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SOFTWARE FOCUS

NMA: Network meta-analysis based on multivariate meta-analysis and meta-regression models in R

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Abstract

Network meta-analysis has become an established methodology within systematic reviews for comparing the effectiveness of multiple treatments and is now a standard approach in comparative effectiveness research. However, the underlying statistical methods are often highly technical for non-statisticians in practice. To complement existing software, we developed `NMA`, a comprehensive R package organized around the multivariate meta-analysis and meta-regression framework and designed to provide a broad range of analytical and graphical tools through simple commands. The `NMA` package provides tools for evidence synthesis, network meta-regression, assessment of heterogeneity and inconsistency, comparative effectiveness analyses, and graphical visualization. It also incorporates higher-order inferential and prediction procedures and data-handling functions that facilitate the integration of arm-level data and summary effect estimates. In this article, we provide a gentle introduction to the `NMA` package and illustrate its application through a case study of a network meta-analysis of antihypertensive drugs.

Highlights

What is already known?

- Several freely available computational packages provide powerful and flexible tools for network meta-analysis. The multivariate meta-analysis and meta-regression framework[1–3] provides a general frequentist formulation for evidence synthesis and inconsistency assessment.

What is new?

- We developed `NMA`, an R package organized around the multivariate meta-analysis and meta-regression framework and designed to complement existing software.
- The `NMA` package brings together a broad range of functions for evidence synthesis, heterogeneity and inconsistency assessment, comparative effectiveness analysis, and graphical visualization within a common analytical workflow.

This article was awarded Open Data and Open Materials badges for transparent practices. See the Data availability statement for details.

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- Key analytical tools—including Higgins' global inconsistency test, network meta-regression, and advanced inferential and prediction methods designed to improve uncertainty quantification[4,5]—are implemented.
- Data-handling tools facilitate the integration of arm-level data and summary effect estimates, providing additional flexibility, particularly for survival outcomes.

Potential impact for RSM readers

- The package facilitates the practical use of network meta-analysis for a broad range of researchers, including non-statisticians, thereby enhancing the accessibility of systematic reviews on important clinical and public health questions.
- By comprehensively covering standard analyses and graphical tools, the `NMA` package is also valuable for educational purposes, serving as a practical resource for students, researchers, and clinicians to learn research methods through real-world case studies.

1. Introduction

In almost all disease areas today, multiple treatment options exist, and the question of which treatment constitutes the best option for each patient has become a central issue.[6] At the same time, with the profound impact of population aging in developed countries, this question has also become increasingly important from the perspectives of health economics and public health policy.[7,8] Conventional pairwise meta-analysis, which has been developed since the 1980s, has substantial limitations for addressing this purpose, and network meta-analysis has become the new standard method for comparative effectiveness research.[9,10] Naci and O'Connor[11] have suggested that network meta-analysis can also be applied at the stage of regulatory approval of new drugs, in order to compare their efficacy and safety with those of existing therapies. The necessity of such approaches is expected to increase substantially in the future.

Several excellent free computational tools for network meta-analysis have already been developed in R (R Foundation for Statistical Computing, Vienna, Austria). For Bayesian approaches, which have been widely adopted since their early development, `gemtc`,[12] `pcnetmeta`,[13] and `multinma`[14] packages are available. For frequentist approaches, the contrast-based approach is comprehensively supported by the `netmeta` package.[15] The `metafor` package[16] also provides extensive functionalities that are highly useful for conducting complex integrated analyses, including network meta-analysis. These packages offer powerful and flexible tools. The `NMA` package is intended to complement them by providing an R implementation organized explicitly around the multivariate meta-analysis and meta-regression framework described by Higgins et al.[1] and White et al.,[2] as implemented in Stata's network suite.[3] `NMA` also incorporates higher-order inferential and prediction procedures designed to address potential underestimation of statistical uncertainty in random-effects models.[4,17,18]

To provide this complementary implementation, we developed the R package `NMA` as a comprehensive computational tool for the practice of network meta-analysis, with an interface designed to facilitate use by non-statisticians. Within this framework, `NMA` implements methods such as Jackson's random inconsistency model[19,20] and the multivariate I^2 statistic.[21] Furthermore, it incorporates new inference and prediction methods for treatment effects based on higher-order asymptotic theory.[4,5] A wide range of graphical tools have also been implemented, including those for assessing transitivity.[22] The package provides enhanced data-handling functionality, with tools that allow the integration of both arm-level data and summary-level data. This provides greater flexibility in network meta-analysis, making it especially useful for studies of survival outcomes.

In this article, we provide an overview of the functions implemented in the `NMA` package and illustrate its use with example programs and case analyses. In Section 2, we briefly describe the example data used in this article. Section 3 presents a summary of the functions implemented in the `NMA` package, and Sections 4–8 demonstrate various applications of the package using the network meta-analysis of antihypertensive drugs reported by Sciarretta et al.[23] as a case study with a binary outcome. Additional

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analytical tools that cannot be fully described in the main text are detailed in the Supplementary Material.

Due to space limitations, the R output has been selectively presented. Complete R programs reproducing all case analyses are available on the authors' GitHub page (https://github.com/nomahi/NMA). In addition, further examples with continuous and survival outcomes are given in e-Appendices A and B in the Supplementary Material, respectively.

2. Illustrative example: Network meta-analysis of antihypertensive drugs

In this article, we present a case analysis of `NMA` using the network meta-analysis of antihypertensive drugs reported by Sciarretta et al.[23] as an example of a binary outcome. Sciarretta et al.[23] conducted a network meta-analysis comparing seven classes of antihypertensive drugs—α-blockers (AB), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers (BBs), calcium channel blockers (CCBs), conventional treatment (CT), and diuretics (DDs)—with placebo. The outcome of interest was the occurrence of heart failure, treated as a binary variable. The dataset included 26 randomized controlled trials conducted between 1997 and 2009, comprising a total of 223,313 participants.

Within the `NMA` package, this is provided as a dataset `heartfailure` and contains arm-level data, including sample sizes (`n`) and event counts (`d`) for each group. In addition, arm-level covariate data are available, including mean baseline systolic and diastolic blood pressure (`SBP, DBP`), as well as year of publication (`pubyear`).

```
> install.packages("NMA")              # Install from CRAN
> library("NMA")
> head(heartfailure, 6)
  study      trial     trt    n  d pubyear   SBP  DBP
1     1   Syst-Eur     CCB 2398 37    1997 173.8 85.5
2     1   Syst-Eur Placebo 2297 49    1997 173.9 85.5
3     2 Syst-China     CCB 1253  4    1998 170.5 86.0
4     2 Syst-China Placebo 1141  8    1998 170.5 86.0
5     3      UKPDS     ACE  400 12    1998 159.0 94.0
6     3      UKPDS      BB  358  9    1998 159.0 93.0
```

3. General overview of the NMA package

3.1. Functionalities and features

The R package `NMA` was developed as a collection of generic computational tools for network meta-analysis. It is based on the multivariate meta-regression framework proposed by White et al.[2] and is designed to apply effective statistical methods available within this model. Table 1 provides an overview of the functions implemented in the package.

The package brings together a range of methods within the multivariate meta-regression framework, including network meta-regression, Higgins's global inconsistency test, Jackson's random inconsistency model,[19] higher-order inference and prediction methods developed by Noma et al.,[4,5] and tools for assessing transitivity. In addition, the package offers data-handling tools that facilitate the integration of arm-based data (e.g., means, standard deviations) with trials reporting only contrast-based effect measures (e.g., mean differences).

To ensure accessibility for non-statisticians, the package has been designed with a user-friendly interface. Once an analysis dataset is generated using the `setup` function, all analytical tools can be applied with simple commands using the generated object. In the following sections, we provide an overview of the purpose of each function, how to use them, and how to interpret their results.

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Table 1. *Main functions of the* `NMA` *package and their descriptions.*

Function	Description	Section
`setup`	Transforming arm-level data into contrast-based summary statistics and creating data objects for all subsequent analyses.	3.2
`trans.armdata`	Transforming reported contrast-based summary statistics into arm-level data.	3.2
`trans.armdataP`	Transforming reported incidence proportion or survival probability data into arm-level data.	3.2
`netplot`	Generating a network diagram.	4.1
`SumPMA`	Pairwise meta-analyses for all directly compared treatment pairs in the network.	4.2
`nma`	Performs a network meta-analysis using a multivariate meta-analysis model and computes heterogeneity measures.	5.3
`nmareg`	Performs a network meta-regression using a contrast-based approach.	5.3
`nmarank`	Calculates ranking statistics for the network meta-analysis.	6.1
`nmaleague`	Generates a league table.	6.2
`nmaforest`	Generates a ranked forest plot of the network meta-analysis results.	6.3
`local.ict`	Local inconsistency tests for all triangular loops in the network.	7.1
`global.ict`	Higgins' global inconsistency test.	7.2
`nmaQ`	Computes the multivariate Q-statistic and its factorization.	7.2
`sidesplit`	Conducts sidesplitting to quantify direct and indirect evidence for all possible treatment pairs and to test inconsistency.	7.3
`random.icm`	Jackson's random inconsistency model.	7.4
`nmafunnel`	Generates a comparison-adjusted funnel plot.	8.1
`nmaweight`	Evaluates study weights and the contribution matrix.	8.2
`transitivity`	Assesses transitivity.	8.3

3.2. Supported data types and setup

The `NMA` package accommodates three types of outcomes—continuous, binary, and survival—as summarized in Table 2. For each outcome type, the package enables estimation using several effect measures, including the mean difference, standardized mean difference, risk difference, risk ratio, odds ratio, hazard ratio, and survival probability difference.

All analyses require that data be prepared in the *arm-level* format. These arm-level datasets are edited by the `setup` function, which edits and creates contrast-based statistics suitable for the analyses using multivariate meta-analysis models. As in conventional meta-analysis, however, mixed data of arm-level and summary-level statistics are often created in practice.[24] The `NMA` package therefore provides dedicated functions for handling such cases. For example, in continuous outcomes, some trials may report mean, standard deviation, and sample size for each arm, whereas others provide only contrast-based effect measures such as the mean difference with a standard error (which can be reconstructed from confidence intervals or p-values). In the latter case, the function `trans.armdata` can be used to back-calculate (pseudo) arm-level data. Note that the reconstructed values will not necessarily reproduce the original arm-level data exactly. However, in practice, the `setup` function transforms all the (pseudo) arm-level data into contrast-based effect measures for analysis, and the resulting summary measures are designed to coincide closely with the originally reported effect measures. Thus, the

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Table 2. *Outcome types supported in the* `NMA` *package and their descriptions.*

Type of outcome	Effect measure	Description
Continuous	Mean difference Standardized mean difference	For the included trials, arm-level data on the mean, standard deviation, and sample size are required. If some trials report only summary statistics, the `trans.armdata` function can be used to back-calculate the corresponding arm-level data (see e-Appendix A in the Supplementary Material).
Binary	Risk difference Risk ratio Odds ratio	For the included trials, arm-level data on the number of events and sample size are required. If some trials report only summary statistics, the `trans.armdata` function can be used to back-calculate the corresponding arm-level data (see Section 3.2).
Survival	Hazard ratio Survival probability difference	For the included trials, either the estimated log-hazard ratio with its standard error or arm-level data on the number of events and sample size are required. For convenience, the `trans.armdata` function can be used to convert the estimated log-hazard ratio, under the proportional hazards assumption, into arm-level data on the number of events and sample size that carry equivalent statistical information. Also, the arm-level data can be estimated from survival probability estimates using the `trans.armdataP` function. When the analysis is performed using the `setup` function, the original hazard ratio estimates are restored, enabling all subsequent analyses to be conducted (see e-Appendix B in the Supplementary Material).

arm-level data generated by `trans.armdata` should be viewed as "working" pseudo-data, serving as a bridge to construct contrast-based summaries.

For survival outcomes, hazard ratios are frequently reported.[25] These summary data can also be passed to `trans.armdata`. Under the proportional hazards assumption, the function applies the complementary log–log transformation to invert the hazard ratio formula,[26,27] thereby generating pseudo-data in the form of reconstructed event counts. Also, arm-specific survival probability data can sometimes be obtained from a Kaplan–Meier plot.[25] These survival probabilities can be converted into (pseudo) event counts and sample sizes using the `trans.armdataP` function. These pseudo-data can then be combined with trials reporting only event counts and sample sizes, producing a dichotomized arm-level dataset across all studies. Passing this dataset to the `setup` function yields contrast-based effect measures expressed as hazard ratios, which reproduce the original estimates.

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Once arm-level data from different-type data are merged into a single dataset, the `setup` function can produce contrast-based effect measures. All subsequent analyses can then be performed using the resulting object with simple commands. If arm-level covariates are available—for example, summary baseline characteristics that can be used in meta-regression or for evaluating transitivity—these variables can be added directly to the dataset in advance. Such data editing may conveniently be carried out in spreadsheet software such as Microsoft Excel (Microsoft, Redmond, WA.).

As an illustrative example for the binary outcome case, the required variables include study identifier (`study`), treatment (`trt`), number of events (`d`), sample size (`n`), and covariates (`z`; optional, multiple allowed). Users must also specify the effect measure of interest (risk difference, risk ratio, or odds ratio) and designate a reference treatment (`ref`).

```
> hf2 <- setup(study=study,trt=trt,d=d,n=n,z=c(SBP,DBP,pubyear),
  measure="OR",ref="Placebo",data=heartfailure)
```

Using the output object generated by the `setup` function as an argument, all subsequent analyses can be executed with simple commands.

4. Summarizing basic information on the network of evidence

4.1. Network diagram

In network meta-analysis, network diagrams[28] are presented in most studies to visualize both the amount and structure of the evidence being synthesized. The `NMA` package facilitates this process through the `netplot` function, which enables users to generate such diagrams in a straightforward manner. The function can be executed using the syntax illustrated below, and its specifications can be flexibly modified according to user preferences. The size of the nodes and the thickness of the edges in the `netplot` function are proportional to the total sample size for each treatment and each direct comparison, respectively.

```
> netplot(hf2)
```

(The figure created is shown in Figure 1.)

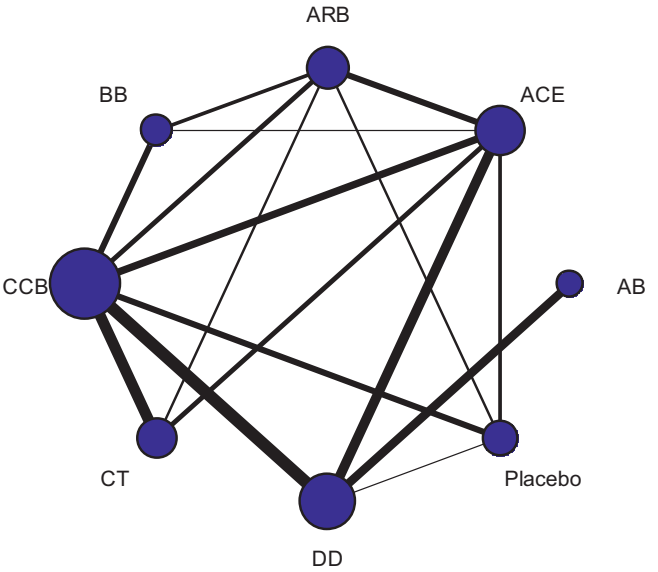


Figure 1. *Network diagram of the antihypertensive drug study created using the* `netplot` *function.*

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4.2. Pairwise meta-analysis for all treatment pairs with direct comparisons

As part of the basic information, the results of pairwise meta-analyses for all direct comparisons in the network can be summarized using the `SumPMA` function. This output includes the results of meta-analyses based on the DerSimonian–Laird-type random-effects model,[29] along with estimates of τ^2, I^2, and H^2 statistics, and Egger's test.[30] By default, the restricted maximum likelihood (REML) method is adopted.

```
> SumPMA(hf2)
Coding:
 code treatment
    1   Placebo
    2        AB
    3       ACE
    4       ARB
    5        BB
    6       CCB
    7        CT
    8        DD

Summary effect measures:
        N Estimate Lower Upper Pr(>|z|)
1 vs. 3 1    0.759 0.663 0.869    0.000
1 vs. 4 2    0.845 0.547 1.304    0.447
1 vs. 6 3    0.678 0.485 0.949    0.023
1 vs. 8 1    0.375 0.228 0.615    0.000
2 vs. 8 1    0.494 0.433 0.564    0.000
3 vs. 4 1    1.052 0.929 1.192    0.424
3 vs. 5 1    0.834 0.347 2.003    0.684
3 vs. 6 3    1.189 1.076 1.314    0.001
3 vs. 7 1    0.878 0.630 1.225    0.445
3 vs. 8 1    1.136 0.818 1.577    0.447
4 vs. 5 1    1.058 0.845 1.325    0.622
4 vs. 6 1    1.145 0.989 1.326    0.070
4 vs. 7 2    1.501 0.991 2.272    0.055
5 vs. 6 1    0.839 0.665 1.057    0.137
6 vs. 7 3    0.865 0.743 1.007    0.061
6 vs. 8 5    0.711 0.644 0.786    0.000

Heterogeneity measures:
        N   tau tau^2   I^2   H^2
1 vs. 3 1 0.000 0.000 0.000 1.000
1 vs. 4 2 0.281 0.079 0.806 5.157
1 vs. 6 3 0.000 0.000 0.000 1.000
1 vs. 8 1 0.000 0.000 0.000 1.000
2 vs. 8 1 0.000 0.000 0.000 1.000
3 vs. 4 1 0.000 0.000 0.000 1.000
3 vs. 5 1 0.000 0.000 0.000 1.000
3 vs. 6 3 0.000 0.000 0.000 1.000
3 vs. 7 1 0.000 0.000 0.000 1.000
3 vs. 8 1 0.000 0.000 0.000 1.000
4 vs. 5 1 0.000 0.000 0.000 1.000
```

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```
4 vs. 6 1 0.000 0.000 0.000 1.000
4 vs. 7 2 0.152 0.023 0.253 1.339
5 vs. 6 1 0.000 0.000 0.000 1.000
6 vs. 7 3 0.000 0.000 0.000 1.000
6 vs. 8 5 0.001 0.000 0.000 1.000
```

5. Network meta-analysis using multivariate meta-analysis models

5.1. Multivariate meta-analysis models and synthesis methods

The contrast-based approach is one of the principal methods used for evidence synthesis in network meta-analysis.[22,31] In this framework, effect measures such as odds ratios, hazard ratios, or mean differences are modeled as outcome measures. This approach can be interpreted as a generalization of the conventional DerSimonian–Laird method for pairwise meta-analysis,[29] whereby study-specific outcomes are treated as multivariate outcomes and modeled within a multivariate meta-analysis framework.[32]

White et al.[2] demonstrated that such multivariate meta-regression models allow for the implementation of contrast-based network meta-analysis, and further showed that this framework provides a general means to evaluate inconsistency through the design-by-treatment interaction model.[1] In this section, we outline the underlying statistical model and corresponding analytical procedures.

Specifically, we consider the synthesis of N trials comparing $p + 1$ treatments. Let Y_{ij} denote the estimator of the treatment effect of the jth treatment relative to a designated reference treatment (e.g., placebo) in the ith trial $(i = 1, 2, \ldots, N; j = 1, 2, \ldots, p)$. Commonly used effect measures include the mean difference, standardized mean difference, risk difference, risk ratio, odds ratio, and hazard ratio, with ratio measures typically modeled on the logarithmic scale. For the contrast-based network meta-regression, we adopt a multivariate meta-analysis model for the outcome variable $\boldsymbol{Y}_i = \left(Y_{i1}, Y_{i2}, \ldots, Y_{ip}\right)^T$,

$$\boldsymbol{Y}_i = \boldsymbol{\theta}_i + \boldsymbol{e}_i \qquad (*)$$

$$\boldsymbol{\theta}_i = \boldsymbol{X}_i^T \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i,$$

where $\boldsymbol{\theta}_i = \left(\theta_{i1}, \theta_{i2}, \ldots, \theta_{ip}\right)^T$ and $\boldsymbol{\beta} = \left(\boldsymbol{\beta}_1^T, \ldots, \boldsymbol{\beta}_p^T\right)^T$. The regression function model $\boldsymbol{X}_i^T \boldsymbol{\beta}$ involves a design matrix,

$$\boldsymbol{X}_i = \begin{pmatrix} \boldsymbol{x}_{i1} & 0 & \cdots & 0 \\ 0 & \boldsymbol{x}_{i2} & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \boldsymbol{x}_{ip} \end{pmatrix},$$

where $\boldsymbol{x}_{ij}$ is a $q_j \times 1$ covariate vector for Y_{ij} (q_j is the number of the covariates) and $\boldsymbol{\beta}_j$ is its $q_j \times 1$ regression coefficient vector. Also, $\boldsymbol{e}_i$ and $\boldsymbol{\varepsilon}_i$ are independent random variation terms within and across studies ($p \times 1$ random vectors), assumed to be distributed $\boldsymbol{e}_i \sim \mathrm{MVN}\left(\boldsymbol{0}, \boldsymbol{S}_i\right)$ and $\boldsymbol{\varepsilon}_i \sim \mathrm{MVN}\left(\boldsymbol{0}, \boldsymbol{\Sigma}\right)$. $\boldsymbol{S}_i$ (a $p \times p$ matrix) is the within-study covariance matrix,

$$\boldsymbol{S}_i = \begin{pmatrix} s_{i1}^2 & \rho_{i12} s_{i1} s_{i2} & \cdots & \rho_{i1p} s_{i1} s_{ip} \\ \rho_{i21} s_{i2} s_{i1} & s_{i2}^2 & \cdots & \rho_{i2p} s_{i2} s_{ip} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{ip1} s_{ip} s_{i1} & \rho_{ip2} s_{ip} s_{i2} & \cdots & s_{ip}^2 \end{pmatrix},$$

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which is usually assumed to be known and fixed to its valid estimate.[33] In addition, $\boldsymbol{\Sigma}$ is the between-studies variance–covariance matrix:

$$\boldsymbol{\Sigma} = \tau^2 \boldsymbol{P} = \tau^2 \begin{pmatrix} 1 & 1/2 & \cdots & 1/2 \\ 1/2 & 1 & \ldots & 1/2 \\ \vdots & \vdots & \ddots & \vdots \\ 1/2 & 1/2 & \cdots & 1 \end{pmatrix}$$

for $\tau^2 > 0$. Note that the correlation structure of $\boldsymbol{\Sigma}$ can be assumed to be unstructured; however, there are rarely enough studies to allow identification of all variance–covariance parameters. Consequently, most network meta-analyses adopt the equal-variance assumption for the p components of $\boldsymbol{\varepsilon}_i$. Under this assumption, and by virtue of the consistency property, all pairwise correlation coefficients are set to 0.50.[34] In the NMA package, we likewise adopt the equal-variance assumption as the standard specification of the model.

For trials that do not include a reference treatment, the data augmentation strategy proposed by White et al.[2] can be applied; in this approach, a quasi-negligible dataset is added to the reference arm (e.g., 0.001 events for 0.01 patients in the case of a binary outcome). In addition, because most individual clinical trials typically involve only two to four arms, we formally employ subvectors or submatrices in the likelihood function.[2]

Standard network meta-analysis without covariates and under the consistency assumption can be expressed as a special case of the model with $\boldsymbol{x}_{ij} = (\mathbf{1})$, a vector of ones. Meta-regression analyses incorporating covariates can then be performed within the same framework. In terms of the classification by Donegan et al.,[35] the multivariate meta-regression model based on the framework proposed by White et al.[2] corresponds to the independent interaction assumption, in which treatment-by-covariate interaction coefficients may differ across treatment comparisons. Accordingly, the regression function is modeled separately for each outcome component. Furthermore, when $\tau^2 = 0$, the model reduces to a fixed-effect model. In the `NMA` package, standard network meta-analyses can be conducted using the `nma` function, while meta-regression can be performed with the `nmareg` function.

Model parameters can be estimated using the standard REML method. Under a random-effects model, as in pairwise meta-analyses, the confidence intervals for $\boldsymbol{\beta}$ may be inaccurate when the number of studies N is small.[4,18,36] The Cochrane Handbook[24] recommends the use of the Hartung–Knapp–Sidik–Jonkman (HKSJ) method[17,37,38] for pairwise meta-analyses. For network meta-analysis, Noma et al.[4] also proposed a higher-order asymptotic correction, which has been adopted as the default method in the `NMA` package.

5.2. Assessment of heterogeneity

The issue of between-trial heterogeneity in treatment effects is also of central importance in network meta-analysis. The conventional measures used in pairwise meta-analysis, such as Cochran's Q-test[39] and Higgins' I^2 statistic,[40] have been extended to the multivariate meta-analysis framework by Jackson et al.,[21] and can be directly computed from model (*). The parameter τ can be interpreted as the heterogeneity standard deviation. In addition, prediction intervals,[41] which represent the expected range of treatment effects in future populations while accounting for between-study heterogeneity, have become widely used in recent meta-analyses. Although prediction intervals have commonly been calculated using approximations based on the t-distribution, concerns about their accuracy have been raised.[36,42] To address this issue, Noma et al.[5] proposed several improved methods. The `NMA` package adopts, as the default method, an approach based on higher-order asymptotic approximations developed by Noma et al.,[5] and these results are reported collectively in the output of the `nma` function.

5.3. Computational tools for primary synthesis methods

The synthesis analysis based on the consistency assumption can be performed by the `nma` function, which adopts the higher-order asymptotic correction methods proposed by Noma et al.[4,5] as default

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(named as "Noma-Hamura" methods). The output also provides various heterogeneity statistics, including τ, τ^2, the H^2 statistic, the I^2 statistic, the Q-test, and the prediction interval. By setting `eform=TRUE`, the estimated effect measures are exponentiated, thereby allowing direct interpretation of effect sizes such as odds ratios, risk ratios, and hazard ratios, which are synthesized on the logarithmic scale under normality assumptions.

```
> nma(hf2, eform=TRUE)
Coding:
 code treatment
    1   Placebo
    2        AB
    3       ACE
    4       ARB
    5        BB
    6       CCB
    7        CT
    8        DD

Reference: Placebo

Number of studies: 26

Method: Noma-Hamura's improved REML-based inference and prediction
methods

Coef. (vs. treat 1):
         Est.    SE Lower Upper Pr(>|z|)
2: cons 1.214 0.165 0.811 1.818    0.284
3: cons 0.714 0.086 0.586 0.870    0.004
4: cons 0.759 0.088 0.626 0.919    0.009
5: cons 0.878 0.133 0.659 1.170    0.345
6: cons 0.843 0.093 0.689 1.033    0.092
7: cons 0.775 0.112 0.611 0.982    0.037
8: cons 0.600 0.113 0.465 0.774    0.001

tau (Between-studies_SD) estimate: 0.099

tau2 (Between-studies_variance) estimate: 0.01

Multivariate H2-statistic: 1.604

Multivariate I2-statistic: 0.594

Test for Heterogeneity: Q(df = 21) = 33.688, p-value = 0.039

95%PI (vs. treat 1):
        Lower Upper
2: cons 0.741 1.990
3: cons 0.525 0.972
4: cons 0.566 1.016
5: cons 0.612 1.258
```

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```
6: cons 0.626 1.136
7: cons 0.563 1.065
8: cons 0.425 0.847
```

Similarly, network meta-regression can be conducted using the `nmareg` function. The example below illustrates an analysis of effect modification for the odds ratio of ACE versus placebo with systolic blood pressure (SBP) included as a covariate. It should be noted that in multivariate meta-regression, a different regression function is specified for each component of the outcome vectors $\boldsymbol{Y}_1, \ldots, \boldsymbol{Y}_N$. The variable to be evaluated as an effect modifier is specified via the argument `z`, and the corresponding outcome components are designated using the argument `treats`. For instance, to perform a meta-regression analysis assessing effect modification of SBP on the odds ratio for treatment 3 versus 1, the following command can be applied. Both `z` and `treats` can be specified as vectors to allow for the inclusion of multiple covariates and outcomes.

```
> nmareg(hf2,z=SBP,treats=3)
Covariates: SBP

Outcomes evaluated the effect modifications: 3 vs. 1

Coefficients:
         Coef.     SE  Lower  Upper Pr(>|z|)
2: cons  0.170 0.165 -0.154  0.493    0.304
3: cons  0.141 0.468 -0.776  1.058    0.763
3: SBP  -0.003 0.003 -0.009  0.003    0.297
4: cons -0.288 0.087 -0.459 -0.118    0.001
5: cons -0.154 0.134 -0.417  0.109    0.250
6: cons -0.203 0.095 -0.389 -0.017    0.032
7: cons -0.306 0.120 -0.540 -0.071    0.011
8: cons -0.535 0.110 -0.751 -0.319    0.000

Between-studies SD: 0.102
```

In addition, estimation of the regression coefficients requires sufficient information and covariate variation in the network to identify the specified meta-regression model. Because the multivariate meta-regression model combines information across the network, identifiability is not determined solely by the number of trials directly comparing the corresponding treatment pair. If the specified model is not identifiable from the available network evidence, estimation will fail and an error will be produced.

6. Analyses of ranking and comparative effectiveness

6.1. Ranking probability and SUCRA

As an analytic approach to comparative effectiveness, treatment ranking methods are widely used.[22] Based on the estimates from model (*), the probabilities of each treatment being ranked best, second, …, or worst can be estimated using a parametric bootstrap procedure.[43] In addition, the bootstrap method can be used to estimate the surface under the cumulative ranking curve (SUCRA).[44] SUCRA is a continuous score ranging from 0 to 1 that indicates the relative position of each treatment within the overall distribution (analogous to a quantile of the distribution). These quantities can be computed using the `nmarank` function, which also provides plots of the ranking probabilities.

```
> nmarank(hf2)
SUCRA:
       SUCRA
DD     0.992
ACE    0.796
```

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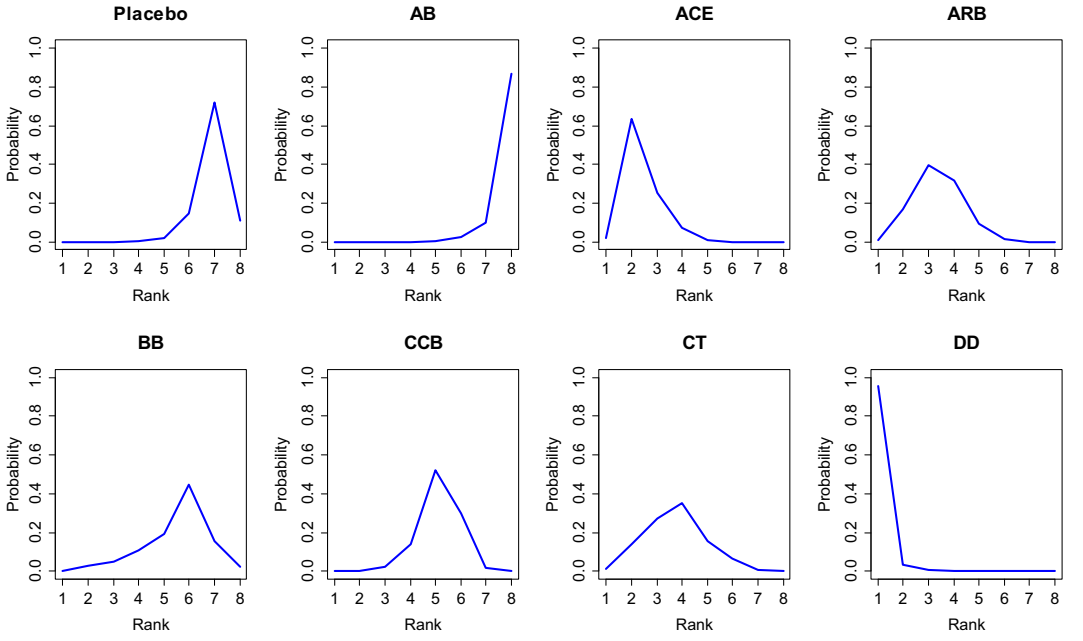


Figure 2. *Ranking probability plot of the antihypertensive drug study created using the* `nmarank` *function.*

```
ARB       0.660
CT        0.612
CCB       0.407
BB        0.354
Placebo   0.155
AB        0.025
```

(The ranking probabilities of each treatment are presented in Figure 2.)

6.2. League table

As another type of output for comparative effectiveness, a league table[44] can also be generated easily using the `nmaleague` function. The league table can additionally be exported in CSV format.

Based on the results of the synthesis analysis, a league table can be created with user-specified options. The number of decimal places can be set via the argument `digits`, and the output file name for CSV export can be specified using `out.csv`. For example:

```
> nmaleague(hf2, eform=TRUE, digits=2, out.csv="nmaleague_out.csv")
```

(The output is omitted here due to space limitations.)

6.3. Ranked forest plot

The results of the synthesis analysis are often presented graphically using a forest plot. For comparative effectiveness analyses, a ranked forest plot,[45] in which treatments are ordered by their estimated effect measures, is frequently employed. Such plots can be easily generated using the `nmaforest` function.

```
> nmaforest(hf2, col.plot="blue")
```

(The forest plot created is shown in Figure 3.)

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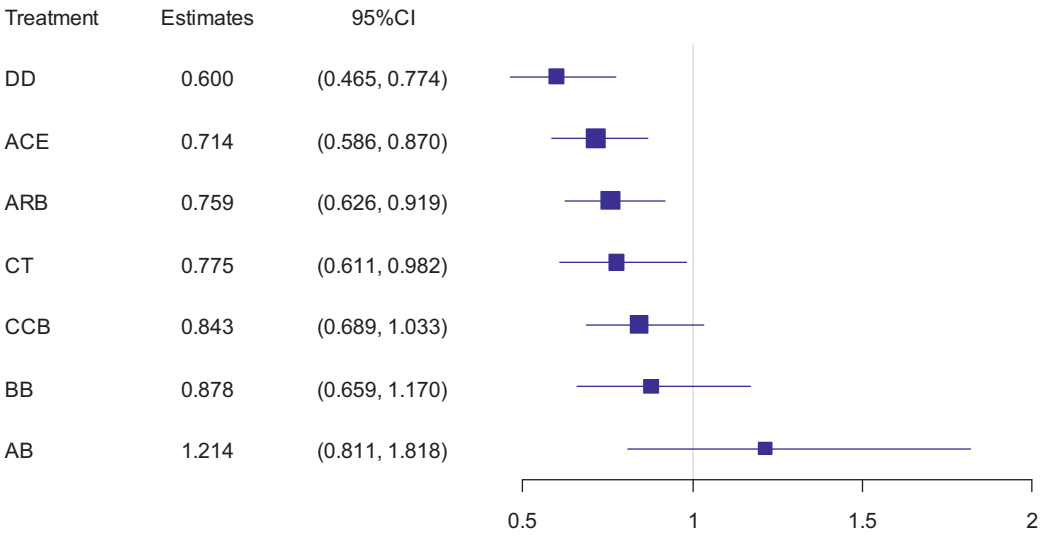


Figure 3. *Ranked forest plot of the antihypertensive drug study created using the* `nmaforest` *function.*

7. Evaluation of inconsistency

7.1. Local inconsistency test

Various statistical methods have been proposed for evaluating inconsistency, and several representative approaches are implemented in the `NMA` package. The first is the local inconsistency test (`local.ict` function). This method extracts triangular loops of three treatments from the evidence network and tests whether the treatment effects obtained from the direct and indirect comparison paths within each loop are consistent.[46,47]

```
> local.ict(hf2)
Local inconsistency tests:
            N   tau X2-statistic df Pr(>X2)
loop: 1-3-4 4 0.281        0.015  1  0.903
loop: 1-3-6 7 0.007        2.218  1  0.136
loop: 1-3-8 4 0.179        2.627  1  0.105
loop: 1-4-6 6 0.203        1.161  1  0.281
loop: 1-6-8 9 0.009        0.664  1  0.415
loop: 3-4-5 3 0.009        0.385  1  0.535
loop: 3-4-6 5 0.008        0.015  1  0.903
loop: 3-4-7 5 0.163        1.644  1  0.200
loop: 3-5-6 5 0.007        1.301  1  0.254
loop: 3-6-7 6 0.008        3.304  3  0.347
loop: 3-6-8 8 0.006        3.538  3  0.316
loop: 4-5-6 3 0.007        1.978  1  0.160
loop: 4-6-7 6 0.009        3.669  1  0.055
```

7.2. Global inconsistency test

The second method is the global inconsistency test (`global.ict` function). While inconsistency within a triangular loop can be readily understood as the discrepancy between direct and indirect comparisons along the loop, it is less straightforward to define inconsistency across more complex networks.

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Higgins et al.[1] formalized this by defining inconsistency as "differences in treatment effects depending on which treatments are being compared," and expressed it through a design-by-treatment interaction framework (where "design" refers to the set of treatments being compared).[48] In this approach, all possible design-by-treatment interactions in the network are modeled within a meta-regression framework, and a test of the global null hypothesis regarding these interactions was proposed as the global inconsistency test.

```
> global.ict(hf2)
Coefficients of the design-by-treatment interaction model:
               Est.    SE  Lower  Upper Pr(>|z|)
2: cons      -0.277 0.343 -0.948  0.395    0.420
3: cons      -0.276 0.171 -0.610  0.059    0.106
4: cons      -0.160 0.147 -0.448  0.129    0.278
4: des_3-4   -0.065 0.281 -0.617  0.486    0.816
5: cons      -0.458 0.503 -1.444  0.529    0.363
5: des_4-5    0.355 0.559 -0.741  1.451    0.526
6: cons      -0.401 0.201 -0.795 -0.007    0.046
6: des_3-6    0.312 0.685 -1.031  1.654    0.649
6: des_3-6-7  0.370 0.327 -0.272  1.011    0.259
6: des_3-6-8  0.280 0.312 -0.331  0.891    0.369
6: des_4-6    0.377 0.303 -0.217  0.972    0.214
6: des_5-6   -0.233 0.576 -1.362  0.897    0.687
7: cons      -0.094 0.259 -0.601  0.413    0.717
7: des_3-7   -0.312 0.302 -0.903  0.280    0.302
7: des_4-7    0.341 0.366 -0.377  1.058    0.352
7: des_6-7   -0.530 0.363 -1.242  0.183    0.145
8: cons      -0.982 0.297 -1.565 -0.399    0.001
8: des_3-6-8  0.525 0.381 -0.222  1.271    0.168
8: des_3-8    0.833 0.412  0.025  1.641    0.043
8: des_6-8    0.156 0.438 -0.703  1.015    0.722

Between-studies SD: 0.156

P-value: 0.459
```

As a supplementary tool, the `nmaQ` function can be used to decompose the *Q*-statistic, providing *Q*-statistics for each design and separating the within-design and between-design components. This allows the results of heterogeneity tests to be obtained for each component.

```
> nmaQ(hf2)
Within designs (individual designs):
      N     n     Q df Pr(>Q)
1-3   1  9297 0.000  0  1.000
1-4   2  7439 5.157  1  0.023
1-6   3 16800 0.502  2  0.778
1-8   1  3845 0.000  0  1.000
2-8   1 24335 0.000  0  1.000
3-4   1 17118 0.000  0  1.000
3-5   1   758 0.000  0  1.000
3-6   1   470 0.000  0  1.000
3-6-7 1  6614 0.000  0  1.000
3-6-8 1 33357 0.000  0  1.000
3-7   1 10985 0.000  0  1.000
```

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```
3-8   1  6083 0.000  0  1.000
4-5   1  9193 0.000  0  1.000
4-6   1 15245 0.000  0  1.000
4-7   2  5129 1.339  1  0.247
5-6   1 19257 0.000  0  1.000
6-7   2 27357 0.074  1  0.786
6-8   4 10031 4.581  3  0.205

Q-statistics:
                     Q df Pr(>Q)
Within designs  11.652  8  0.167
Between designs 22.036 13  0.055
Total           33.688 21  0.039
```

7.3. Sidesplitting

The third method is side-splitting (`sidesplit` function). This approach summarizes the direct and indirect evidence for a specific pair of treatments and tests whether their pooled quantities are in disagreement. When multi-arm trials with three or more arms are included, special considerations are required to avoid bias.[49,50] The `NMA` package adopts the approach proposed by Noma,[49] which is based on network meta-regression.

```
> sidesplit(hf2)
Direct evidence:
          Est.    SE  Lower  Upper Pr(>|z|)
1 vs. 3 -0.276 0.143 -0.556  0.005    0.054
1 vs. 4 -0.155 0.131 -0.411  0.101    0.234
1 vs. 6 -0.392 0.180 -0.744 -0.040    0.029
1 vs. 8 -0.982 0.261 -1.493 -0.471    0.000

Indirect evidence:
          Est.    SE  Lower  Upper Pr(>|z|)
1 vs. 3 -0.407 0.126 -0.654 -0.160    0.001
1 vs. 4 -0.440 0.137 -0.708 -0.172    0.001
1 vs. 6 -0.100 0.092 -0.280  0.081    0.278
1 vs. 8 -0.428 0.093 -0.611 -0.245    0.000

Difference between direct and indirect evidence with inconsistency test:
          Est.    SE  Lower  Upper Pr(>|z|)
1 vs. 3  0.131 0.191 -0.242  0.505    0.491
1 vs. 4  0.284 0.189 -0.086  0.655    0.133
1 vs. 6 -0.292 0.202 -0.688  0.103    0.148
1 vs. 8 -0.554 0.277 -1.097 -0.011    0.045
```

(Due to space limitations, only the top four rows of results are presented.)

7.4. Random inconsistency model

The fourth method is the random inconsistency model proposed by Jackson et al.[19] (`random.icm` function). This approach extends the design-by-treatment interaction meta-regression model of Higgins et al.[1] by treating the design effects as random effects.[19,20] In this model, inconsistency can be evaluated by testing the variance component associated with the random design effects. In addition, this model

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provides I^2 statistics for heterogeneity, for inconsistency, and for the overall model that jointly accounts for both heterogeneity and inconsistency.

```
> random.icm(hf2)
Number of designs: 18

Coef. (vs. treat 1):
         Coef.    SE  95%CL  95%CU P-value
2: cons  0.188 0.169 -0.144  0.519   0.267
3: cons -0.342 0.088 -0.514 -0.171   0.000
4: cons -0.283 0.091 -0.461 -0.106   0.002
5: cons -0.139 0.136 -0.406  0.129   0.310
6: cons -0.177 0.094 -0.360  0.006   0.058
7: cons -0.260 0.114 -0.483 -0.036   0.023
8: cons -0.517 0.112 -0.736 -0.299   0.000

Between-studies SD: 0.092

Between-designs SD: 0.055

Likelihood ratio tests for the variance components:
                             X2-statistic df P-value
Heterogeneity                       0.479  1   0.489
Inconsistency                       0.039  1   0.843
Heterogeneity + Inconsistency       0.519  2   0.772

Heterogeneity and inconsistency statistics:
                           R-statistic I2-statistic
Heterogeneity                    1.523        0.569
Inconsistency                    1.051        0.095
Heterogeneity + Inconsistency    1.602        0.610
```

8. Other graphical tools

8.1. Comparison-adjusted funnel plot

In network meta-analysis, the assessment of publication bias is challenging because multiple treatments are compared and the direction of publication bias may differ across trials. One approach is the comparison-adjusted funnel plot,[43] in which the results of trials with direct comparisons against a specified reference treatment are adjusted to share a common center line, thereby allowing a descriptive evaluation of publication bias across the network. Such plots can be generated using the `nmafunnel` function.

```
> nmafunnel(hf2,legends="bottomright")
```

(The comparison-adjusted funnel plot created is shown in Figure 4.)

8.2. Study weights and contribution matrix

In network meta-analysis, it is important to assess how individual studies influence the synthesized results. Jackson et al.[51] and Noma et al.[50] demonstrated that contribution rates can be estimated using factorized information, and that contribution weight matrices can be derived accordingly. In the `NMA`

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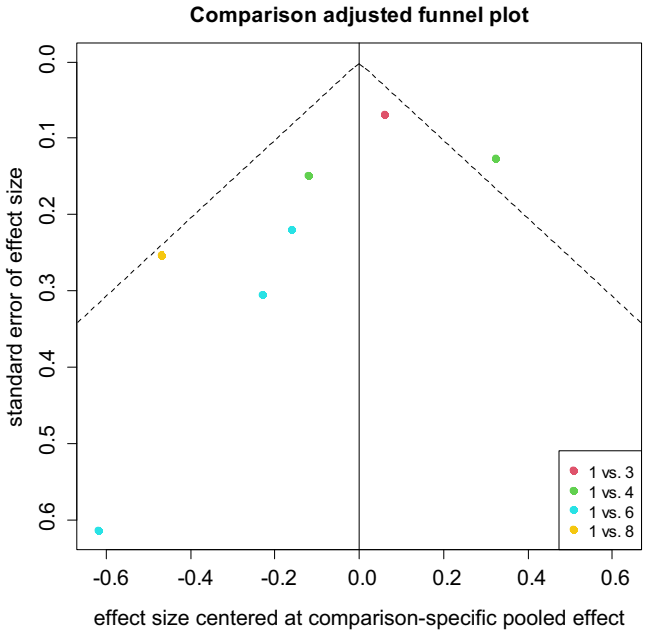


Figure 4. *Comparison-adjusted funnel plot of the antihypertensive drug study created using the* `nmafunnel` *function.*

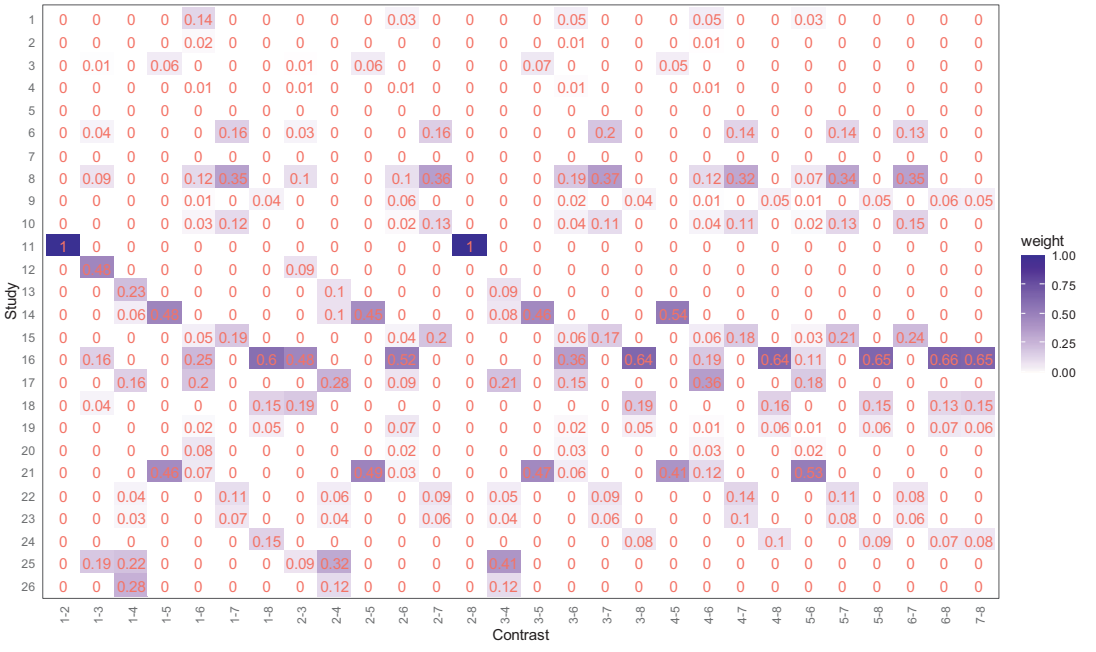


Figure 5. *Heat plot of the contribution weights of individual studies in the antihypertensive drug study created using the* `nmaweight` *function.*

package, the `nmaweight` function allows users to compute these contribution weight matrices and to visualize them graphically as a heatmap.

```
> nmaweight(hf2)
```

(*The heat plot created is shown in Figure 5.*)

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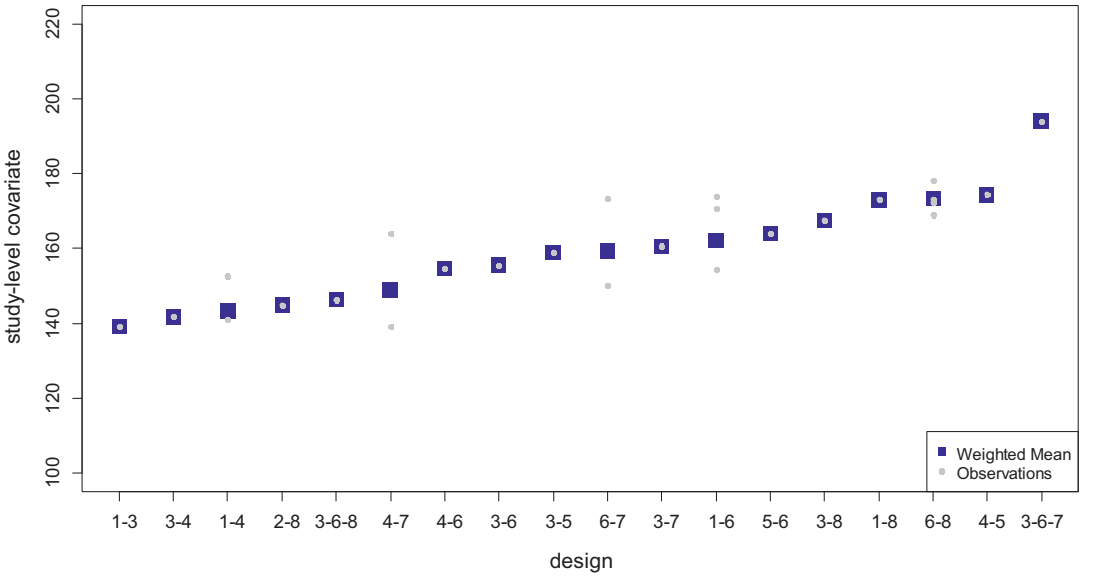


Figure 6. *Side-by-side boxplot for assessing transitivity in the antihypertensive drug study created using the* `transitivity` *function.*

8.3. Check of transitivity

In network meta-analysis, not only consistency but also transitivity is regarded as a fundamental and essential assumption,[22] as it underpins the premise that indirect comparisons are theoretically valid even in the absence of direct evidence. To date, no standard statistical method has been firmly established for evaluating transitivity. However, Cipriani, Furukawa, Salanti et al.[52] illustrated an approach in which the distributions of key covariates are compared across designs using side-by-side boxplots, thereby enabling an assessment of heterogeneity in covariate distributions. In the `NMA` package, the `transitivity` function generates such side-by-side boxplots to facilitate the evaluation of transitivity.

```
> transitivity(hf2, SBP, yrange=c(100,220))
```

(*The side-by-side boxplot created is shown in Figure 6.*)

9. Concluding remarks

Network meta-analysis is now a well-established methodology within systematic reviews and has already become widely adopted as a standard approach for comparative effectiveness research.[24,53] However, the statistical methods are often highly technical for non-statisticians. In the practice of systematic reviews, statistical experts are not always involved, and many researchers lack either the time or the technical skills to implement their own programming. Therefore, the availability of user-friendly software with versatile functionality is of critical importance for enabling practitioners to conduct research on important clinical and public health questions. Graphical user interface systems such as `NMAstudio`[54] and `MetaInsight`[55] facilitate network meta-analysis through interactive workflows. The `NMA` package complements these tools by supporting flexible, customizable, script-based analyses within R, including higher-order inferential and prediction procedures. We hope that the `NMA` package will encourage more researchers and practitioners to undertake network meta-analysis and will contribute to the generation of new evidence that can ultimately improve clinical practice and public health.

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Author contributions. Conceptualization: H.N. and K.M.; Formal analysis: H.N.; Investigation: H.N. and K.M.; Methodology: H.N., K.M., S.T., and T.A.F.; Supervision: S.T. and T.A.F.; Writing—original draft: H.N.; Writing—review and editing: H.N., K.M., S.T., and T.A.F.

Competing interest statement. The authors declare that no competing interests exist.

Data availability statement. All datasets used in this article are available in the `NMA` package on CRAN (https://doi.org/10.32614/CRAN.package.NMA). Complete R programs reproducing all case analyses are available on the authors' GitHub page (https://github.com/nomahi/NMA) and archived on Zenodo: https://zenodo.org/records/21972821.

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Supplementary material. To view supplementary material for this article, please visit http://doi.org/10.1017/rsm.2026.10122.

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