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Multilevel network meta-regression

Methods and implementation

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Multilevel Network Meta-Regression (ML-NMR)

- Applicable in networks of all sizes

- Avoids aggregation bias

- Correctly handles non-collapsible effect measures

- Produces estimates in any target population for decision making

- Extends the standard network meta-analysis (NMA) framework, reducing to:

  - IPD network meta-regression with full IPD

  - Standard NMA with no adjustment

- Allows assumptions to be tested/relaxed in larger networks (Phillippo et al. 2023)

- Implemented in R package *multinma*

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ML-NMR

1. Define an individual-level regression model
   - IPD network meta-regression (gold-standard approach)

2. Average (integrate) this over the aggregate population(s) to form the aggregate-level model

Individual:

$$y_{ijk} \sim \pi_{\mathrm{Ind}}(\theta_{ijk})$$

$$g(\theta_{ijk}) = \eta_{jk}(\boldsymbol{x}_{ijk}) = \mu_j + \boldsymbol{x}_{ijk}^{\mathsf{T}}(\boldsymbol{\beta}_1 + \boldsymbol{\beta}_{2,k}) + \gamma_k$$

Aggregate:

1. $$y_{\bullet jk} \sim \pi_{\mathrm{Agg}}(\theta_{\bullet jk})$$

2. $$\theta_{\bullet jk} = \int_{\mathfrak{X}} g^{-1}\big(\eta_{jk}(\boldsymbol{x})\big) f_{jk}(\boldsymbol{x})\, d\boldsymbol{x}$$

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ML-NMR

1. **From individual to aggregate likelihood**

$$y_{ijk} \sim \pi_{\text{Ind}}(\theta_{ijk}) \longrightarrow y_{\bullet jk} \sim \pi_{\text{Agg}}(\theta_{\bullet jk})$$

2. **Integration over a population**

$$\theta_{\bullet jk} = \int_{\mathfrak{x}} g^{-1}\big(\eta_{jk}(\boldsymbol{x})\big) f_{jk}(\boldsymbol{x}) \, d\boldsymbol{x}$$

Straightforward in many cases
- E.g. Normal or Poisson outcomes
- Binomial approx. for binary outcomes

Use numerical integration
- Quasi Monte-Carlo
- Copula for correlations

Not always easy or possible to determine aggregate likelihood
- Survival outcomes with censoring

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ML-NMR for survival outcomes

- Most common type of population adjustment analysis
- IPD studies
  - Individual event/censoring times
  - Individual covariate values
- Aggregate studies
  - Individual event/censoring times (e.g. reconstructed from KM curves)
  - Covariate summaries
- We cannot write down the aggregate-level model
  - Motivates a more general approach

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ML-NMR for survival outcomes

Work directly with the likelihood contributions from each level of the model

1. Define individual-level regression model

   - IPD network meta-regression, survival outcome with censoring

2. Integrate the likelihood for each aggregate data point over the joint covariate distribution

| Individual | $L_{ijk|x}(\boldsymbol{\xi}; t, y, \boldsymbol{x}) = S_{jk}(t|\boldsymbol{x})\lambda_{jk}(t|\boldsymbol{x})^y$ |

| Aggregate | $L_{ijk}(\boldsymbol{\xi}; t, y) = \int_{\mathfrak{x}} S_{jk}(t|\boldsymbol{x})\lambda_{jk}(t|\boldsymbol{x})^y f_{jk}(\boldsymbol{x})\, d\boldsymbol{x}$ |

Survival $S_{jk}(t|\boldsymbol{x})$ and hazard $\lambda_{jk}(t|\boldsymbol{x})$ functions may be of any form (parametric PH or AFT, splines or fractional polynomial etc.)

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Predicting quantities of interest for a target population

The target population could be represented by

- A randomised trial
- An observational study

- A registry dataset
- …

With IPD covariate information	With summary statistics
1. Make predictions for each individual	1. Generate integration points from joint covariate distribution
2. Summarise these for the population	2. Integrate over the target population

For quantities on linear predictor scale (e.g. average treatment effects) both are equivalent to "plugging-in" mean covariate values:

$$d_{ab(P)} = \bar{\boldsymbol{x}}_{(P)}^{\mathsf{T}}(\boldsymbol{\beta}_{2,b} - \boldsymbol{\beta}_{2,a}) + \gamma_b - \gamma_a$$

Not true in general, need full integration (e.g. event probabilities, survival curves, etc.)

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The multinma R package
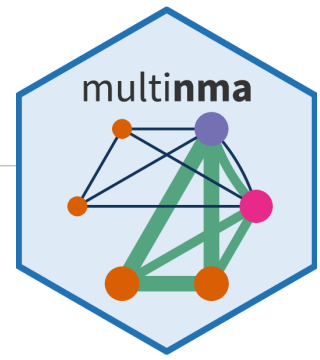
- NMA and ML-NMR with individual patient data and/or aggregate data

- Bayesian framework using Stan, code highly optimised

- Outcomes, likelihoods, link functions:

  - Binary/count – Bernoulli/binomial (logit, probit, cloglog)

  - Rate – Poisson (log)

  - Ordered categorical – Multinomial (logit, probit, cloglog)

  - Continuous – Normal (identity, log)

  - Survival – Exponential (PH/AFT), Weibull (PH/AFT), Gompertz, log-Normal, log-Logistic, Gamma, Generalised Gamma, M-spline, piecewise exponential

- Fixed and random effects, unrelated mean effects, node-splitting

Outline of NMA in multinma
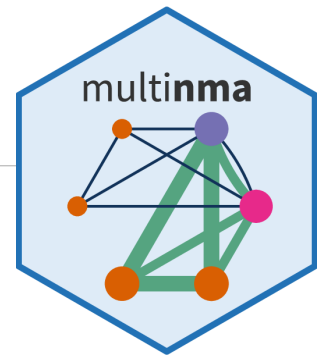
- Data in long ("tidy") format
  - One row per arm/contrast per study, or per individual in IPD
  - One row per event time for survival outcomes
- Define the network
  - `set_agd_arm()` `set_agd_contrast()` `set_agd_surv()` `set_ipd()`
  - `combine_network()`
- Specify prior distributions, run analysis
  - `nma()`
- Checking convergence, model fit, results
  - `print()`   `plot()`   `dic()`
  - `relative_effects()` `predict()`   `posterior_ranks()`

Outline of ML-NMR in multinma
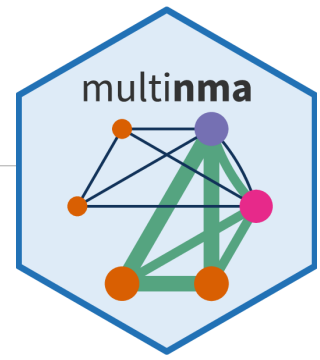
- Data in long ("tidy") format
- Define the network
  - `set_agd_arm()` `set_agd_contrast()` `set_agd_surv()` `set_ipd()`
  - `combine_network()`
- Set up numerical integration
  - `add_integration()`   `distr()`
- Specify prior distributions, run analysis
  - `nma()`
- Checking convergence, model fit, results
  - `print()`   `plot()`   `dic()`
  - `relative_effects()` `predict()`   `posterior_ranks()`

Example: Newly-diagnosed multiple myeloma

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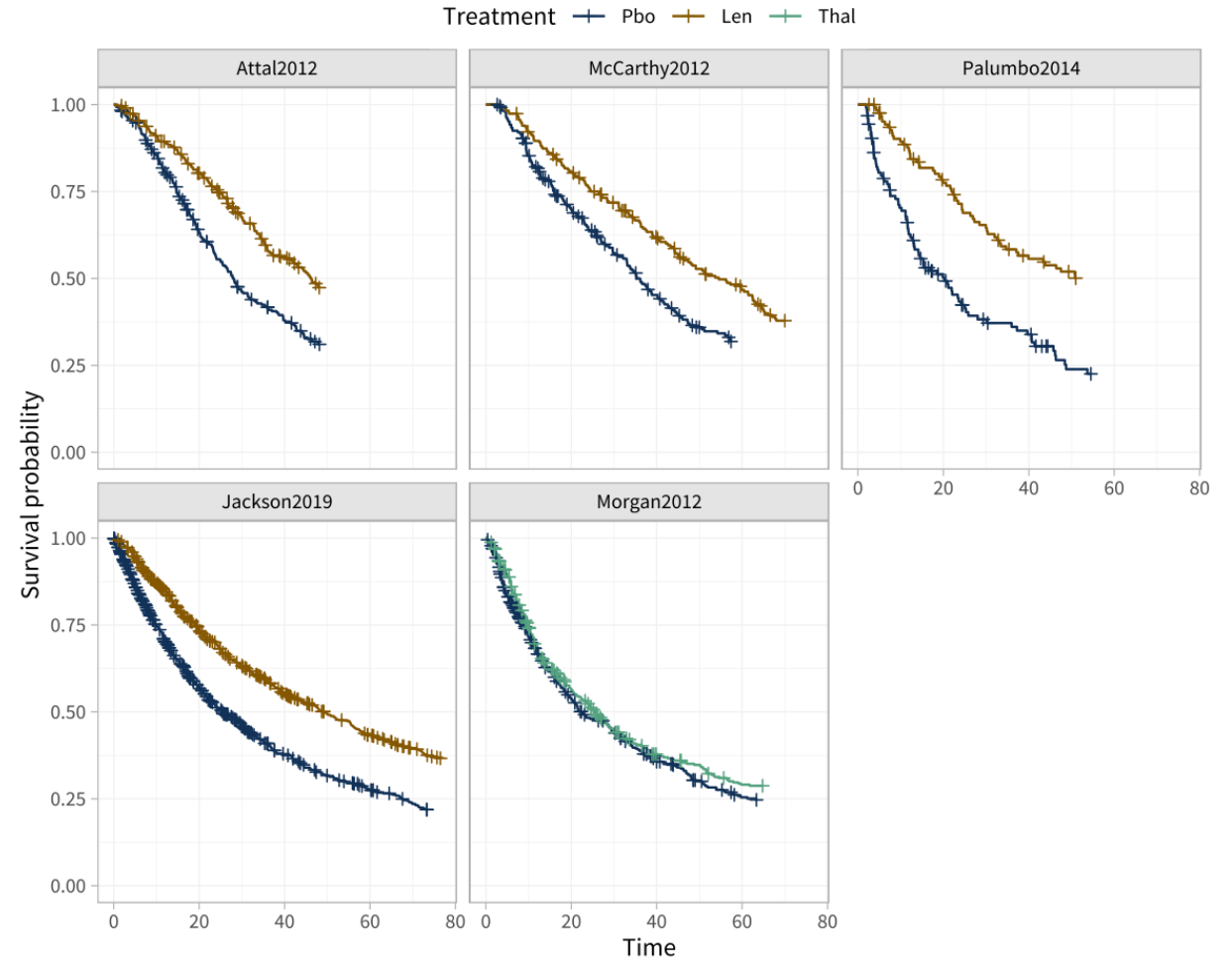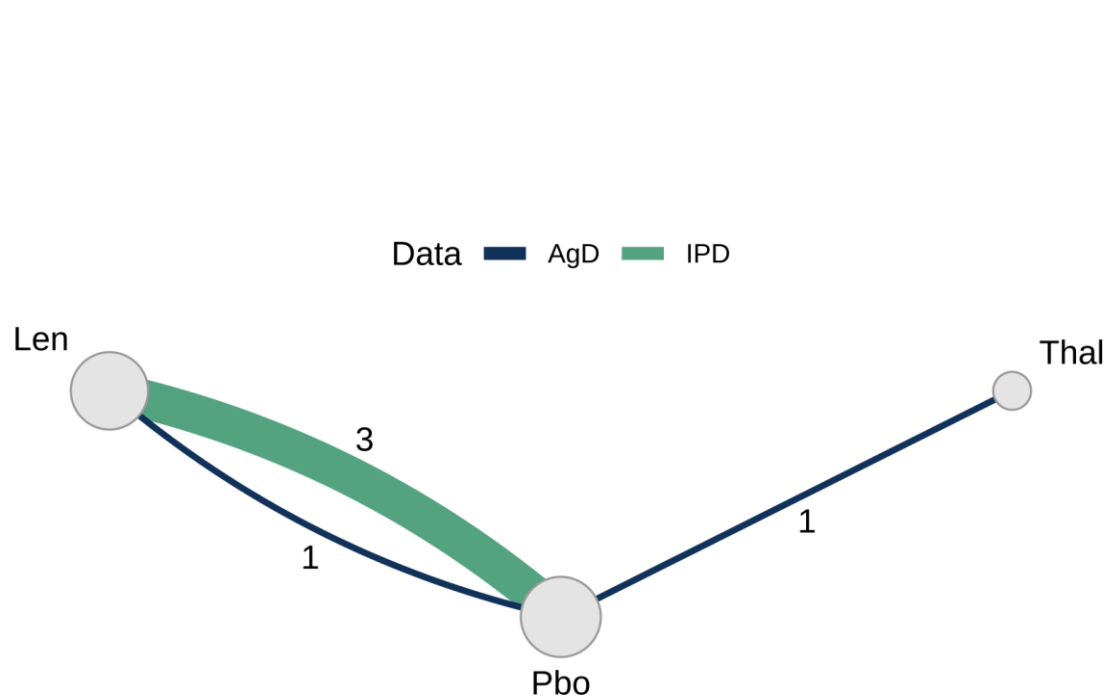
ML-NMR in the multinma package (survival outcomes)
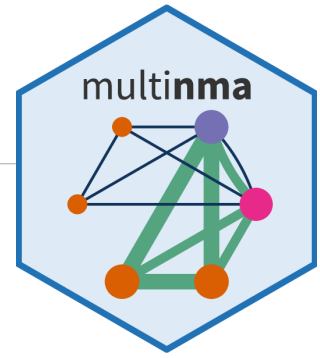
```r
# Set up network
ndmm_net <- combine_network(
  set_ipd(ndmm_ipd, study = studyc, trt = trtc,
          Surv = Surv(eventtime, status), trt_class = trtclass),
  set_agd_surv(ndmm_agd, study = studyc, trt = trtc,
               Surv = Surv(eventtime, status), trt_class = trtclass,
               covariates = ndmm_agd_covs))

# Add integration
ndmm_net <- add_integration(ndmm_net,
  age = distr(qgamma, mean = age_mean, sd = age_sd),
  iss_stage3 = distr(qbern, iss_stage3),
  response = distr(qbern, response),
  male = distr(qbern, male))

# Fit M-spline ML-NMR model in Stan
ndmm_fit <- nma(ndmm_net,
  likelihood = "mspline",                            # M-spline model
  regression = ~(age + iss_stage3 + response + male)*.trt,   # Regression
  prior_intercept = normal(scale = 100),             # Priors
  prior_trt = normal(scale = 10),
  prior_reg = normal(scale = 10),
  prior_aux = half_normal(1))

# Plot population-average survival curves
plot(predict(ndmm_fit, type = "survival"))
```
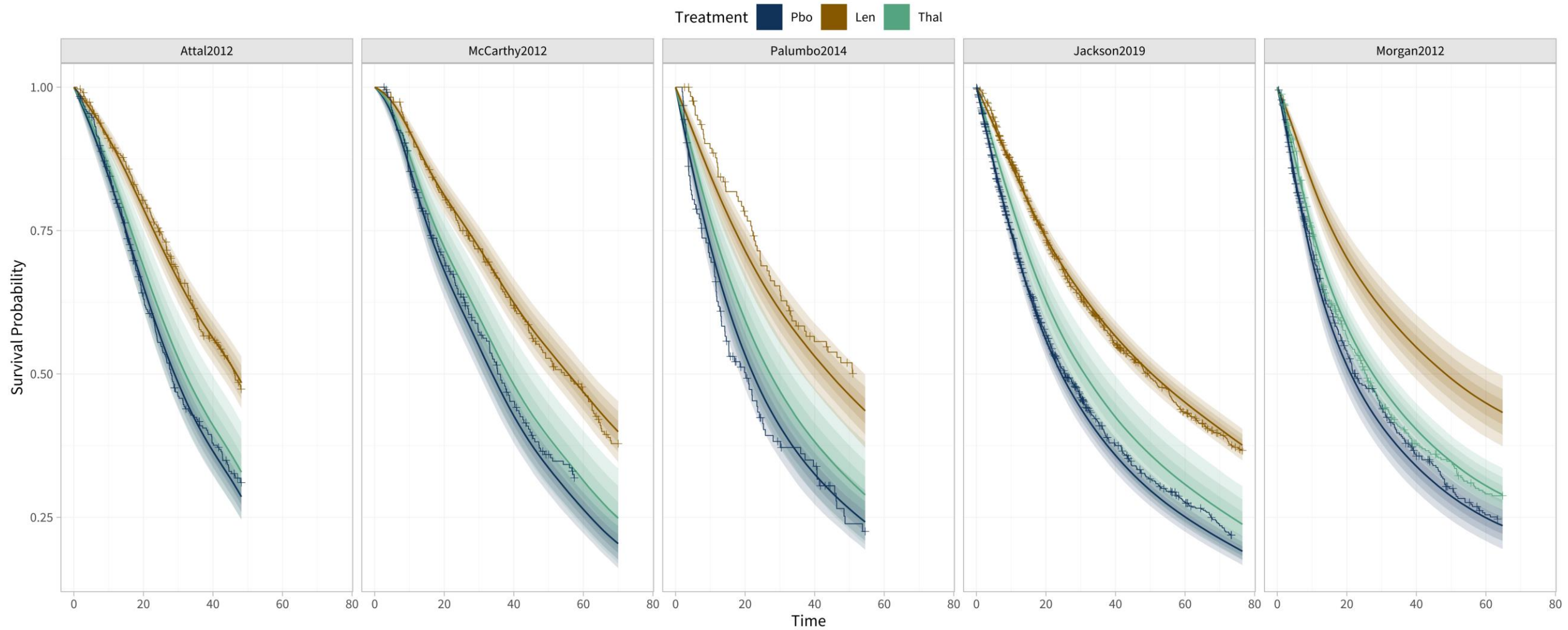
set_ipd()
set_agd_surv()
combine_network()

add_integration()

nma()

predict()
plot()

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Example: Newly-diagnosed multiple myeloma

Summary

- ML-NMR is a flexible and general method for synthesising evidence from mixtures of individual and aggregate level data in networks of all sizes, for a range of outcomes including survival

- Has several advantages over previous population-adjustment methods

- Decision making is aided by the production of effect estimates relevant to the decision target population

- Implemented in **multinma** R package
  - Website: dmphillippo.github.io/multinma
  - Documentation, example analyses
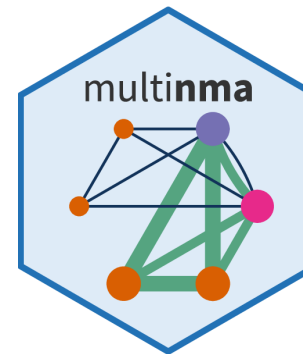
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Funding and References

Phillippo, DM et al. (2020) Multilevel Network Meta-Regression for population-adjusted treatment comparisons. *Journal of the Royal Statistical Society: Series A*, 183(3):1189-1210. DOI: 10.1111/rssa.12579.

Phillippo, DM et al. (2020) Assessing the performance of population adjustment methods for anchored indirect comparisons: A simulation study. *Statistics in Medicine*, 39(30):4885-4911. DOI: 10.1002/sim.8759

Phillippo DM et al. (2023) Validating the assumptions of population adjustment: application of multilevel network meta-regression to a network of treatments for plaque psoriasis. *Medical Decision Making*, 43(1):53-67. DOI: 10.1177/0272989X221117162.

Phillippo, DM (2019) *Calibration of treatment effects in network meta-analysis using individual patient data.* PhD Thesis, University of Bristol. Available from research-information.bristol.ac.uk.

R package *multinma*, see dmphillippo.github.io/multinma for details

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