Meta-Analysis in Stata:

An Updated Collection from the Stata Journal

Second Edition

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Introduction to the second edition

We are delighted that this second edition of *Meta-Analysis in Stata* reflects the continuing innovations in meta-analysis software made by the Stata community since the publication of the first edition in 2009. This new collection of articles about meta-analysis from the *Stata Technical Bulletin* and the *Stata Journal* includes 27 articles, of which 11 are new additions.

The main Stata meta-analysis command `metan` has been widely used by researchers and, according to Google Scholar, has to date been cited by over 300 articles (adding the citations for Bradburn, Deeks, and Altman [1998], Harris et al. [2008], and its listing on the Statistical Software Components archive). We hope that this collection will facilitate the widespread use of both the existing and new commands.

The new articles reflect recent methodological developments in meta-analysis and provide new commands implementing these methods. The second edition extends the structure of the first edition by including parts on multivariate meta-analysis, individual participant data (IPD) meta-analysis, and network meta-analysis.

Part 1 is concerned with fitting meta-analysis models. It additionally includes the article by Kontopantelis and Reeves (2010) describing the `metaan` command, which provides additional estimators for random-effects meta-analysis and can report alternative measures of heterogeneity.

Part 2 remains unchanged from the first edition.

Part 3 is concerned with investigation of bias. It additionally includes the article by Crowther, Abrams, and Lambert (2012) describing the `extfunnel` command, which can be used to examine the impact of a hypothetical additional study on a meta-analysis by augmenting the funnel plot with statistical significance or heterogeneity contours.

Part 4, which addresses multivariate (multiple outcomes) meta-analysis, discusses a substantial update to the `mvmeta` command for multivariate outcome meta-analysis as described by White (2011). The update includes multivariate meta-regression and additional postestimation reporting features, such as I^2 statistics for each outcome.

Part 5 is a new collection of commands for IPD meta-analysis. The article by Kontopantelis and Reeves (2013) describes the `ipdforest` command, which performs IPD meta-analysis using either hierarchical linear or logistic regression and can provide a forest plot. A two-stage approach to IPD meta-analysis is described by Fisher (2015) and implemented in the `ipdmetan` command. The command can incorporate studies reporting both IPD and study-level (aggegrate) data and has options to fine tune the forest plots in such settings.

Part 6 includes three new articles on network meta-analysis, which is a major recent development in meta-analysis methodology (Bucher et al. 1997, Caldwell, Ades, and Higgins 2005; Salanti et al. 2008; Salanti 2012). The first article, by Miladinovic et al. (2014), concerns comparisons of treatments in the absence of direct evidence between them (so-called indirect comparisons). The second article, by White (Forthcoming), presents the `network` suite of commands for network meta-analysis, which is centered around fitting network meta-analysis models with the multivariate normal approach using `mvmeta`. Third the article, by Chaimani and Salanti (Forthcoming), describes the `network_graphs` package of graphical commands for network meta-analysis. These commands have been designed to work with the same data structures as those provided by the `network` suite.

Part 7 includes articles on various advanced meta-analysis methods. New articles include that by Crowther et al. (2013), which provides the `metasim`, `metapow`, and `metapowplot` commands. These estimate the probability that the conclusions of a meta-analysis will change given the inclusion of a hypothetical new study and are based on the methodology of Sutton et al. (2007). Stata 12 and 13 introduced the `sem` and `gsem` commands for structural equation modeling. These commands are very flexible and allow a wide range of constraints to be placed on the parameters in the model. Palmer and Sterne (Forthcoming) describe how these features enable these commands to fit fixed- and random-effects meta-analysis models, including meta-regression and multivariate meta-analysis models. Cumulative meta-analysis was discussed in the first edition by Sterne (1998). Through their `metacumbounds` command, Miladinovic, Hozo, and Djulbegovic (2013) automate the use of the "ldbounds" package for R (Casper and Perez 2014). This command implements trial sequential boundaries for cumulative meta-analyses for controlling the type I error of the meta-analysis.

Information about user-written commands for meta-analysis can be obtained by typing `help meta` in Stata. In addition to this, Stata maintains a frequently asked questions on meta-analysis at

http://www.stata.com/support/faqs/statistics/meta-analysis/

We hope that this second edition of articles about meta-analysis repeats the success of the first edition and continues to encourage users to implement the latest methods for meta-analysis in new Stata commands.

Tom M. Palmer and Jonathan A. C. Sterne
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The data formats provided by White (Forthcoming) and used by the `network` package of commands have been adopted by Chaimani et al. (2013) within the package `network_graphs` of graphical commands for network meta-analysis. This article has been updated for the *Stata Journal* by Chaimani and Salanti (Forthcoming). The package includes commands for assessing the assumptions of the network meta-analysis models including plotting maps of the network (`networkplot`), plotting the contribution each direct treatment comparison to the network summary estimates (`netweight`), evaluating inconsistency in each closed loop of the network (`ifplot`), and plotting comparison-adjusted funnel plots (`netfunnel`). It also includes commands for viewing the results of network meta-analysis models, including plots of confidence and prediction intervals about summary estimates (`intervalplot`), plots of ranking probabilities for each treatment (`sucra`), plots of league tables of all possible pairwise comparisons (`netleague`, new in the updated article), and additional plots ranking the pairwise treatment comparisons (`mdsrank` and `clusterank`).

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Indirect treatment comparison

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Abstract. This article presents a command, `indirect`, for the estimation of effects of multiple treatments in the absence of randomized controlled trials for direct comparisons of interventions.

Keywords: st0325, indirect, Bucher, network meta-analysis

1 Introduction

Traditional meta-analyses that combine treatment effects across trials comparing the same interventions have been used in clinical medicine since the 1980s. In the absence of direct comparisons between two interventions, under certain conditions, a network of evidence can be constructed so that interventions may be compared indirectly (Glenny et al. 2005). The methods for indirect treatment comparison can be broadly categorized as frequentist or Bayesian. The frequentist methods are those described by Bucher et al. (1997), Lumley (2002), and White et al. (2012). The main difference between the two is that the former, also known as the adjusted indirect treatment comparison (AITC) method, is intended for situations where there is no direct evidence and comparisons are made pairwise. The Lumley method, like the Bayesian one, combines both direct and indirect comparisons within a total network of evidence. The Bayesian methods are statistically more flexible but computationally intensive and complex. They revolve around the choice of a prior estimate and depend on multiple-chain Monte Carlo simulations for the posterior estimates of treatment effects (Lu and Ades 2004; Caldwell, Ades, and Higgins 2005; Jansen et al. 2008). Interested readers are directed toward a special issue of *Research Synthesis Methods* for further information

(Salanti and Schmid 2012), especially about how network meta-analysis can accommodate more complicated networks in Stata (White et al. 2012; Chaimani et al. 2013). Motivated by AITC's desirability for simple networks, we implemented it as the Stata command `indirect`.

2 Adjusted indirect treatment comparison

The adjusted indirect method allows for the comparison of two treatments by using information from randomized controlled trials comparing each of the interventions with a common comparator. It assumes that the treatment effectiveness is the same across all trials used in the comparison. Formally and following notation by Wells et al. (2009), given k number of treatments $T_1, T_2, \ldots, T_k$ such that all consecutive pairs have been compared (T_1 versus T_2, T_2 versus $T_3, \ldots, T_{k-1}$ versus T_k), the indirect $100(1-\alpha/2)\%$ confidence interval (CI) estimator of the measure of association $\widehat{A}$ for a pair of treatments (T_i, T_{i+1}) is given by

$$\sum_{i=1}^{k-1} \widehat{A}_{T_i T_{i+1}} \pm Z_{\frac{\alpha}{2}} \sqrt{\sum_{i=1}^{k-1} \mathrm{Var}\left(\widehat{A}_{T_i T_{i+1}}\right)}$$

where $\sum_{i=1}^{k-1} \widehat{A}_{T_i T_{i+1}}$ is the indirect estimator of treatments T_1 and T_k. The measure of association $\widehat{A}$ can be in the form of an odds ratio, a risk ratio, a hazard ratio (HR), a risk difference, or a mean difference. The test statistic for testing the indirect association between treatments T_1 and T_k for n number of studies used is

$$\chi^2_{df=n} = \frac{\sum_{i=1}^{k-2} \sum_{j=i+1}^{k-1} \left(\sum_{j=1}^{n} W_{T_i T_{i+1}, j}\right) \left(\sum_{j=1}^{n} W_{T_j T_{j+1}, j}\right) \left(\widehat{A}_{T_i T_{i+1}} - \widehat{A}_{T_j T_{j+1}}\right)^2}{\sum_{i=1}^{k-1} \sum_{j=1}^{n} W_{T_i T_{i+1}, j}}$$

where the weight assigned for the jth study evaluating treatments (T_i, T_{i+1}) is defined as

$$W_{T_i T_{i+1}, j} = \left\{\mathrm{Var}\left(\widehat{A}_{T_i T_{i+1}, j}\right)\right\}^{-1}$$

AITC can calculate indirect treatment estimates for the networks given in figure 1 (star, ladder, and single loop) as long as the comparisons are made pairwise.

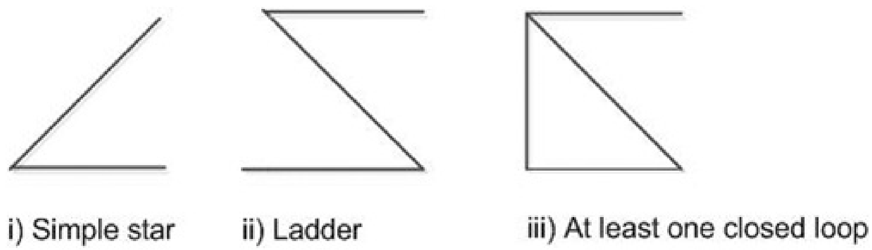

Figure 1. Examples of network patterns for the AITC

2.1 Syntax for indirect

Our command `indirect` assumes that Stata's `metan` command (Harris et al. 2008) has been installed. Because of the complexity of the syntax and to facilitate the ease of its implementation, we have included a dialog-box file, `indirect.dlg` (figure 2).

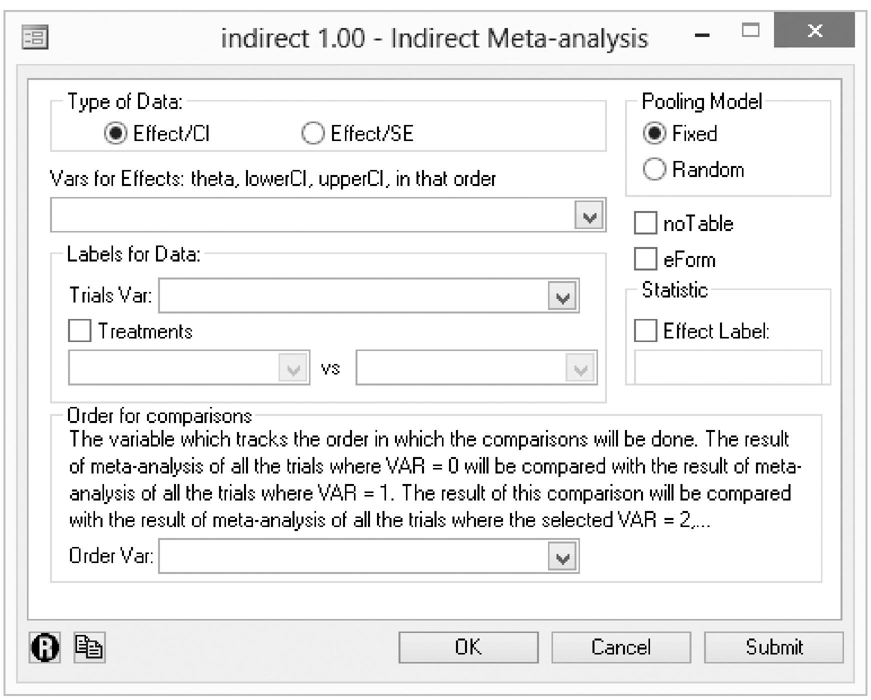

Figure 2. Dialog box used to process `indirect`