Bivariate network meta-analysis with second order consistency assumption and application to surrogate endpoint evaluation.

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Surrogate endpoints are very important in early regulatory decision-making in health care, when evidence on effectiveness of new health technologies may be limited due to the long follow-up time required to measure their effect on the final clinical outcome. Shorter-term surrogate endpoints can then be used if they are good predictors of clinical benefit. We develop bivariate network meta-analysis (bvNMA) methods to model the association patterns between the treatment effects on the surrogate and final outcomes within and across treatment contrasts.

Network meta-analysis (NMA) combines data from trials investigating heterogeneous treatment contrasts and has the advantage of estimating treatment effects for all contrasts individually in a single analysis. In the bivariate form, NMA models treatment effects on two correlated outcomes for all treatments in the network. It is a common practice to assume homogeneity of the between-studies covariance matrices across treatment contrasts in bvNMA, in particular when the number of studies per contrast is small. In our models, we allow for the heterogeneity parameters and the correlations to vary across treatment contrasts in order to describe the heterogeneous surrogate relationships that may vary between treatments. To take into account the constraints on the variances and correlations imposed by the network structure, we extend the method by Lu and Ades (Biostatistics 2009(10):792–805, introducing the consistency assumption for the second order moments) to the bivariate case. Additional exchangeability assumption is made when some data in the network are missing, for example the effect of a new treatment on the final outcome.

We apply bvNMA to model heterogeneous surrogate relationships across multiple trials (different populations) within each treatment contrast and across different treatment contrasts. This allows us to make predictions of the treatment effect on the final outcome either for a new study of an existing treatment but in a new population or for a trial investigating a new treatment. Modelling techniques are illustrated using simulated data and an applied example in advanced colorectal cancer. When the strength of the surrogate relationship varies across treatment contrasts, bvNMA has the advantage of identifying treatments for which surrogacy holds, thus leading to better predictions.