rnmamod: An R Package for Conducting Bayesian Network Meta-analysis with Missing Participants

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Abstract The development of several R packages for conducting network meta-analysis has enhanced the popularity of this evidence synthesis tool. The available R packages facilitate the implementation of most models to conduct and evaluate network meta-analysis and provide the necessary results, conforming to the PRISMA-NMA statement. The rnmamod package is a novel contribution to conducting aggregate network meta-analysis using Bayesian methods, as it allows addressing missing participants properly in all models, even if a handful of the included studies report this information. Importantly, rnmamod is the first R package to offer a rich, user-friendly visualisation toolkit that turns a "parameter-dense" output of network meta-analysis into several comprehensive graphs. Furthermore, the package functions on various models allow processing their output to create visualisations tailored to the user preferences. Therefore, rnmamod aids the thorough appraisal and interpretation of the results, the cross-comparison of different models and the manuscript preparation for journal submission.

Introduction

Evidence-based medicine is the backbone of informed decisions for the benefit of the patients, stemming from a meticulous and judicious use of the available evidence, while taking into account also the clinical experience and patient values (Sackett et al. 1996). However, the medical community is faced daily with several intervention options and dosages, challenging the optimal practice of evidence-based medicine (Lee 2022). Systematic reviews with pairwise meta-analysis summarise the evidence of pairs of interventions, providing fragmented evidence that does not serve the clinical needs. Moreover, evidence in the comparability of different interventions at the trial level is also fragmented, as it is not feasible to compare all intervention options for a condition in one trial. These limitations led to the development and later establishment of network meta-analysis (NMA), also known as multiple treatment comparison, a new generation evidence synthesis tool (Salanti 2012). Network meta-analysis is an extension of pairwise meta-analysis for collecting all relevant pieces of evidence for a specific condition, patient population, and intervention options to provide coherent evidence for all possible intervention comparisons, and allow ordering the investigated interventions from the best to worst option for a specific outcome (Caldwell 2014). Indirect evidence (obtained from different sets of trials sharing a common comparator) plays a central role in the development and prominence of NMA.

Since the introduction of indirect evidence and early development of the relevant methodology (Higgins and Whitehead 1996; Bucher et al. 1997), the NMA framework has undergone substantial progress conceptually and methodologically. The fast-pace publications of relevant methodological articles and systematic reviews with NMA attest to the increasing popularity of NMA in the wide medical and evidence synthesis community (Efthimiou et al. 2016; Petropoulou et al. 2017). Needless to say that the availability of statistical analysis software is the driving force to the advances and wide dissemination of NMA. A review of the methodology and software for NMA (Efthimiou et al. 2016) listed several statistical software tools used to promote NMA, with the **R** software (R Core Team 2022) being the most popular to develop and compare methods for NMA, followed by **Stata** (StataCorp 2021) and **SAS software** (SAS Institute 2020).

In the last decade, there has been a raise in the R packages for NMA with various functionalities (Dewey and Viechtbauer 2022). These packages can be categorised by, among others:

- *the analysis framework*: **frequentist** (**netmeta** (Rücker et al. 2022), and **NMAoutlier** (Petropoulou et al. 2027)), **Bayesian** (**bnma** (Seo and Schmid 2022), **gemtc** (van Valkenhoef and Kuiper 2021), **metapack** (Lim et al. 2022), **multinma** (David M. Phillippo 2022), **NMADiagT** (Lu et al. 2020), **nmaINLA** (Guenhan 2021), and **pcnetmeta** (Lin et al. 2017)), or **both** (**nmaplateplot** (Z. Wang et al. 2021), **nmarank** (Nikolakopoulou, Schwarzer, and Papakonstantinou 2021) which is mainly frequentist-driven but can be easily applied to Bayesian results (Papakonstantinou et al. 2022), and **nmathresh** (David M. Phillippo et al. 2018) which is mainly Bayesian-driven but can be naturally applied to the frequentist framework);
- *the assumed distribution of the input data*: exact distribution, known as **one-stage approach** (typical in the Bayesian framework), or normality approximation, known as **two-stage approach** (typical

in the frequentist framework);
- *the modeling approach*: **arm-based** (**NMADiagT** (Lu et al. 2020), and **pcnetmeta** (Lin et al. 2017)), or **contrast-based** (the remaining R packages);
- *the scope breadth*: **address part of the NMA framework** (**metapack** (Lim et al. 2022), **NMADiagT** (Lu et al. 2020), **NMAoutlier** (Petropoulou et al. 2027), **nmaplateplot** (Z. Wang et al. 2021), **nmarank** (Nikolakopoulou, Schwarzer, and Papakonstantinou 2021), and **nmathresh** (David M. Phillippo et al. 2018)) or **conduct NMA and assess heterogeneity and inconsistency** (the remaining R packages);
- *the outcome structure*: **mixture of aggregate and individual patient data** (**multinma** (David M. Phillippo 2022)) or **aggregate data** only (the remaining R packages)); and
- *the outcome data type*: **binary**, **continuous**, **multinomial** (**bnma** (Seo and Schmid 2022) only), and so on. See Table 1.

Most packages fall into many categories. For instance, **gemtc** (van Valkenhoef and Kuiper 2021), probably the most popular R package for Bayesian NMA, allows both for one-stage and two-stage approaches using contrast-based modeling, has a wide scope, and deals with aggregate outcome data of many types. **netmeta** (Rücker et al. 2022) is currently the only R package developed exclusively for NMA in the frequentist framework based on the graph theory (Ruecker 2012), allows only for a two-stage approach (contrast-based modeling), has also a wide scope, and accommodates binary, rates, and continuous aggregate outcome data. On the other side, R packages, such as **nmathresh** (David M. Phillippo et al. 2018), **nmaplateplot** (Z. Wang et al. 2021), and **nmarank** (Nikolakopoulou, Schwarzer, and Papakonstantinou 2021) do not perform NMA, but use the NMA results (obtained using other R packages or statistical software tools) as an input to provide, for instance, decision-invariant bias-adjustment thresholds and intervals (**nmathresh** (David M. Phillippo et al. 2018)), various league tables in heatplot style with all intervention comparisons (**nmaplateplot** (Z. Wang et al. 2021)), or an intervention hierarchy approach tailored to the research question (**nmarank** (Nikolakopoulou, Schwarzer, and Papakonstantinou 2021)).

Due to the complexity and the wide scope of NMA, the researchers are faced with a large volume of results, necessary to understand the evidence base, assess the underlying assumptions, evaluate the quality of the estimated parameters (model diagnostics), and properly answer the research question, for instance, concerning the comparative effectiveness of the competing interventions and their hierarchy. To address the challenges associated with the best reporting of NMA results, the PRISMA-NMA statement (Hutton et al. 2015) was developed expanding on the PRISMA statement for pairwise meta-analysis (Page et al. 2021) to provide an extensive checklist with the essential items pertaining to the NMA results, ensuring completeness in the reporting of systematic reviews with multiple interventions. The R packages **PRISMAstatement** (Wasey 2019) and **metagear** (Lajeunesse 2021) facilitate the creation of the PRISMA flow chart and the process of article screening and data extraction, conforming to the PRISMA statement (Page et al. 2021), and are also relevant for systematic reviews with multiple interventions. The additional items in the PRISMA-NMA statement that apply to the NMA framework, such as presentation and summary of network geometry, inconsistency assessment, league tables and presentation of intervention hierarchy, are addressed in most R packages either in a targeted manner (e.g., **nmaplateplot** (Z. Wang et al. 2021), and **nmarank** (Nikolakopoulou, Schwarzer, and Papakonstantinou 2021)) or collectively (**bnma** (Seo and Schmid 2022), **netmeta** (Rücker et al. 2022), **gemtc** (van Valkenhoef and Kuiper 2021), and **pcnetmeta** (Lin et al. 2017)).

Most methodological studies on and systematic reviews with NMA have implemented Bayesian methods (Efthimiou et al. 2016; Petropoulou et al. 2017). The advantages of the Bayesian framework (e.g., flexible modeling, allowance of uncertainty in all model parameters, incorporation of external relevant information and facilitation of probabilistic statements) (Sutton and Abrams 2001), in conjunction with the dominance of the BUGS software (Lunn et al. 2009) during the springtime of the NMA framework, may be attributed to the popularity of Bayesian NMA. The rise of R packages on Bayesian NMA also demonstrates the acclaim of Bayesian methods from the evidence synthesis community. The rest of the section pertains to R packages on Bayesian NMA published in the **CRAN Task View 'Meta-Analysis'** (Dewey and Viechtbauer 2022) that feature a wide methodological and reporting scope: **bnma** (Seo and Schmid 2022), **gemtc** (van Valkenhoef and Kuiper 2021), **pcnetmeta** (Lin et al. 2017), and **rnmamod** (Spineli 2022) (a recent novel contribution).

The R packages **bnma** (Seo and Schmid 2022), **gemtc** (van Valkenhoef and Kuiper 2021), and **pcnetmeta** (Lin et al. 2017) conduct hierarchical NMA using Markov chain Monte Carlo methods through the JAGS program (Plummer 2003). However, these packages differ in their methodological and reporting breadth to some extent: **bnma** (Seo and Schmid 2022) and **gemtc** (van Valkenhoef and Kuiper 2021) have a greater common basis on methods and outputs than **pcnetmeta** (Lin et al. 2017). This may be attributed to using the contrast-based modeling approach, which is the established approach to meta-analysis (trial-specific relative treatment effects, such as log odds ratio, are pooled across the trials), whilst **pcnetmeta** (Lin et al. 2017) considers the arm-based modeling approach, which deviates from the standard meta-analysis practice (Dias and Ades 2016) and is less

Table 1: Features of R packages for network meta-analyses (CRAN Task View)

Package	Analysis		Modeling approach		Scope breadth		Outcome structure	
	Bayesian	Frequentist	Contrast	Arm	Wide	Narrow	AD & IPD	AD
bnma	X		X		X		X	
gemtc	X		X		X		X	
metapack	X		X			X	X	
multinma^{1}	X		X		X			X
netmeta		X	X		X		X	
NMADiagT	X			X		X	X	
nmaINLA^{2}	X		X		X		X	
NMAoutlier		X	X			X	X	
nmaplateplot	X	X	X			X	X	
nmarank^{3}	X	X	X			X	X	
nmathresh^{4}	X	X	X			X	X	
pcnetmeta	X			X	X		X	

Note:

AD, aggregate data; IPD, individual patient data.

[1] Estimation using the probabilistic programming language Stan.

[2] Use of integrated nested Laplace approximation.

[3] Mainly frequentist-driven but can be easily applied to Bayesian results.

[4] Mainly Bayesian-driven but can be naturally applied to the frequentist framework.

widespread. Currently, the package **pcnetmeta** (Lin et al. 2017) does not contain any function to conduct inconsistency evaluation and meta-regression, is limited only to rankograms in terms of hierarchy measures (Salanti et al. 2022), and considers only the trace plots as a visual diagnostic tool. On the contrary, **bnma** (Seo and Schmid 2022) and **gemtc** (van Valkenhoef and Kuiper 2021) offer at least one method for inconsistency evaluation, allow conducting meta-regression and consider a wider variety of hierarchy measures and diagnostic tools. However, all three R packages provide a small-sized toolkit with functions regarding the presentation of the relative treatment effects: a league table for one outcome that appears only in the console, and a forest-plot or table on the relative treatment effects of all comparisons with the selected intervention.

Furthermore, other common features of the R packages **bnma** (Seo and Schmid 2022), **gemtc** (van Valkenhoef and Kuiper 2021), and **pcnetmeta** (Lin et al. 2017) include: (i) the undue reliance on the function `print()` (the results appear in the console) than visualisation, and (ii) presenting the results mostly in isolation, restricting the ability to gain further insights into the performance of the NMA models and contextualise the results in the light of the strengths and limitations in the analysis. The package

rnmamod provides 'dynamic' graphs by combining plots.

Background

Some packages on interactive graphics include **plotly** (Sievert 2020) that interfaces with Javascript for web-based interactive graphics, **crosstalk** (Cheng and Sievert 2021) that specializes cross-linking elements across individual graphics. The recent R Journal paper **tsibbletalk** (E. Wang and Cook 2021) provides a good example of including interactive graphics into an article for the journal. It has both a set of linked plots, and also an animated gif example, illustrating linking between time series plots and feature summaries.

Customizing tooltip design with ToOoOlTiPs

ToOoOlTiPs is a packages for customizing tooltips in interactive graphics, it features these possibilities.

A gallery of tooltips examples

The **palmerpenguins** data (Horst, Hill, and Gorman 2020) features three penguin species which has a lovely illustration by Alison Horst in Figure 1.

Table 2 prints at the first few rows of the `penguins` data:

Figure 2 shows an plot of the penguins data, made using the **ggplot2** package.

```
penguins %>%
```

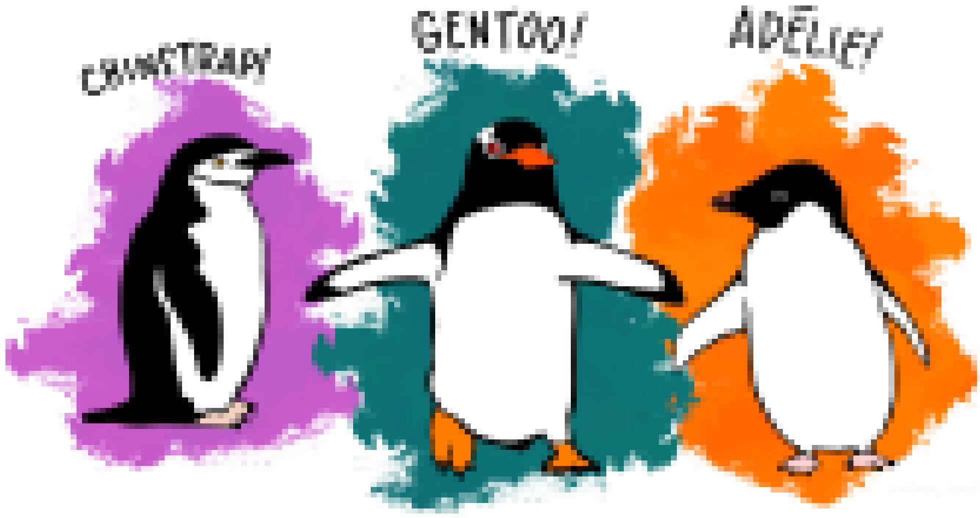

Figure 1: Artwork by allison_horst

Table 2: A basic table

species	island	bill_length_mm	bill_depth_mm	flipper_length_mm	body_mass_g	sex	year
Adelie	Torgersen	39.1	18.7	181	3750	male	2007
Adelie	Torgersen	39.5	17.4	186	3800	female	2007
Adelie	Torgersen	40.3	18.0	195	3250	female	2007
Adelie	Torgersen	NA	NA	NA	NA	NA	2007
Adelie	Torgersen	36.7	19.3	193	3450	female	2007
Adelie	Torgersen	39.3	20.6	190	3650	male	2007

```
ggplot(aes(x = bill_depth_mm, y = bill_length_mm,
           color = species)) +
geom_point()
```

Summary

We have displayed various tooltips that are available in the package **ToOoOlTiPs**.

References

Bucher, H C, G H Guyatt, L E Griffith, and S D Walter. 1997. "The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials." *J Clin Epidemiol* 50 (6): 683–91. https://doi.org/10.1016/s0895-4356(97)00049-8.

Caldwell, Deborah M. 2014. "An Overview of Conducting Systematic Reviews with Network Meta-Analysis." *Syst Rev* 3: 109. https://doi.org/10.1186/2046-4053-3-109.

Cheng, Joe, and Carson Sievert. 2021. *crosstalk: Inter-Widget Interactivity for HTML Widgets*. https://CRAN.R-project.org/package=crosstalk.

Dewey, Michael, and Wolfgang Viechtbauer. 2022. *CRAN Task View: Meta-Analysis*. https://CRAN.R-project.org/view=MetaAnalysis.

Dias, Sofia, and A E Ades. 2016. "Absolute or Relative Effects? Arm-Based Synthesis of Trial Data." *Res Synth Methods* 7 (1): 23–28. https://doi.org/10.1002/jrsm.1184.

Efthimiou, Orestis, Thomas P. A. Debray, Gert van Valkenhoef, Sven Trelle, Klea Panayidou, Karel G. M. Moons, Johannes B. Reitsma, Aijing Shang, Georgia Salanti, and GetReal Methods Review Group. 2016. "GetReal in Network Meta-Analysis: A Review of the Methodology." *Res Synth Methods* 7 (3): 236–63. https://doi.org/10.1002/jrsm.1195.

Guenhan, Burak Kuersad. 2021. *nmaINLA: Network Meta-Analysis Using Integrated Nested Laplace Approximations*. https://CRAN.R-project.org/package=nmaINLA.

Higgins, J P, and A Whitehead. 1996. "Borrowing Strength from External Trials in a Meta-Analysis." *Stat Med* 15 (24): 2733–49.

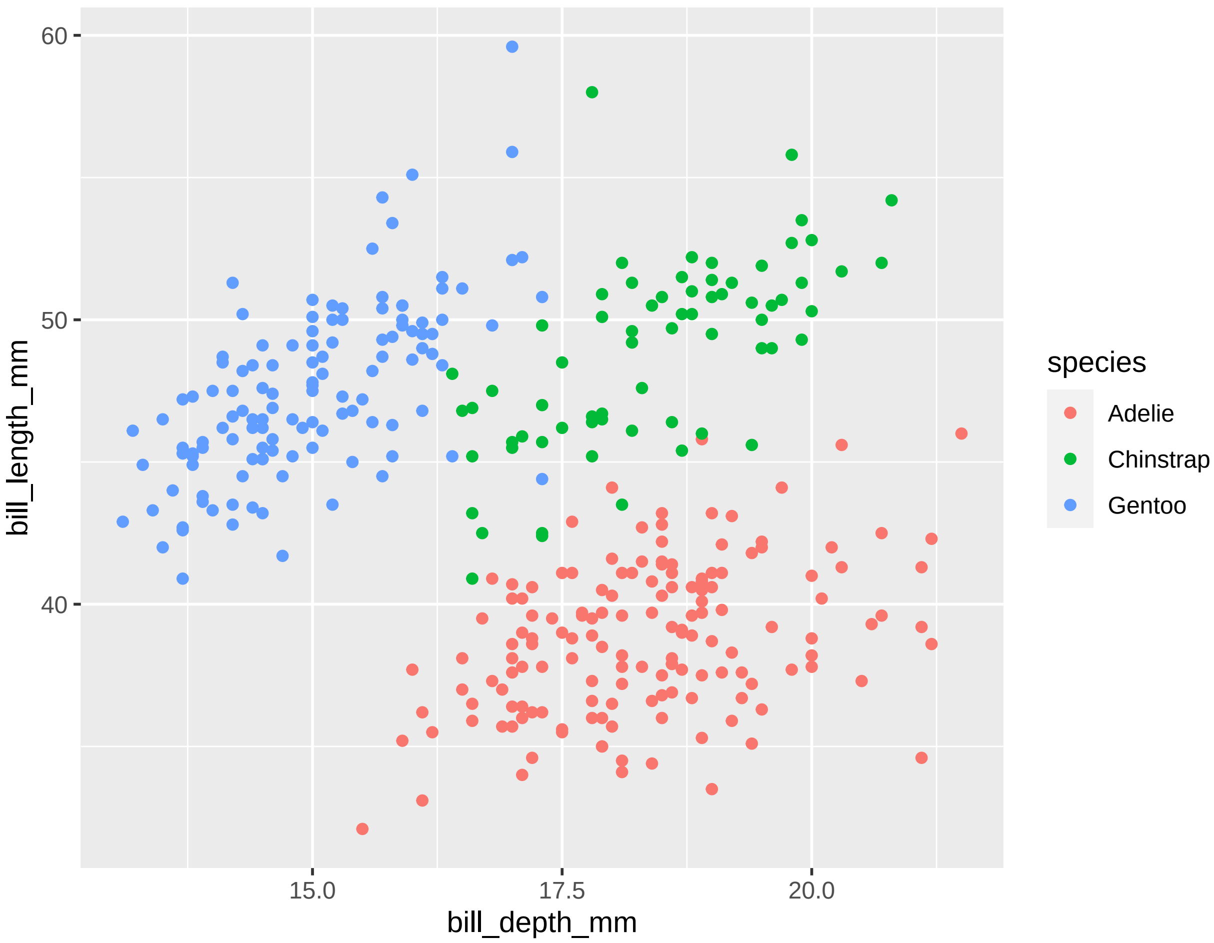

Figure 2: A basic non-interactive plot made with the ggplot2 package on palmer penguin data. Three species of penguins are plotted with bill depth on the x-axis and bill length on the y-axis. Visit the online article to access the interactive version made with the plotly package.

Horst, Allison Marie, Alison Presmanes Hill, and Kristen B Gorman. 2020. *palmerpenguins: Palmer Archipelago (Antarctica) Penguin Data*. https://allisonhorst.github.io/palmerpenguins/.

Hutton, Brian, Georgia Salanti, Deborah M Caldwell, Anna Chaimani, Christopher H Schmid, Chris Cameron, John P A Ioannidis, et al. 2015. "The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions: Checklist and Explanations." *Ann Intern Med* 162 (11): 777–84. https://doi.org/10.7326/M14-2385.

Lajeunesse, Marc J. 2021. *Metagear: Comprehensive Research Synthesis Tools for Systematic Reviews and Meta-Analysis*. https://CRAN.R-project.org/package=metagear.

Lee, Andrew. 2022. "The Development of Network Meta-Analysis." *J R Soc Med* 115 (8): 313–21. https://doi.org/10.1177/01410768221113196.

Lim, Daeyoung, Ming-Hui Chen, Sungduk Kim, Joseph Ibrahim, Arvind Shah, and Jianxin Lin. 2022. *Metapack: Bayesian Meta-Analysis and Network Meta-Analysis*. https://CRAN.R-project.org/package=metapack.

Lin, Lifeng, Jing Zhang, James S. Hodges, and Haitao Chu. 2017. "Performing Arm-Based Network Meta-Analysis in R with the pcnetmeta Package." *Journal of Statistical Software* 80 (5): 1–25. https://doi.org/10.18637/jss.v080.i05.

Lu, Boyang, Qinshu Lian, James S. Hodges, Yong Chen, and Haitao Chu. 2020. *NMADiagT: Network Meta-Analysis of Multiple Diagnostic Tests*. https://CRAN.R-project.org/package=NMADiagT.

Lunn, David, David Spiegelhalter, Andrew Thomas, and Nicky Best. 2009. "The BUGS Project: Evolution, Critique and Future Directions." *Stat Med* 28 (25): 3049–67. https://doi.org/10.1002/sim.3680.

Nikolakopoulou, Adriani, Guido Schwarzer, and Theodoros Papakonstantinou. 2021. *Nmarank: Complex Hierarchy Questions in Network Meta-Analysis*. https://CRAN.R-project.org/package=nmarank.

Page, Matthew J, Joanne E McKenzie, Patrick M Bossuyt, Isabelle Boutron, Tammy C Hoffmann, Cynthia D Mulrow, Larissa Shamseer, et al. 2021. "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews." *BMJ* 372: n71. https://doi.org/10.1136/bmj.n71.

Papakonstantinou, Theodoros, Georgia Salanti, Dimitris Mavridis, Gerta Rücker, Guido Schwarzer, and Adriani Nikolakopoulou. 2022. "Answering Complex Hierarchy Questions in Network Meta-Analysis." *BMC Med Res Methodol* 22 (1): 47. https://doi.org/10.1186/s12874-021-01488-3.

Petropoulou, Maria, Adriani Nikolakopoulou, Areti-Angeliki Veroniki, Patricia Rios, Afshin Vafaei, Wasifa Zarin, Myrsini Giannatsi, et al. 2017. "Bibliographic Study Showed Improving Statistical Methodology of Network Meta-Analyses Published Between 1999 and 2015." *J Clin Epidemiol* 82: 20–28. https://doi.org/10.1016/j.jclinepi.2016.11.002.

Petropoulou, Maria, Guido Schwarzer, Agapios Panos, and Dimitris Mavridis. 2027. *NMAoutlier: Detecting Outliers in Network Meta-Analysis*. https://CRAN.R-project.org/package=NMAoutlier.

Phillippo, David M. 2022. *Multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data*. https://CRAN.R-project.org/package=multinma.

Phillippo, David M, Sofia Dias, A E Ades, Vanessa Didelez, and Nicky J Welton. 2018. "Sensitivity of Treatment Recommendations to Bias in Network Meta-Analysis." *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 181 (3): 843–67. https://doi.org/10.1111/rssa.12341.

Plummer, Martyn. 2003. *JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling*. Edited by Kurt Hornik, Friedrich Leisch, and Achim Zeileis. Technische Universität Wien, Vienna, Austria. https://www.R-project.org/conferences/DSC-2003/Proceedings/Plummer.pdf.

R Core Team. 2022. *R: A Language and Environment for Statistical Computing. Foundation for Statistical Computing, Vienna, Austria*. https://www.R-project.org/.

Rücker, Gerta, Ulrike Krahn, Jochem König, Orestis Efthimiou, Annabel Davies, Theodoros Papakonstantinou, and Guido Schwarzer. 2022. *Netmeta: Network Meta-Analysis Using Frequentist Methods*. https://CRAN.R-project.org/package=netmeta.

Ruecker, Gerta. 2012. "Network Meta-Analysis, Electrical Networks and Graph Theory." *Res Synth Methods* 3 (4): 312–24. https://doi.org/10.1002/jrsm.1058.

Sackett, David L, William M Rosenberg, J A Gray, R B Haynes, and W S Richardson. 1996. "Evidence Based Medicine: What It Is and What It Isn't." *BMJ* 312 (7023): 71–72. https://doi.org/10.1136/bmj.312.7023.71.

Salanti, Georgia. 2012. "Indirect and Mixed-Treatment Comparison, Network, or Multiple-Treatments Meta-Analysis: Many Names, Many Benefits, Many Concerns for the Next Generation Evidence Synthesis Tool." *Res Synth Methods* 3 (2): 80–97. https://doi.org/10.1002/jrsm.1037.

Salanti, Georgia, Adriani Nikolakopoulou, Orestis Efthimiou, Dimitris Mavridis, Matthias Egger, and Ian R White. 2022. "Introducing the Treatment Hierarchy Question in Network Meta-Analysis." *Am J Epidemiol* 191 (5): 930–38. https://doi.org/10.1093/aje/kwab278.

SAS Institute. 2020. *The SAS System for Windows. Release 9.4. Cary, NC: SAS Inst*. https://www.sas.com.

Seo, Michael, and Christopher Schmid. 2022. *Bnma: Bayesian Network Meta-Analysis Using 'JAGS'*. https://CRAN.R-project.org/package=bnma.

Sievert, Carson. 2020. *Interactive Web-Based Data Visualization with r, Plotly, and Shiny*. Chapman;

Hall/CRC. https://plotly-r.com.

Spineli, Loukia M. 2022. *Rnmamod: Bayesian Network Meta-Analysis with Missing Participants*. https://CRAN.R-project.org/package=rnmamod.

StataCorp. 2021. *Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC*. http://www.stata.com.

Sutton, Alex J, and Keith R Abrams. 2001. "Bayesian Methods in Meta-Analysis and Evidence Synthesis." *Stat Methods Med Res* 10 (4): 277–303. https://doi.org/10.1177/096228020101000404.

van Valkenhoef, Gert, and Joel Kuiper. 2021. *Gemtc: Network Meta-Analysis Using Bayesian Methods*. https://CRAN.R-project.org/package=gemtc.

Wang, Earo, and Dianne Cook. 2021. "Conversations in Time: Interactive Visualisation to Explore Structured Temporal Data." *The R Journal*. https://doi.org/10.32614/RJ-2021-050.

Wang, Zhenxun, Lifeng Lin, Shanshan Zhao, and Haitao Chu. 2021. *Nmaplateplot: The Plate Plot for Network Meta-Analysis Results*. https://CRAN.R-project.org/package=nmaplateplot.

Wasey, Jack O. 2019. *PRISMAstatement: Plot Flow Charts According to the "PRISMA" Statement*. https://CRAN.R-project.org/package=PRISMAstatement.

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