Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1. Literature Search for Articles on Network Meta-analysis

We searched for full-length articles with original data of network meta-analyses from 2010 to 2018, and we excluded letters, commentaries, news, and research methodology and reporting. The literature search was conducted via the official websites of JAMA (https://jamanetwork.com/advanced-search), the Lancet (https://www.thelancet.com/search/advanced), and BMJ (https://www.bmj.com/search/advanced). We downloaded articles with the term “meta analysis”, “meta analyses”, “meta epidemiological”, “network meta analysis”, “network meta analyses”, “mixed treatment comparison(s)”, or “multiple treatment(s)” in their titles. Then, we looked at the articles’ contents, and excluded articles if they were not network meta-analyses of multiple treatments. Some articles were also excluded when they presented data of multiple treatments but did not formally perform network meta-analyses to simultaneously synthesize their evidence. Of note, although most articles with the term “meta analysis”, “meta analyses”, or “meta epidemiological” were conventional pairwise meta-analyses, some were actually network meta-analyses; therefore, these terms were retained in our literature search. In addition, we compared the obtained articles with the network meta-analyses collected by Nikolakopoulou et al.¹ (searched before 2014), Bafeta et al.²,³ (searched before 2013), and Trinquart et al.⁴ (searched before 2013 with restrictions on model types). Missed articles were added to our final list (eTable 1).
eAppendix 2. Example of Producing Prediction Intervals in Network Meta-analysis

eTable 2 presents software programs for NMAs and the corresponding commands for producing prediction intervals. All commands are simple and do not require much additional effort in the analyses. This appendix applies the available software programs to the example dataset of smoking cessation. The following statistical analyses estimated odds ratios on a logarithmic scale with 95% confidence/credible intervals and prediction intervals. The specific commands for producing prediction intervals are highlighted in the following statistical code.

Stata

If the Stata routines for network meta-analysis have not been installed yet, type the following command in Stata

```
.net from http://www.homepages.ucl.ac.uk/~rmjwiww/stata/
```

Click the link meta and install the packages network and mvmeta. Also, type the following command

```
.net from http://www.stata-journal.com/software/sj15-4/
```

Install the package st0411. The detailed instructions of these Stata routines have been provided by Chaimani et al.,5 Chaimani and Salanti,6 and White.7

The smoking cessation dataset is stored in the file “smokingcessation.dta”. By typing

```
.list, noobs clean
```

the dataset can be displayed as follows

```
study  rA  nA  rB  nB  rC  nC  rD  nD
1    9  140  .  .  23  140  10  138
2     .  .  11  78  12  85  29  170
3    75  731  .  .  363  714  .  .
4    2  106  .  .   9  205  .  .
5   58  549  .  .  237  1561  .  .
6  .5  34  .  .   9.5  49  .  .
7    3  100  .  .  31  98  .  .
8  1  31  .  .  26  95  .  .
9  6  39  .  .  17  77  .  .
10  79  702  77  694  .  .  .  .
11  18  671  21  535  .  .  .  .
12  64  642  .  .  107  761  .  .
13  5  62  .  .  8  90  .  .
14  20  234  .  .  34  237  .  .
15  .5  21  .  .  .  .  9.5  21
16   8  116  19  149  .  .  .  .
17  95  1107  .  .  143  1031  .  .
18  15  187  .  .  36  504  .  .
19  78  584  .  .  73  675  .  .
20  69  1177  .  .  54  888  .  .
21  .  .  20  49  16  43  .  .
22  .  .  7  66  .  .  32  127
23  .  .  .  .  12  76  20  74
24  .  .  .  .  9  55  3  26
```

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Note that the continuity correction of 0.5 is applied to each study that contains zero event in a certain treatment arm. Then, we run the following commands to implement network meta-analysis and derive 95% prediction intervals:

```
.network setup r n, studyvar(study)
.network table
.network meta consistency
.intervalplot, pred
```

The last command returns the following results:

The intervalplot command assumes that the saved results from mvmeta or network meta commands have been derived from the current dataset.

| Comparison | Effect Size | Standard Error | LCI   | UCI   | LPrI   | UPrI   |
|------------|-------------|----------------|-------|-------|--------|--------|
| y_B        | .3971683    | .3297603       | -2.4915 | 1.043487 | -1.180223 | 1.97456 |
| y_C        | .7090092    | .1982125       | .1982125 | 1.097499 | -0.7671354 | 2.185154 |
| y_D        | .868733     | .3749113       | .749113 | 1.253146 | -1.603546 | 2.490396 |
| y_C-y_B    | .3118409    | .3391682       | -0.3529166 | .9765984 | -1.274405 | 1.898087 |
| y_D-y_B    | .4715647    | .4058903       | -3.239657 | 1.627095 | -1.182962 | 2.126092 |
| y_D-y_C    | .1597238    | .3534939       | -0.533115 | .8525591 | -1.440384 | 1.759832 |

R package “netmeta”

If the R package “netmeta” has not been installed yet, type the following command in R to install this package:

```
> install.packages("netmeta")
```

Load this package:

```
> library("netmeta")
```

This package contains the smoking cessation dataset, which can be used by typing:

```
> data(smokingcessation)
```

The following commands produce the estimated log odds ratios and their 95% confidence intervals and 95% prediction intervals:

```
> pair <- pairwise(list(treat1, treat2, treat3),
+ event = list(event1, event2, event3), n = list(n1, n2, n3),
+ data = smokingcessation, sm = "OR")
> out.netmeta <- netmeta(pair, prediction = TRUE)
> est.netmeta <- out.netmeta$TE.random
> CI.lower.netmeta <- out.netmeta$lower.random
> CI.upper.netmeta <- out.netmeta$upper.random
> PrI.lower.netmeta <- out.netmeta$lower.predict
> PrI.upper.netmeta <- out.netmeta$upper.predict
```

Here, the argument prediction in the R function netmeta() specifies whether prediction intervals are produced (TRUE) or not (FALSE). The results can be displayed as follows:

```
> est.netmeta
A  B  C  D
A 0.0000000 -0.4162377 -0.7334060 -0.9022982
```

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The five objects est.netmeta, CI.lower.netmeta, CI.upper.netmeta, PrI.lower.netmeta, and PrI.upper.netmeta accordingly contain the point estimates of overall log odds ratios of all treatment comparisons, their 95% confidence intervals’ lower and upper bounds, and their 95% prediction intervals’ lower and upper bounds. Each object is a 4 x 4 matrix, and each matrix element corresponds to a comparison of a pair of treatments. Specifically, each treatment comparison result is interpreted as the treatment corresponding to its row vs. the treatment corresponding to its column.

**WinBUGS (implemented via R package “R2WinBUGS”)**

If the software program WinBUGS has not been downloaded, it is available at https://www.mrc-bsu.cam.ac.uk/wp-content/uploads/2018/11/winbugs143_unrestricted.zip. After unzipping the downloaded file, the software program “WinBUGS14.exe” is located in the folder “WinBUGS14”. If the R package “R2WinBUGS” has not been installed yet, type the following command in R to install this package:

```r
> install.packages("R2WinBUGS")
```

This package implements BUGS models via the R platform. Load the R package “R2WinBUGS”:

```r
> library("R2WinBUGS")
```

The BUGS model for network meta-analysis can be specified in the following R function:

```r
BayesianNMAModel <- function(){
  for(i in 1:NS){
    w[i,1] <- 0
    delta[i,t[i,1]] <- 0
```

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mu[i] ~ dnorm(0, 0.0001)  # vague priors for trial baselines
for(k in 1:na[i]){  
  r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])  # binomial likelihood
  logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]  # model
}
for(k in 2:na[i]){  # trial-specific LOR
  delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], tau[i,t[i,k]])
  md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]  # mean of LOR
  tau[i,t[i,k]] <- tau*2*(k - 1)/k  # precision of LOR
  # adjustment of multi-arm trials
  w[i,k] <- delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]]
  sw[i,k] <- sum(w[i,1:(k-1)])/k - 1}
}
d[1] <- 0
for(k in 2:NT){
  d[k] ~ dnorm(0, 0.0001)
}
tau <- pow(sd, -2)
sd ~ dunif(0, 2)  # uniform prior for random effects standard deviation

# pairwise ORs
for(c in 1:(NT - 1)){
  for(k in (c + 1):NT){
    lor[c,k] <- d[k] - d[c]
    lor.new[c,k] ~ dnorm(lor[c,k], tau)  # predicted LOR
  }
}

Alternatively, the BUGS model can be stored in a separate text file in the working directory. Note that the last line lor.new[c,k] ~ dnorm(lor[c,k], tau) is the additional part for producing prediction intervals, and all remaining parts are the conventional code to perform Bayesian network meta-analysis. After specifying the BUGS model, we type the following R code to prepare the smoking cessation dataset in the format of the above BUGS model:

```r
> NS <- dim(smokingcessation)[1]
> NT <- 4
> na <- c(rep(3, 2), rep(2, NS - 2))
> r <- as.matrix(smokingcessation[,c("event1", "event2", "event3")])
> n <- as.matrix(smokingcessation[,c("n1", "n2", "n3")])
> treat <- smokingcessation[,c("treat1", "treat2", "treat3")]
> t <- matrix(NA, NS, 3)
> for(i in 1:NS){
+   for(j in 1:3){
+     if(treat[i,j] == "A") t[i,j] <- 1
+     if(treat[i,j] == "B") t[i,j] <- 2
+     if(treat[i,j] == "C") t[i,j] <- 3
+     if(treat[i,j] == "D") t[i,j] <- 4
+   }
+ }
```

Based on the above reformatted data, we specify the objects of data and the parameters’ initial values (used to initialize the Markov chain Monte Carlo algorithm) in the BUGS model as follows:
> data <- list(NS = NS, NT = NT, na = na, r = r, n = n, t = t)
> inits <- list(
+   list(mu = rep(0, NS), d = rep(0, 4), sd = 1),
+   list(mu = rep(0.5, NS), d = rep(-0.5, 4), sd = 2),
+   list(mu = rep(-0.5, NS), d = rep(0.5, 4), sd = 0.5))

Consequently, the following code performs Bayesian network meta-analysis by invoking WinBUGS from R:

> set.seed(1234)
> out.bugs <- bugs(data = data, inits = inits,
+   parameters.to.save = c("lor", "lor.new", "sd"),
+   model.file = BayesianNMAModel,
+   n.chains = 3, n.iter = 50000, n.burnin = 20000, n.thin = 2,
+   bugs.directory = bugs.dir)
> out.bugs.smry <- out.bugs$summary
> est.bugs <- CI.lower.bugs <- CI.upper.bugs <-
+   PrI.lower.bugs <- PrI.upper.bugs <- matrix(0, 4, 4)
> for(i in 1:4){
+   for(j in 1:4){
+     if(i < j){
+       est.bugs[j, i] <-
+         out.bugs.smry[paste0("lor\[", i, ",", j, "]"), "50%"]
+       est.bugs[i, j] <- -est.bugs[j, i]
+       CI.lower.bugs[j, i] <-
+         out.bugs.smry[paste0("lor\[", i, ",", j, "]"), "2.5%"]
+       CI.lower.bugs[i, j] <-
+         -out.bugs.smry[paste0("lor\[", i, ",", j, "]"), "97.5%"]
+       CI.upper.bugs[j, i] <-
+         out.bugs.smry[paste0("lor\[", i, ",", j, "]"), "97.5%"]
+       CI.upper.bugs[i, j] <-
+         -out.bugs.smry[paste0("lor\[", i, ",", j, "]"), "2.5%"]
+       PrI.lower.bugs[j, i] <-
+         out.bugs.smry[paste0("lor.new\[", i, ",", j, "]"), "2.5%"]
+       PrI.lower.bugs[i, j] <-
+         -out.bugs.smry[paste0("lor.new\[", i, ",", j, "]"), "97.5%"]
+       PrI.upper.bugs[j, i] <-
+         out.bugs.smry[paste0("lor.new\[", i, ",", j, "]"), "97.5%"]
+       PrI.upper.bugs[i, j] <-
+         -out.bugs.smry[paste0("lor.new\[", i, ",", j, "]"), "2.5%"]
+     }
+   }
+ }

Here, the first line set.seed(1234) specifies a seed to generate random numbers for starting the Markov chain Monte Carlo algorithm, so that all results can be exactly reproduced. The argument model.file = BayesianNMAModel in the function bugs() specifies the BUGS model; here, recall that BayesianNMAModel is an R function containing the BUGS model as defined above. If a separate text file is used to specify the BUGS model, the argument model.file should be a character string of the text file’s name (and the path to this file if the working directory is not pre-specified). In addition, the argument bugs.dir specifies the path to the location of the WinBUGS software program on the user’s PC; usually, it has the form of ".../WinBUGS14".

The results are obtained using three Markov chains (specified by the argument n.chains), each having 30,000 iterations (which is the argument n.iter minus the argument n.burnin) after a 20,000-
run burn-in period (specified by the argument `n.burnin`) with thinning rate 2 (specified by the argument `n.thin`) for reducing sample autocorrelations. The results can be displayed as follows:

```r
> est.bugs
[,1]    [,2]    [,3]    [,4]
[1,] 0.0000  -0.4823  -0.8357  -1.0940
[2,] 0.4823   0.0000   -0.3558  -0.6093
[3,] 0.8357   0.3558   0.0000  -0.2541
[4,] 1.0940   0.6093   0.2541   0.0000
> CI.lower.bugs
[,1]      [,2]       [,3]       [,4]
[1,] 0.0000000  -1.290025   -1.3360000  -1.996000
[2,] -0.2917000   0.0000000   -1.1740000  -1.598025
[3,]  0.3954000   0.4515000     0.0000000  -1.083000
[4,]  0.2681825  -0.3220000   -0.5437125   0.000000
> CI.upper.bugs
[,1]     [,2]    [,3]       [,4]
[1,] 0.000000  0.2917000  0.3954000   0.2681825
[2,]  1.290025  0.0000000  1.1740000   1.598025
[3,]  1.3360000  1.1740000   0.0000000   1.5437125
[4,]  1.9960000  1.5980250  1.0830000   0.0000000
> PrI.lower.bugs
[,1]      [,2]      [,3]      [,4]
[1,] 0.0000000  -2.390025   -2.6440000  -3.065000
[2,] -1.3750000   0.0000000  -2.2650255  -2.567025
[3,] -0.8928025  -1.5380000   0.0000000  -2.169025
[4,] -0.7721050  -1.3100255  -1.6160250   0.000000
> PrI.upper.bugs
[,1]     [,2]      [,3]     [,4]
[1,] 0.0000000   1.3750000   0.8928025  0.772105
[2,]  2.3900255   0.0000000  1.5380000  1.310025
[3,]  2.6440000   2.2650255  0.0000000  1.616025
[4,]  3.0650000   2.5670255  2.1690250   0.000000
```

The interpretation of these results is similar to that of the results produced by the R package “netmeta” in the above section. The objects `CI.lower.bugs` and `CI.upper.bugs` represent the lower and upper bounds of 95% credible intervals (under the Bayesian framework), instead of 95% confidence intervals as in the results produced by the R package “netmeta” (under the frequentist framework).

**Remarks**

As shown in the above statistical code, prediction intervals can be feasibly produced by all three software programs with a few additional commands. The results of the network meta-analysis of smoking cessation are visualized in the Figure in the main content. The point estimates of odds ratios produced by the three software programs are generally similar for each treatment comparison. The lower and upper bounds of the 95% confidence/credible intervals and the 95% prediction intervals produced by different software programs may have some noticeable differences. These differences may be due to the different model assumptions and specifications used in the different software programs for network meta-analysis.

**Research reproducibility**

The results produced in this article were based on Stata/SE version 13.0, R version 3.5.3, R package “netmeta” version 1.0-1, R package “R2WinBUGS” version 2.1-2, and WinBUGS version 1.4.3.
**eTable 1. Characteristics of Articles on Network Meta-analyses**

| Article                      | Year | Journal | Statistical method used to perform network meta-analysis | Prediction intervals reported (yes/no) |
|------------------------------|------|---------|--------------------------------------------------------|---------------------------------------|
| Phung et al.11               | 2010 | *JAMA*  | Bayesian RE model                                      | No                                    |
| Anothaisintawee et al.12     | 2011 | *JAMA*  | Frequentist RE model                                    | No                                    |
| Castellucci et al.13         | 2014 | *JAMA*  | Bayesian FE/RE model                                    | No                                    |
| Johnston et al.14            | 2014 | *JAMA*  | Bayesian RE model                                       | No                                    |
| Bratton et al.15             | 2015 | *JAMA*  | Frequentist RE model                                    | No                                    |
| Isayama et al.16             | 2016 | *JAMA*  | Bayesian RE model                                       | No                                    |
| Khera et al.17               | 2016 | *JAMA*  | Bayesian RE model                                       | No                                    |
| Palmer et al.18              | 2016 | *JAMA*  | Frequentist RE model                                    | No                                    |
| Tricco et al.19              | 2017 | *JAMA*  | Frequentist RE model                                    | No                                    |
| Gregori et al.20             | 2018 | *JAMA*  | Bayesian RE model                                       | No                                    |
| Mitra et al.21               | 2018 | *JAMA*  | Bayesian RE model                                       | No                                    |
| Zheng et al.22               | 2018 | *JAMA*  | Bayesian FE/RE model                                    | No                                    |
| Cipriani et al.23            | 2011 | *Lancet*| Bayesian RE model                                       | No                                    |
| Palmerini et al.24           | 2012 | *Lancet*| Bayesian RE model                                       | No                                    |
| Leucht et al.25              | 2013 | *Lancet*| Bayesian RE model                                       | No                                    |
| Palmer et al.26              | 2015 | *Lancet*| Frequentist RE model                                    | No                                    |
| Palmerini et al.27           | 2015 | *Lancet*| Bayesian RE model                                       | No                                    |
| Singh et al.28               | 2015 | *Lancet*| Bayesian FE/RE model                                    | No                                    |
| Siontis et al.29             | 2015 | *Lancet*| Frequentist RE model                                    | No                                    |
| Cipriani et al.30            | 2016 | *Lancet*| Bayesian RE model                                       | No                                    |
| da Costa et al.31            | 2017 | *Lancet*| Bayesian RE model                                       | No                                    |
| Jinatongthai et al.32        | 2017 | *Lancet*| Frequentist RE model                                    | No                                    |
| Cipriani et al.33            | 2018 | *Lancet*| Bayesian RE model                                       | No                                    |
| Wandel et al.34              | 2010 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Baldwin et al.35             | 2011 | *BMJ*   | Bayesian/frequentist RE model                           | No                                    |
| Hartling et al.36            | 2011 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Trelle et al.37              | 2011 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Bangalore et al.38           | 2012 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Daniels et al.39             | 2012 | *BMJ*   | Bayesian FE/RE model                                    | No                                    |
| Haas et al.40                | 2012 | *BMJ*   | Bayesian RE model                                       | Yes                                   |
| Hutton et al.41              | 2012 | *BMJ*   | Bayesian RE model                                       | Yes                                   |
| Bangalore et al.42           | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Castellucci et al.43         | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Chatterjee et al.44          | 2013 | *BMJ*   | Bayesian RE model                                       | No*                                   |
| Naci and Ioannidis45         | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Navarese et al.46            | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Stegeman et al.47            | 2013 | *BMJ*   | Frequentist RE model                                    | No                                    |
| Uthman et al.48              | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Wu et al.49                  | 2013 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Bangalore et al.50           | 2014 | *BMJ*   | Frequentist RE model                                    | No                                    |
| Loymans et al.51             | 2014 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Naci et al.52                | 2014 | *BMJ*   | Bayesian FE/RE model                                    | No                                    |
| Price et al.53               | 2014 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Tricco et al.54              | 2014 | *BMJ*   | Frequentist RE model                                    | Yes                                   |
| Windecker et al.55           | 2014 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Alfrevic et al.56            | 2015 | *BMJ*   | Bayesian FE/RE model                                    | No                                    |
| Giacoppo et al.57            | 2015 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Li et al.58                  | 2015 | *BMJ*   | Bayesian RE model                                       | No                                    |
| Article                                    | Year | Journal | Statistical method used to perform network meta-analysis | Prediction intervals reported (yes/no) |
|-------------------------------------------|------|---------|----------------------------------------------------------|----------------------------------------|
| Luangasatanatip et al.59                  | 2015 | BMJ     | Bayesian RE model                                        | No                                     |
| Dulai et al.60                            | 2016 | BMJ     | Bayesian RE model                                        | No                                     |
| Hazelwood et al.61                        | 2016 | BMJ     | Bayesian RE model                                        | No                                     |
| Lopez-Lopez et al.62                      | 2017 | BMJ     | Bayesian FE model                                        | No                                     |
| Lopez-Lopez et al.63                      | 2017 | BMJ     | Bayesian FE model                                        | No                                     |
| Moser et al.64                            | 2017 | BMJ     | Frequentist RE model                                     | No                                     |
| Wang et al.65                             | 2017 | BMJ     | Frequentist RE model                                     | Yes                                    |
| Siontis et al.66                          | 2018 | BMJ     | Frequentist RE model                                     | No                                     |
| Tricco et al.67                           | 2018 | BMJ     | Bayesian RE model                                        | Yes                                    |
| Xu et al.68                               | 2018 | BMJ     | Bayesian RE model                                        | No                                     |

Prediction intervals were reported only for pairwise meta-analyses, not for network meta-analyses. Acronym: FE, fixed effects; NA, not applicable; RE, random effects. These articles are sorted by their journals, publication years, and first authors’ surnames.
eTable 2. Summary of Software Programs for Producing Prediction Intervals in Network Meta-analysis

| Software program | Model type | Command for producing prediction intervals |
|------------------|------------|---------------------------------------------|
| Stata            | Frequentist| Use `intervalplot` with the `predictions` option after running the `network meta` command |
| R package “netmeta” | Frequentist | Specify the argument `prediction` as `TRUE` in the function `netmeta()` |
| WinBUGS\(^a\) | Bayesian   | Within the BUGS model, draw further samples from the predictive distribution \( \delta_{jk,\text{new}} \sim N(d_{jk}, \sigma^2) \) for the treatment comparison of \( k \) vs. \( j \), where \( d_{jk} \) and \( \sigma^2 \) are the overall relative effect and between-study variance; form the prediction interval based on the posterior quantiles of \( \delta_{jk,\text{new}} \) |

\(^a\)Other software programs that support the Markov chain Monte Carlo algorithm (e.g., JAGS, OpenBUGS, SAS, Stan) can be also used to perform Bayesian network meta-analyses, and thus readily produce prediction intervals.
eFigure. Estimated Overall Odds Ratios of 6 Treatment Comparisons in the Network Meta-analysis of Smoking Cessation Using Stata, R Package netmeta, and WinBUGS

A indicates no intervention; B, self-help; C, individual counseling; and D, group counseling.
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