Supplemental Material S3. Specifications of the fixed effects and random effects models.

3.1 Fixed effects model

To allow for comparisons of multiple treatments, we used a notation that distinguishes between arm k of trial i and the treatment compared in that arm, since not all studies will compare the same treatments. With continuous outcome data, the meta-analysis was based on the sample means, y_{ik}, which are approximately normally distributed, with likelihood

$$y_{ik} \sim \text{Normal}(\theta_{ik}, se_{ik}^2) \tag{3.1}$$

where θ_{ik} is the linear predictor in arm *k* of trial *i*. The treatment in arm 1 (no-training control group) is taken to be the reference in the analysis. The parameter of interest is the mean, θ_{ik}, with

$$\theta_{ik} = \mu_i + d_{t_{i1},t_{ik}} \tag{3.2}$$

where μ_i are the trial-specific baseline effects of the treatment in arm 1 of trial i, and $d_{t_{i1},t_{ik}} =$

$d_{1,t_{ik}} - d_{1,t_{i1}}$ represents the mean effect of the treatment in arm *k* in trial *i*, t_{ik}, compared with the treatment in arm 1 of trial *i*, t_{i1}, and $d_{11} = 0$. The basic parameters d_{1k}, $k = 2, \ldots, S$, representing the pooled effects of treatments 2, …, 8 compared with treatment 1 (the reference treatment) are estimated. The basic parameters were assigned non-informative prior distributions

$$d_{1k} \sim \text{Normal}(0, 100^2) \tag{3.3}$$

3.2 Random effects model

The random effects model is obtained by replacing equation (3.2) with

$$\theta_{ik} = \mu_i + \delta_{ik} \tag{3.4}$$

where δ_{ik} are the trial-specific treatment effects of the treatment in arm *k*, relative to the treatment in arm 1 in that trial. The relative effect of the treatment in arm 1 compared with itself to zero, $\delta_{i1} = 0$ and for $k > 1$

$$\delta_{ik} \sim \text{Normal}(d_{t_{i1},t_{ik}}, \sigma^2) \tag{3.5}$$

where σ^2 represents the between-trial variability in treatment effects (heterogeneity). The prior distribution for the between-trial heterogeneity standard deviation σ is chosen as

$$\sigma \sim \text{Uniform}(0,5) \tag{3.6}$$

We used the conditional univariate distribution to estimate the random effects for multi-arm ($k > 2$) studies so that the between-arm correlations between parameters are taken into account (Raiffa & Schlaiffer, 2000):

$$\delta_{i,1k} \left| \begin{pmatrix} \delta_{i,12} \\ \vdots \\ \delta_{i,1(k-1)} \end{pmatrix} \right. \sim \text{Normal}\left(\left(d_{1,t_{ik}} - d_{1,t_{i1}}\right) + \frac{1}{k-1}\sum_{j=1}^{k-1}\left[\delta_{i,1j} - \left(d_{1,t_{ij}} - d_{1,t_{i1}}\right)\right], \frac{k}{2(k-1)}\sigma^2 \right) \tag{3.7}$$

3.3 Meta-regression models

To extend the standard network meta-analysis model specification described above to include study-level covariates, we introduce interaction terms, β_{12}, β_{13}, …, β_{1S}. Each of these added terms represents the additional (interaction) treatment effect per unit increase in the covariate value in comparisons of treatments 2, 3, …, S to treatment 1. These terms are exactly parallel to the main effects d_{12}, d_{13}, …, d_{1S}. As with the main effects, the interaction term would be the difference between the interaction terms on the effects relative to treatment 1. The random effects model is obtained by replacing equation (3.4) with

$$\theta_{ik} = \mu_i + \delta_{ik} + \beta_{t_{i1},t_{ik}}(x_i - m_x) \tag{3.8}$$

$$\beta_{t_{i1},t_{ik}} = \beta_{1,t_{ik}} - \beta_{1,t_{i1}} \tag{3.9}$$

where x_i is the trial-level covariate for trial i, which can represent a subgroup, a continuous covariate; for continuous covariates it is generally advisable to center the covariate to improve convergence, m_x represent the centering value; and β_{ck} the regression coefficient for the covariate effect in comparisons of treatment k to c, which can be written as the difference in interactions with the reference treatment ($\beta_{1k} - \beta_{1c}$). In this model δ_{ik} represent the relative effect of the treatment in arm k compared with the treatment in arm 1 of trial i at the centering value m_x. Similarly, the pooled effects d_{1k} will be the relative effects of treatments k = 2, …, S compared with the reference treatment at the centering value m_x.

In a network meta-analysis context, there are a very large number of models that can be proposed for the interaction terms, β, each with very different implications. Three possible model specifications that make different assumptions regarding the covariate effects on each treatment are described below.

(1) Independent treatment-by-covariate interactions

This model assumes that all treatment-by-covariate interactions are different for each treatment vs the control comparator and entirely unrelated to each other by including a separate regression coefficient for each treatment in the network (excluding the control comparator). Each regression coefficient is given an independent non-informative prior distribution, such that for treatment k = 2, …, S

$$\beta_{1k} \sim \text{Normal}(0, 100^2)\ . \tag{3.10}$$

(2) Exchangeable treatment-by-covariate interactions

This model assumes that the interaction effects for each treatment are different but related. The interaction terms are drawn from a random distribution with a common mean and between-treatment variance, so for treatment *k* = 2, …, *S*

$$\beta_{1k} \sim \text{Normal}(b, \sigma_b^2) \tag{3.11}$$

where b is the overall mean and σ_b^2 its corresponding between treatment heterogeneity in covariate effect. Independent prior distributions are given for b and σ_b^2.

(3) Common treatment-by-covariate interactions

In this more restrictive model, there is a single interaction term b that applies to relative effects of all the treatments relative to treatment 1. For all treatments *k* = 2, …, *S*, we set

$$\beta_{1k} = b\,. \tag{3.12}$$

References

Dias, S., Ades, A. E., Welton, N. J., Jansen, J. P., & Sutton, A. J. (2018). *Network meta-analysis for decision-making*. John Wiley & Sons, Ltd.

Raiffa, H., & Schlaiffer, R. (2000). *Applied statistical decision theory*. Wiley Interscience.