
# Bivariate network meta-analysis for surrogate endpoint evaluation

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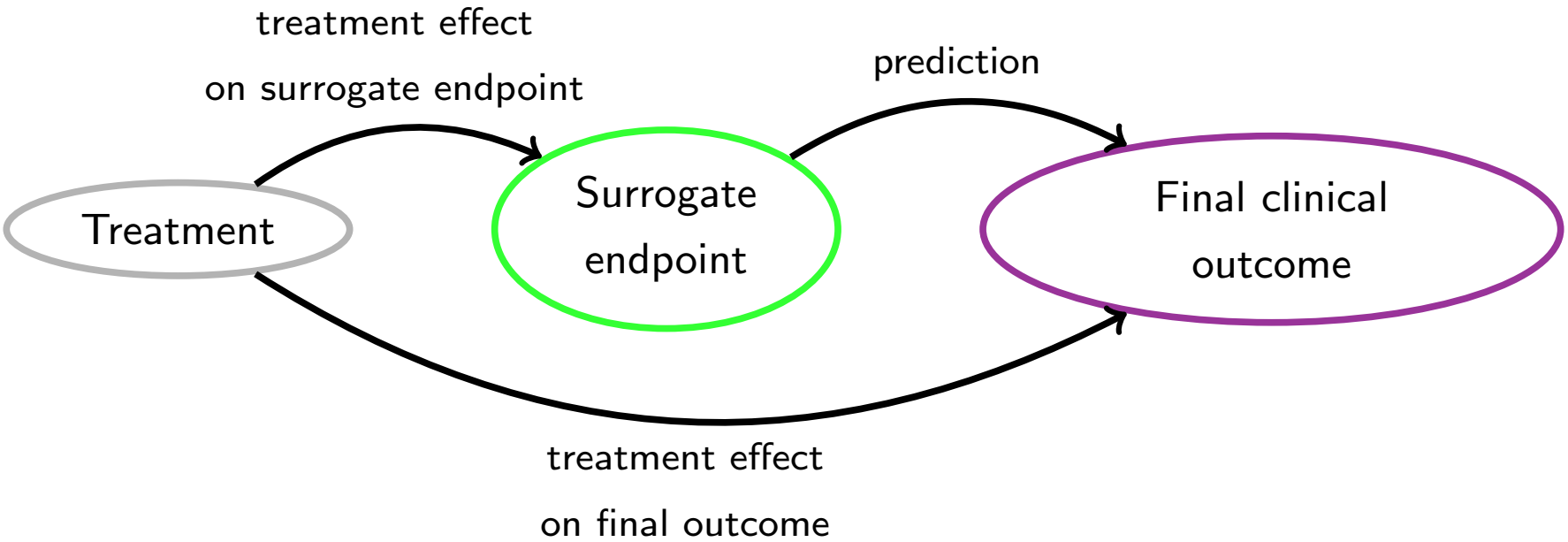
# Outline

# Surrogate endpoints




**Surrogate outcome:** A biomarker that is intended to substitute for a clinical (final) outcome.
A surrogate end point is expected to predict clinical benefit

*Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001.*

# Surrogate endpoints: importance

Surrogate endpoints are **of interest in drug development process** if they can be measured

- less costly
- less invasively
- or require shorter follow-up time

compared to a target (final) clinical outcome.

They are increasingly important **in health technology assessment**

- at the early stages of drug development
- conditional licensing based on a biomarker
- evidence on treatment effectiveness on a target outcome limited

# Examples of potential surrogate endpoints

- In oncology, a number of putative surrogate endpoints for overall survival have been investigated, which include measures of response or time to non-mortality event (such as progression).
- Examples include:
  - Progression free survival (PFS) in advanced colorectal cancer
    *(Buyse et al. Journal of Clinical Oncology 2007,*
    *Ciani et al. Journal of Clinical Epidemiology 2015)*
  - Event free survival (EFS) in gastric cancer
    *(Oba et al, Journal of the National Cancer Institute 2013)*
  - Cytogenetic response or molecular response in chronic myeloid leukaemia
    *(Ciani et al, Value in health 2013)*
- But also in other diseases:
  - CD4 count as a surrogate to AIDS or death in HIV infection
    *(Daniels MJ, Hughes MD. Statistics in Medicine 1997.)*
  - Relapse rate as a surrogate to disability progression in multiple sclerosis
    *(Sormani MP et al. Neurology 2010; **75**:302–309.)*

# Surrogate endpoints in decision making

- Use of surrogate endpoints may bring another level of uncertainty if the surrogate relationship (between the treatment effects on the surrogate and final outcomes) is not properly evaluated.
- For example, between Jan 2008 and Dec 2012, FDA made 36 of 54 cancer drug approvals (67%) on the basis of a surrogate endpoint: 19 based on response rate and 17 based on PFS or disease free survival. At further follow up, 5 drugs were subsequently shown to improve OS, 18 drugs failed to improve OS, and 13 drugs continued to have unknown survival effects.
  *(Kim and Prasad, JAMA Internal Medicine 2015)*
- Appropriate validation of surrogate endpoints is required before they can be used in HTA decision making.

# Methods for Surrogate Endpoint Validation

- **Validation on three levels**

  *(Taylor and Elston, Health Technology Assessment 2009)*

  - biological plausibility of association between outcomes
  - patient-level association between outcomes
  - study-level association

    **A surrogate endpoint is expected to predict clinical benefit**
- For HTA decision-making, a modelling framework is required
  - to establish the strength of the surrogate relationship between the treatment effects on the surrogate and the final outcome
  - and to predict the likely treatment effect on the final outcome for the new health technology

# Methods for Surrogate Endpoint Validation

- Relying solely on patient level association not sufficient when evaluating surrogate endpoints, in particular when individual level association evaluated based on data from a single trial

  *(Fleming and DeMets, Annals of internal medicine 1996)*
- A single trial validation cannot guarantee that an association between effects confirmed based on individual data under one treatment will hold in other interventions.
- A meta-analytic approach, based on data from a number of trials to establish the association between the treatment effects on the candidate surrogate endpoint and on the final outcome is more appropriate for evaluation of surrogate endpoints.

# Methods for Surrogate Endpoint Validation

- Putative surrogate endpoints are validated by estimating the pattern of association between the treatment effects on surrogate and final endpoints across trials.
- Bivariate meta-analysis methods, that take account of the correlations between the average treatment effects on surrogate and final outcomes, are suitable tools for modelling surrogate endpoints *(Bujkiewicz et al, NICE DSU Technical Support Document 20; October 2019)*.
- Individual patient data hierarchical methods can be used to evaluate surrogate endpoint at both patients and study levels *(Buyse et al. Biostatistics 2000, Burzykowski et al. Journal of Royal Statistical Society A 2004)*.
- Bivariate methods for summary data can be used to model study-level surrogacy *(Daniels and Hughes, Statistics in Medicine 1997, Bujkiewicz et al. Statistical Methods in Medical Research 2018)*.

# Bivariate random-effects meta-analysis (BRMA)

**within–study model**

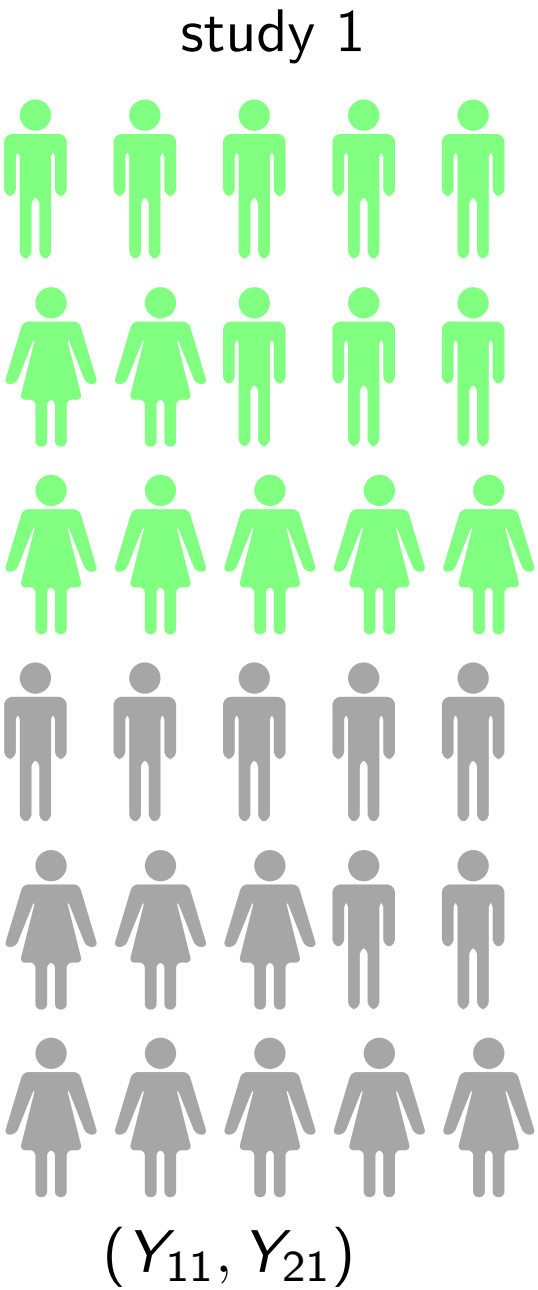
$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right),$$

**between–study model**

$$\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \mathbf{T} = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}\right).$$

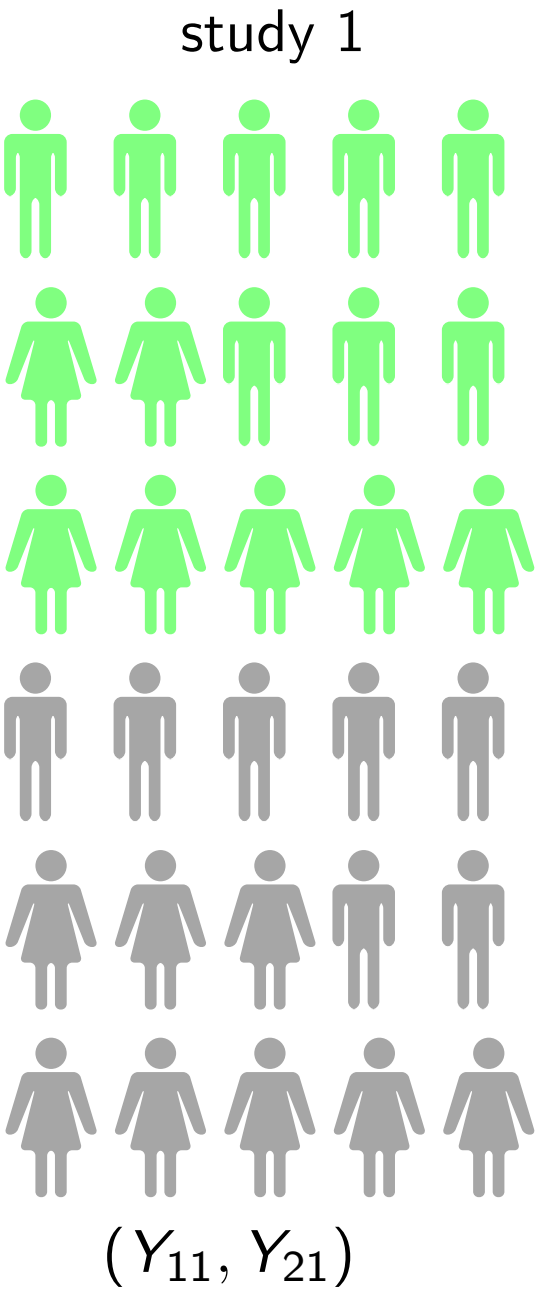
Hierarchical framework:

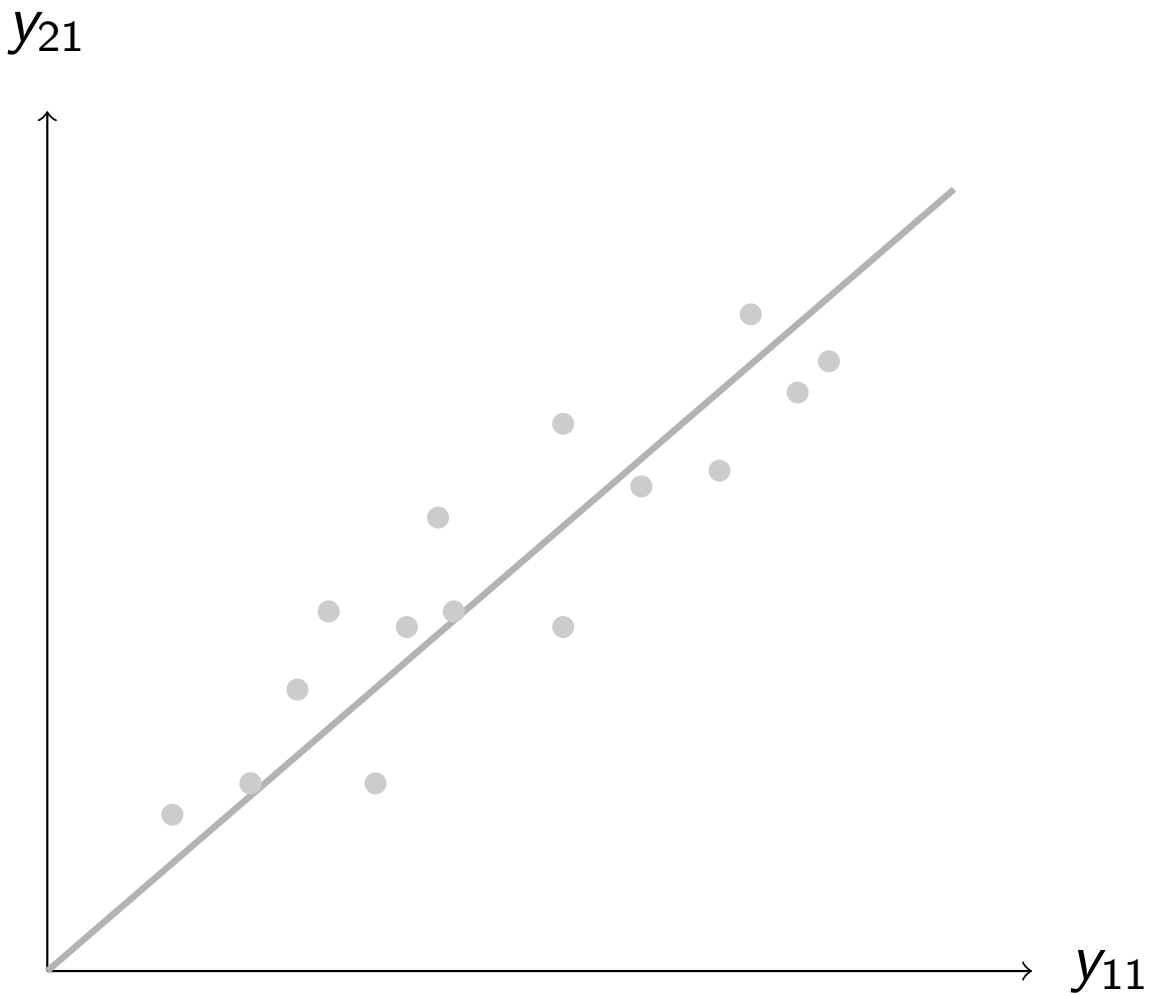
- $Y_{1i}$, $Y_{2i}$ – estimates of correlated treatment effects $\delta_{1i}$, $\delta_{2i}$
- $\mathbf{\Sigma_i}$ – within-study covariance matrices of the estimates.
- $\delta_{1i}$, $\delta_{2i}$ – true treatment effects in the population
- $(d_1, d_2)$ – pooled estimates
- $\mathbf{T}$ – between-study covariance matrix.

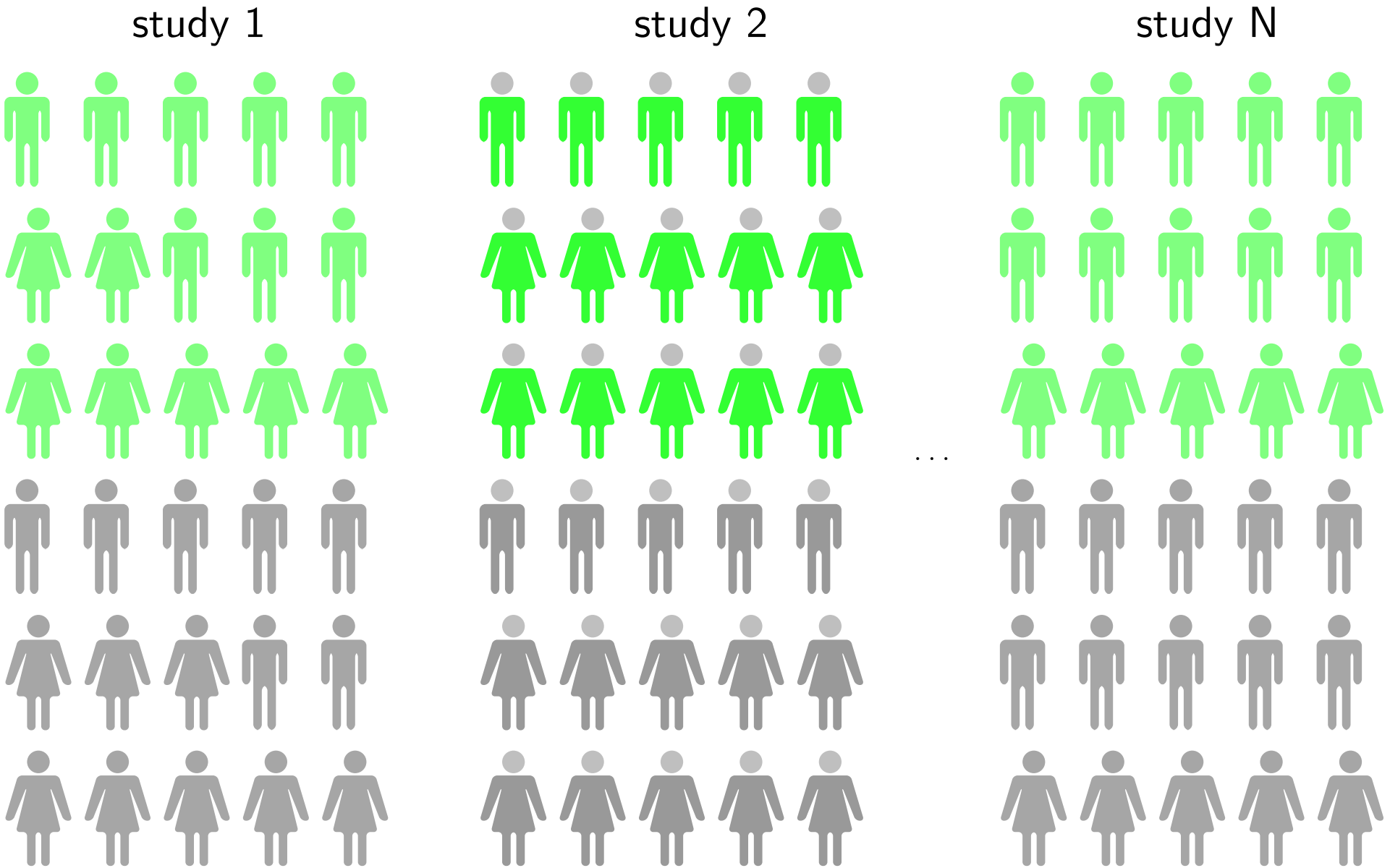



Data on two outcomes,
such as systolic blood pressure
and diastolic blood pressure,
are collected from all individuals
randomised to two treatments.

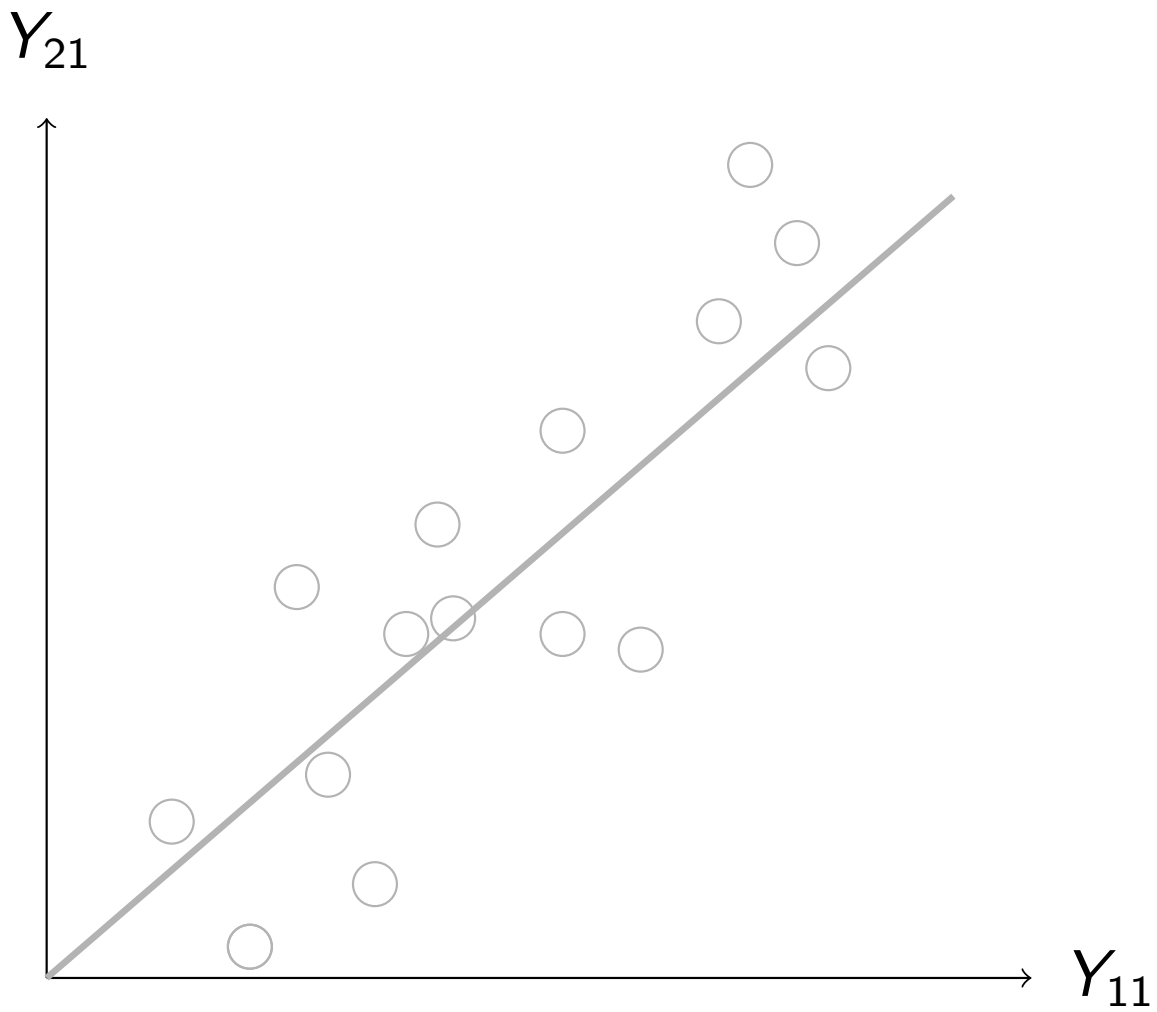
Patients may differ in their
baseline characteristics
leading to variability
between effects


study 1
$(Y_{11}, Y_{21})$


$y_{21}$
$y_{11}$


study 1
study 2
study N
...
$(Y_{11}, Y_{21})$
$(Y_{12}, Y_{22})$
$(Y_{1N}, Y_{2N})$

# Bivariate random-effects meta-analysis




Summary data on two outcomes, collected from multiple studies.
Patient populations may differ leading to between-studies variability

# Bivariate random effects meta-analysis (2)

**within–study model**

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right),$$

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$$\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \mathbf{T} = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}\right).$$

$Y_{1i}$ and $Y_{2i}$ – estimates of the treatment effects on two outcomes
$\delta_{1i}$ and $\delta_{2i}$ – correlated true effects in the population

**Prior distributions** are placed on the parameters:
the between-studies heterogeneity parameters: $\tau_j \sim U(0, 2)$
between-studies correlation $\rho = r * 2 - 1$, $r \sim Beta(1.5, 1.5)$
pooled effects $d_j \sim N(0, 1000)$.

# Bivariate random effects meta-analysis (3)

**within–study model**

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right),$$

**between–study model**

$$\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \mathbf{T} = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}\right).$$

$Y_{1i}$ and $Y_{2i}$ – estimates of the treatment effects on two outcomes
$\delta_{1i}$ and $\delta_{2i}$ – correlated true effects in the population

**Surrogacy criteria:**
perfect surrogacy means that $\rho = \pm 1 \text{ and } \delta_{1i} = 0 \Leftrightarrow \delta_{2i} = 0.$

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$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right),$$

**between–study model**

$$\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \mathbf{T} = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}\right).$$

$Y_{1i}$ and $Y_{2i}$ – estimates of the treatment effects on two outcomes
$\delta_{1i}$ and $\delta_{2i}$ – correlated true effects in the population

**Surrogacy criteria:**

perfect surrogacy means that $\rho = \pm 1 \text{ and } \delta_{1i} = 0 \Leftrightarrow \delta_{2i} = 0.$
Trial-level (adjusted) $R^2 = \rho^2 = 1$.

(Buyse et al Biostatistics 2000, Burzykowski et al RSS A 2001, Renfro et al Stat Med 2012)

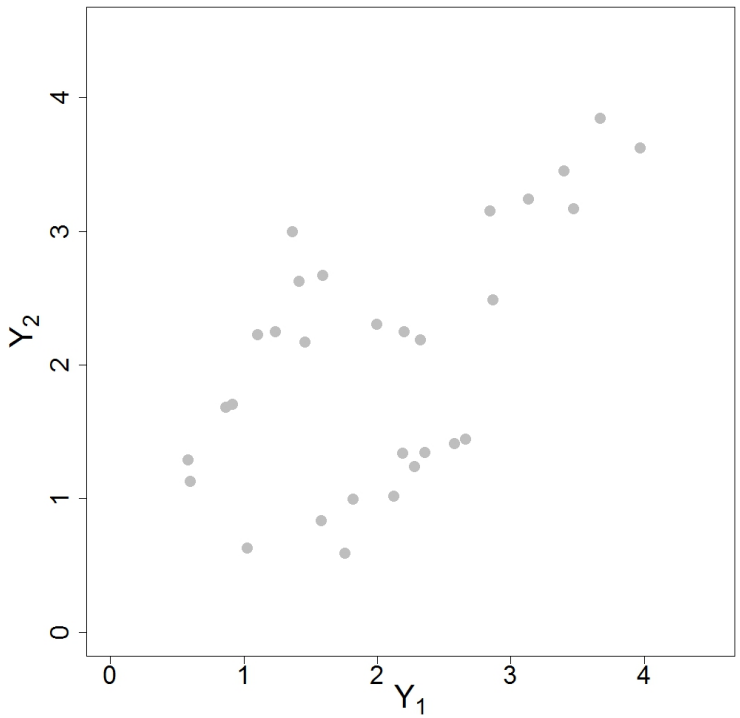
# Data requirements for surrogate endpoint validation

- Data from all relevant studies on the treatment effect on both outcomes (the surrogate endpoint and the final clinical outcome) are typically included in the analysis.
- Relevant studies are typically identified through a systematic review.
- For a strong surrogate endpoint (a good predictor of clinical benefit) the surrogate relationship will not depend on a treatment or a subpopulation – data from all trials in all subgroups of patients in a given disease area would be used.
- Often subsets of interventions or population may only be included.
- For example when the differences in mechanism of action between treatment types or patients subgroups affect the estimates of the treatment effect on the surrogate and final outcomes in different ways, thus affecting the estimates of the surrogate relationship.

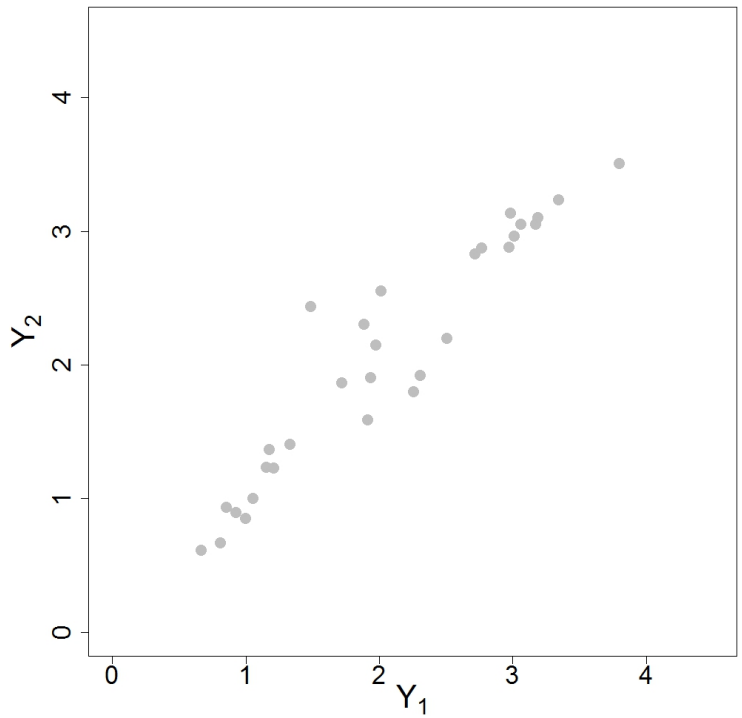
# Mixed treatment evidence

# Illustrative simulated scenarios

Scenario 1




Scenario 2



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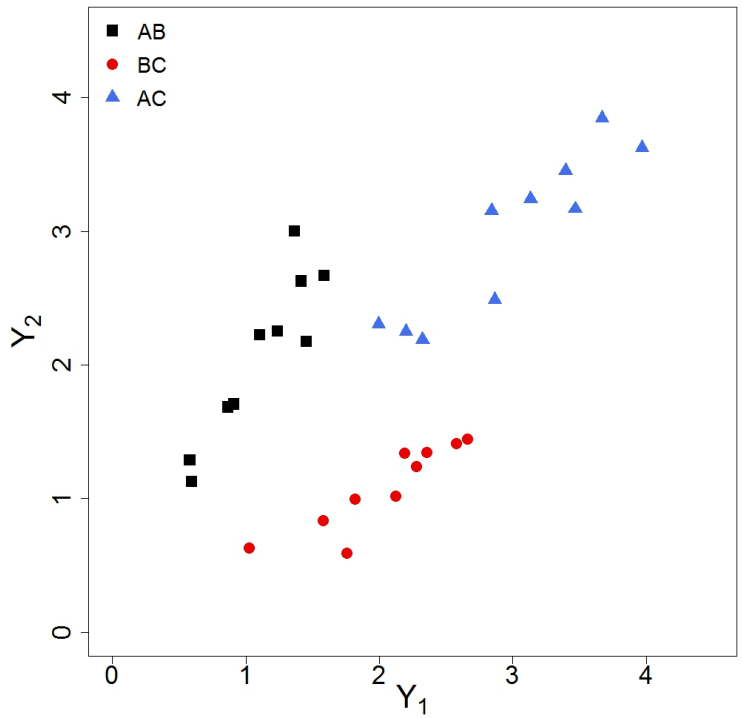


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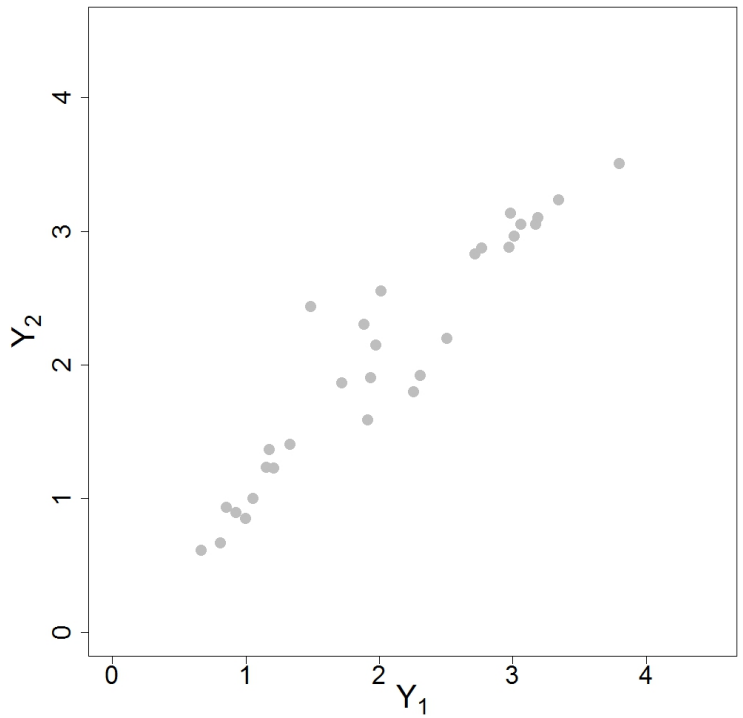

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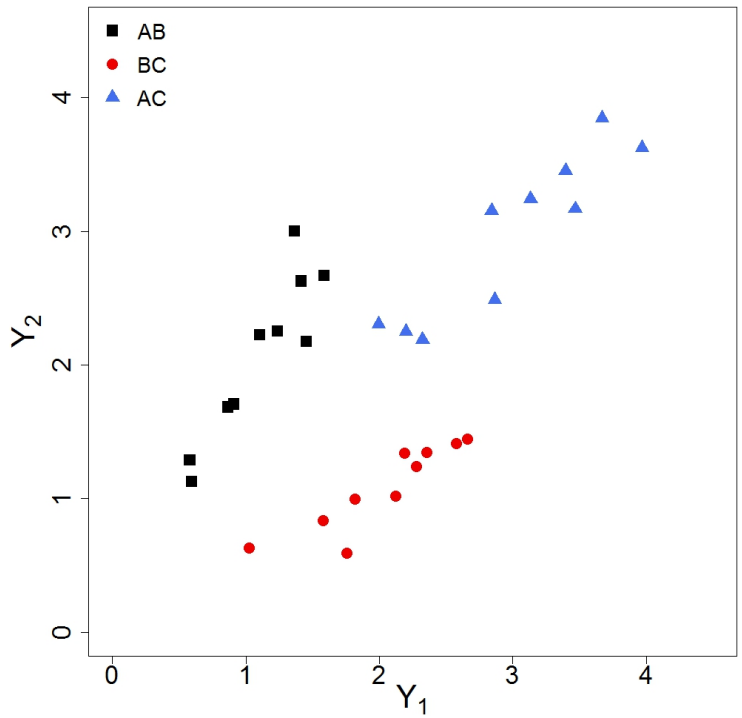


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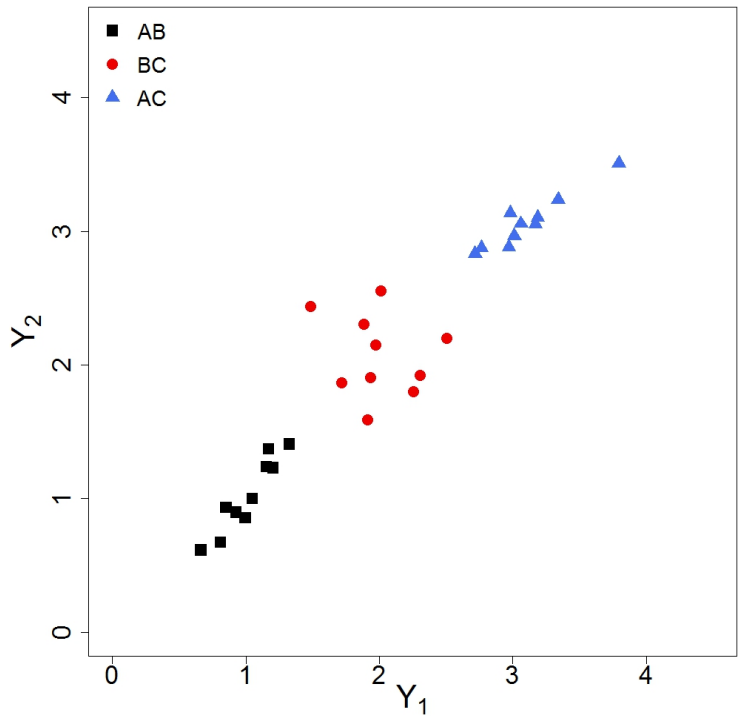

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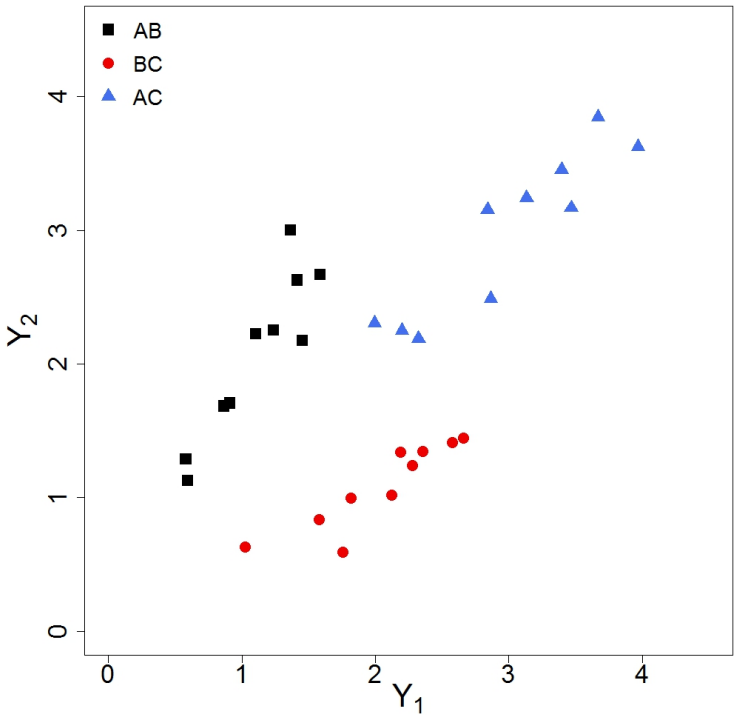


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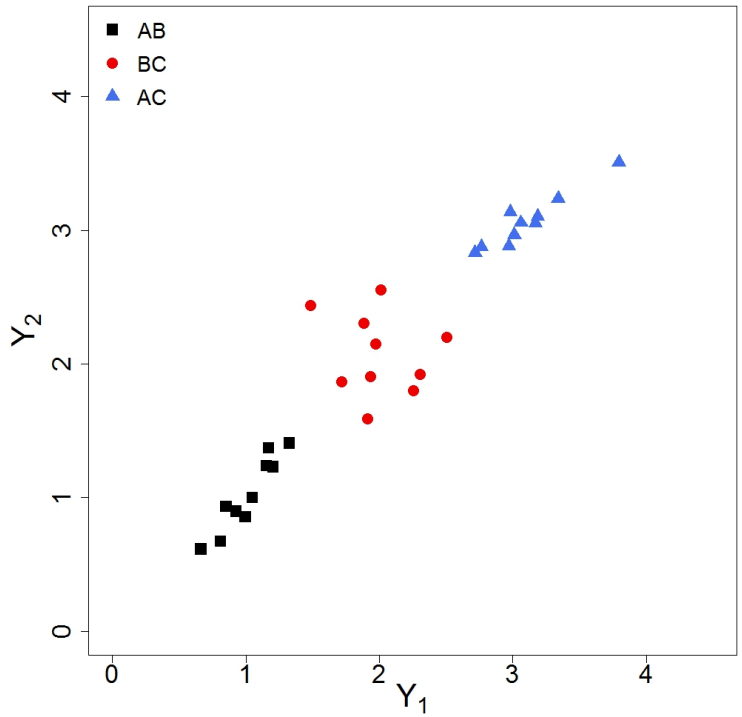


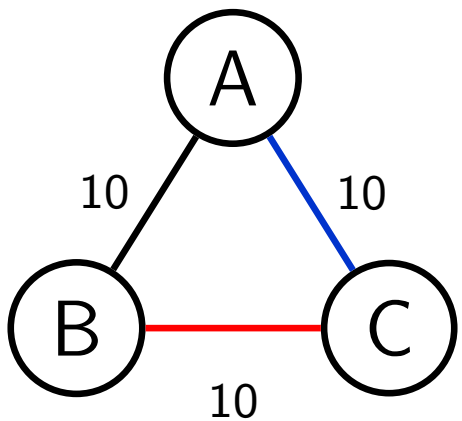

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RESEARCH ARTICLE

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# Bivariate network meta-analysis for surrogate endpoint evaluation

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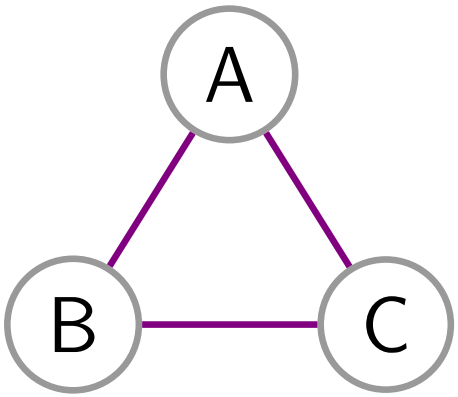
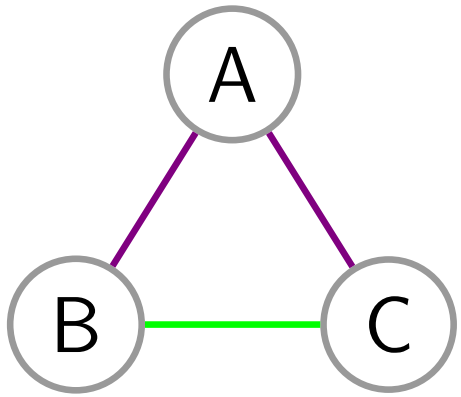
Surrogate endpoints are very important in regulatory decision making in healthcare, in particular if they can be measured early compared to the long-term final clinical outcome and act as good predictors of clinical benefit. Bivariate meta-analysis methods can be used to evaluate surrogate endpoints and to predict the treatment effect on the final outcome from the treatment effect measured on a surrogate endpoint. However, candidate surrogate endpoints are often imperfect, and the level of association between the treatment effects on the surrogate and final outcomes may vary between treatments. This imposes a limitation on methods which do not differentiate between the treatments. We develop bivariate network meta-analysis (bvNMA) methods, which combine data on treatment effects on the surrogate and final outcomes, from trials investigating multiple treatment contrasts. The bvNMA methods estimate the effects on both outcomes for all treatment contrasts individually in a single analysis. At the same time, they allow us to model the trial-level surrogacy patterns within each treatment contrast and treatment-level surrogacy, thus enabling predictions of the treatment effect on the final outcome either for a new study in a new population or for a new treatment. Modelling assumptions about the

# Network meta-analysis

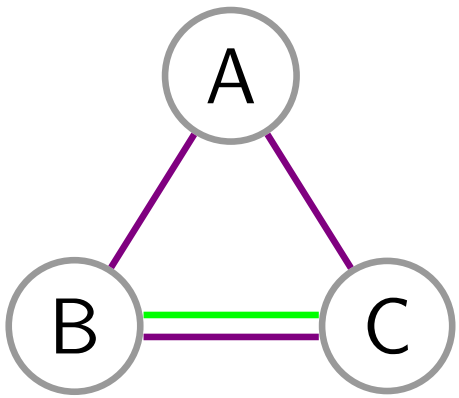
Direct comparison




Indirect comparison




Mixed comparisons




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

# Bivariate network meta-analysis (bvNMA)

$$\begin{pmatrix} Y_{1kli} \\ Y_{2kli} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1kli} \\ \delta_{2kli} \end{pmatrix}, \begin{pmatrix} \sigma^2_{1kli} & \sigma_{1kli}\sigma_{2kli}\rho_{wkli} \\ \sigma_{1kli}\sigma_{2kli}\rho_{wkli} & \sigma^2_{2kli} \end{pmatrix}\right)$$

$$\begin{pmatrix} \delta_{1kli} \\ \delta_{2kli} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} d_{1kl} \\ d_{2kl} \end{pmatrix}, \mathbf{T_{kl}} = \begin{pmatrix} \tau^2_{1kl} & \tau_{1kl}\tau_{2kl}\rho_{kl} \\ \tau_{1kl}\tau_{2kl}\rho_{kl} & \tau^2_{2kl} \end{pmatrix}\right)$$

$k$, $l$ – baseline (control) and experimental treatment in a study $i$,
$\delta_{jkli}$ – true treatment effects ( $l$ vs. $k$) for outcome $j$ in study $i$
$d_{jkl}$ – mean treatment effect of $l$ vs. $k$ for outcome $j$.

Achana FA, Cooper NJ, Bujkiewicz S, et al. *BMC Med Res Meth* 2014; **14**:92.
Efthimiou O, et al. *Statistics in Medicine* 2014; **33**:2275–87.

# bvNMA: consistency assumptions

## First order consistency assumption:

$$\begin{pmatrix} d_{1kl} \\ d_{2kl} \end{pmatrix} = \begin{pmatrix} d_{1bl} - d_{1bk} \\ d_{2bl} - d_{2bk} \end{pmatrix}$$

$b = 1$ – common reference treatment in the network

$d_{j,1k}$ – **basic parameters**, $j = 1, 2,\ k = 1, \ldots, n_t$

$d_{j,11} = 0$, prior distributions: $d_{j,1k} \sim N(0, 10^3)$.

## Second order consistency assumption:

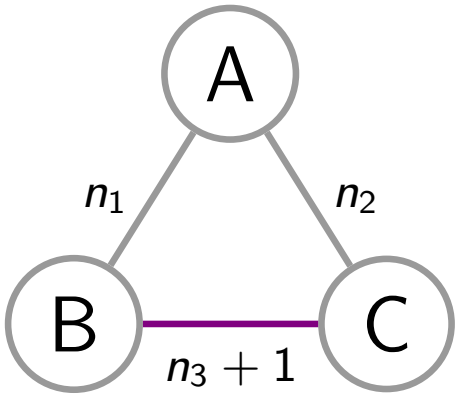
- Triangle inequalities: $|\tau_{jbl} - \tau_{jbk}| \leq \tau_{jkl} \leq \tau_{jbl} + \tau_{jbk}$
- and further constraints on the covariances:

$$\tau_{1kl}\tau_{2kl}\rho_{1kl,2kl} =$$
$$\tau_{1bl}\tau_{2bl}\rho_{1bl,2bl} + \tau_{1bk}\tau_{2bk}\rho_{1bk,2bk} - \tau_{1bl}\tau_{2bk}\rho_{1bl,2bk} - \tau_{1bk}\tau_{2bl}\rho_{1bk,2bl}$$

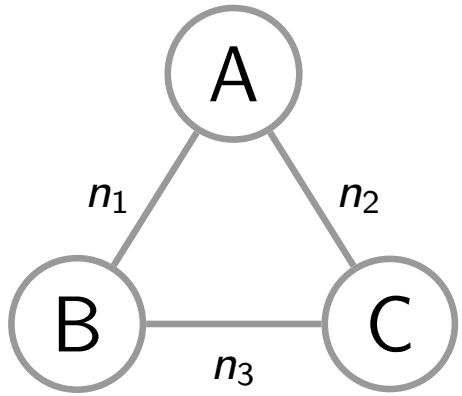
Prior distributions for $T_{kl}$ constructed:

- ensuring the **second-order consistency** assumption (*Lu and Ades, Biostatistics 2009*)
- Cholesky separation strategy – to ensure matrix is **positive semi-definite** (*Wei and Higgins, Statistics in Medicine 2013*).

# Surrogacy across different populations




surrogate endpoint

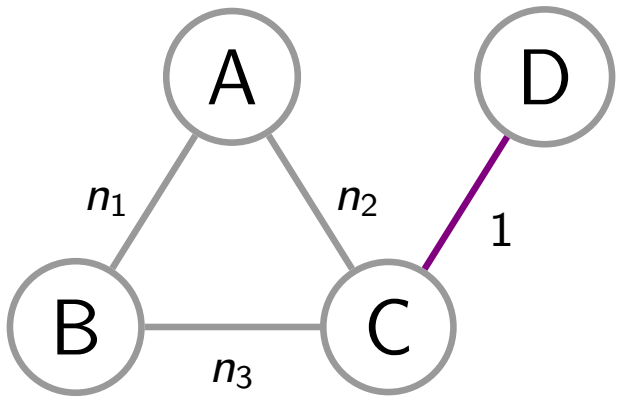



final outcome

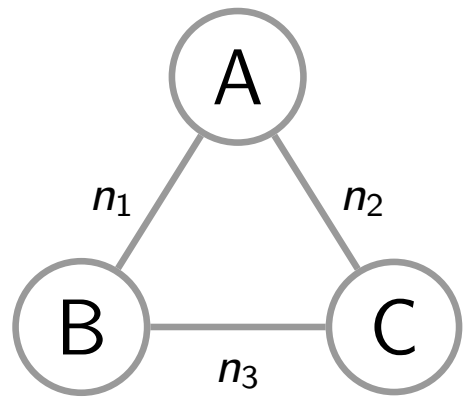
**Surrogacy criteria:**
within treatment contrast $kl$, perfect surrogacy:

$$\rho_{1kl,2kl} = \pm 1 \text{ and } \delta_{1kli} = 0 \Leftrightarrow \delta_{2kli} = 0$$

# Surrogacy across different treatments




surrogate endpoint




final outcome

# bvNMA 2: exchangeability of treatments

For each treatment arm $k$; ancillary parameters $\theta_{jk}$, such that $d_{j1k} = \theta_{jk} - \theta_{j1},\ k > 1$ are assumed exchangeable and correlated.

This implies the association between the average effects:

$$\begin{pmatrix} d_{1kl} \\ d_{2kl} \end{pmatrix} \sim N\left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \omega_1^2 & \omega_1\omega_2\rho_t \\ \omega_1\omega_2\rho_t & \omega_2^2 \end{pmatrix} \right\},$$

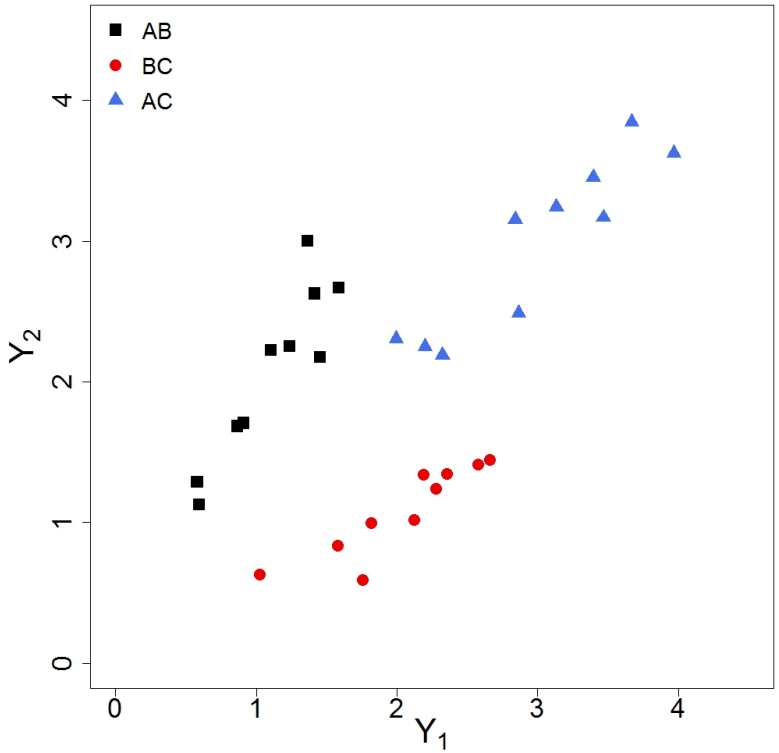
$k \neq l,\ k, l = 1, \ldots, n_t$.

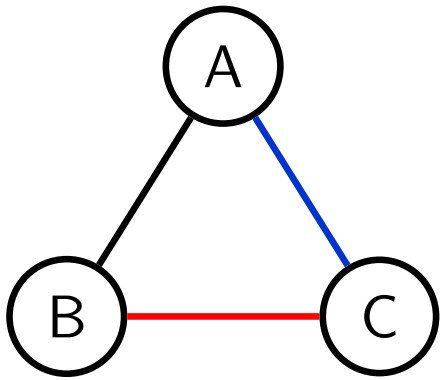
**Across-treatments surrogacy:**

$$\rho_t = \pm 1, \text{ and } d_{1,kl} = 0 \ \Leftrightarrow\ d_{2,kl} = 0$$

Prior distributions:
$\omega_j \sim Unif(0, 2)$
and $\rho_t = r * 2 - 1$ with $r \sim Beta(1.5, 1.5)$.

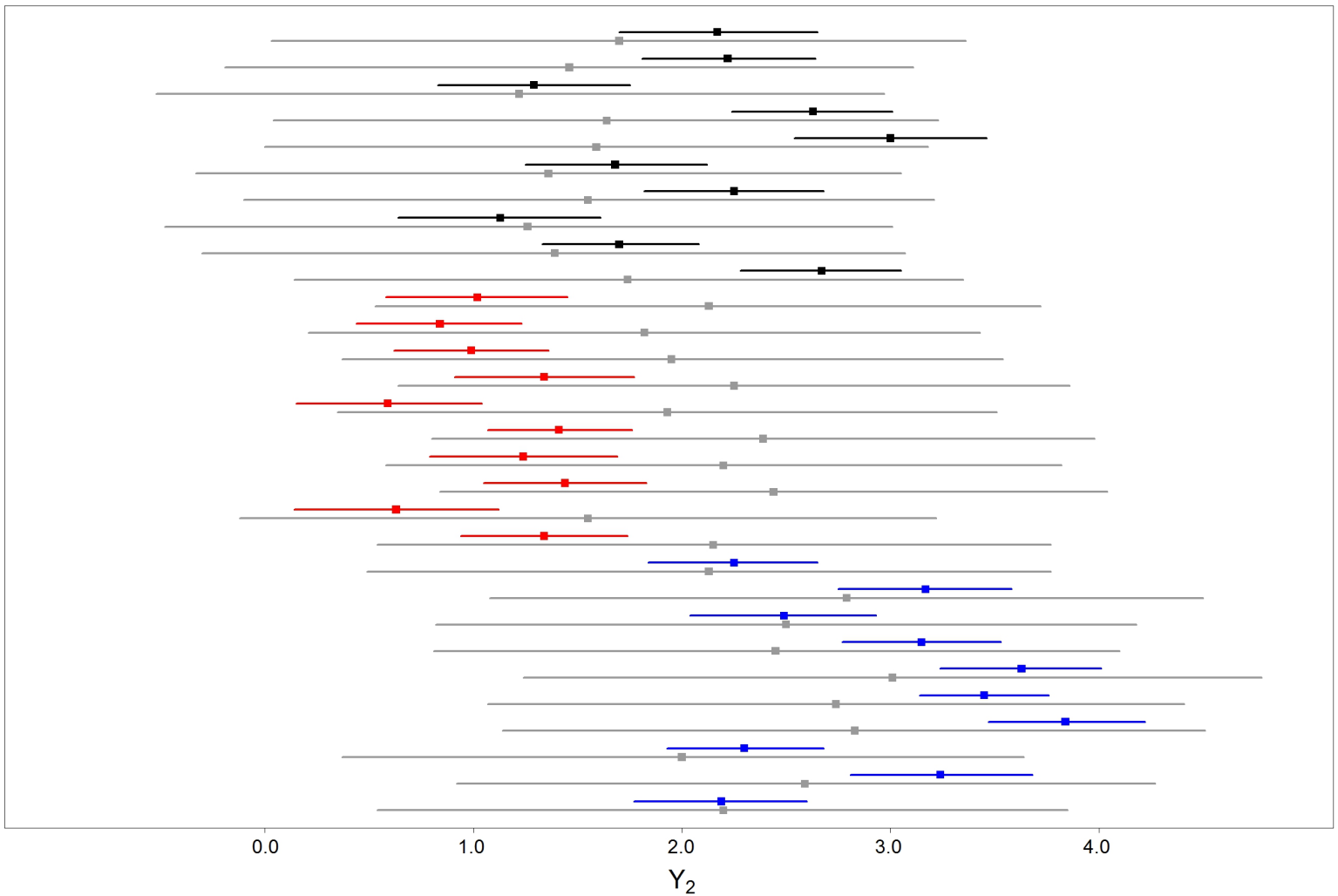
# Results: scenario 1



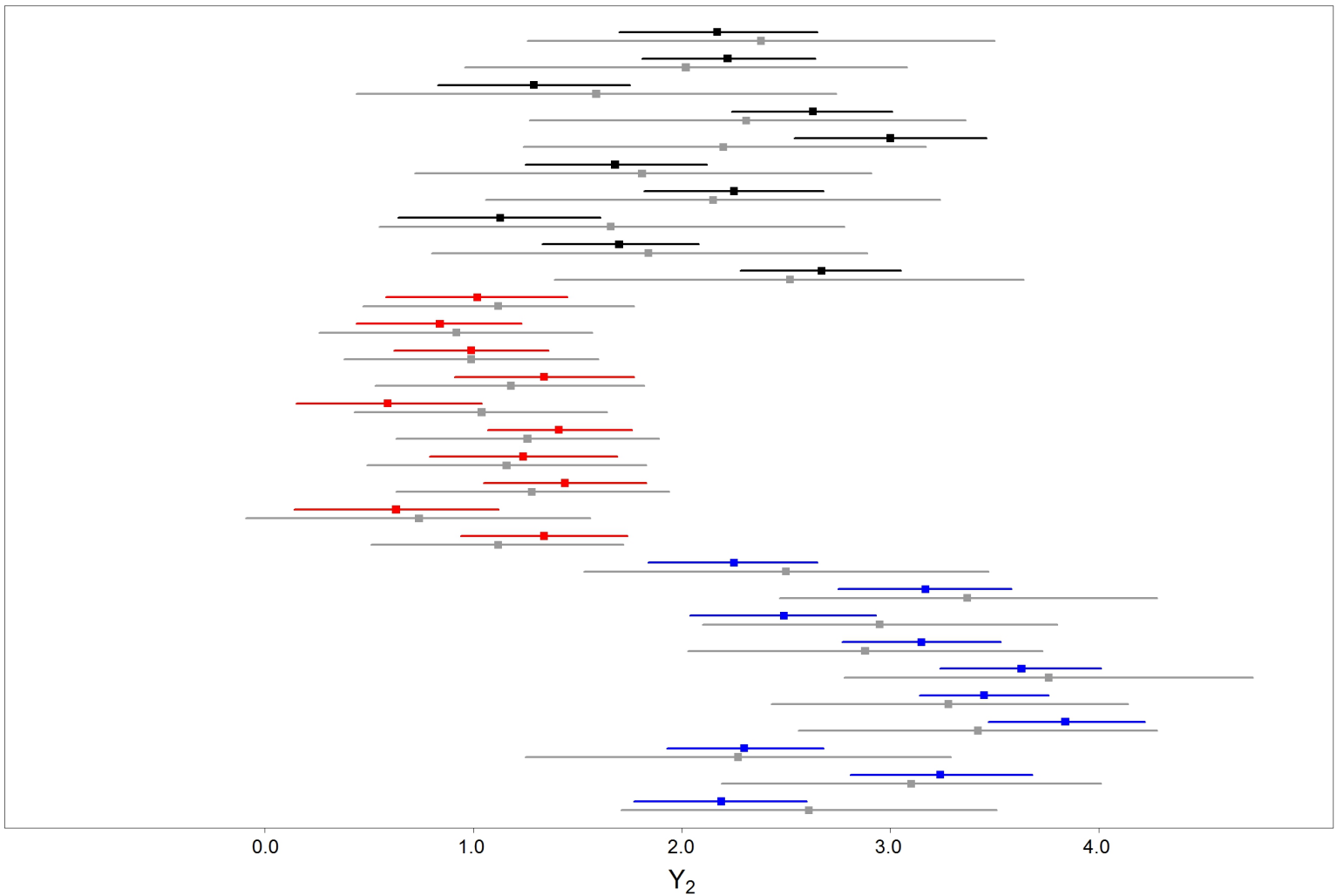




| model | AB | BC | AC |
|---|---|---|---|
| *correlations* | | | |
| BRMA | | 0.57 (0.27, 0.79) | |
| bvNMA | 0.88 (0.55, 0.99) | 0.74 (0.22, 0.97) | 0.9 (0.66, 0.99) |

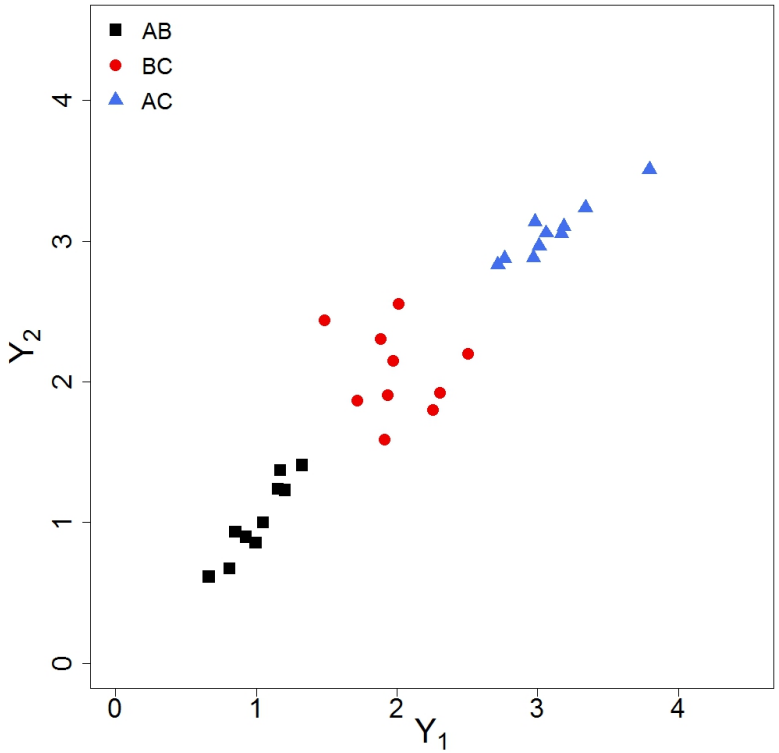
# Scenario 1: Predicted effect from BRMA

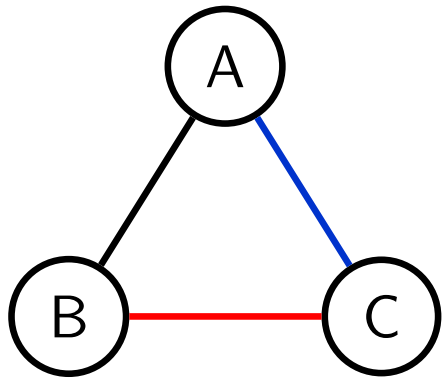


# Scenario 1: Predicted effect from bvNMA



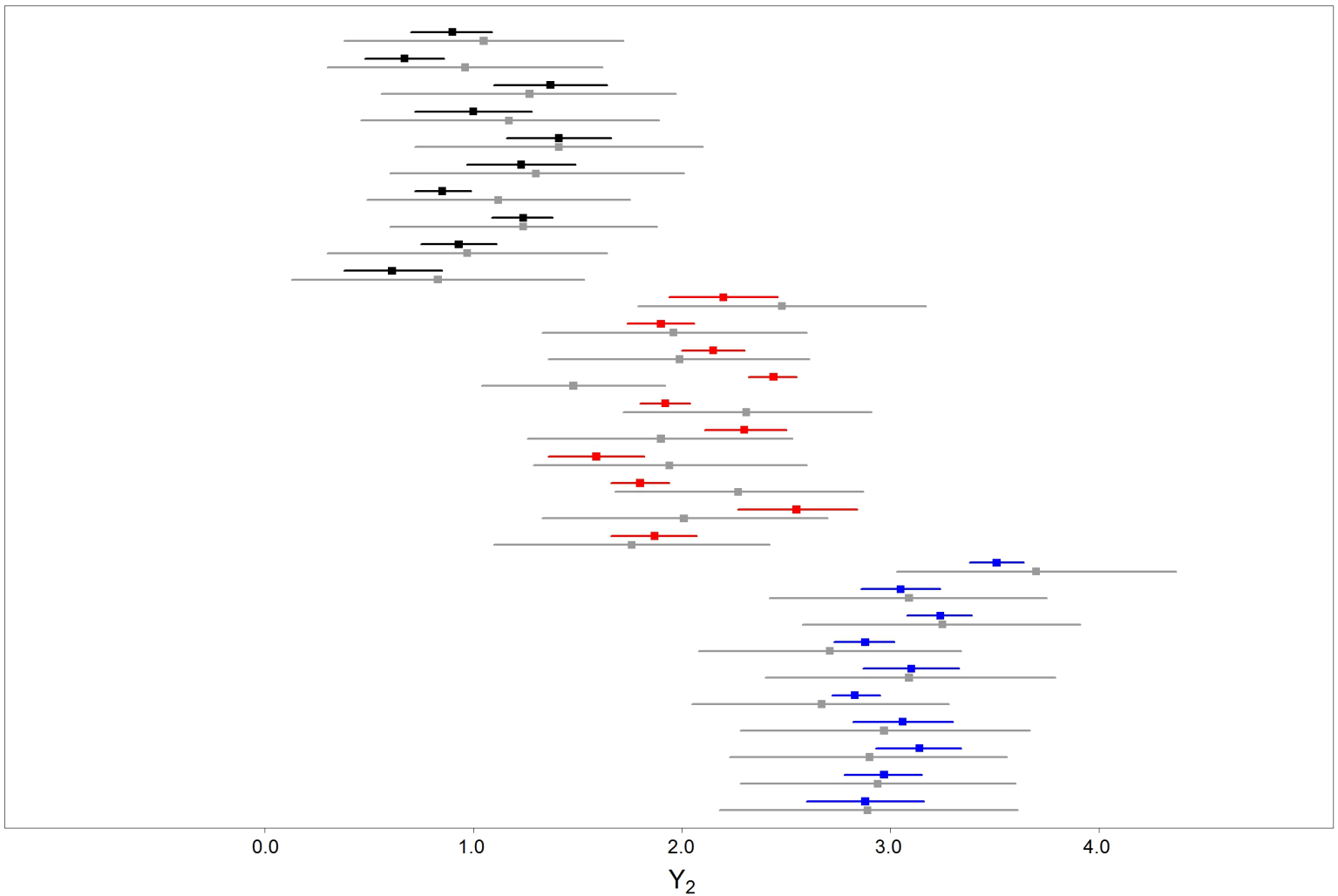
# Results: scenario 2



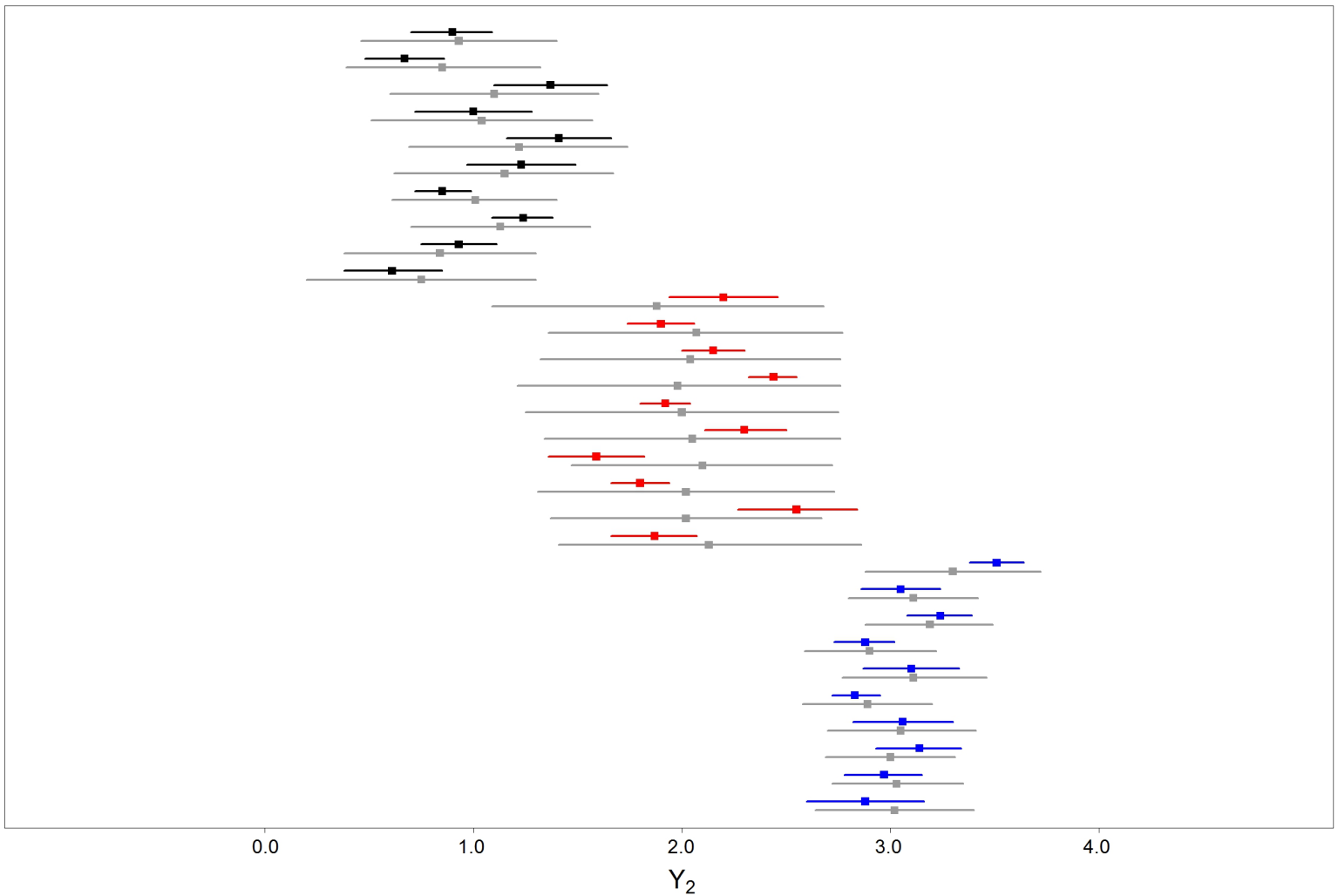



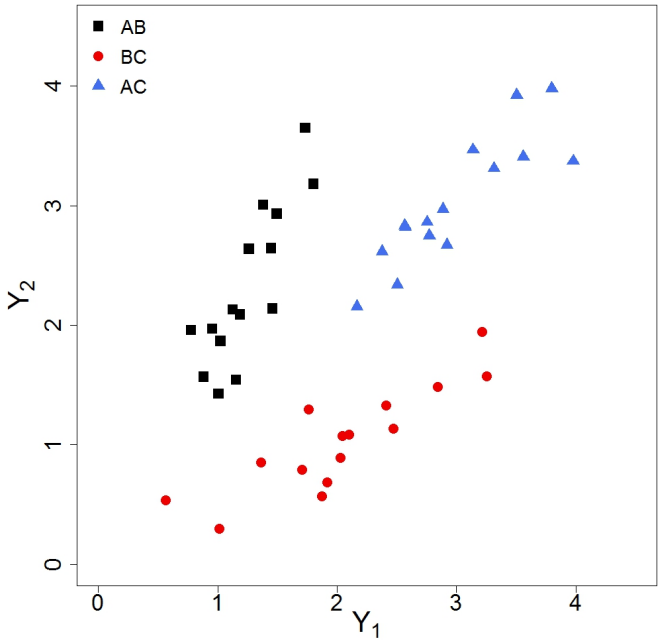

| model | AB | BC | AC |
|---|---|---|---|
| *correlations* | | | |
| BRMA | | 0.94 (0.88, 0.98) | |
| bvNMA | 0.78 (0.20, 0.99) | -0.05 (-0.60, 0.53) | 0.80 (0.26, 0.99) |

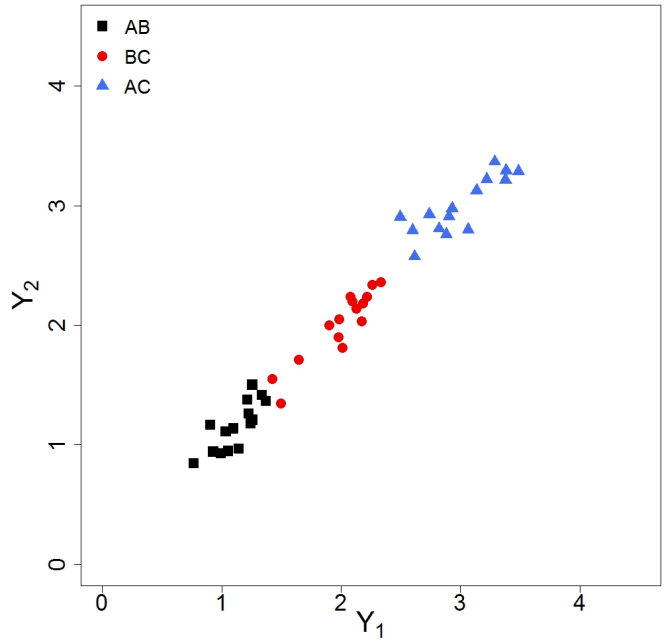
# Scenario 2: Predicted effect from BRMA



# Scenario 2: Predicted effect from bvNMA




AB
BC
AC
$Y_2$
$Y_1$
0
1
2
3
4


AB
BC
AC
$Y_2$
$Y_1$
0
1
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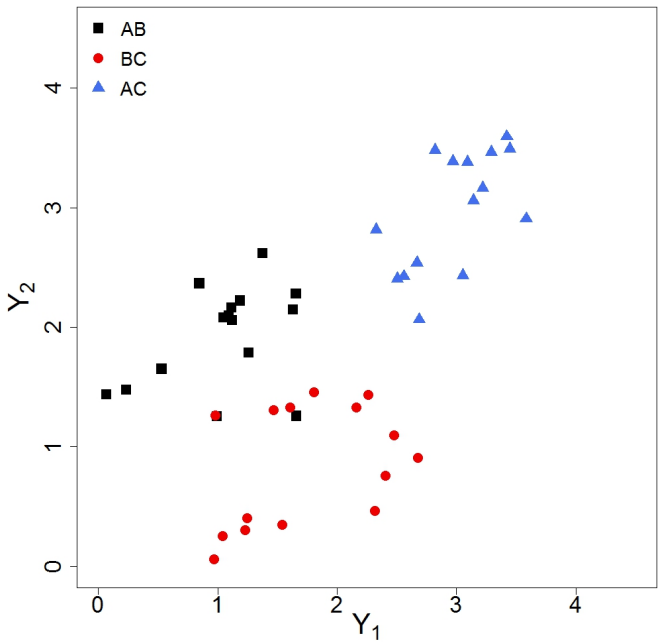
3
4


AB
BC
AC
$Y_2$
$Y_1$
0
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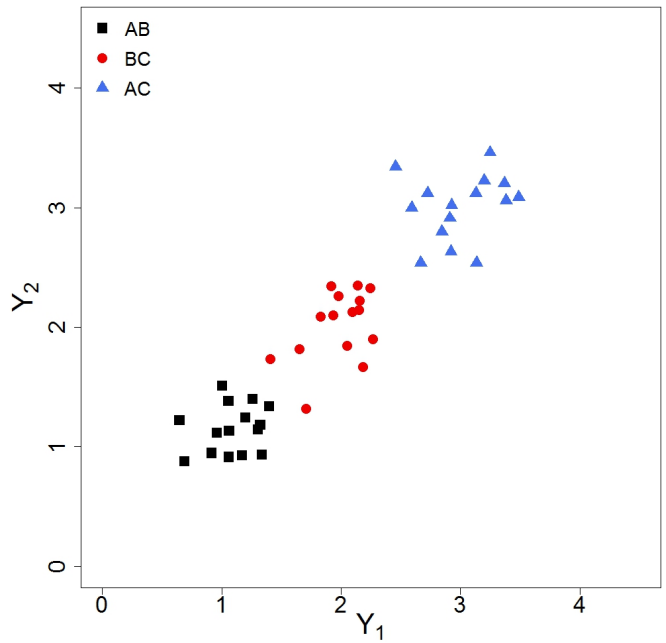
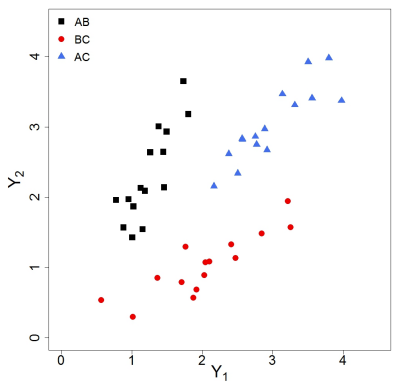
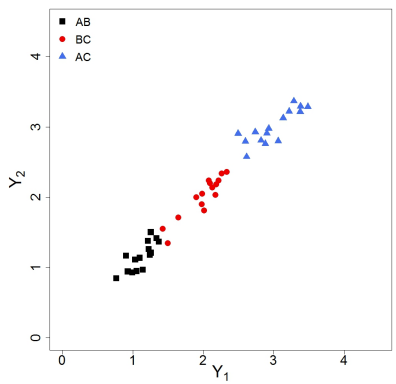

AB
BC
AC
$Y_2$
$Y_1$
0
1
2
3
4

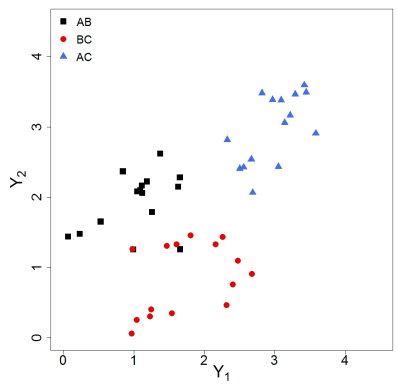
| | mean $\rho_{kl}$ / wCrI | | |
|---|---|---|---|
| | AB | BC | AC |
| *scenario 1: true correlations* $\rho_{kl} = 0.9$ | | | |
| BRMA | | 0.55 / 0.42 | |
| bvNMA 1a | 0.73 / 0.70 | 0.74 / 0.68 | 0.82 / 0.43 |
| bvNMA 1b | 0.77 / 0.58 | 0.72 / 0.62 | 0.84 / 0.40 |
| bvNMA 1d | | 0.77 / 0.30 | |
| *scenario 2: true correlations* $\rho_{kl} = 0.9$ | | | |
| BRMA | | 0.99 / 0.02 | |
| bvNMA 1a | 0.80 / 0.47 | 0.80 / 0.46 | 0.80 / 0.47 |
| bvNMA 1b | 0.82 / 0.40 | 0.80 / 0.47 | 0.81 / 0.41 |
| bvNMA 1d | | 0.82 / 0.22 | |
| *scenario 3: true correlations* $\rho_{kl} = 0.25$ | | | |
| BRMA | | 0.42 / 0.49 | |
| bvNMA 1a | 0.16 / 1.08 | 0.16 / 1.07 | 0.16 / 1.07 |
| bvNMA 1b | 0.19 / 1.04 | 0.16 / 1.01 | 0.19 / 1.03 |
| bvNMA 1d | | 0.22 / 0.66 | |
| *scenario 4: true correlations* $\rho_{kl} = 0.25$ | | | |
| BRMA | | 0.92 / 0.09 | |
| bvNMA 1a | 0.17 / 1.02 | 0.17 / 1.00 | 0.17 / 1.02 |
| bvNMA 1b | 0.19 / 0.98 | 0.18 / 0.98 | 0.19 / 0.98 |
| bvNMA 1d | | 0.21 / 0.62 | |

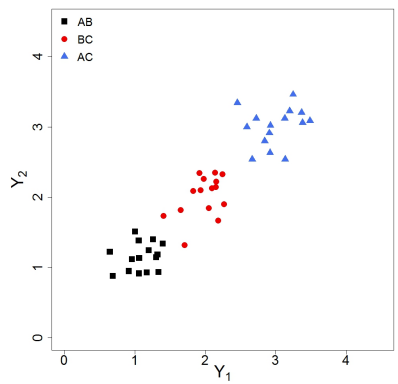
BRMA – bivariate random effects meta-analysis (pair wise)
1a – model with first order consistency, 1b – second order consistency,
1d – heterogeneity of the between-studies variances and correlations

| | AB | | | BC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| model | coverage | RMSE | wCrIr | coverage | RMSE | wCrIr | coverage | RMSE | wCrIr |
| *scenario 1* | | | | | | | | | |
| BRMA | 0.99 | 0.72 | | 0.99 | 0.72 | | 1.00 | 1.10 | |
| bvNMA 1a | 0.99 | 0.41 | 0.57 | 0.98 | 0.42 | 0.57 | 0.98 | 0.19 | 0.27 |
| bvNMA 1b | 0.98 | 0.41 | 0.51 | 0.97 | 0.42 | 0.51 | 1.0 | 0.18 | 0.29 |
| bvNMA 1d | 0.95 | 0.44 | 0.43 | 0.95 | 0.45 | 0.43 | 0.98 | 0.26 | 0.45 |
| *scenario 2* | | | | | | | | | |
| BRMA | 0.93 | 0.19 | | 0.95 | 0.18 | | 0.98 | 0.15 | |
| bvNMA 1a | 0.98 | 0.19 | 1.15 | 0.97 | 0.18 | 1.16 | 0.98 | 0.15 | 0.92 |
| bvNMA 1b | 0.96 | 0.19 | 1.04 | 0.96 | 0.18 | 1.05 | 0.99 | 0.15 | 0.96 |
| bvNMA 1d | 0.93 | 0.20 | 0.90 | 0.94 | 0.19 | 0.90 | 0.99 | 0.15 | 0.92 |
| *scenario 3* | | | | | | | | | |
| BRMA | 1.0 | 0.57 | | 1.0 | 0.59 | | 0.95 | 1.07 | |
| bvNMA 1a | 0.97 | 0.40 | 0.51 | 0.97 | 0.42 | 0.51 | 0.98 | 0.40 | 0.52 |
| bvNMA 1b | 0.97 | 0.40 | 0.50 | 0.98 | 0.42 | 0.50 | 0.98 | 0.39 | 0.52 |
| bvNMA 1d | 0.98 | 0.39 | 0.47 | 0.97 | 0.41 | 0.47 | 0.99 | 0.39 | 0.48 |
| *scenario 4* | | | | | | | | | |
| BRMA | 0.95 | 0.35 | | 0.95 | 0.35 | | 0.97 | 0.30 | |
| bvNMA 1a | 0.97 | 0.31 | 0.96 | 0.98 | 0.31 | 0.96 | 0.98 | 0.25 | 0.83 |
| bvNMA 1b | 0.96 | 0.30 | 0.88 | 0.97 | 0.31 | 0.89 | 0.98 | 0.25 | 0.83 |
| bvNMA 1d | 0.95 | 0.30 | 0.75 | 0.95 | 0.31 | 0.75 | 0.97 | 0.25 | 0.76 |









# Illustrative example: advanced colorectal cancer (aCRC)

**50 randomized controlled trials** (RCTs) investigating use of

- anti-VEGF with chemotherapy vs. chemotherapy alone (15 RCTs)
- EGFRi with chemotherapy vs. chemotherapy alone (24 RCTs)
- EGFRi with chemotherapy vs. anti-VEGF with chemotherapy (4 RCTs)
- EGFRi with anti-VEGF and chemotherapy vs. anti-VEGF with chemotherapy (4 RCTs)
- anti-IgG2 with EGFRi and chemotherapy vs. EGFRi with chemotherapy (1RCT, 2 subgroups)
- anti-IGF1R with chemotherapy vs. chemotherapy alone (1 RCT)
- EGFRi with anti-VEGF and chemotherapy vs. chemotherapy alone (1 RCT)

anti-VEGF – antiangiogenic treatments targeting vascular endothelial growth factor
EGFRi – epidermal growth factor receptor inhibitors
anti-IgG2 – humanised monoclonal antibody targeting integrin receptors
anti-IGF1R – monoclonal antibody targeting the type 1 insulin-like growth factor receptor

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- anti-IgG2 with EGFRi and chemotherapy vs. EGFRi with chemotherapy (1RCT, 2 subgroups)
- anti-IGF1R with chemotherapy vs. chemotherapy alone (1 RCT)
- EGFRi with anti-VEGF and chemotherapy vs. chemotherapy alone (1 RCT)

Wagner et al. Cochrane Database of Systematic Reviews. 2009;(3):1–75
Chan et al. Cochrane Database of Systematic Reviews. 2017;(6):1–175
Mocellin et al. Cochrane Database of Systematic Reviews. 2017;(1):1–121
Kumachev et al. PloS one. 2015;10(10):e0140187.

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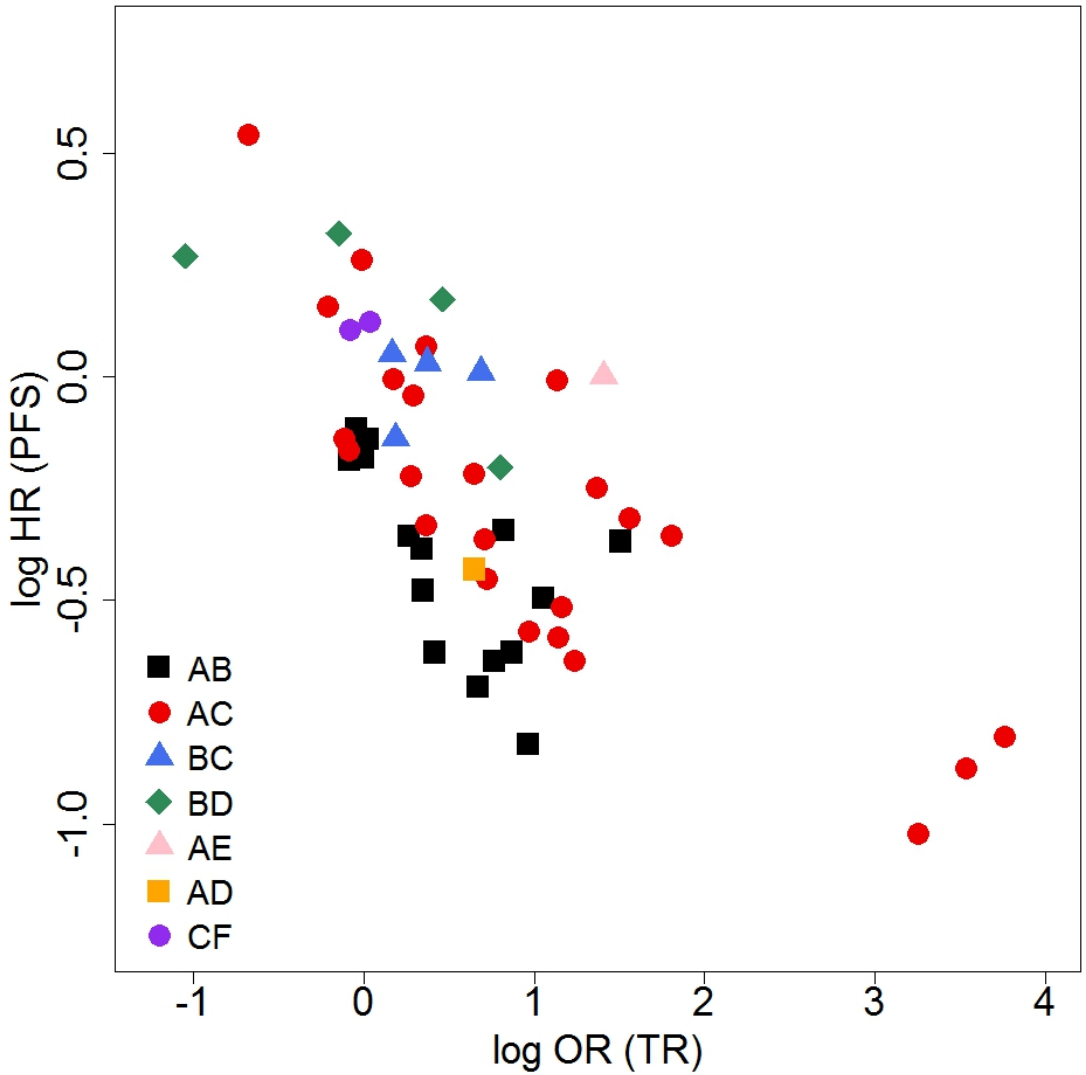
- anti-IGF1R with chemotherapy vs. chemotherapy alone (1 RCT)
- EGFRi with anti-VEGF and chemotherapy vs. chemotherapy alone (1 RCT)

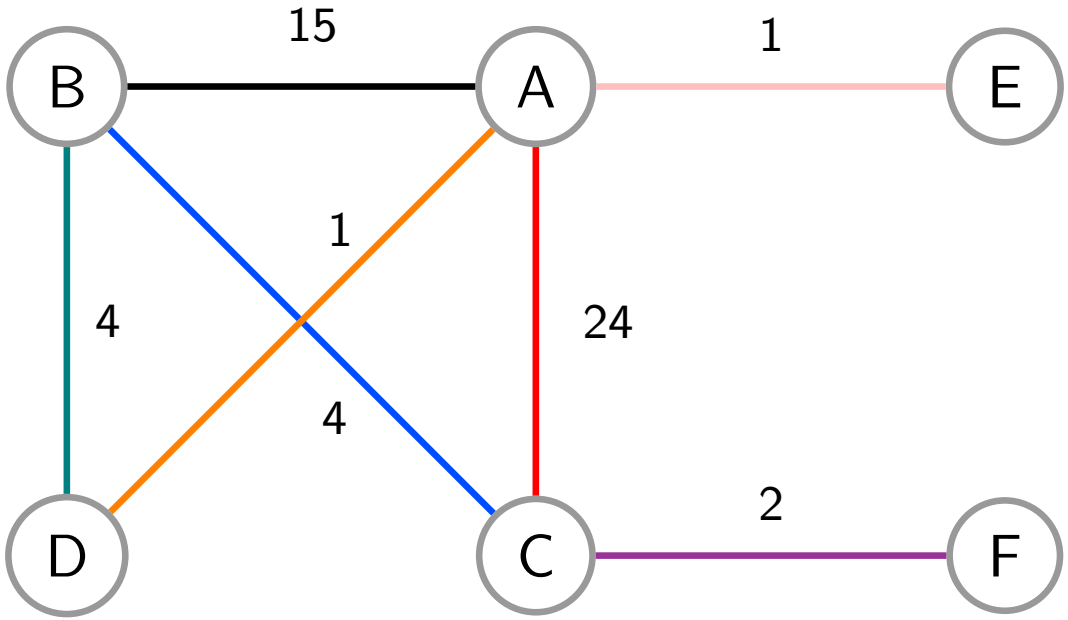
Outcomes and measure of treatment effect:

- potential **surrogate endpoint**: tumour response (TR), log OR
- **final outcome**: progression free survival (PFS), log HR

# Data for the aCRC example



# Network diagram for the aCRC example




A: chemotherapy alone,
B: anti-VEGF therapies + chemotherapy,
C: EGFRi + chemotherapy,
D: EGFRi + anti-VEGF therapies + chemotherapy,
E: anti-IGF1R ,
F: anti-IgG2 + chemotherapy

# Comparison of results across models

| | | BRMA | bvNMA | bvNMA 2* |
|---|---|---|---|---|
| $\rho_{kl}$ | AB | | **-0.69 (-0.96, -0.18)** | -0.70 (-0.95, -0.19) |
| | AC | | **-0.83 (-0.97, -0.57)** | -0.83 (-0.97, -0.56) |
| | BC | | -0.29 (-0.91, 0.67) | -0.28 (-0.91, 0.68) |
| | BD | **-0.73 (-0.89, -0.49)** | -0.28 (-0.89, 0.58) | -0.29 (-0.90, 0.56) |
| | AE | | -0.08 (-0.89, 0.83) | -0.07 (-0.89, 0.84) |
| | AD | | -0.32 (-0.95, 0.72) | -0.35 (-0.95, 0.70) |
| | CF | | -0.02 (-0.84, 0.82) | -0.04 (-0.85, 0.82) |
| $\rho_t$ | – | NA | NA | **-0.34 (-0.92, 0.56)** |

* *Model with across-treatment exchangeability*

$\rho_{kl}$ – within-treatment contrast between-studies correlations
$\rho_t$ – across-treatment correlations obtained from the models allowing for exchangeability
A – chemotherapy alone,
B – anti-VEGF therapies + chemotherapy,
C – EGFRi + chemotherapy,
D – EGFRi + anti-VEGF therapies + chemotherapy

# Discussion of NMA for surrogate endpoint evaluation: summary

- Surrogate relationship may depend on the mechanism of action of treatments or treatment classes.
- When this is the case, surrogate relationship may be investigated in subgroups.
- Data included in such analysis will be limited to a certain class of treatments, which may dramatically reduce evidence base for surrogate endpoint evaluation.
- The bivariate network meta-analytic method for surrogate endpoint evaluation can overcome this limitation
- The method allows for modelling surrogate relationships in each treatment contrast individually whilst borrowing information from other treatment contrasts by taking into account the network structure of the data.

# Discussion of NMA for surrogate endpoint evaluation

- An extension of the method, in addition to modelling the study-level surrogate relationship (within each treatment contrast), models also a treatment-level surrogacy by assuming additional similarity between the treatments.
- This extended method allows for predicting treatment effect on the final outcome for a new study and a new treatment.
- Limitations:
  - There may be insufficient number of studies per contrast.
  - Consistency assumption may not be valid.

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RESEARCH ARTICLE

Statistics in Medicine WILEY

# Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data

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**Abstract**

Surrogate endpoints play an important role in drug development when they can be used to measure treatment effect early compared to the final clinical outcome and to predict clinical benefit or harm. Such endpoints are assessed for their predictive value of clinical benefit by investigating the surrogate relationship between treatment effects on the surrogate and final outcomes using meta-analytic methods. When surrogate relationships vary across treatment classes, such validation may fail due to limited data within each treatment class. In this paper, two alternative Bayesian meta-analytic methods are introduced which allow for borrowing of information from other treatment classes when exploring the surrogacy in a particular class. The first approach extends

# Discussion of NMA for surrogate endpoint evaluation: limitation and further work

- Another method has recently been developed by Papanikos et al.:
  - a pair wise approach
  - allows for borrowing information about surrogate relationships between treatment classes
- Two versions of the method are proposed:
  - assuming exchangeability (similarity) of the surrogate relationships across the treatment classes
  - a model which relaxes this assumption by allowing for partial exchangeability, i.e. the level of exchangeability is defined by a probability of similarity which is learned from the data.

# Standard surrogacy model: Daniels and Hughes

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \mathrm{N}\left( \begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix} \right)$$

$$\delta_{2i} \mid \delta_{1i} \sim N(\lambda_0 + \lambda_1 \delta_{1i}, \psi^2),$$

Prior distributions:
$\delta_{1i} \sim N(0, 1000)$, $\lambda_0 \sim N(0, 1000)$, $\lambda_1 \sim N(0, 1000)$, $\psi \sim Unif(0, 2)$.

Surrogacy criteria for a perfect surrogate relationship:
$\lambda_0 = 0$ – no treatment effect on the surrogate endpoint implies no treatment effect on the final clinical outcome
$\lambda_1 \neq 0$ – establishing a relationship between treatment effects on the surrogate and final clinical outcomes.
$\psi^2 = 0$ – conditional variance measures the strength of the association

Daniels and Hughes, Statistics in Medicine 1997

# Exchangeability model

$$\begin{pmatrix} Y_{1ij} \\ Y_{2ij} \end{pmatrix} \sim \mathrm{N}\left( \begin{pmatrix} \delta_{1ij} \\ \delta_{2ji} \end{pmatrix}, \begin{pmatrix} \sigma^2_{1ij} & \sigma_{1ij}\sigma_{2ij}\rho_{wij} \\ \sigma_{1ij}\sigma_{2ij}\rho_{wij} & \sigma^2_{2ij} \end{pmatrix} \right)$$

$$\delta_{2ij} \mid \delta_{1ij} \sim N(\lambda_{0j} + \lambda_{1j}\delta_{1ij}, \psi^2_j),$$

$$\lambda_{0j} \sim N(\beta_0, \xi^2_0), \quad \lambda_{1j} \sim N(\beta_1, \xi^2_1)$$

Prior distributions:
$\delta_{1ij} \sim N(0, 1000)$, $\beta_0 \sim N(0, 1000)$, $\beta_1 \sim N(0, 1000)$, $\psi_j \sim Unif\,(0, 2)$, $\xi_{0,1} \sim Unif\,(0, 2)$.
Surrogacy criteria for a perfect surrogate relationship within each treatment class:
$\lambda_{0j} = 0$ – no treatment effect on the surrogate endpoint implies no treatment effect on the final clinical outcome
$\lambda_{1j} \neq 0$ – establishing a relationship between treatment effects on the surrogate and final clinical outcomes.
$\psi^2_j = 0$ – conditional variance measures the strength of the association

# Partial exchangeability model

$$\begin{pmatrix} Y_{1ij} \\ Y_{2ij} \end{pmatrix} \sim \mathrm{N}\left( \begin{pmatrix} \delta_{1ij} \\ \delta_{2ji} \end{pmatrix}, \begin{pmatrix} \sigma^2_{1ij} & \sigma_{1ij}\sigma_{2ij}\rho_{wij} \\ \sigma_{1ij}\sigma_{2ij}\rho_{wij} & \sigma^2_{2ij} \end{pmatrix} \right)$$

$$\delta_{2ij} \mid \delta_{1ij} \sim N(\lambda_{0j} + \lambda_{1j}\delta_{1ij}, \psi^2_j),$$

$$\lambda_{0j} \sim N(\beta_0, \xi^2_0),$$

$$\begin{cases} \lambda_{1j} \sim N(\beta_1, \xi^2_1) & \text{if } p_j = 1 \\ \lambda_{1j} \sim N(0, 10^3) & \text{if } p_j = 0 \end{cases}$$

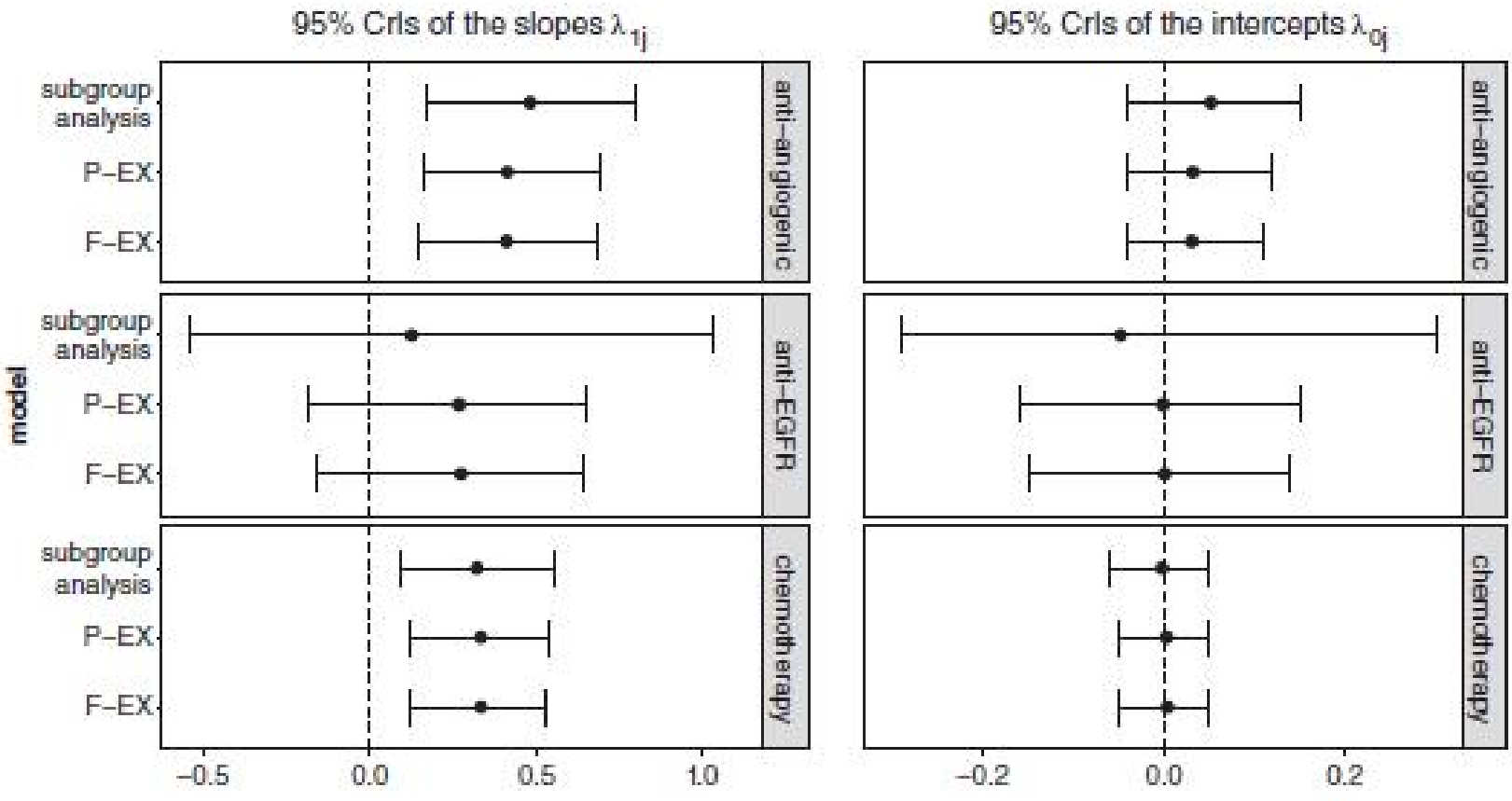
Prior distributions:

$\delta_{1ij} \sim N(0, 1000)$, $\beta_0 \sim N(0, 1000)$, $\beta_1 \sim N(0, 1000)$, $p_j \sim Bernoulli(\pi_j)$
$\psi_j \sim Unif(0, 2)$, $\xi_{0,1} \sim Unif(0, 2)$.

Papanikos T et al, Statistics in Medicine, published online 28 January 2020.

# Results in aCRC

## Surrogacy between treatment effects on PFS and OS




Papanikos T et al, Statistics in Medicine, published online 28 January 2020.

# Discussion

- Bivariate meta-analysis models surrogate relationships between treatment effects (ignoring differences in treatments between studies).
- Bivariate network meta-analysis methods allow us to model
  - the surrogacy patterns across multiple trials (different populations) within a treatment contrast
  - and across treatment contrasts

  thus enabling predictions of the treatment effect on the final outcome for a new study
  - in a new population
  - or investigating a new treatment.

# Discussion

- The models can be extended to evaluate jointly multiple surrogate endpoints
  - Showed improved precision of predictions when using multiple surrogate endpoints in multiple sclerosis (Bujkiewicz et al, Statistics in Medicine 2016)
  - but not in advanced colorectal cancer (Elia EG, Städler N, Ciani O, Taylor RS, Bujkiewicz S, Combining tumour response and progression free survival as surrogate endpoints for overall survival in advanced colorectal cancer. Cancer Epidemiology, 5 January 2020.)
- The models can be extended to take into account correlation between arms in multi-arm trials (Achana et al BMC MRM 2014).

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