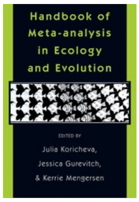

Schmid, C.H., Stewart, G.B., Rothstein, H.R., Lajeunesse, M.J. and Gurevitch, J. (2013) Software for statistical meta-analysis. In J. Koricheva, J. Gurevitch, and K. Mengersen, editors. Handbook of meta-analysis in ecology and evolution (pp. 174 −194). Princeton University Press, Princeton, New Jersey, USA.

12

Software for Statistical Meta-analysis

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Disclaimer: Authors of this chapter have participated in authoring several of the software packages discussed in this chapter. CHS is a coauthor of MetaAnalyst, HR is a coauthor of Comprehensive Meta-Analysis, MJL is the author of phyloMeta, and JG is a coauthor of MetaWin.

To conduct a meta-analysis, a researcher will need to use computer software to perform all but the simplest calculations. There are three types of software that can be used, depending upon the needs of the user. The first option is a spreadsheet, the second is a general purpose statistical package, and the third option is a program developed expressly to carry out meta-analysis.

The most basic meta-analytic tools, such as weighted averages for fixed- and random-effects models, can be programmed by a knowledgeable user in a spreadsheet, such as Microsoft Excel. In the past, spreadsheets have often been used to carry out many of the meta-analyses published in the scientific literature, but we advise that these should no longer be used in research. This is because of the likelihood of programming and transcriptional errors, and because many of the statistical and graphical analyses that have now become standard are not available using spreadsheet analyses, though they are available elsewhere.

General purpose statistical software varies in its ease of use and flexibility for meta-analysis. These packages cannot be used "as is" because their base algorithms are designed primarily for the statistical analysis of primary studies, and thus produce erroneous results applied directly to meta-analysis. Fortunately, a variety of books and journal articles have included code for adapting one or more of these packages for meta-analysis and, for each of the major software packages, meta-analysts have developed publicly available macros and subroutines. We describe some of these in this chapter for SAS, SPSS, Stata, S-Plus, R, and BUGS. Stata, in particular, has become a popular tool because of its relatively intuitive commands and the availability of macros to perform most of the standard and many of the not-so-standard analyses written and promoted by methodological leaders in meta-analysis (Sterne et al. 2009).

Users who are familiar with these packages, and who have the requisite programming and statistical ability, may find it worthwhile to use these programs, or even to create their own routines, functions, or macros; these could be particularly useful for complex analyses such as the multivariate, Bayesian, and longitudinal analyses described in Chapters 11 and 16. These chapters give code for some of the most common types of analyses. However, most nonstatisticians will find this difficult. These statistical packages generally have steep learning curves and require a large investment of time, very little of which is specific to meta-analysis. Several are also quite expensive.

Finally, there are stand-alone packages for meta-analysis that come in many different flavors. We focus on those that are the most flexible and the most suited to the types of analyses carried out by ecologists and evolutionary biologists. Thus, we pass over the many limited programs that are either specialized for other fields, such as psychometric meta-analysis (the Hunter-Schmidt package; Roth 2008), the meta-analysis of diagnostic tests (MetaDiSc; Zamora et al. 2006), or that were written in outdated formats such as MS-DOS in the early years of meta-analysis (e.g., DStat and True Epistat; Normand 1995).

The most well-known and widely available of the general stand-alone programs are Comprehensive Meta-Analysis (CMA), MetaWin, MIX, MetaAnalyst, and RevMan. In general, all these packages are easier to use for meta-analysis than the general purpose packages, but they vary substantially in their ability to import and export data, compute effect sizes and variances for the data from each primary study, handle complex data structures (such as multiple subgroups, outcomes, time-points, or comparisons), use different statistical models, conduct subgroup analyses and meta-regression, perform sensitivity and small study/publication bias analyses, and provide presentation quality graphics. They also differ in user friendliness, technical support, documentation, and price. Thus, their attractiveness depends on which features are important to individual users.

We first review the stand-alone programs (see Table 12.1 for comparison), then discuss the general purpose software (see Table 12.2 for comparison), and finally briefly review two programs that can extract the data underlying a graphical display. Readers will need to keep in mind that software features, cost, and availability all change fairly rapidly over time; while some of the specific information here may be out of date by the time you are reading this chapter, the general issues and principles we discuss in choosing software for meta-analysis will have a longer half-life. Web searches, the Methods sections of recent research syntheses, and professional meetings where research synthesis results and methods are presented, are good resources for keeping up with both software availability and developments in methodology.

STAND-ALONE META-ANALYSIS SOFTWARE

Comprehensive Meta-analysis (CMA)

CMA is a popular package that has been developed under the consultation of a team of meta-analytic experts. It offers an accessible user interface with many options, excellent graphics, and most standard non-Bayesian analyses that do not require iterative computations.

Data entry

Summary data from each study are entered into a spreadsheet. One of the strengths of CMA is the variety of types of summary data it will accept and then convert to the effect size of interest. Additionally, CMA allows the user to select a different format for each study, if needed. For example, the user can provide correlations and sample sizes, correlations and standard errors, or *P*-values and sample sizes. For binary data, the user can provide the number of events and nonevents, odds ratios and confidence intervals, or chi-square statistics and sample sizes. Altogether, CMA accepts summary data in over 100 different formats. It also allows the user to import data from other Windows-based spreadsheet programs, such as Excel.

Analysis

CMA can perform meta-analysis for the following effect sizes: raw mean difference, standardized mean difference (Cohen's *d* and Hedges' *g*—the latter is referred to as Hedges' *d* in

TABLE 12.1. Comparison of stand-alone software capability for meta-analysis.

	Rev Man	MetaAnalyst	MIX	MetaWin	CMA
Operating System	Windows	Windows	Windows	Windows	Windows
Distributor	Cochrane Collaboration	J Lau, C Schmid	Private	Private	Biostat, Inc
Website	www.cc-ims.net	http://tuftscaes.org/meta_analyst/	http://www.meta-analysis-made-easy.com/	www.metawinsoft.com	www.metaanalysis.com
Version	5.1	Beta 3.13	2.0	2.1.5	2.2
Price (US $)	FREE	FREE	FREE	60	various
Spreadsheet	∅	✓	✓	✓	✓
Import data	∅	✓	✓	✓	✓
MA interface	✓	✓	✓	✓	✓
Regression	∅	✓	✓	✓	✓
Single group	∅	✓	✓†	✓	✓
Fixed Effects	✓	✓	✓	✓	✓
Random Effects	✓	✓	✓	✓	✓
Multilevel Models	∅	✓	∅	∅	∅
Random Effects Regression	∅	✓	∅	✓	✓
Bayesian Models	∅	✓	∅	∅	∅
Cumulative MA	∅	✓	✓	✓	✓
Small sample/Publication Bias Tests	∅	∅	✓	✓	✓
Binary Data	✓	✓	✓	✓	✓
Continuous Data	✓	✓	✓	✓	✓
Multivariate	∅	✓	∅	∅	∅
Documentation	✓	✓	∅	✓	✓
Forest Plot	✓	✓	✓	✓	✓
Funnel Plot	✓	✓	✓	✓	✓
Data Export options	∅	✓	✓	✓	✓
Technical Support	✓	✓	✓	✓	✓
Programming capabilities	∅	∅	∅	∅	∅
Automated Leave one out sensitivity	∅	✓	∅	✓	✓

† One group analysis available for continuous outcomes only.

ecological literature), odds ratio (and log odds ratio), risk ratio (and log risk ratio), risk difference, correlation (and Fisher's z), rate ratio, and hazard ratio. It will also compute point estimates in single group designs, such as the mean, proportion, or rate in a single group. Finally, the program will work with a generic effect size.

Menus and toolbars are used to customize the analyses, and the way they are displayed. The user has the option of choosing either fixed- or random-effects models, or selecting both. The user can also tailor the statistics that will be displayed. Options include any or all of the following: effect size, variance, standard error, P-value, confidence interval, study weights, and heterogeneity statistics including τ^2, τ, and $I^{2.}$

The program can manage complex data structures, including multiple subgroups, outcomes, time-points, and/or comparisons. Several options are provided for dealing with the various data structures. For example, if some studies include several independent subgroups, the user can restrict an analysis to only some subgroups or combine data across subgroups within studies. Similarly, when some or all studies have more than one time-point at which outcome data were collected, the user can (1) limit the analysis to one or more of the time-points, (2) use the average across time-points, or (3) compare effects in different outcomes at different time-points. However, the program cannot perform an appropriate multivariate analysis across time, as discussed in Chapter 16.

The program can perform analyses using a single categorical (analysis of variance analogue or subgroup analysis) or continuous modifier (weighted regression on continuous data).

Several methods are available to assess small study/publication bias. These include the Begg and Mazumdar (1994) and Egger, Davey Smith, Schneider, et al. (1997) tests, the file drawer method (Orwin 1983), trim and fill (Duval and Tweedie 2000a, 2000b), and cumulative meta-analysis ordered by sample size or precision (Lau et al. 1995).

Sensitivity analysis options include an *omit one* analysis where the meta-analysis is run repeatedly, with one study removed on each pass. Another option is the ability to exclude sets of user-selected studies from the analysis.

Although CMA can do subgroup analyses and fixed-effects meta-regression, it cannot fit Bayesian models.

Graphics

CMA can produce forest plots with many user customizable features. Results can be exported to Microsoft Word or Powerpoint, or can be printed as a high resolution graph. CMA also produces funnel plots and forest plots for cumulative meta-analysis.

Documentation

CMA comes with an online manual, free tutorial examples in PDF form, and free technical support by phone or email. CMA was tested for accuracy against the Stata macros and the RevMan program. The formulas for conducting the synthesis are documented in Borenstein et al. (2009), and the formulas for computing effect sizes are documented in Borenstein et al. (2010a).

Cost and availability

All versions of the software may be downloaded from www.meta-analysis.com, including a fully functional demo program that runs for 10 days, with an on-request extension to one month. Costs vary depending upon whether the purchaser is a student, academic user, or commercial (for-profit company) user, whether a site license or individual use license is needed, and whether the program is obtained through an annual lease that includes free updates, or a perpetual license with optional updates. There are also several versions with different features. As of July 2012, a single perpetual license costs \$1295 at the corporate rate, \$795 at the academic rate and \$395 at the student rate. The price drops to \$395 and \$265 for corporate and academic institutions if 40 or more copies are purchased. Annual leases for teaching are \$95 per copy.

MetaWin 2.0

MetaWin is the only meta-analysis program written by ecologists and specifically designed for ecological data, although it can be used more broadly. MetaWin is easy to use and has options not available in other stand-alone meta-analysis packages, including randomization and bootstrapping procedures. But it can only handle basic analyses, with no facilities for more complex meta-analysis modeling. Its ease of use may tempt novice users to analyze data without necessarily thinking through or fully understanding their choices.

Data entry

Data can be entered directly into a spreadsheet, or imported from a Windows-based spreadsheet such as Excel. The size of the file is limited only by the storage capacity of the user's computer. The spreadsheet can be manipulated with simple commands (save, print, clear cells, cut and paste, insert column, etc.). Effect sizes and their variances can be calculated from means, standard deviations, and sample sizes (Hedges' d, ln response ratio), or from two by two contingency data (odds ratio, rate difference, and relative rate). Statistical functions can be transformed using the MetaWin calculator (e.g., Student's t can be transformed to r, Cohen's d can be transformed to r, F can be transformed to Cohen's d, and so on). Effect sizes of the user's choosing can also be directly input by the user. If correlation coefficients and sample sizes are input, MetaWin will calculate Fisher's z-transform. All commands are carried out by clicking on "radio buttons" to indicate one's choices.

Analysis

Grand mean effect size and its confidence intervals, weighted mean effect sizes for categories of studies (moderators or covariates), and confidence intervals can be calculated using parametric or bootstrap (including bias-corrected bootstrap) techniques. Weighted regressions on continuous moderators can also be computed. Heterogeneity tests (Q statistics) offer the option of parametric or randomization tests. MetaWin does not offer the heterogeneity statistics I^2 and τ^2 for random-effects analyses. Calculations can be based on fixed-effects or random-effects models. Ordinarily, the inverse of the sampling variance is chosen for the weights in the analyses, but the user can choose any other weights desired, or can do unweighted analyses (by inputting a column of ones for the weights). The program will omit any studies with undefined values for means or sampling variances from the analysis, and will indicate in the output which studies were eliminated.

Additional options are the "Refine Categories" and "Refine Studies" tabs. These allow the user to remove studies belonging to particular categories, to remove individual studies (singly or any number of them) and rerun the analyses, or to focus on particular groups; they additionally can be used for sensitivity analysis. One can also perform fail-safe calculations using either Orwin's method (Orwin 1983) or Rosenthal's method (Rosenthal 1979), with options to alter the probability level. Cumulative meta-analyses is available, but not for subgroups. The user can choose any quantitative variable to order the studies for the cumulative analysis.

Graphics

Graphics are directed to data exploration and include normal quantile plots, scatterplots, forest plots, weighted histograms, funnel plots, regression plots, radial plots for odds ratios, and cumulative meta-analysis plots. All can be generated by clicking on the appropriate radio buttons after indicating which data are to be plotted. Most options for detecting small study/publication bias are available except for trim and fill, which is not an automatic option. Graphical output is not of publication quality.

Documentation

MetaWin has an online manual and help buttons. Users can also purchase a printed version of the manual.

Cost and availability

MetaWin 2.0 was published by a commercial scientific textbook publisher, Sinauer Associates, but went out of print before this book was published. Its original cost was $150, discounted for students and for multiple-user licenses (e.g., for teaching). While it is no longer offered or supported by the publisher, it is available for downloading at a reduced price from the original package ($60 as of July 2012). Information about how to purchase it online is available on the MetaWin home page, currently at http://www.metawinsoft.com/.

MIX

MIX is a program for meta-analysis that works as an add-on to Microsoft Excel (Bax et al. 2006). It is easy to use, but is limited in its capabilities.

Data entry

Data are initially input manually through a spreadsheet or by reading in an Excel or text file or a built-in MIX data set. Data may be entered as raw counts for one or two group data, or as summary effect sizes for comparative data. Data can be saved in an internal format.

Analysis

MIX uses computational tools in Excel to do its calculations, but has its own interface that allows the user to choose from different meta-analytic tools. Menus and toolbars are used to customize the analysis. The user can choose to set significance levels, weighting methods, metrics, models, sorting orders, continuity correction for zero cells, graphical output formats, and use of the normal or *t*-distribution. Graphs are Excel objects and so can be edited with the features of Excel graphs. Data can be saved as text files, .csv files, .xls files, or as MIX data sets. Output can be exported as a graphics object only in .gif or .png format.

MIX can perform basic analyses, but has no sophisticated modeling options and no programming capabilities. MIX fits fixed- and random-effects (DerSimonian-Laird) summary models for both binary and continuous outcomes. Binary metrics include the risk ratio, risk difference, and odds ratio. Continuous metrics include the weighted mean difference, Hedges' *g* and Cohen's *d* statistics, and Fisher's *z* for correlations. For single groups, it supports a generic effect size. The program can do cumulative meta-analysis and fixed-effects regression. It reports only τ^2 as a heterogeneity statistic.

Graphics

MIX has a variety of graphics including the boxplot, normal quantile plot, residual histogram, forest plots, funnel plot, L'Abbé plot (L'Abbé et al. 1987), and radial plot (Galbraith 1994). It also has a variety of quantitative tools for examining small-study/publication bias effects including the fail-safe *N*, Egger and Begg/Mazumdar tests, and trim and fill. Sensitivity analysis options include an *omit one* analysis where the meta-analysis is run repeatedly, with one study removed on each pass, as well as the ability to exclude sets of user-selected studies from the analysis.

Documentation

Currently, no documentation is available, but this is planned at the next major update.

Cost and availability

MIX is a free add-on to Microsoft Excel and can be downloaded at http://www.meta-analysis-made-easy.com/. A new version 2.0 is now available. This will be distributed in two formats. The professional version will include all features and will require purchase of a license. As of July 2012, fees range from $75 for a student license to $210 for a personal license (for those not at academic or educational institutions). Users in developing countries can get the professional version for $50. A scaled-down "lite" version will be given for free but will not allow the user to save or build data sets. Interested users should check the website for final specifications.

PhyloMeta

PhyloMeta is a simple Windows console program developed for integrating phylogenetic information into all the conventional statistics of ecological and evolutionary meta-analyses (Lajeunesse 2011a). Here the user inputs their meta-analytical data (effect sizes and variances) and a hypothesis on the phylogenetic history connecting these effects (see details in Chapter 17). This phylogenetic hypothesis is then converted into a correlation matrix that is applied to regression models assuming fixed- or random-effects models (described in Lajeunesse 2009). It also calculates model selection criteria (AIC scores) to help distinguish the fit of these different meta-analytical models. It was designed to complement the nonphylogenetic analyses of MetaWin. It is easy to use, but has limited capability for running more elaborate regression models or for testing more sophisticated evolutionary hypotheses.

Data entry

The data entry is simple and requires the input of two text files; one contains the effect size data and moderator groupings, and the other contains the hypothesized phylogeny in NEWICK format. These effect sizes and variances must be computed externally before the analyses. PhyloMeta also cannot analyze multiple effect sizes for single species—users must pool all the effects for a single species prior to phylogenetic meta-analyses. There is also no restriction on the type of effect size metric used to quantify experimental outcomes.

Analysis

The user does not specify what analyses to perform; all are performed simultaneously in a single run of phyloMeta (e.g., fixed- and random-effects, within- and between-study *Q*-tests, analyses with and without phylogenetic information, or subgroup analyses). This design is meant to facilitate the calling of phyloMeta in R for simulation analyses or for visualizing results. It does not perform meta-regressions or advanced multilevel, multivariate, or Bayesian models. All analyses are outputted to the console screen and to a text file.

Graphics

PhyloMeta is a console program in Windows, and only provides tables of results in text format.

Documentation

Additional details on the implementation of phyloMeta are found in Lajeunesse (2011a). PhyloMeta also has a manual that describes how to perform analyses and includes troubleshooting tips for conducting phylogenetic meta-analyses. This manual is free and currently available on Marc Lajeunesse's website at http://lajeunesse.myweb.usf.edu/publications.html.

Cost and availability

PhyloMeta can be obtained at no cost as a Windows executable file on the web at http://lajeunesse.myweb.usf.edu/publications.

RevMan

RevMan (Review Manager) was developed by the Cochrane Collaboration for use with Cochrane reviews, though its use is not restricted to this application. RevMan is designed to manage all stages of a systematic review, rather than solely to conduct a meta-analysis. Users enter the protocol and the complete review, including text, characteristics of studies, comparison table, and study data. This is different than the other software reviewed in this chapter. Furthermore, since RevMan is designed for health care applications, it is primarily used for analysis of binary data, although it will also analyze mean differences.

The advantage of consistency gained by providing a standardized procedure and software for all reviews also limits its utility. The Cochrane process is quite specific and incorporates many features relevant to research in health fields. Geographically scattered review groups combine to publish reviews intended to be accessible to all interested parties. Thus, it excludes the use of advanced statistical analysis, such as regression, multilevel, multivariate, and Bayesian models, and has very limited capacity to account for random effects. It is not suitable for describing the heterogeneous types of data ecologists and evolutionary biologists frequently encounter.

Data entry

RevMan accepts data in only four formats: events and sample size; means, standard deviations and sample size; observed minus expected frequencies, standardized by the variance;

and a generic effect size. All studies must be entered in the same format. In order to deal with summary data in different formats, the user must compute the effect size and variance for each study externally and then manually input the computed effect size and variance into RevMan. Users can import summary data from spreadsheet programs, such as Excel.

The program can perform meta-analyses using raw mean differences, standardized mean differences (Hedges' *g*), odds ratios, risk ratios, risk differences, and a generic effect size.

Analysis

The user can specify the model (fixed or random effects), statistical method (e.g., Mantel-Haenszel, inverse variance, or one-step), and effect size measure. RevMan provides Q, I^2, and τ^2 as heterogeneity statistics. If data are entered for subgroups, RevMan can conduct a separate analysis for each subgroup, and can also compare effects across subgroups for fixed-effects inverse-variance based methods. It cannot, however, carry out meta-regressions or any advanced multilevel, multivariate, or Bayesian models. Sensitivity analysis in RevMan is limited to the ability to exclude sets of user-selected studies from the analysis.

Graphics

The results are displayed as a forest plot. RevMan does not carry out statistical tests for small-study/publication bias, but it will produce a funnel plot.

Documentation

The Cochrane Collaboration publishes a large handbook which serves as a standard reference for doing systematic reviews, as well as a manual for using RevMan (Higgins and Green 2011). This is available for a free download at http://handbook.cochrane.org.

Cost and availability

RevMan can be downloaded for free at http://ims.cochrane.org/RevMan.

MetaAnalyst

MetaAnalyst is a Windows-based enhancement of an old MS-DOS program distributed for many years as shareware by Joseph Lau. The update implements many advanced analytic capabilities for meta-analysis. Currently, it is undergoing a major revision that will enable it to directly interface with both the R and BUGS languages (Wallace et al. 2012).

Data entry

MetaAnalyst currently supports manual input of data through a spreadsheet format, as well as data imported from Microsoft Excel (.xls) and Comma Separated Value (.csv) formats. Users are prompted as to what type of data (e.g., one or two arm, continuous/binary/diagnostic) they wish to enter and are presented with the appropriate spreadsheet that includes study identifier, study name, and year. Data may be saved in internal format. Summary metrics are automatically calculated in the spreadsheet and displayed in a variety of formats (e.g., odds ratio, risk ratio, or risk difference for binary data), along with confidence intervals. Covariates may be added and removed at any time. Column labels may also be changed.

Analysis

MetaAnalyst supports a large number of analyses. Users can perform analyses of continuous data effects (means, standardized means, Hedges' *g*), binary data effects (risk difference, risk ratio, and odds ratio), and diagnostic accuracy metrics (e.g., sensitivity and specificity). Users may perform fixed-effects analyses with inverse variance, Mantel-Haenszel, and Peto weights; random-effects analyses using the DerSimonian-Laird weights; maximum likelihood fit by the EM algorithm, and Bayesian analyses. Meta-regression is supported for fixed, random, and Bayesian analyses, and allows the use of any number of covariates, including the baseline risk (McIntosh 1996, Schmid et al. 2004). Users may specify the confidence or credible (Bayesian confidence) levels desired. The program supports analyses of subgroups and allows exclusion of any arbitrary set of studies; it will perform sensitivity analyses leaving one study out at a time.

The Bayesian analyses use OpenBUGS (the open source version of WinBUGS, http://www.openbugs.info/w/) to perform Markov chain Monte Carlo (MCMC) analyses. Users may select different inverse gamma prior distributions for variance parameters. Bayesian analyses produce summaries of quantiles of the posterior distribution, as well as posterior probabilities of summary effects. MetaAnalyst currently implements specific OpenBUGS script files, but will shortly have the capacity for users to implement their own script files. The Gelman-Rubin diagnostic (Gelman et al. 2004) is automatically calculated to help diagnose convergence. Users can define the convergence parameter as well as the number of simulations to run and to save. Various other output statistics can be requested, including summaries and plots of the chains run; these encompass the means, medians, and percentiles of each parameter, their autocorrelations, and plots of their empirical probability densities. Numerical output is saved as .rtf files.

Graphics

Graphic types supported include forest plots for single and cumulative meta-analyses, L'Abbé plots, and funnel plots. Plots of parameter traces and autocorrelations, as well as kernel density plots of the parameters are available for Bayesian models. Plots of the observed risk and their shrinkage to posterior estimates are also included. All of these plots can be edited within MetaAnalyst and are saved as .png images.

Documentation

MetaAnalyst has online help and documentation that come with the downloaded program.

Cost and availability

MetaAnalyst is free and available for download from http://tuftscaes.org/meta_analyst/.

MACROS FOR GENERAL PURPOSE STATISTICAL SOFTWARE

Meta-analytic models can be fit with a standard regression or analysis of variance program in any of the major statistical packages, but require modifications to the standard output because of their specific within-study weights. Each of the major packages also has user-written routines that have implemented specific meta-analytic macros. We first describe the manipulations necessary to use standard statistical software for meta-analysis, and then describe meta-analysis macros that can be obtained for each of the four major packages.

TABLE 12.2. Comparison of general purpose statistical software capability for meta-analysis.

	Stata/BUGS	SAS	SPSS	R/BUGS
Operating System	Windows, Mac (only Stata), Linux, Unix	Windows, Linux, Unix	Windows, Mac, Linux	Windows, Mac (only R), Linux, Unix
Distributor	Stata Corp	SAS Corp	SPSS	R Project
Website	www.stata.com	www.sas.com	www-01.ibm .com/software/ analytics/spss/ products/ statistics	www.r-project.org
Version	12	9.3	20	2.15
Price (US $)	From 595 for annual license (Intercooled version)	Various	Various	FREE
Spreadsheet	✓	∅	✓	✓
Import data	✓	✓	✓	✓
MA interface/routines	Macros	Macros	Macros	Macros
Regression	✓	✓	✓	✓
Single group	✓	✓	✓	✓
Fixed Effects	✓	✓	✓	✓
Random Effects	✓	✓	✓	✓
Multilevel Models	✓	✓	✓	✓
Random Effects Regression	✓	✓	✓	✓
Bayesian Models	✓	✓	∅	✓
Cumulative MA	✓	✓	✓	✓
Publication Bias	✓	✓	✓	✓
Binary Data	✓	✓	✓	✓
Continuous	✓	✓	✓	✓
Multivariate	✓	✓	✓	✓
Documentation	✓	✓	✓	✓
Forest Plot	✓	✓	✓	✓
Funnel Plot	✓	✓	✓	✓
Data Export options	✓	✓	✓	✓
Technical Support	✓	✓	✓	✓
Programming capabilities	✓	✓	✓	✓
Automated Leave one out sensitivity	✓	✓	✓	✓

As described in earlier chapters, meta-analytic models are estimated by method of moments, maximum likelihood, and Bayesian methods. With method of moments, the meta-analytic estimate is a weighted average and can thus be calculated by using a regression program supplying weights as an option. When the inverse variance study weights are assumed to be known, however, a slight modification to the regression output is required. This arises because weighted regression programs typically assume that the weights supplied are proportional to the study variances (not equal to them), with the constant of proportionality defined as the residual mean squared error, σ^2. Therefore, the proper standard errors for the meta-analytic estimates require dividing the standard errors output (as provided by the programs) by the estimate of σ. When using a mixed model routine as in Chapter 10 for maximum likelihood, the variance parameters are specified explicitly, so this correction is not needed. Instead, the proper likelihood is calculated from the model specified by the user. Likewise, the Bayesian analysis specifies the within-study variances explicitly, although it is also possible to model a common proportionality constant as well. Whitehead (2002) provides more information and example code for manipulating software packages to do meta-analysis.

Stata

Stata is a general purpose computer package that has considerable flexibility, responds well to user requests, and provides a suite of meta-analytic programs contributed by users (Sterne et al. 2009). Stata has no graphical user interface for meta-analysis and must be used in a command-line format instead. On the other hand, the program syntax is straightforward and most analyses only require one line of code, usually giving the name of the program, the data, and the options required for the analysis. Stata has clean graphics, particularly for the funnel plot, and appears in many publications of meta-analyses. It also has an interface to BUGS (see below) called *winbugsfromstata*, so it is possible to run Bayesian analyses and return the results to Stata. Thus, Stata can be used for data entry, manipulation, and presentation, leaving BUGS to do the calculation.

Data entry

Data are passed into the meta-analytic routines through Stata. Users can input cell frequencies from two by two tables for binary outcomes, means and standard deviations for numerical outcomes, or estimates and standard errors; these are placed in the Stata meta-analysis functions.

Analysis

Stata provides several commands for meta-analysis. *Metan* is the main meta-analysis command; it provides a comprehensive range of methods for meta-analysis using fixed- and random-effects models, and creates new variables containing the treatment effect estimate and its standard error for each study. These variables can then be used as input to other Stata meta-analysis commands. Meta-analyses may be conducted in subgroups by using the by( ) option. *Metacum* is a command for implementing cumulative meta-analysis and *metap* performs meta-analysis of *P*-values. Meta-regression is implemented in the *metareg* command. Stata also has commands for implementing advanced methods, including *glst* for generalized least squares that is used for trend estimation of summarized dose-response data (Berlin et al. 1993), *mvmeta* for maximum likelihood, restricted maximum likelihood, or method of moments estimation of random-effects multivariate models; and *metamiss* for meta-analysis with binary outcomes when some or all studies have missing data. *Metabias* implements tests for asymmetry in funnel plots and *metatrim* does trim and fill.

Graphics

Stata implements the funnel plot with the *metafunnel* command, and the contour enhanced funnel plot with *confunnel*. Other graphics include the forest plot with *metan*, and the L'Abbé plot with *labbe*.

Documentation

The Stata meta-analysis commands are not part of the official Stata release, but they can be downloaded from the central repository for Stata packages at http://www.repec.org, which is also directly accessible through Stata. Within Stata, you can get help for a description of these commands, as well as their installation instructions. They have been collected and updated by Sterne et al. (2009). Another useful source is the book by Egger et al. (2001). Stata itself comes with documentation and also publishes *Stata Journal* (www.stata-journal.com), a quarterly journal that describes Stata computing resources. The *winbugsfromstata* connection to BUGS can be downloaded at http://www2.le.ac.uk/departments/health-sciences/research/gen-epi/Progs/winbugs-from-stata/.

Cost and availability

Stata can be ordered from www.stata.com. As of July 2012, the price for the Intercooled version 12 for a government/nonprofit single user is $595 for the annual license and $1195 for the perpetual license.

R

R is the open source version of the S programming language. Users have contributed many packages to its CRAN repository that implement new statistical methods. These can be installed in the local computing environment. The best R package for meta-analysis is *metafor*, developed by Wolfgang Viechtbauer (www.wvbauer.com/downloads.html). It is described below.

Data entry

Data are passed into the meta-analytic routines through R, which means that they can be entered directly or read in through a wide variety of formats using R import functions. The package has a function to calculate common effect size metrics from raw data.

Analysis

The functions available allow users to carry out method of moments analyses for binary and continuous outcomes, including fixed-effects models (Mantel-Haenszel, Peto, and inverse variance weighting methods) and random-effects models (various methods for estimating the between-study variance), meta-regression using generalized least squares, cumulative meta-analysis, tests for small sample/publication bias, and the trim and fill method. Various functions enable users to extract summary statistics, such as estimates and confidence intervals from the fitted model objects, and to work with residuals. Sensitivity analyses leaving one study out at a time are also available.

More sophisticated analyses can be implemented in two ways with R. First, users can write their own functions in the R programming language. Second, users desiring to perform Bayesian analyses can use the R packages *R2WinBUGS*, *R2jags,* and *BRugs* to enable R to call the BUGS environment (see below).

Graphics

The metafor package implements forest plots, funnel plots, residual diagnostic and influence plots, normal probability plots, the radial plot, and plots of the sensitivity of estimates to leaving out one study at a time. Users also have R's powerful graphics facilities available to develop and customize their own presentation quality figures.

Documentation

R packages can be downloaded from http://cran.r-project.org/web/packages/. All R packages have associated help files that are installed when the package is loaded. These explain the various R functions that comprise the package. A variety of books are available for programming in R, including many online documents. The metafor package is described in Viechtbauer (2010).

Cost and availability

R is an open source program available for free download at www.r-project.org. User-contributed packages stored at www.cran.r-project.org/web/packages/ may be downloaded from within R.

SPSS

SPSS is the most widely used statistical package in the social sciences. Mark Lipsey and David Wilson have written a set of macros for doing method of moments calculations for random- and fixed-effects meta-analysis and for meta-regression. These analyses must be performed from the syntax window using the command line interface rather than from the pull-down menus in SPSS.

Data entry

The Lipsey and Wilson macros use the effect size and its standard error as inputs. Therefore, these values must already have been calculated in the SPSS data set including any transformations, such as small sample size bias corrections, the Fisher's z transformation for correlations, or the logarithmic transformation for odds ratios and response ratios that are necessary for analysis.

Analysis

After initialization, each macro is run with the inputted effect size and standard error. *MeanES* calculates basic statistics, such as mean effect size, confidence intervals, z-test, and a test of homogeneity for fixed- and random-effects models. *MetaF* performs the analog to the one-way ANOVA analysis and allows specification of either a fixed-effects model, or three methods of estimating mixed-effects (random-effects) models: method of moments, full-information maximum likelihood, and restricted-information maximum likelihood. It is useful for testing differences across mean effect sizes for a categorical variable, such as treatment. *MetaReg* performs weighted generalized least squares regression for a fixed-effects model, or mixed-effects (random-effects) models using method of moments, full-information maximum likelihood, and restricted-information maximum likelihood.

Graphics

Plots must be created from the output of the macros using SPSS graphics facilities.

Documentation

A "read me" file with instructions for the macros is part of the download (see "cost and availability," below). SPSS itself has extensive documentation that comes with the program.

Cost and availability

The Lipsey and Wilson macros are available for a free download from http://mason.gmu.edu/~dwilsonb/ma.html. SPSS itself has recently been bought by IBM, and the statistics package is now named IBM SPSS and can be purchased from http://www-01.ibm.com/software/analytics/spss/products/statistics/. Reduced pricing is available for educational purposes and for students. There are also discounts for bulk purchasing.

SAS

SAS is the most widely used statistical package, particularly in the corporate world. In fact, SAS is no longer merely a statistical package but a data environment (which is why you no longer find its original name of Statistical Analysis System anywhere in its documentation). SAS produces many books that show users how to apply SAS coding to statistical problems. Wang and Bushman (1999) have written one for meta-analysis. Kuss and Koch (1996) also provide meta-analysis macros for SAS. Lipsey and Wilson's macros described above for SPSS are also written for SAS. Below, we discuss the use of the macros developed for meta-analysis that are described in Wang and Bushman (1999), and Kuss and Koch (1996). Sophisticated users may also use PROC MIXED (Van Houwelingen et al. 2002) and PROC NLMIXED (Macaskill 2004) to fit all sorts of different meta-analytic models, but these require familiarity with the programming language.

Data entry

Data are input and manipulated using standard SAS programming code. SAS also has a user interface SAS Enterprise Guide that allows input into a spreadsheet type format. SAS stores data in databases that are accessed through programming code in data steps. Point and click options in the guide are automatically translated into SAS programming code.

Analysis

Wang and Bushman (1999) show how to use SAS commands and statistical procedures to fit fixed- and mixed- (random) effects models for continuous and categorical data and correlations. Kuss and Koch (1996) provide several macros, including *metacalc* for fixed- and random-effects meta-analysis of the risk difference, log risk ratio, or log odds ratio (inverse variance, Mantel-Haenzel, or Peto weights).

Graphics

Wang and Bushman (1999) show how to use SAS graphics and macros to make forest plots, funnel plots, quantile plots, and other descriptive plots. Kuss and Koch (1996) provide the macro *metafunn* for producing a funnel plot, *metaci* for a forest plot, and *metagalb* for a radial plot. They also include *metasens* macro for a sensitivity plot that describes the change in the mean estimate as the between-study variance estimate changes.

Documentation

The book by Wang and Bushman (1999) and the paper by Kuss and Koch (1996) provide instructions on using the code. SAS itself has voluminous documentation and a whole library of books on using SAS statistical procedures.

Cost and availability

The Lipsey and Wilson macros can be downloaded at no cost at http://mason.gmu.edu/~dwilsonb/ma.html. The Kuss and Koch and Bushman and Wang macros are available in their publications. SAS itself can be ordered from www.sas.com and is individually priced according to the configurations of the client. Although there is not one standard price, it is very expensive since it requires purchase of a yearly license for at least the SAS/Base and SAS/Stat modules.

BUGS

BUGS (Bayesian inference Under Gibbs Sampling) is the most widely used software for doing Bayesian analysis. It performs Markov chain Monte Carlo (MCMC; Chapter 11) using an intelligent algorithm that determines the appropriate numerical routine from the model structure provided by the user. These include Gibbs sampling, adaptive rejection sampling, and Metropolis-Hastings (in order of increasing complexity). BUGS is implemented in three different versions: WinBUGS, OpenBUGS, and JAGS (Just Another Gibbs Sampler). They use different numerical algorithms so that simulation results can differ slightly. In particular, models may converge at different rates. More importantly, OpenBUGS and JAGS are open source programs that are being maintained, while WinBUGS is no longer updated. OpenBUGS works in the Microsoft Windows environment, whereas JAGS works on Windows, Mac, and Linux/Unix.

All packages can be used in stand-alone form, but interfaces to general purpose software (R and Stata) are also available. These include the R packages *R2WinBUGS*, *R2jags,* and *BRugs,* and the Stata package *winbugsfromstata*. These interfaces offer routines to run the BUGS commands within the R or Stata environment so that MCMC output can be manipulated from within the statistical environment. Because Stata and R have extremely flexible graphic capabilities, quite exceptional plots can be made showing the benefits of using these complex models (see some examples in Chapter 11). We next describe the capabilities of the BUGS environments, independent of their potential inside R or Stata.

Data entry

To run the MCMC algorithm, the user must provide three files: (1) a short program defining the probabilistic structure of the problem including the prior distribution, (2) data for each fixed variable and outcome, and 3) starting values for the parameters of the MCMC algorithm.

Analysis

After compiling the input files, the analyst starts the simulation with a graphical user interface. BUGS decides which type of MCMC algorithm is best and generates simulations from the joint posterior distribution. The user may then investigate these simulations through a variety of statistical summaries and graphical displays. The user supplies the number of simulations to run, and can then check on convergence of the algorithm with a variety of diagnostics available from pull-down menus. Various other output statistics can be requested, including summaries and plots of the chains run; the plots include the means, medians, and percentiles of each parameter. These statistics and plots are useful for diagnosing convergence and for understanding the joint posterior density of the parameters.

Graphics

BUGS implements a variety of graphical summaries that include traces of the parameters simulated, autocorrelations, empirical probability densities (kernel density plots), and Gelman-Rubin-Brooks convergence diagnostics. These displays cannot be directly exported outside of BUGS without an interface to a statistical package. The outputs of the chains can also be saved in text files and read into programs, such as the R package CODA, that make use of these simulations.

Documentation

Online manuals are available and downloaded with the program. These include three volumes of examples that show how to implement various statistical analyses in BUGS. Two of these are written explicitly for meta-analysis. Bayesian meta-analytic methods described in the statistical literature generally use BUGS, and authors often provide code in the papers. Four books by Peter Congdon also provide many examples with code (Congdon 2003, 2005, 2007, 2010).

Cost and availability

WinBUGS is developed and distributed by the Medical Research Council in Great Britain and is available free of charge from www.mrc-bsu.cam.ac.uk; however, a software key is needed to enable the full power for large data sets. This key will be sent to the user upon registration. OpenBUGS is an open source version available at http://www.openbugs.info/w/, and JAGS is open source available at http://mcmc-jags.sourceforge.net.

SOFTWARE FOR DIGITIZING DATA FROM GRAPHS

Before conducting a meta-analysis, the research synthesist must collect the primary data that will go into the meta-analysis. In many papers in the fields of ecology, evolution, and conservation, the data are often presented in graphical form, including bar graphs, points with confidence intervals for means, scatter graphs, and so forth. Although contacting authors to obtain the numerical data is an option, it may be a slow and frustrating process. Many meta-analysts in these fields therefore rely upon using software to convert scanned images of graphs to the underlying numbers, and thus allow inclusion of that study in the meta-analysis.

Many different programs are available to digitize graphs. They are generally quite inexpensive, and include various other functions, depending on the package. They digitize data automatically from scanned files or manually with mouse clicks. The programs generally accept many image file formats and run on common platforms such as Windows, Linux, and less commonly, Macintosh. For most applications any of these will work.

Free programs include DigitizeIt (http://www.digitizeit.de/), Engauge Digitizer (http://digitizer.sourceforge.net/), DataThief (http://www.datathief.org/), ImageJ (http://rsbweb.nih.gov/ij/), and GrabIt! (http://www.datatrendsoftware.com/home.html), which works with Excel. Commercial packages include Dagra (http://www.blueleafsoftware.com/Products/Dagra/) and Ungraph (http://www.biosoft.com/w/ungraph.htm).

Various issues and limitations are involved in accurately digitizing data from graphs. For example, points may be hidden behind other points, accuracy is limited by the resolution of the digitized image, and the translation to numbers may be limited by the accuracy of locating the mouse clicks in some programs. However, we are of the opinion that “pretty good” information is often much better than no information at all, given that users recognize the limitations of the data with which they are working.

CONCLUSIONS

Doing all but the simplest meta-analytic calculations requires a computer and appropriate software. Many different general purpose software packages have statistical and graphical tools that enable users to carry out meta-analyses, but these packages usually require knowledgeable programming and do not include specific tools for meta-analysis. Users without sufficient methodologic and programming background to understand the statistical subtleties may struggle to work out how to correctly implement meta-analyses with these general purpose statistical packages. For nontechnical users, one of the stand-alone packages may be much easier to use, although the modeling options differ considerably among packages. Meta-analysis is becoming a more common scientific enterprise and in the health sciences, it already has a higher citation impact than any other research design (Patsopoulos et al. 2005); as it is increasingly used, the associated software will undoubtedly continue to become more widely available, more flexible, and easier to use.

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