

# Network Meta-Analysis using Individual Participant Data When do benefits arise?

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Moons KGM on behalf of GetReal work package 4

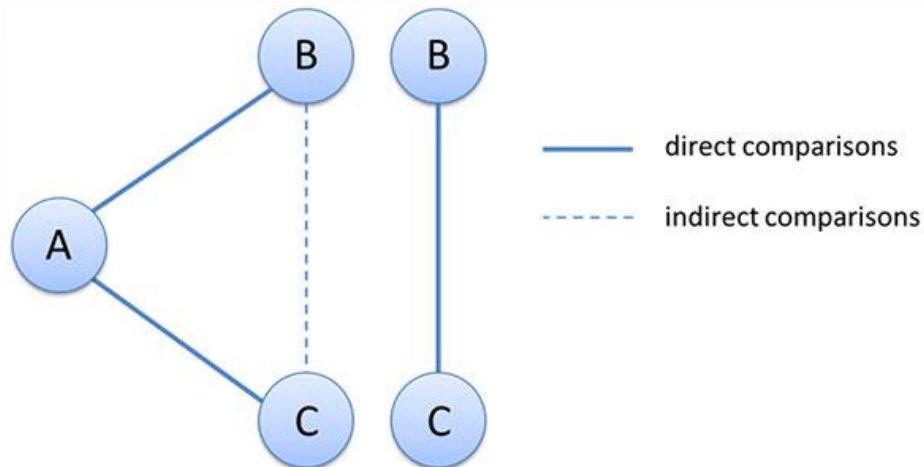
# IMI GETREAL

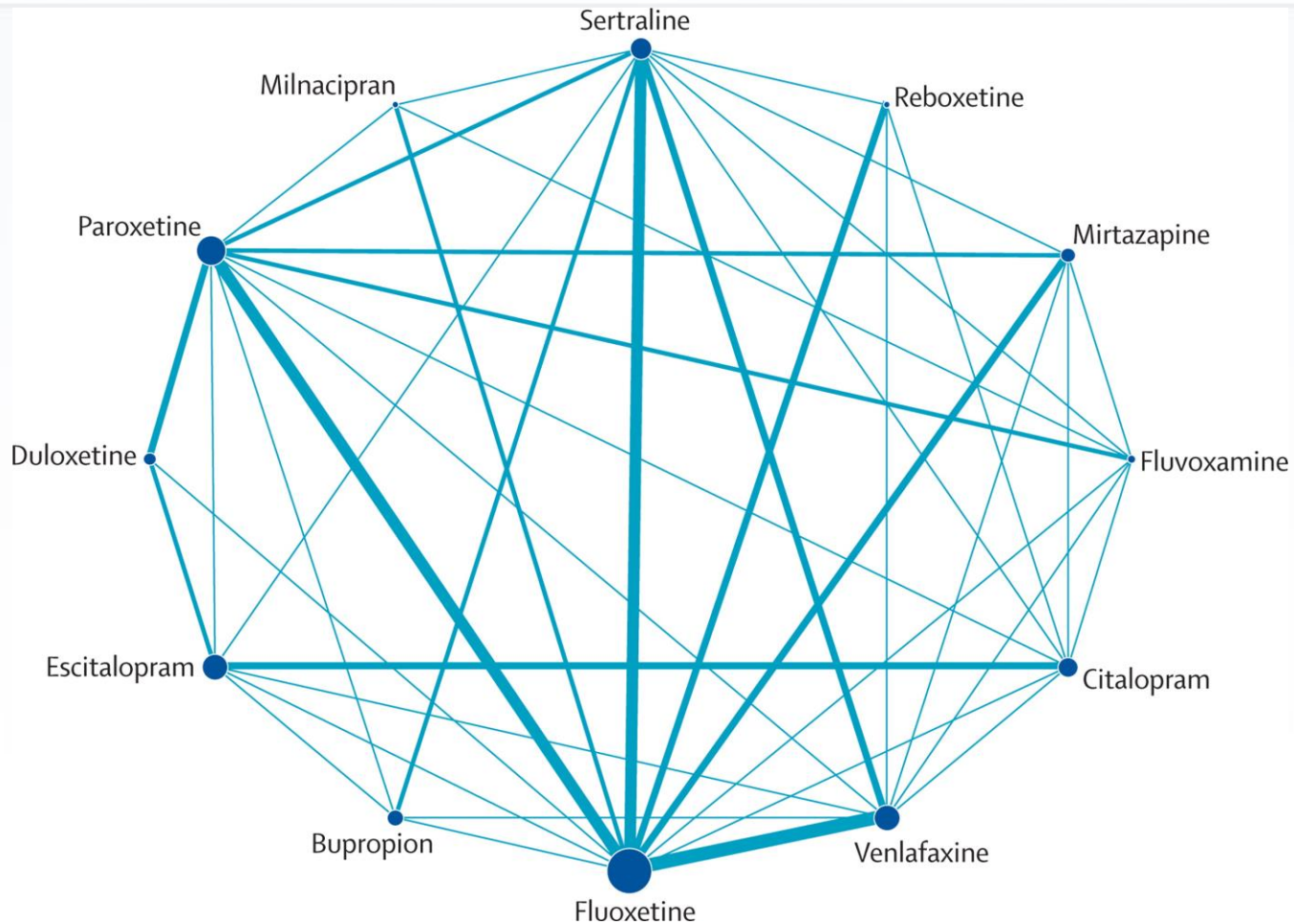


## Background

### Network meta-analysis

Synthesize results from studies that compare multiple competing interventions for the same condition





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## Background


- Network meta-analysis (NMA) often based on aggregate data (AD)
- Concerns regarding validity of indirect comparisons
- About 1/8 of AD-NMA suffer from network inconsistency
- Heterogeneity may also degrade usefulness of NMA
- NMA framework used for inclusion non-randomized studies

**What can we gain by obtaining Individual Participant Data (IPD)?**

## Background

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Tutorial


### Get real in individual participant data (IPD) meta-analysis: a review of the methodology

Thomas P. A. Debray [✉](#), Karel G. M. Moons, Gert van Valkenhoef, Orestis Efthimiou, Noemi Hummel, Rolf H. H. Groenwold, Johannes B. Reitsma, on behalf of the GetReal methods review group

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 score 1



[Funding Information](#)


An overview of the members of the GetReal methods review group is given in Supporting Information 1.



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Tutorial

### GetReal in network meta-analysis: a review of the methodology

Orestis Efthimiou [✉](#), Thomas P. A. Debray, Gert van Valkenhoef, Sven Trelle, Klea Panayidou, Karel G. M. Moons, Johannes B. Reitsma, Aijing Shang, Georgia Salanti, on behalf of GetReal Methods Review Group


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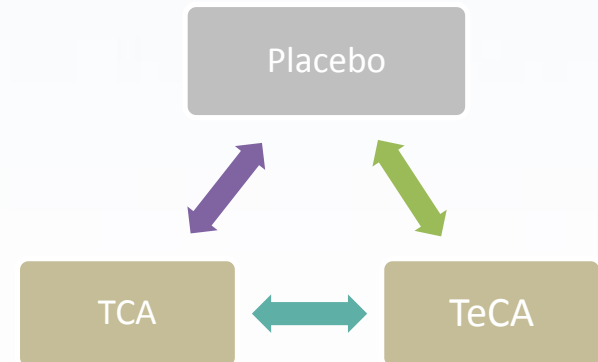
Network meta-analysis of 18 anti-depressant trials

# CASE STUDY



## Case study

- 18 anti-depressant trials
  - Adults diagnosed with major depressive disorder
  - Follow-up of 2 – 6 weeks
- Comparison of 3 types of treatment
  - Tricyclic antidepressants
  - Tetracyclic antidepressants
  - Placebo
- Evaluation of Hamilton Depression score (HAMD)
  - Rating scale of 17 items
  - Score ranges between 0 (no depression) and 54 (severe depression)





No access to IPD

# SCENARIO 1

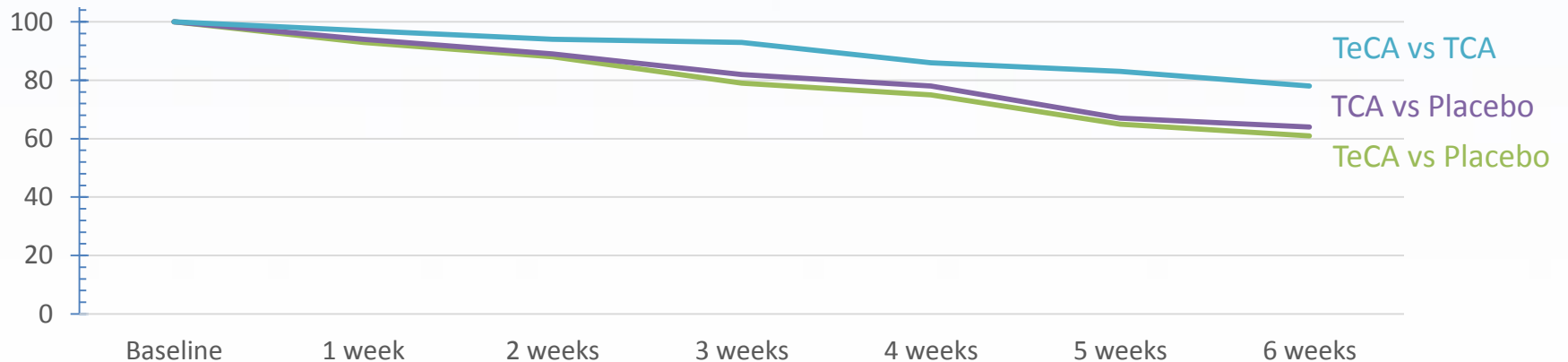


## Scenario 1: no access to IPD

- Aim
  - Investigate the relative change in HAMD score between TeCA and TCA after 6 weeks
  - Explore heterogeneity & network inconsistency
- Common methods for meta-analysis of aggregate data
  - Pairwise meta-analysis
  - Network meta-analysis
  - Network meta-regression (Tx: baseline HAMD score)

## Problem: drop-out

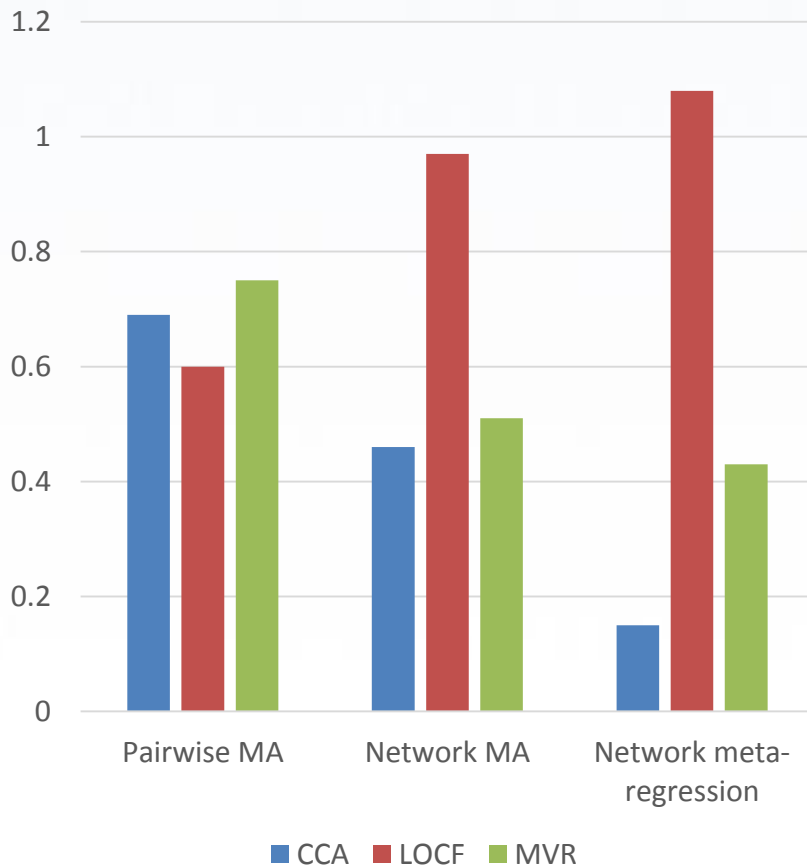
Available response data



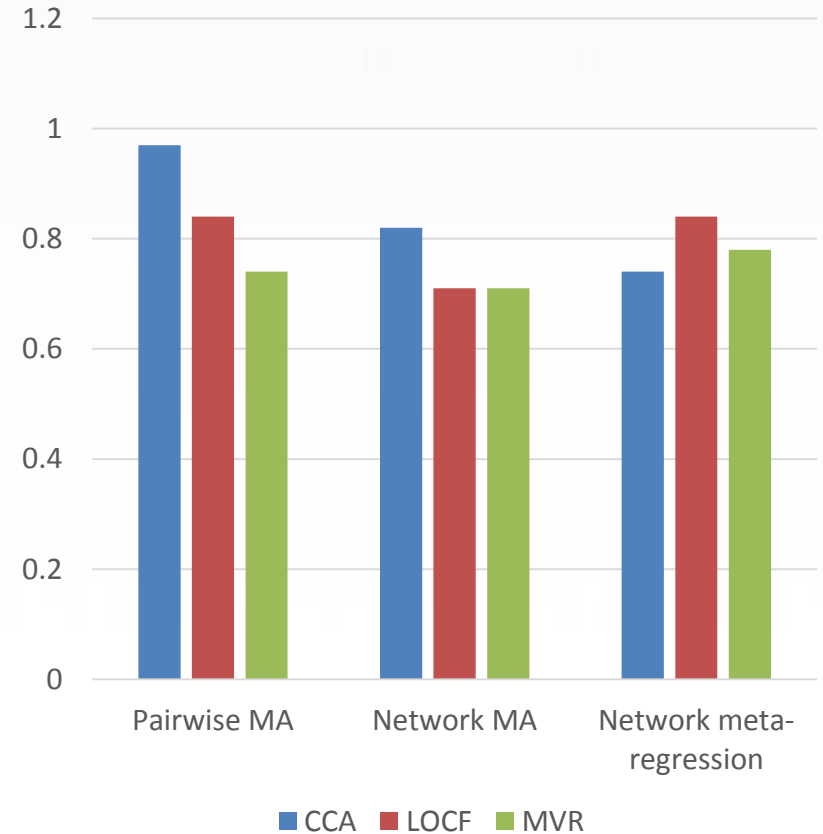
Generate aggregate data according to:

- Complete case analysis (CCA)
- Last observation carried forward (LOCF)
- Multivariate linear regression (MVR)

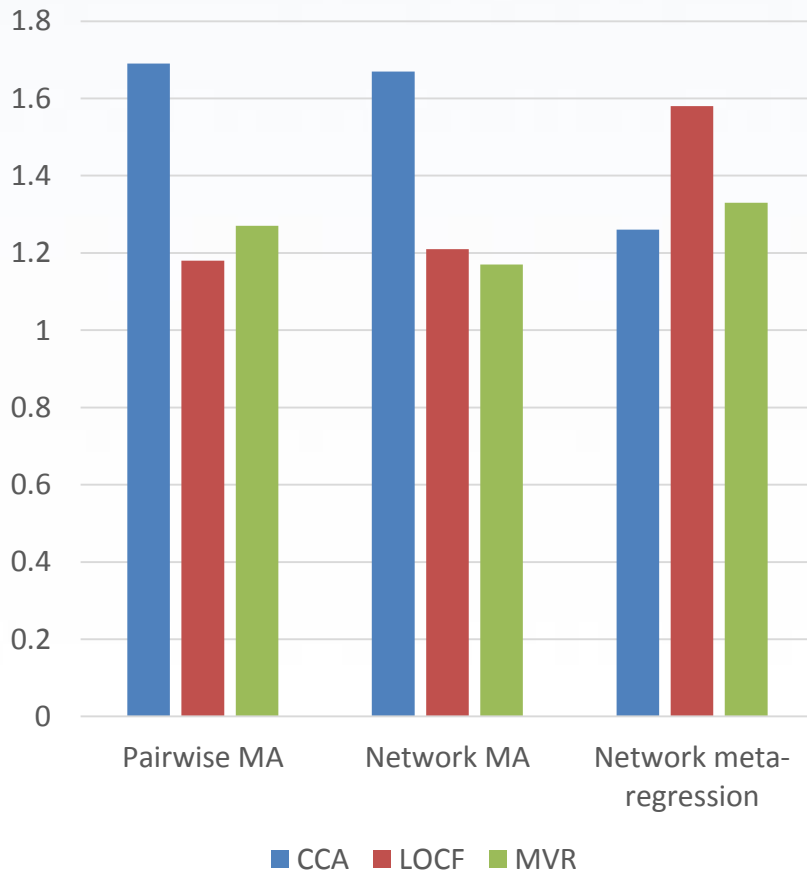
Effect size



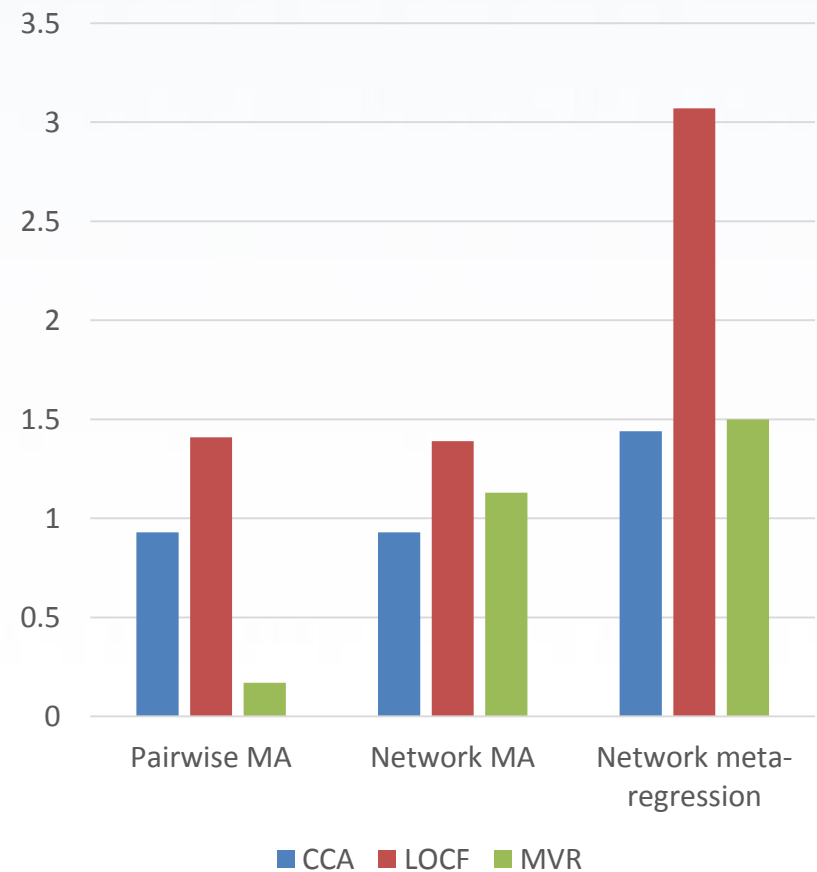
Standard error of effect size



Heterogeneity ( $\tau$ )



Network inconsistency



IPD available for all trials

## SCENARIO 2



## Option 2: Standard one-stage pairwise meta-analysis (PMA)

$$\begin{aligned}
 H_{ijk6} &\sim \mathcal{N}(\mu_{ijk}, \sigma_{i6}^2) \\
 \mu_{ijk6} &= \begin{cases} \alpha_i & : j = b \\ \alpha_i + \delta_i & : j \neq b \end{cases} \\
 \delta_i &\sim \mathcal{N}(d_{tib_i}, \tau_{tib_i}^2)
 \end{aligned}$$

Missing HAMD responses are considered ignorable!

## Option 2: Standard one-stage network meta-analysis (NMA)

$$H_{ijk6} \sim \mathcal{N}(\mu_{ijk}, \sigma_{i6}^2)$$

$$\mu_{ijk6} = \begin{cases} \alpha_i & : j = b \\ \alpha_i + \delta_i & : j \neq b \end{cases}$$

$$\delta_i \sim \mathcal{N}(d_{t_i} - d_{b_i}, \tau^2) \quad \text{with} \quad d_1 = 0$$

Consistency equations

Missing HAMD responses are considered ignorable!



## Option 3: Adjust for confounders/prognostic factors (NMA-PF)

$$\begin{aligned}
 H_{ijk6} &\sim \mathcal{N}(\mu_{ijk}, \sigma_{i6}^2) \\
 \mu_{ijk6} &= \begin{cases} \alpha_i + \gamma_i x_{ijk} & : j = b \\ \alpha_i + \gamma_i x_{ijk} + \delta_i & : j \neq b \end{cases} \\
 \delta_i &\sim \mathcal{N}(d_{i_i} - d_{b_i}, \tau^2) \quad \text{with } d_1 = 0
 \end{aligned}$$

Missing HAMD responses are considered ignorable!

## Option 4: Adjust for effect modifiers (NMA-TX)

$$\begin{aligned}
 H_{ijk6} &\sim \mathcal{N}(\mu_{ijk}, \sigma_{i6}^2) \\
 \mu_{ijk6} &= \begin{cases} \alpha_i + \gamma_i x_{ijk} & : j = b \\ \alpha_i + \gamma_i x_{ijk} + \theta_i x_{ijk} + \delta_i & : j \neq b \end{cases} \\
 \delta_i &\sim \mathcal{N}(d_{t_i} - d_{b_i}, \tau^2) \quad \text{with } d_1 = 0
 \end{aligned}$$

### Notes:

- Missing HAMD responses are considered ignorable
- Ideally  $\theta_i$  should ideally be separated to distinguish between within- and across-trial interaction

## Option 5: Multivariate network meta-analysis (MNMA)

$$\begin{pmatrix} H_{ijk1} \\ \vdots \\ H_{ijk6} \end{pmatrix} \sim \text{MVN} \left( \begin{pmatrix} \mu_{ijk1} \\ \vdots \\ \mu_{ijk6} \end{pmatrix}, R_i \right)$$

$$\begin{pmatrix} \mu_{ijk1} \\ \vdots \\ \mu_{ijk6} \end{pmatrix} = \begin{cases} \begin{pmatrix} \alpha_{i1} \\ \vdots \\ \alpha_{i6} \end{pmatrix} & : j = b \\ \begin{pmatrix} \alpha_{i1} \\ \vdots \\ \alpha_{i6} \end{pmatrix} + \begin{pmatrix} \delta_{i1} \\ \vdots \\ \delta_{i6} \end{pmatrix} & : j \neq b \end{cases}$$

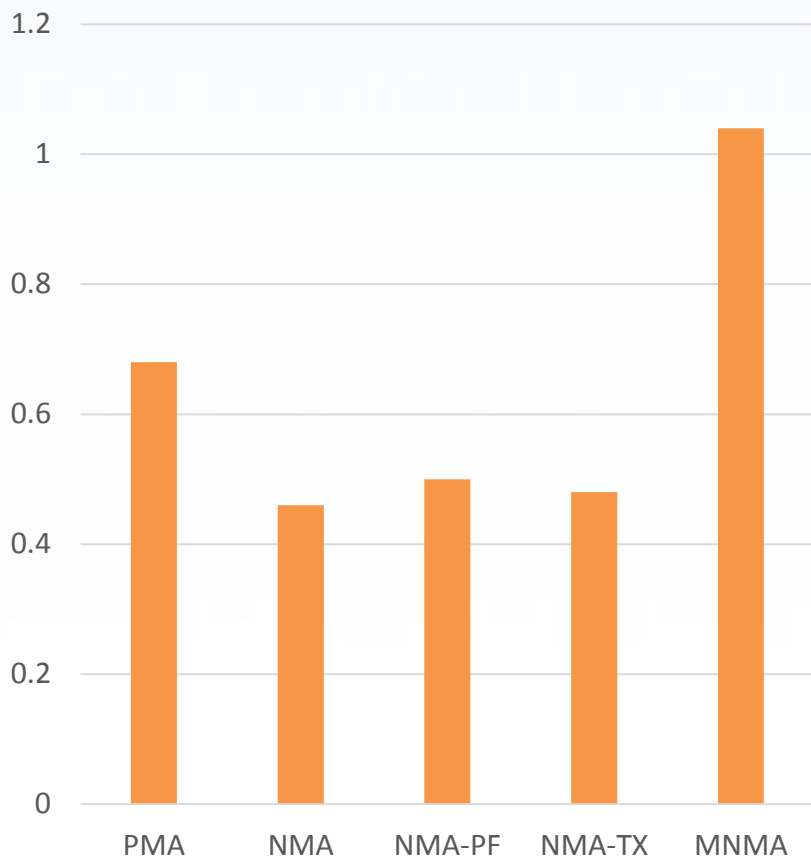
$$\begin{pmatrix} \delta_{i1} \\ \vdots \\ \delta_{i6} \end{pmatrix} \sim \text{MVN} \left( \begin{pmatrix} d_{i1} - d_{b1} \\ \vdots \\ d_{i6} - d_{b6} \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \zeta \tau_1 \tau_2 & \dots & \zeta^5 \tau_1 \tau_6 \\ \zeta \tau_2 \tau_1 & \tau_2^2 & \dots & \zeta^4 \tau_2 \tau_6 \\ \vdots & \vdots & \ddots & \vdots \\ \zeta^5 \tau_6 \tau_1 & \zeta^4 \tau_6 \tau_2 & \dots & \tau_6^2 \end{pmatrix} \right)$$

$$R_i \sim \text{Wishart}^{-1}(\nu, \Lambda)$$

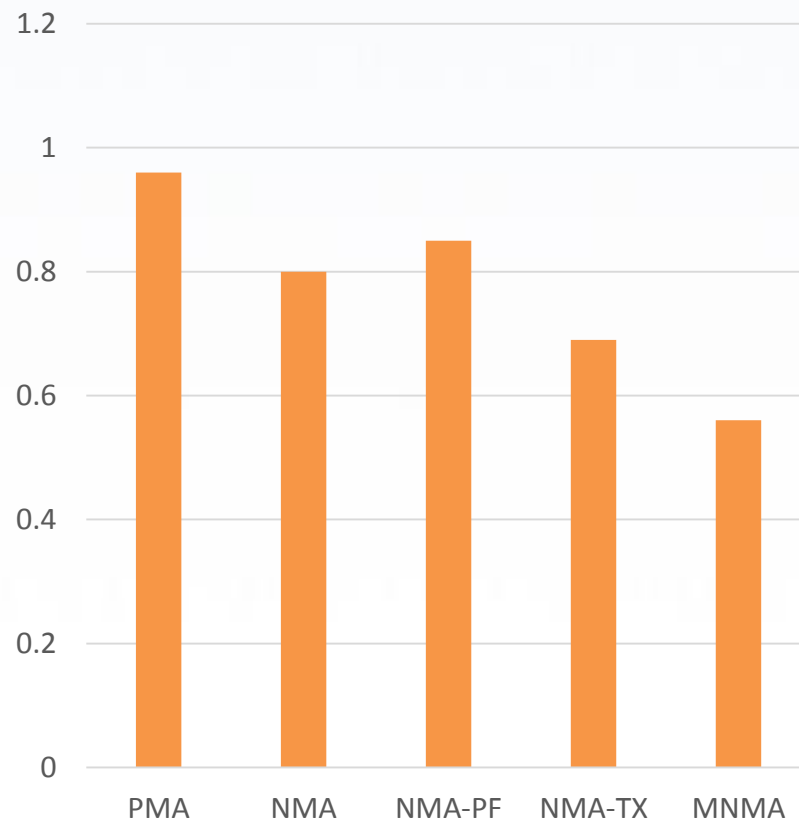
Auto-regressive heterogeneity matrix

Model distribution of within-study covariance matrices to allow imputation of studies with incomplete follow-up

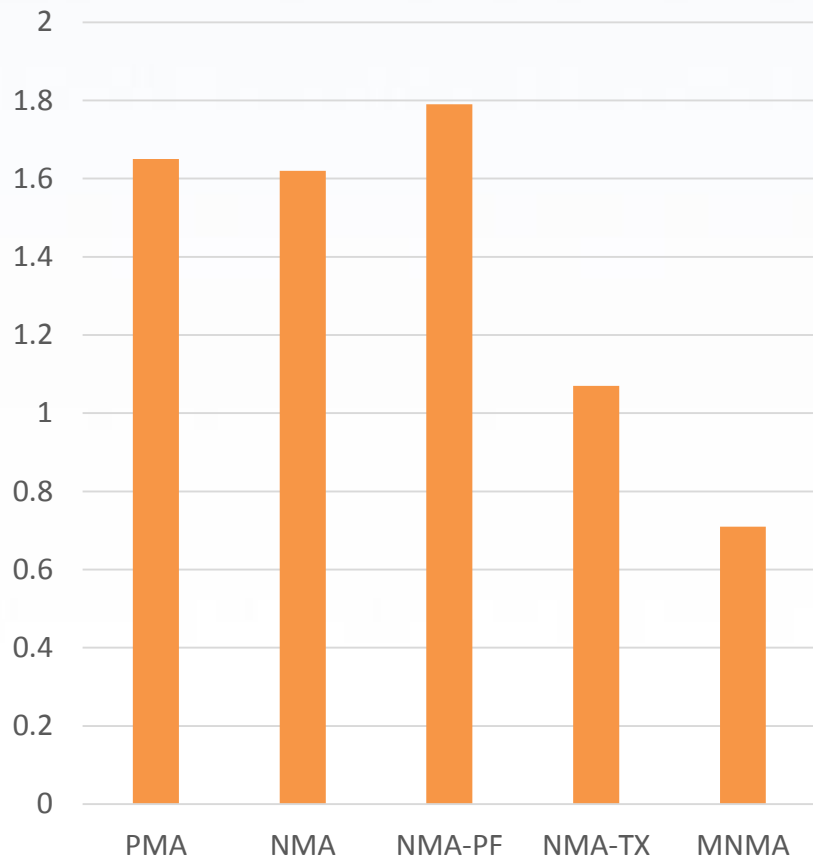
Effect size



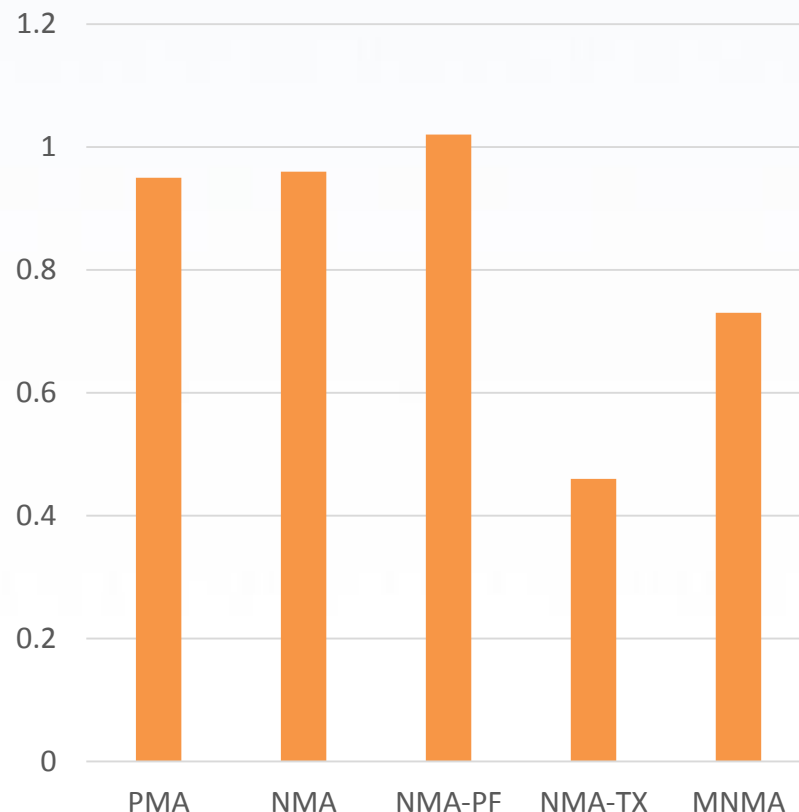
Standard error of effect size



Heterogeneity ( $\tau$ )



Network inconsistency



## Conclusions

- AD-NMA leads to excessive network inconsistency and/or heterogeneity
- IPD-NMA models achieved higher precision
- IPD-NMA models achieved improved consistency and less heterogeneity
  - By modelling longitudinal outcomes with informative drop-out
  - By allowing for participant-level treatment-covariate interaction

Our findings confirm the recommendations from the literature, and indicate that access to IPD may be helpful to improve the validity and usefulness of summary estimates of relative treatment effect.

## Recommendations

### Prioritization of IPD retrieval

- Presence of network inconsistency
- Presence of heterogeneity
- Publications with inappropriate summary statistics

## Overview of statistical methods & source code

Article



# An overview of methods for network meta-analysis using individual participant data: when do benefits arise?

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Johannes B Reitsma,<sup>1,2</sup> John PA Ioannidis,<sup>3</sup> Georgia Salanti,<sup>4,5,6</sup>  
and Karel GM Moons<sup>1,2</sup> on behalf of GetReal Workpackage4

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