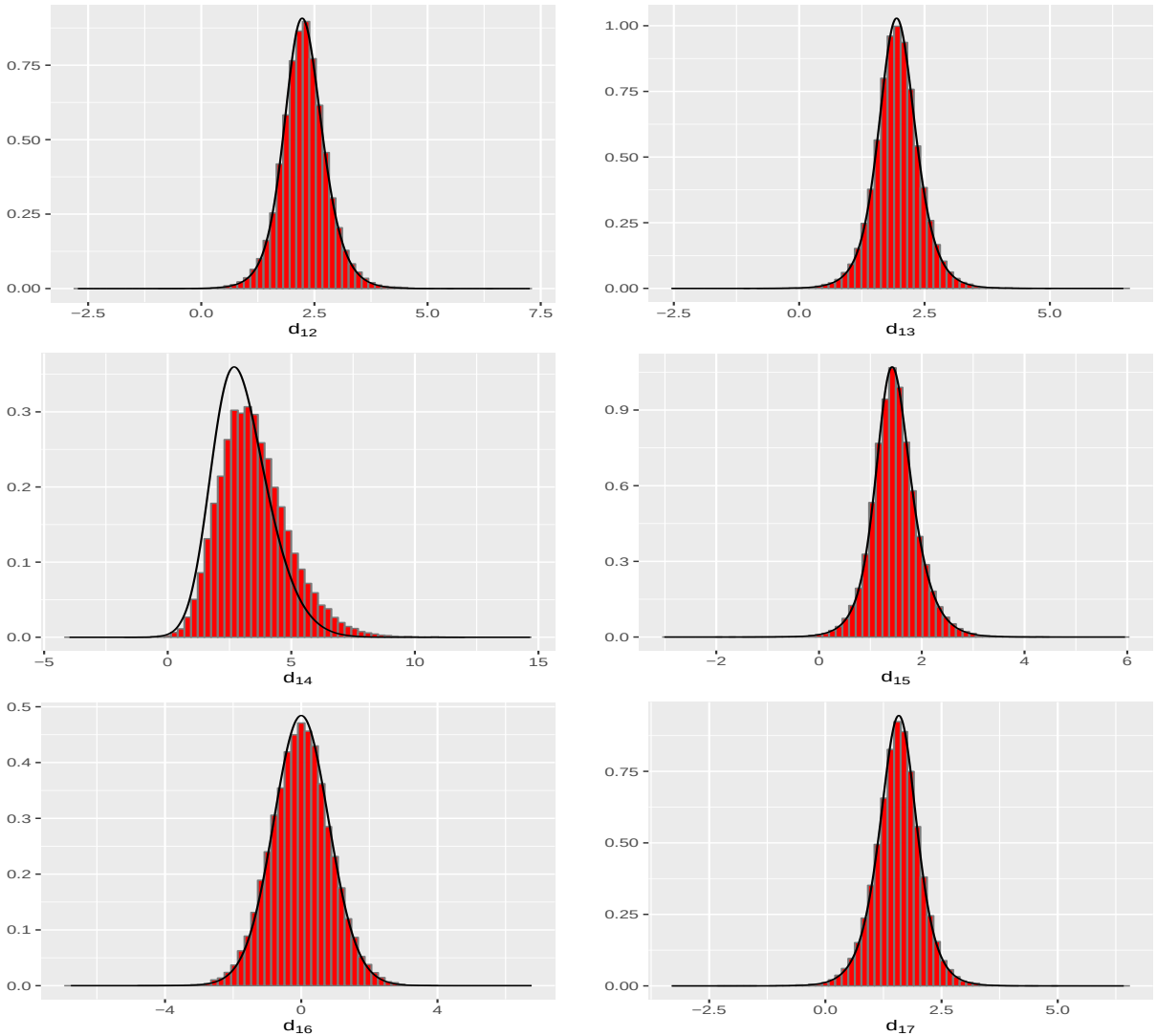
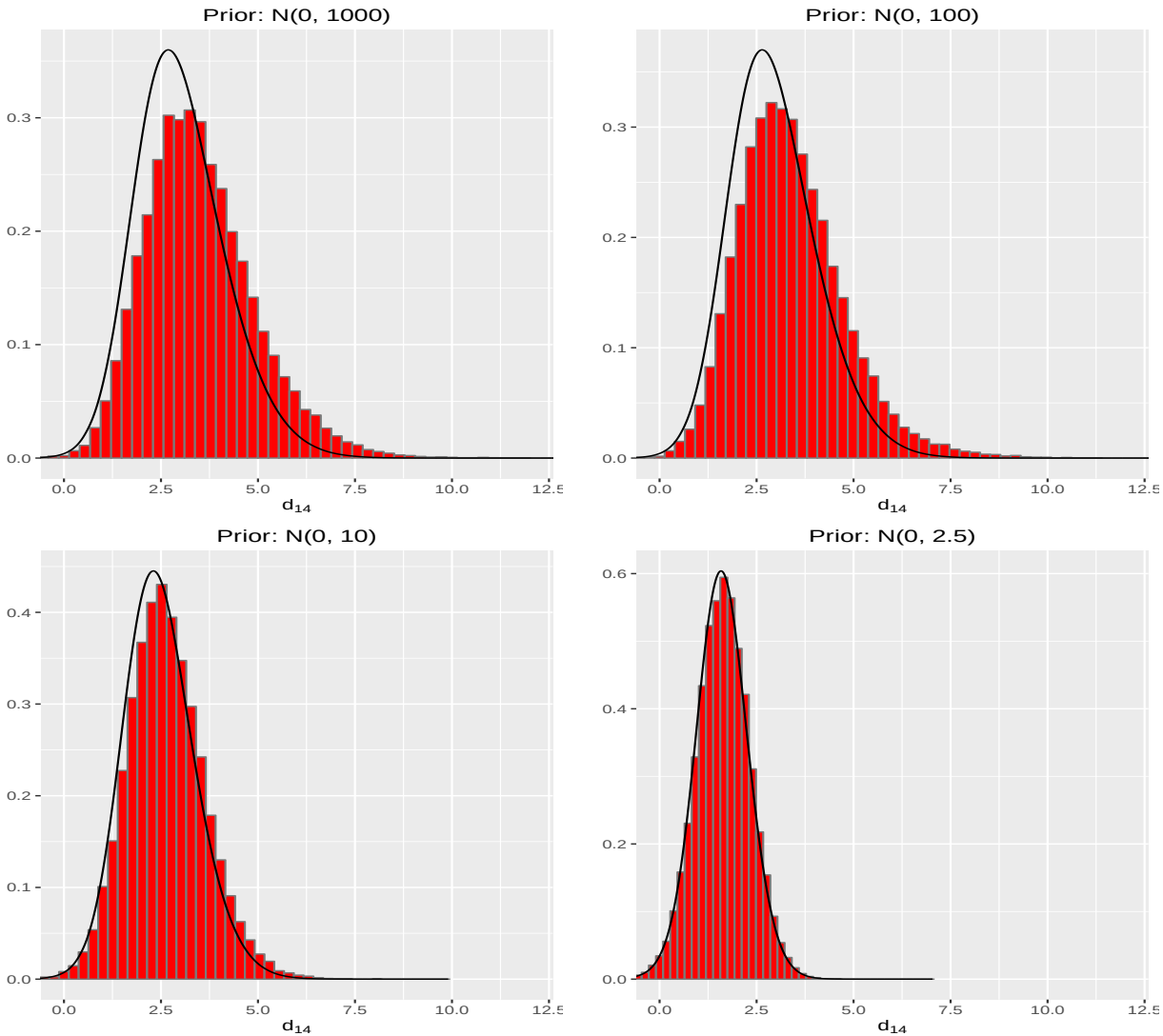
Extra slides

- **Transitivity**: indirect comparison validly **estimates** unobserved comparison
- It can be tested epidemiologically, but not statistically

INLA inaccuracy



Using informative priors



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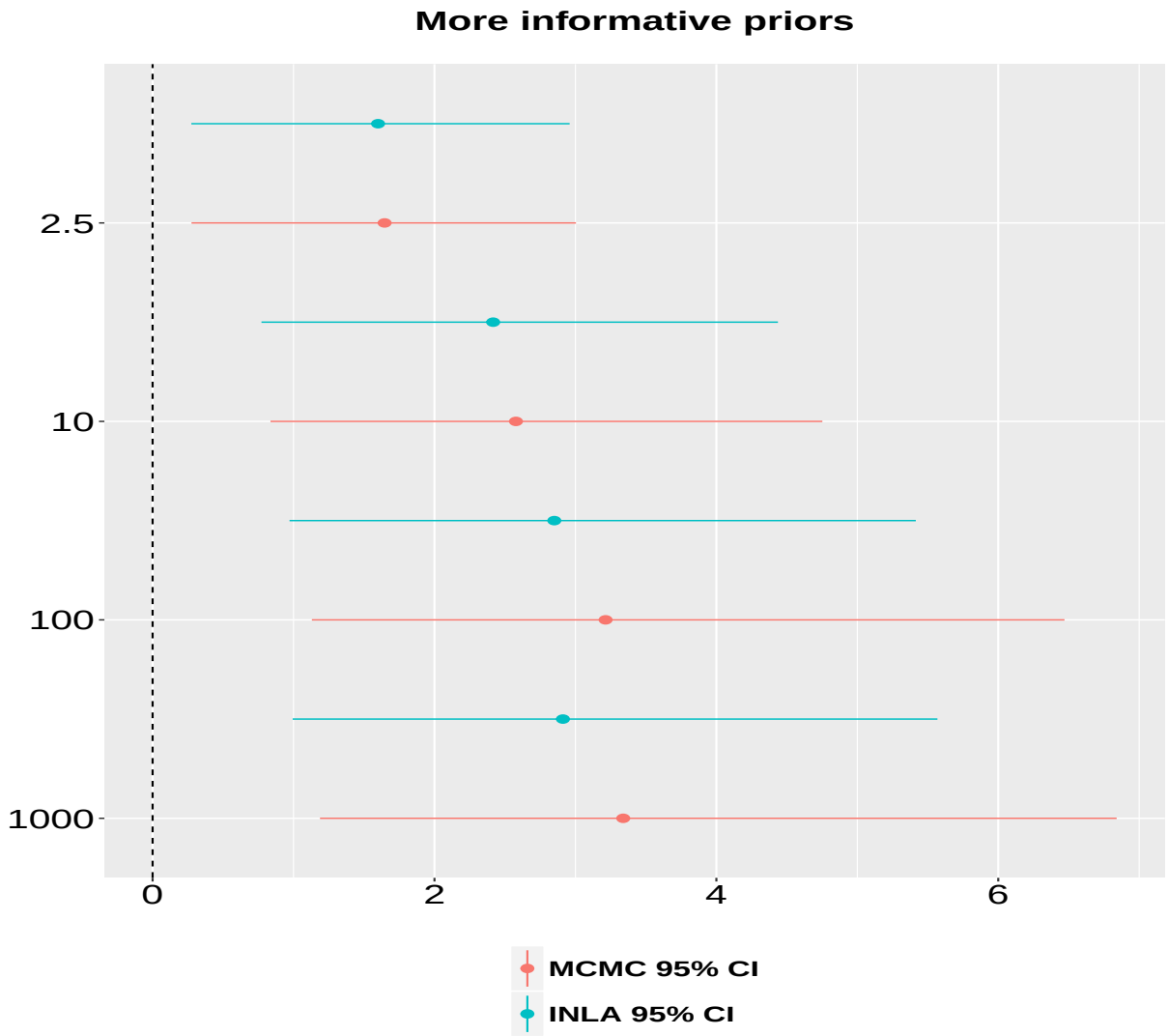
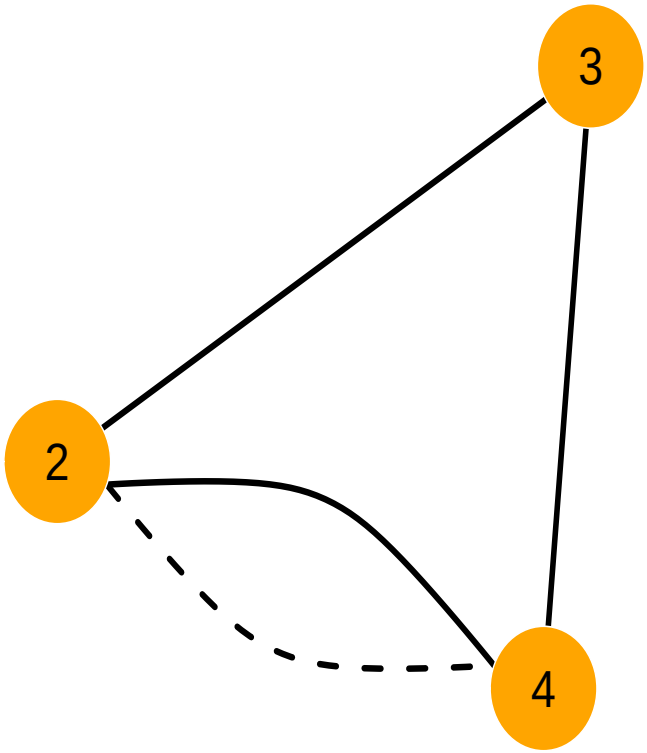


But why?



- Design inconsistency between 2-4 (from two-arm trial) and 2-4 (from three-arm trial)
- Only **some** Lu-Ades models allow this inconsistency.