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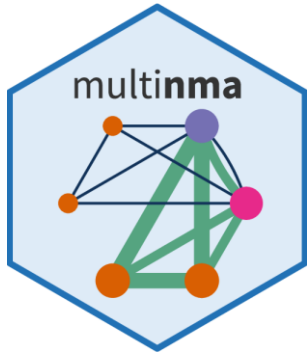
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multinma

A comprehensive R package for network meta-analysis of survival outcomes with aggregate data, individual patient data, or a mixture of both

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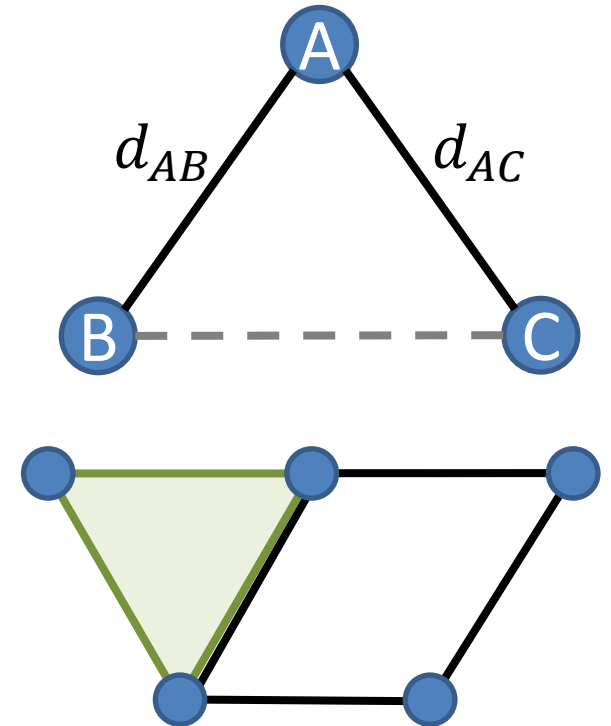
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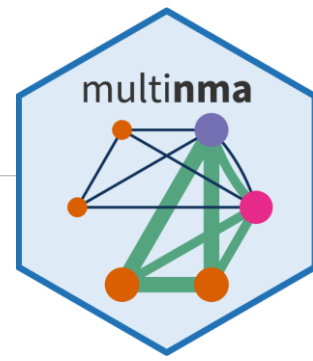
Background

We wish to compare multiple treatments, but not all are studied in the same trial

- Network meta-analysis (NMA) combines evidence on multiple treatments from several studies
- Survival outcomes are common, e.g. oncology
 - Synthesise log hazard ratios (HRs)
 - Restricted to proportional hazards (PH) assumption
 - Synthesise KM data
 - Assess and relax PH assumption
 - Covariate adjustment with individual participant data (IPD)
 - Requires complex bespoke modelling code



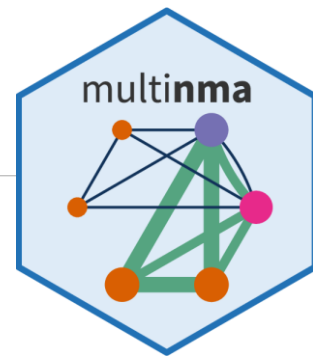
The multinma R package



A user-friendly and comprehensive suite of tools for performing

- Aggregate data (AgD) NMA
 - Individual participant data (IPD) NMA
 - Multilevel network meta-regression with mixed IPD and AgD
-
- Models fitted in a Bayesian framework using Stan
 - First released June 2020, with regular updates and new features since
 - **Survival analysis features** added in v0.6.0 (January 2024)

The multinma R package



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

Outline of NMA in multinma

Data Long (“tidy”) format

- One row per arm/contrast in each AgD study, or per individual in IPD
- One row per event time for survival outcomes

Network setup

- `set_agd_arm()` `set_agd_contrast()` `set_agd_surv()` `set_ipd()`
- `combine_network()`

Fitting Specify model and prior distributions, run analysis

- `nma()`

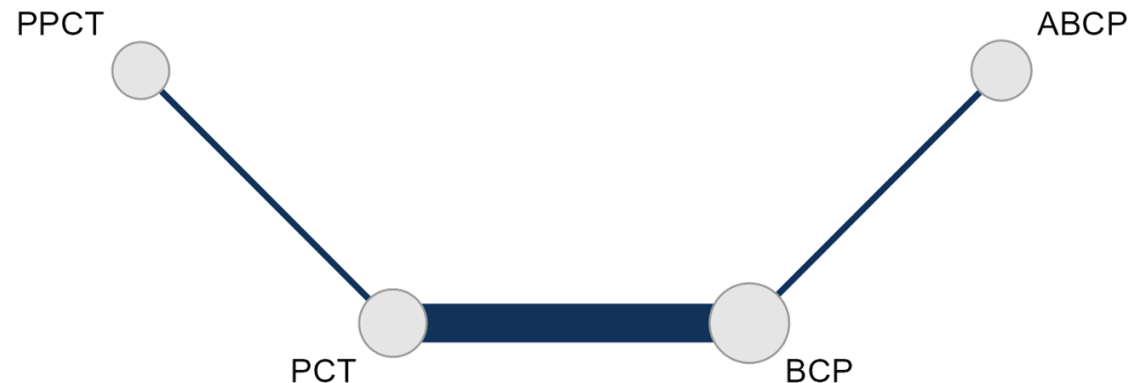
Posterior analysis Checking convergence, model fit and comparison, results

- `dic()` `loo::loo()` `loo::waic()`
 - `relative_effects()` `predict()` `marginal_effects()`
 - `posterior_ranks()` `posterior_rank_probs()`
- } `plot()`

Example: Non-small cell lung cancer

Four studies comparing first-line treatments for NSCLC

- PCT = platinum chemotherapy
- PPCT = pembrolizumab + platinum chemotherapy
- BCP = bevacizumab, carboplatin, paclitaxel
- ABCP = atezolizumab + bevacizumab, carboplatin, paclitaxel

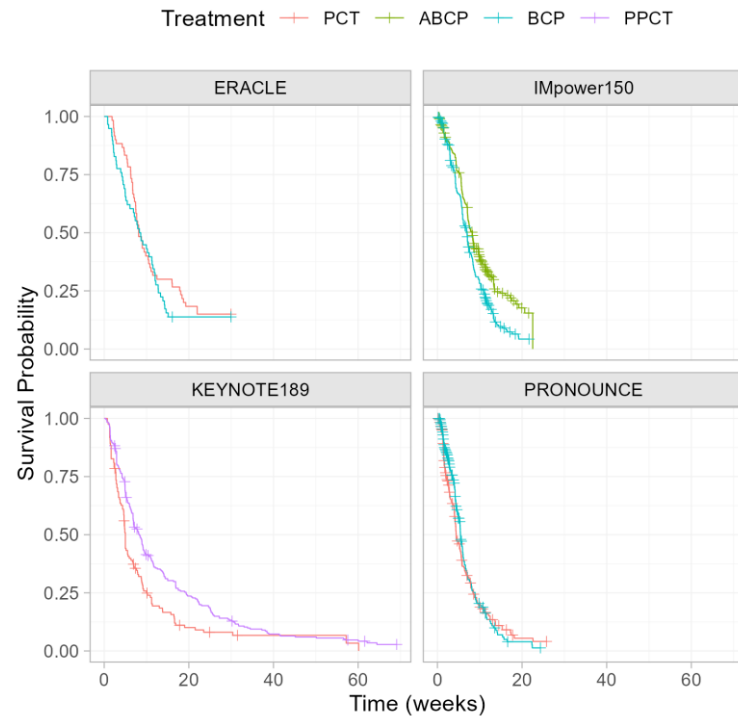


`plot(nsclc_net)`

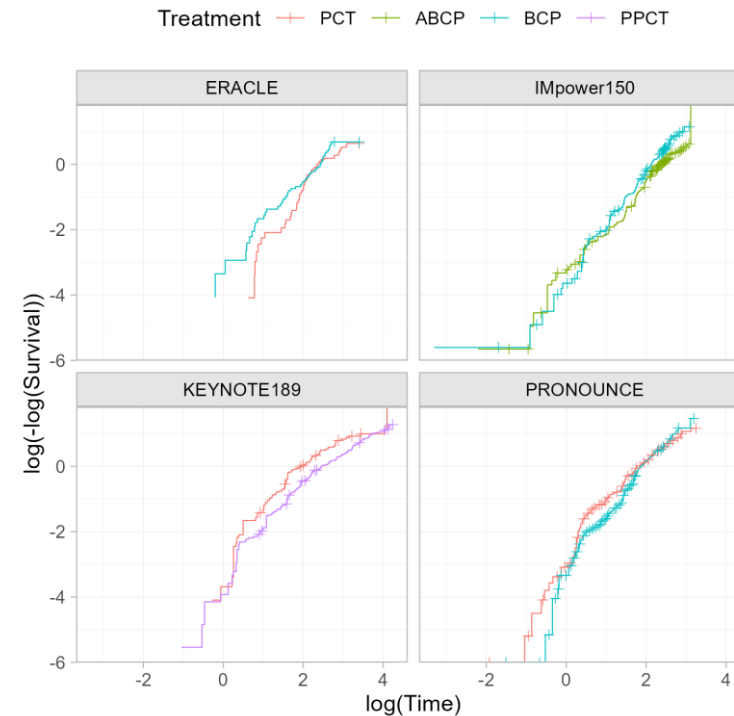
Example: Non-small cell lung cancer

- Survival and censoring times digitised from KM plots
- Evidence for non-proportional hazards

`geom_km()`



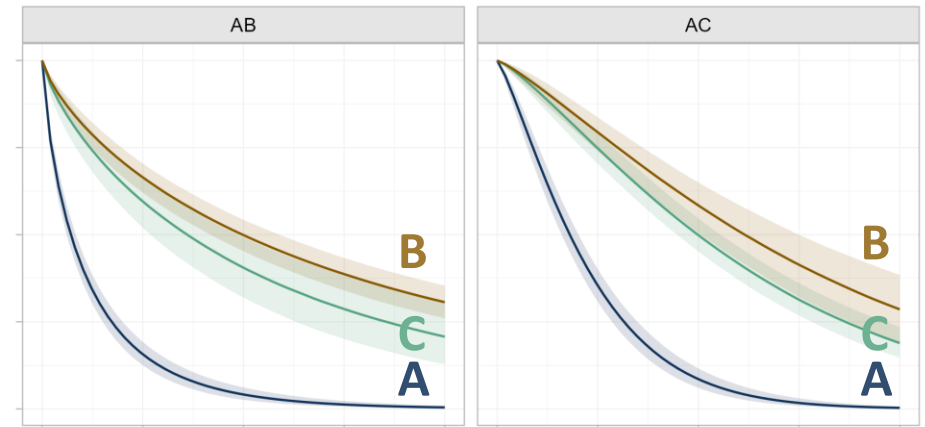
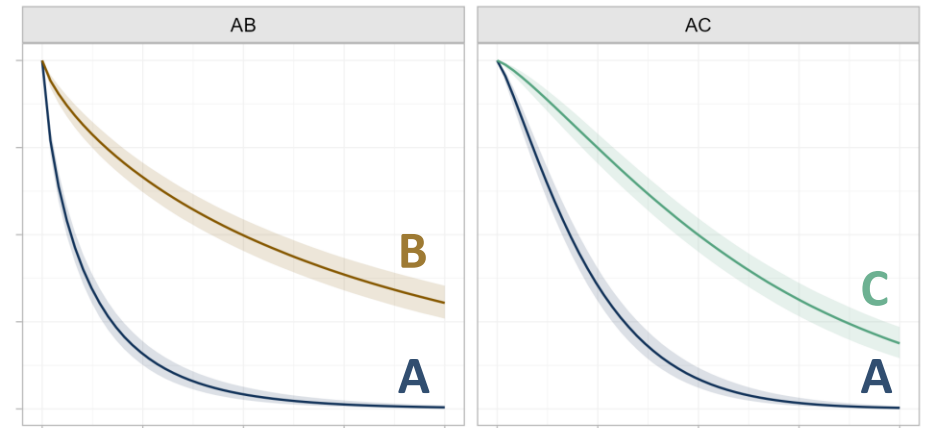
`geom_km(transform = "cloglog")`



- Flexible M-spline baseline hazard model
- Avoids overfitting with a novel random walk prior on spline coefficients
 - Shrinks towards a prior constant baseline hazard
 - Random walk constructed to be invariant to the number and location of knots, and to the timescale
 - Does provide appropriate shrinkage, unlike other priors
 - No shrinkage with Dirichlet (rstanarm, Brilleman 2020)
 - Insufficient shrinkage with random effects (survextrap, Jackson 2024)
 - Avoids the need to fit multiple models (Fractional Polynomials)

Options for modelling non-PH in multinma

- Stratify shape parameters by treatment arm
 - `aux_by = c(.study, .trt)`
 - Fewest assumptions
 - No predictions for unobserved treatment arms
- Treatment effects on shape parameters
 - `aux_regression = ~.trt`
 - Predictions for any treatment in any population
- IPD covariates in NMA model
 - `regression = ~(x1 + x2)*.trt`



NSCLC analysis: network setup

```
# Set up network
nsc1c_net <- set_agd_surv(
  nsc1c_dat,
  study = studyc,
  trt = trtc,
  Surv = Surv(eventtime, status))
```

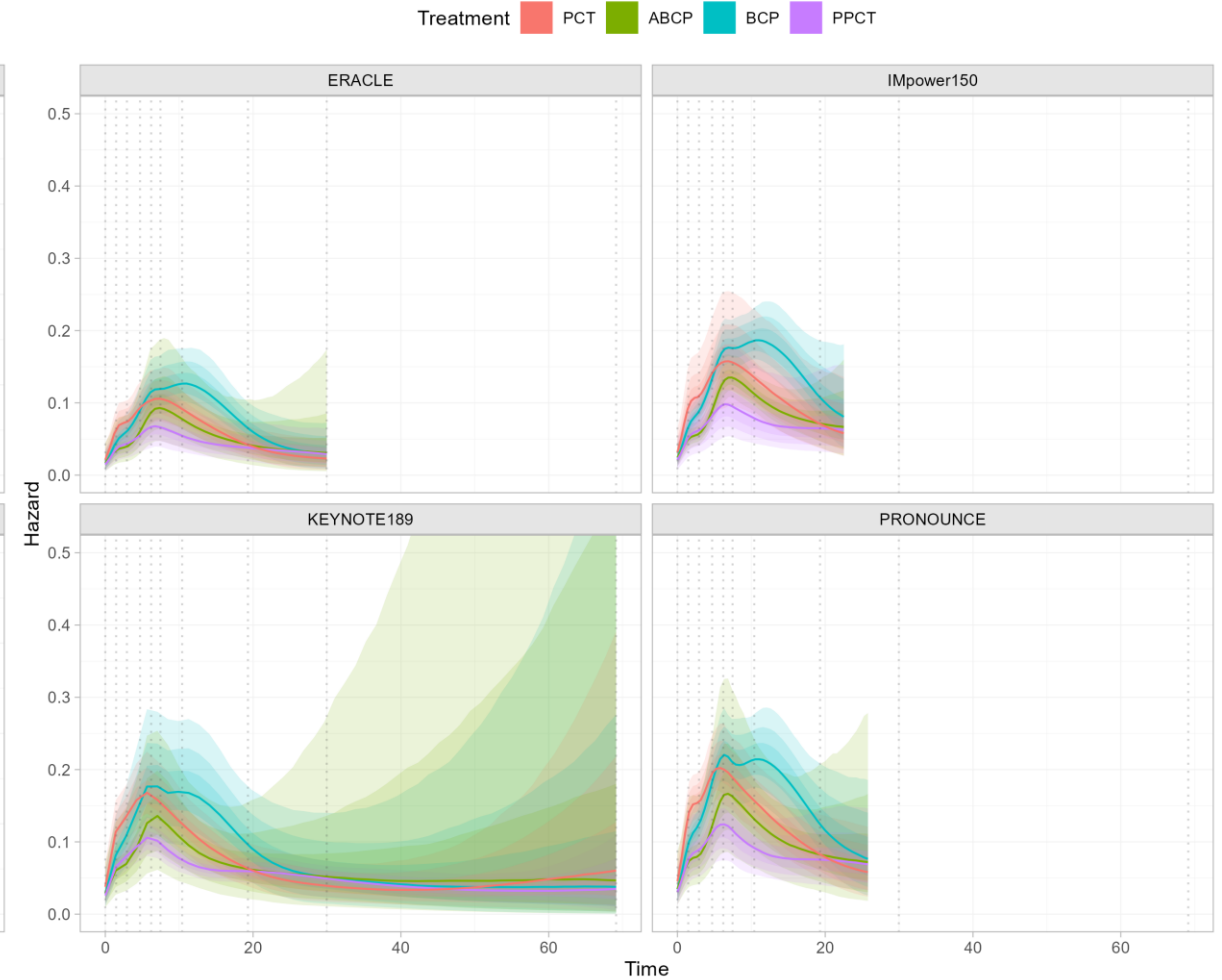
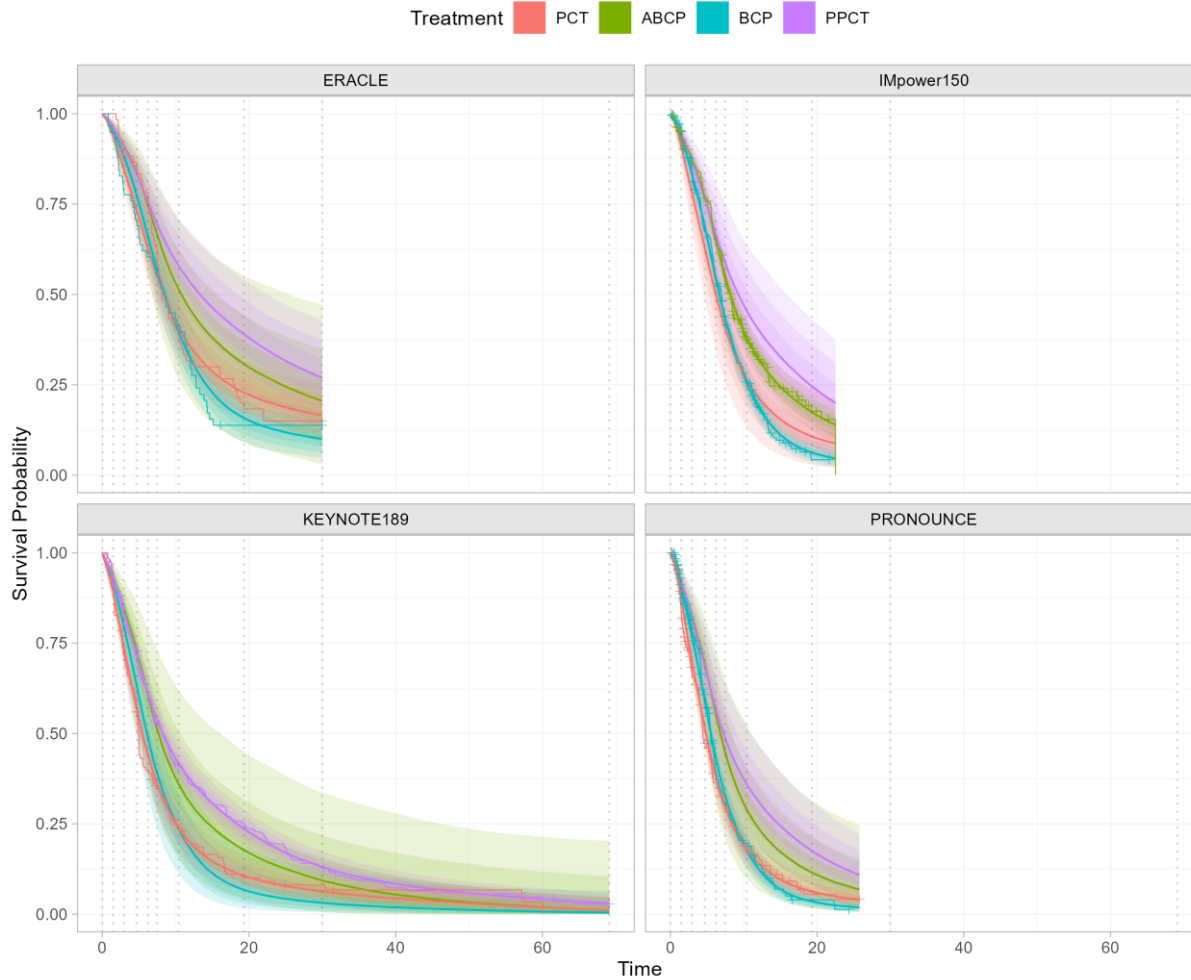
NSCLC analysis: model fitting

```
# Fit non-PH M-spline NMA
nsclc_fit <- nma(nsclc_net,
  likelihood = "mspline",          # M-spline likelihood
  aux_regression = ~.trt,          # Regression on spline coeffs
  prior_intercept = normal(scale = 100), # Priors
  prior_trt = normal(scale = 10),
  prior_aux = half_normal(1),
  prior_aux_reg = half_normal(1))
```

NSCLC analysis: fitted survival and hazard curves

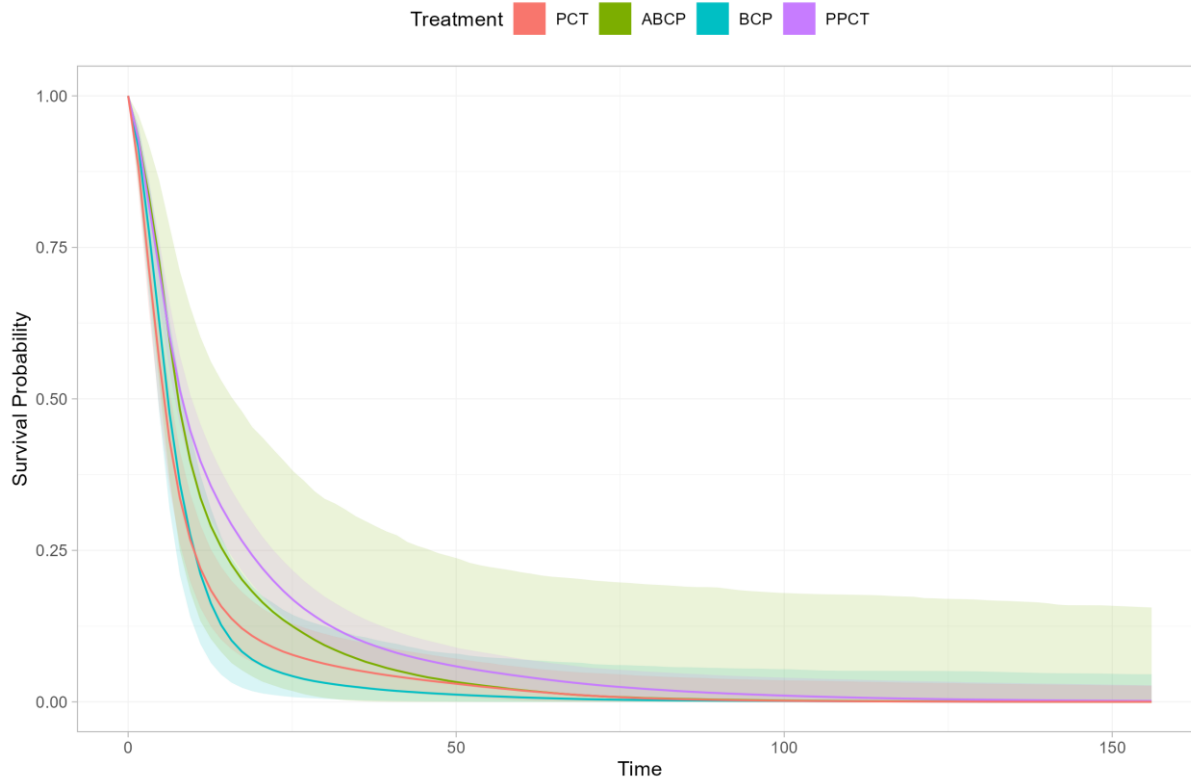
```
plot(predict(nsclc_fit, type = "survival"))
```

```
plot(predict(nsclc_fit, type = "hazard"))
```

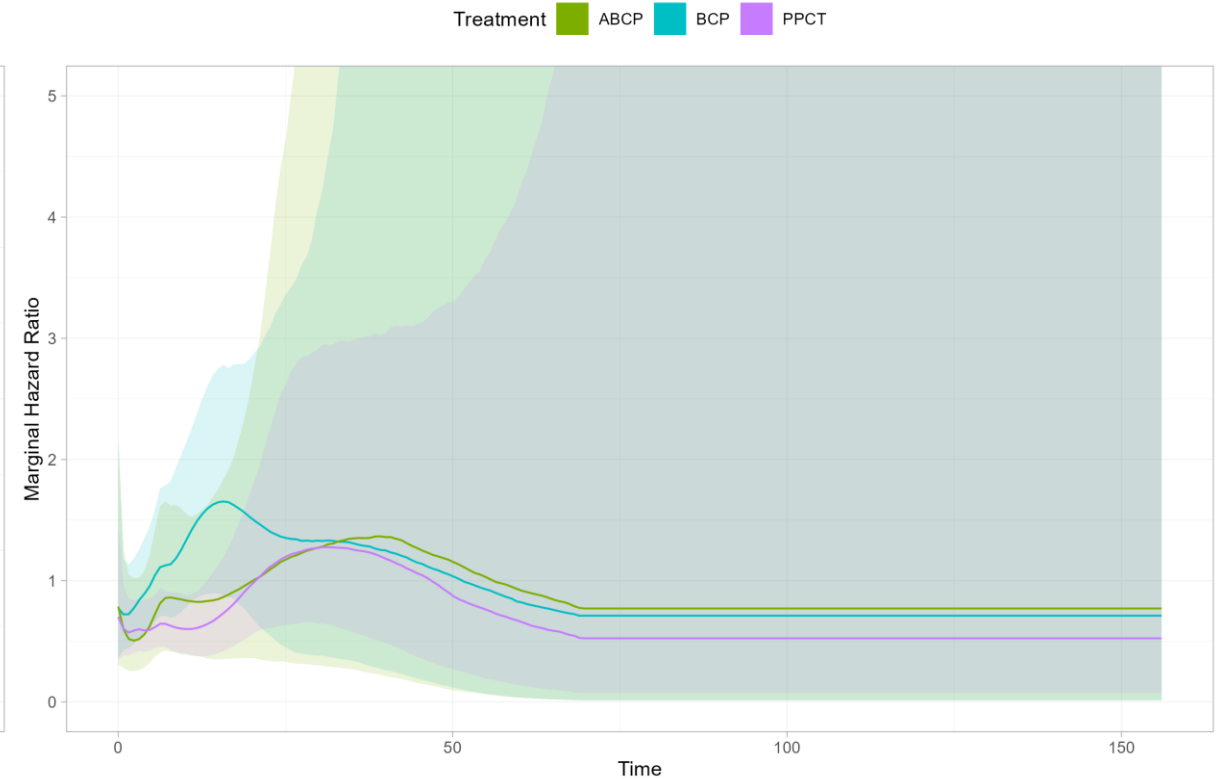


NSCLC analysis: 3-year survival extrapolations and HRs for KEYNOTE

```
plot(predict(nsclc_fit, type = "survival",  
  times = seq(0, 52 * 3, length.out = 100),  
  baseline="KEYNOTE189", aux="KEYNOTE189"))
```



```
plot(marginal_effects(nsclc_fit,  
  type = "hazard", mtype = "ratio",  
  times = seq(0, 52 * 3, length.out = 100),  
  baseline="KEYNOTE189", aux="KEYNOTE189"))
```

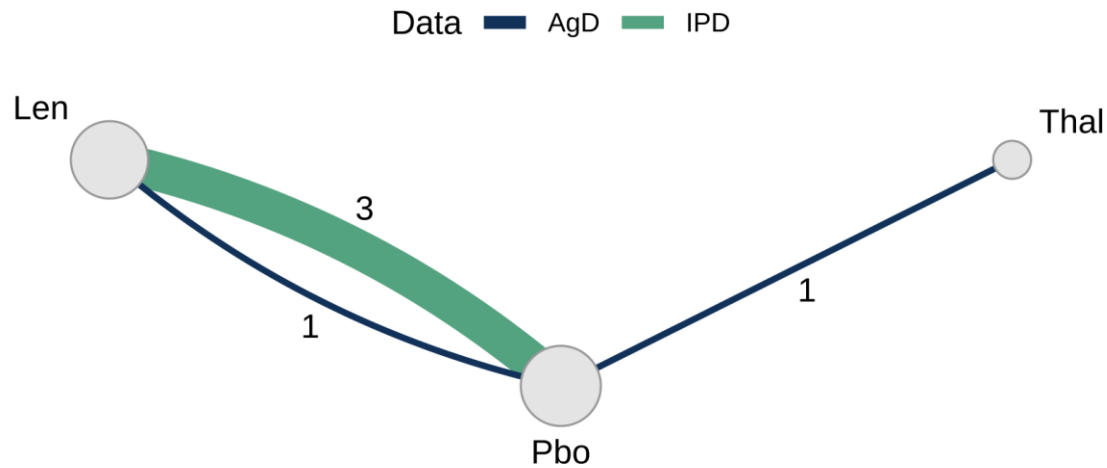


- The `predict()` function can produce:
 - Survival curves
 - Hazard and cumulative hazard curves
 - Median and quantiles of survival times
 - Mean and restricted mean survival times
- The `marginal_effects()` function produces differences or ratios of these, e.g.
 - Time-varying marginal hazard ratios
 - Relative survival ratios over time
 - Differences in RMST or median survival times

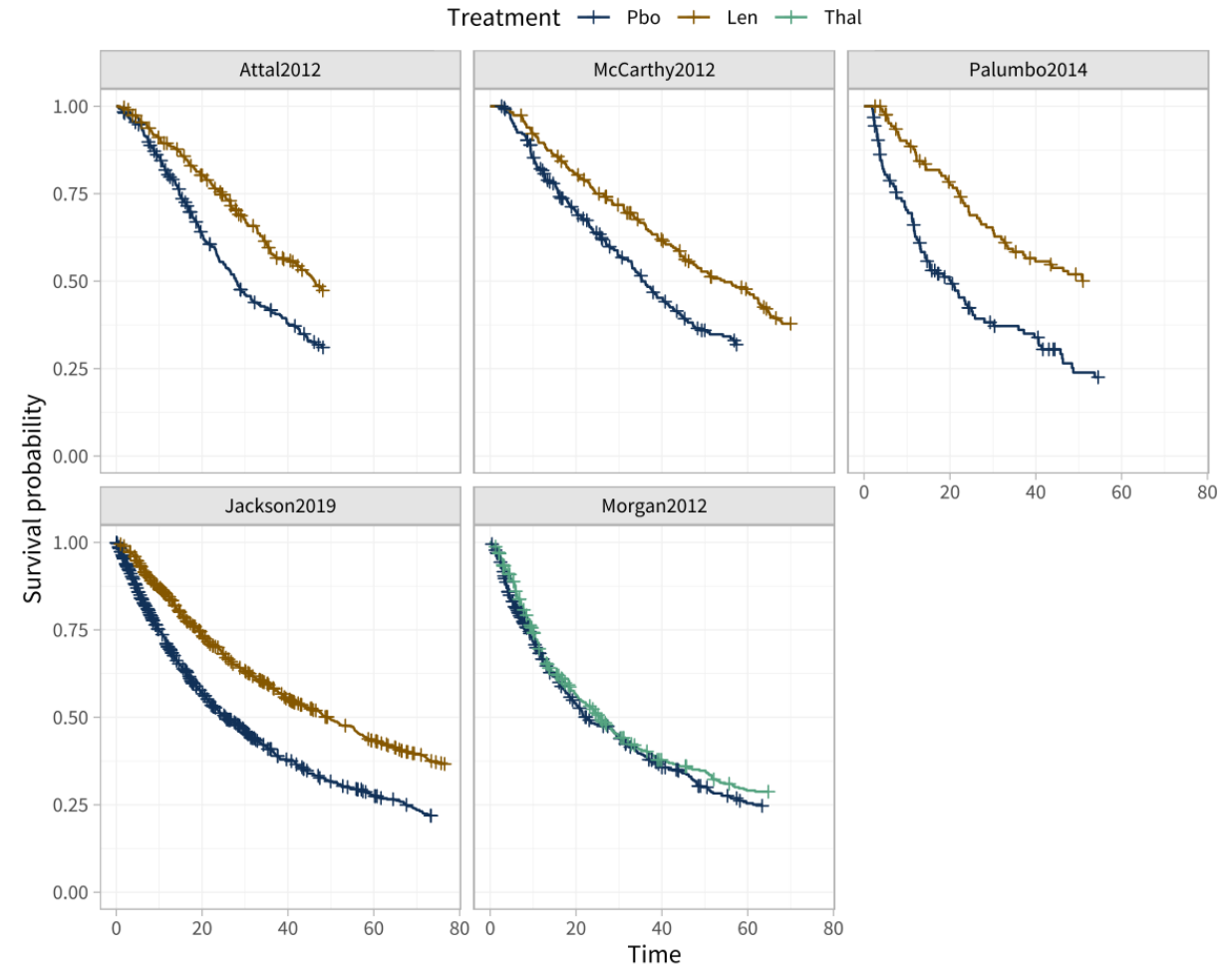
Example: Newly-diagnosed multiple myeloma

- Lenalidomide, Thalidomide, Placebo
- 3 IPD studies, 2 AgD studies
- Four potentially effect-modifying covariates
 - Age, ISS stage, response category, sex

`plot(ndmm_net)`

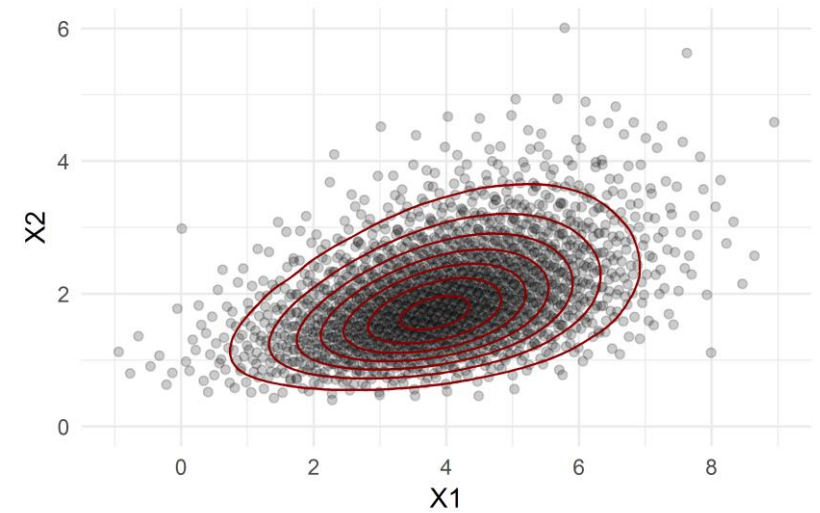


`geom_km()`



Extends full-IPD NMA to coherently incorporate AgD

- Avoids aggregation bias by **integrating** the individual-level model over the aggregate populations
 - Using numerical integration
- Adjust for differences in effect-modifying covariates between populations
- Produce estimates in a target population of interest for decision making



Outline of ML-NMR in multinma

Data Long (“tidy”) format

Network setup

- `set_*`() `combine_network()`

Numerical integration setup

- `add_integration()` `distr()`

Fitting Specify model and prior distributions, run analysis

- `nma()`

Posterior analysis Checking convergence, model fit and comparison, results

- `dic()` `loo::loo()` `loo::waic()`
 - `relative_effects()` `predict()` `marginal_effects()`
 - `posterior_ranks()` `posterior_rank_probs()`
- } `plot()`

NDMM analysis code

```
# 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))
```

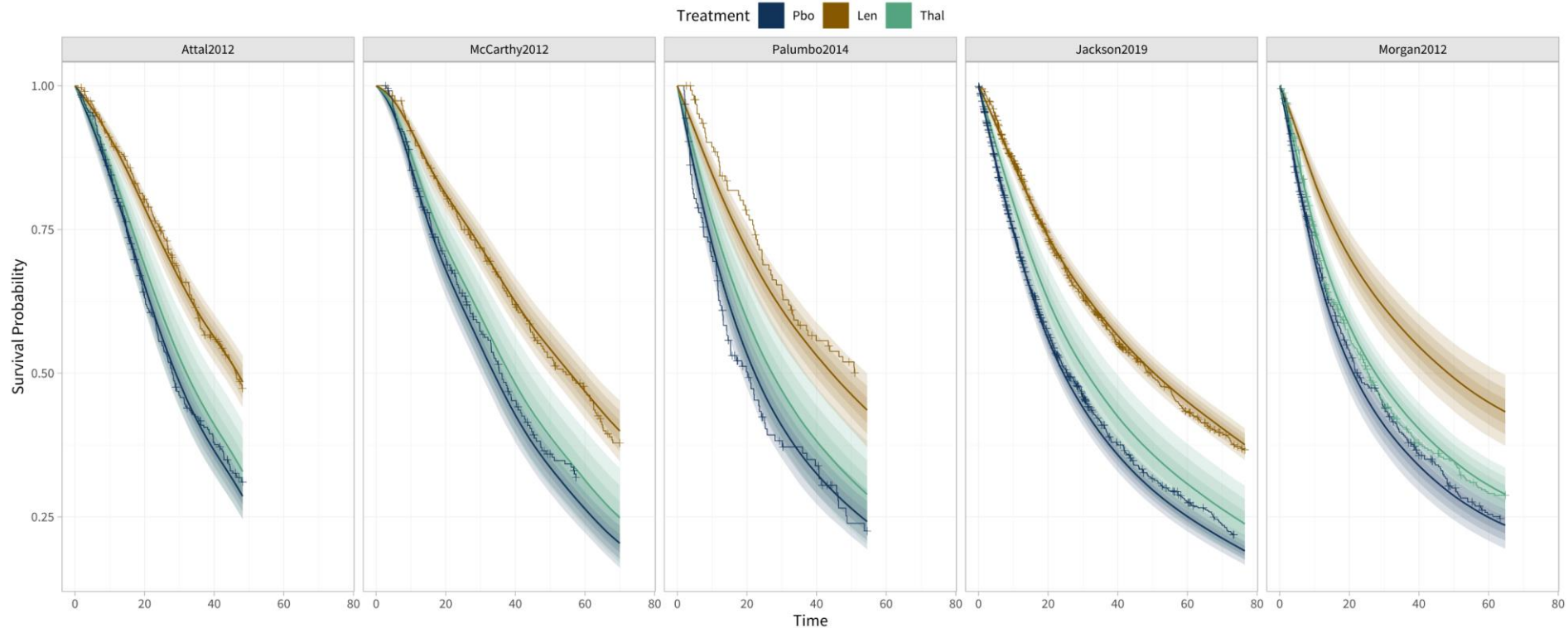
```
set_ipd()
set_agd_surv()
combine_network()
```

```
add_integration()
```

```
nma()
```

Population-average survival curves

```
plot(predict(ndmm_fit, type = "survival"))
```



- Median survival estimates vary by up to a year across populations:
Placebo 20.75 to 33.30 months Thalidomide 26.55 to 38.44 months Lenalidomide 44.95 to 55.92 months
- Evidence of non-PH in unadjusted model, removed by covariate adjustment

Package website

dmphillippo.github.io/multinma



Network meta-analysis models



Source: [R/mma.R](#)
The `nma` function fits network meta-analysis and (multilevel) network meta-regression models in Stan.

Usage

```
nma(  
  network,  
  consistency = c("consistency", "ume", "nodesplit"),  
  trt_effects = c("fixed", "random"),  
  regression = NULL,  
  class_interactions = c("common", "exchangeable", "independent"),  
  likelihood = NULL,  
  link = NULL,  
  ...,  
  nodesplit = get_nodesplits(network, include_consistency = TRUE),  
  prior_intercept = .default(normal(scale = 100)),  
  prior_trt = .default(normal(scale = 10)),  
  prior_het = .default(half_normal(scale = 5)),  
  prior_het_type = c("sd", "var", "prec"),  
  prior_reg = .default(normal(scale = 10)),  
  prior_aux = .default(),  
  prior_aux_reg = .default(),  
  aux_by = NULL,  
  aux_regression = NULL,  
  QR = FALSE,  
  center = TRUE,  
  adapt_delta = NULL,  
  int_thin = 0,  
  int_check = TRUE,  
  mspline_degree = 3,  
  n_knots = 7,  
  knots = NULL,  
  mspline_basis = NULL  
)
```

Arguments

network
An `nma_data` object, as created by the functions `set_*`, `combine_network()`, or `add_integration()`.

consistency
Character string specifying the type of (in)consistency model to fit, either "consistency", "ume", or "nodesplit".

trt_effects
Character string specifying either "fixed" or "random" effects.

regression
A one-sided model formula, specifying the prognostic and effect-modifying terms for a regression model. Any references to treatment should use the `.trt` special variable, for example specifying effect modifier interactions as `variable:.trt` (see details).

class_interactions
Character string specifying whether effect modifier interactions are specified as "common", "exchangeable", or

On this page

- Usage
- Arguments
- Value
- Details
- Likelihoods and link functions
- Auxiliary parameters
- References
- Examples

Overview of Examples



Source: [vignettes/vignette_overview.Rmd](#)
This package contains a number of vignettes, each one walking through an example analysis. The table below gives an overview.

Many of these examples recreate analyses from the series of Technical Support Documents published by the NICE Decision Support Unit ([Dias et al. 2011](#)). The exceptions are atrial fibrillation ([Cooper et al. 2009](#)), white blood cell transfusion ([Turner et al. 2012](#)), and plaque psoriasis multilevel network meta-regression ([Phillippo et al. 2020, 2022](#)).

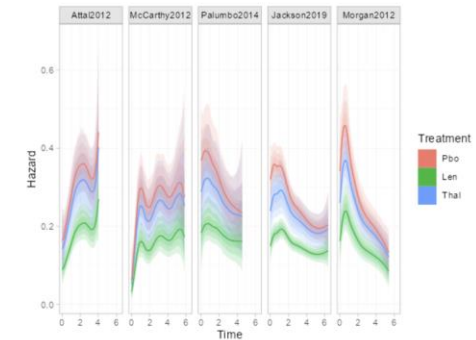
Title	Outcome type	Likelihood	Link function	Notable features
Blocker	Counts	Binomial	logit	Pairwise MA
Dietary fat	Rates	Poisson	log	Analysis of log rate ratios from rate data
Diabetes	Counts with time at risk	Binomial	cloglog	Analysis of log hazard ratios from count data with time at risk
Parkinson's	Continuous	Normal	Identity	Analysis of arm-based data, contrast-based data, and a mixture of both
HTA plaque psoriasis	Ordered	Multinomial (ordered)	probit	Analysis of ordered categorical outcomes
Statins	Counts	Binomial	logit	Meta-regression with subgroups
BCG vaccine	Counts	Binomial	logit	Meta-regression with a continuous covariate, predictive distributions
Smoking cessation	Counts	Binomial	logit	Assessing inconsistency with unrelated mean effects and node-splitting models

Plotting hazards

Let us look at the estimated hazard functions under this model.

By default, the `predict()` function with `type = "hazard"` will produce plots of the population-average marginal hazards (`level = "aggregate"`, which is the default). These can then be plotted using the `plot()` function.

```
plot(predict(ndmm_fit, type = "hazard", level = "aggregate"))
```



We can also look at the individual-level baseline hazards. This is again possible using the `predict()` function, this time with `level = "individual"`. Since we want to show the baseline hazard for the reference level of the covariates, we'll create a data frame to pass to `predict()` as `newdata`.

```
refdat <- tibble(study = ndmm_net$studies,  
  age = ndmm_fit$xbars["age"],  
  iss_stage3 = 0,  
  response_cr_vgpr = 0,  
  male = 0)
```

Since we are providing a new data frame for prediction, we also need to provide the times to predict at and the distributions of the baseline (intercept) and auxiliary (spline coefficient) parameters. We will predict at evenly spaced times between time 0 and the last event/censoring time in each study. We specify a named list of the study names for both `baseline` and `aux`, to use the posterior distributions from each study for these parameters.

```
# At evenly spaced times between the boundary knots  
tdat <- purrr::imap_dfr(ndmm_fit$basis,  
  ~tibble(study = factor(.y, levels = ndmm_net$studies),  
    lower = attr(.x, "boundary.knots")[1],  
    upper = attr(.x, "boundary.knots")[2],  
    times = seq(lower, upper, length = 50)))  
refdat <- left_join(refdat, tdat, by = "study")  
studies <- as.list(setNames(nm = levels(ndmm_net$studies)))
```

Then we produce the predictions and plot:

On this page

- Setup data
- Setup
- ML-NMR models with M-spline baseline hazards
- Plotting hazards
- Assessing the proportional hazards assumption
- Comparison to unadjusted NMA
- Producing population-average estimates
- References

Summary

- multinma is a comprehensive suite of tools for NMA and ML-NMR with AgD, IPD, or mixtures of both
- Now with survival analysis features
 - Parametric and flexible models, non-PH modelling
 - Without complex bespoke modelling code
- ML-NMR coherently combines IPD and AgD, produces population-adjusted estimates in specific target populations for decision making
- M-spline baseline hazards are a novel approach with advantages over alternative flexible methods
 - Provide appropriate shrinkage via random walk prior
 - Closed form likelihood, single model fit (unlike Fractional Polynomials)

Funding and References



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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. (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 et al. (2024) Multilevel network meta-regression for general likelihoods: synthesis of individual and aggregate data with applications to survival analysis. Preprint, *arXiv:2401.12640* [stat.ME]

Phillippo DM (2024). *multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data*. R package version 0.7.0. DOI: 10.5281/zenodo.3904454. URL: dmphillippo.github.io/multinma. CRAN: cran.r-project.org/package=multinma