MetaXL User Guide

Version 5.3

Jan J Barendregt & Suhail A Doi

ABN 51 134 897 411
Sunrise Beach, Queensland, Australia, 2011-2016

Web: www.epigear.com
Email: info@epigear.com

Contents

Introduction

Meta-analysis in Excel

MetaXL is a tool for meta-analysis in Microsoft Excel. It extends Excel with several functions for input and output of meta-analysis data, and a menu that offers access to output (both in table and graphical format), options, examples, and this *User Guide*, among other things.

MetaXL employs the same meta-analysis methods that can be accessed in general statistical packages (such as Stata™) and in dedicated meta-analysis software, but makes two additional methods available: the inverse variance heterogeneity (IVhet) and Quality Effects (QE) models. In addition, a new way to detect publication bias, the Doi plot, has been implemented. For details, see the section on Meta-analysis methods below.

Starting with version 4.0, MetaXL has extended its methods by offering a powerful, yet simple to implement, way of doing network meta-analysis. See the entry on the MANetwork function and the section on Indirect comparisons and Network meta-analysis below.

Installation

MetaXL has been tested with Excel 2000, 2003, 2007, 2010, 2013, and 2016[1].

Installation is usually straightforward: make sure Excel is not running, and run the MetaXLSetup executable. If all goes well, the MetaXL commands will be present in Excel (in the main Excel menu for Excel version 2003 and earlier, in the MetaXL ribbon tab in version 2007 and later), the MetaXL functions will be visible in the Excel Function Wizard (in the function category 'MetaXL'), and you can open the example spreadsheets without seeing any "#NAME?" errors. See the section on 'Trouble shooting' when this is not the case.

The installation program installs an Excel add-in (called 'MetaXL.xll'), together with this documentation file and a few example spreadsheets. For Excel 2007 and later, an additional add-in (called 'MetaXLRibbon.xlam') is installed. In the Windows Start menu a MetaXL entry gives access to the example spreadsheets, this *User Guide*, and an Uninstall program. For a detailed discussion of the installation issues, see the Technical Appendix below.

License

MetaXL is free, but copyrighted software. MetaXL may be installed on as many computers as the user owns or employs, and can be freely distributed to third parties. However, modification of the installation software and distribution of the software to third parties for a fee are strictly prohibited.

Please contact Epigear (info@epigear.com) if you have any questions about this license arrangement.

Features

MetaXL has a number of features:

[1] MetaXL supports both the 32-bit and 64-bit versions of Excel 2010 and higher. The default Excel installation is 32 bit.

1. Fixed effects (inverse variance, Mantel Haenszel, Peto), random effects (DerSimonian & Laird), inverse variance heterogeneity (Doi *et al*), and quality effects (Doi & Thalib) models.
2. Both binary (relative risk, odds ratio, risk difference, rate-ratio's and rate difference) and continuous (weighted mean difference, Cohen's d, Hedges' g, Glasss's Δ) methods.
3. Indirect comparisons and network meta-analysis.
4. Cumulative meta-analysis.
5. Single arm methods: pooled prevalence, correlations and rates methods.
6. Heterogeneity statistics: Cochran's Q, I^2, τ^2.
7. Sensitivity analysis and study exclusion option.
8. A wide range of input format options.
9. Output in table and graphical (forest, funnel and Doi plots) formats, with various ways to copy or save results.

These features are discussed in sections below.

Design issues

MetaXL has been developed with academic research in mind. This implies that transparency of the methods used is deemed important. We have aimed to reference all the algorithms used, or to describe them in sufficient detail in this *User Guide* for algorithms unique to MetaXL. If you have any questions on MetaXL methods left after consulting this *User Guide* and the referenced literature, please contact us.
One of the big advantages of MetaXL being Excel based is that it can very easily be combined with Excel based Monte Carlo simulation software, such as EpiGear's Ersatz. Using Ersatz and MetaXL together makes research into, for example, coverage properties of the various models a breeze, with thousands of meta-analysis calculations done within a minute.
Another important design objective was ease of use. The interface has been kept very simple (and therefore, hopefully, easy to navigate). For users of Excel, MetaXL should pose no hurdles.

Operation

Running MetaXL is done from within Excel. To see how it operates, start Excel, and open one of the example spreadsheets (accessible through the MetaXL menu, which is located in the main Excel menu for Excel version 2003 and earlier, in the MetaXL ribbon tab in version 2007 and later). The example spreadsheets contain tables with study results, and several input table functions (MAInputTable). In addition, there are some functions that report results: MaPooledEffect, and MAPooledEffectLCI and MAPooledEffectHCI for the pooled result and its confidence interval respectively. See the section on MetaXL functions below for a detailed description of these functions and the parameters they take.
Full results are accessed by choosing 'Results' from the MetaXL menu. This will produce a list of choices, one entry for each MAInputTable, MASubgroups, and MANetwork function in the workbook. Clicking one of these produces a pop-up window with tabs giving access to various outputs such as a table and forest, funnel and Doi plots.
Results can be saved to file by choosing 'File|Save results', and can be saved to the clipboard (and then pasted into, for example, Excel or Word) by choosing 'Options|Copy to clipboard', or by right-clicking and choosing 'Copy'.

The MetaXL menu also gives access to input templates for setting up your own meta-analysis, see the discussion of the MAInputTable function below.

This User Guide

Although in the remainder we will discuss the various methods of meta-analysis, this *User Guide* is certainly not meant as an introduction to these issues. The reader is kindly referred to the literature, see the references for some examples. The aim of this document is to make the user familiar with MetaXL and its interface, possibilities, and quirks.

Technical note

Please consult the Technical Appendix below for statistical and other technical details.

MetaXL functions

Introduction

In this section we will describe the functions MetaXL makes available in Excel. All MetaXL functions start with 'MA', and are accessible through Excel's Function Wizard (for Excel 2003 and earlier: Insert|Function in Excel's main menu, for 2007 and later: Formulas|Insert Function, or click the icon to the left of the formula bar) in the category 'MetaXL'. Check out the Function Wizard if you don' know it.
Of the functions described in this section, only the MAInputTable is essential: it determines the input and output and the meta-analysis method used.

MAInputTable

MAInputTable(Name,IOType,Method,Table): returns the Name parameter (if all is well) or an error message (if not).

Table 1: parameters of the MAInputTable function

Parameter	Type	Description
Name	text	A unique name for each MAInputTable function in the workbook (and across workbooks if you have more than one workbook open at a time). The Name should be more than 0 and less than 256 characters long.
IOType	text	One of: NumRR, NumOR, NumRD, RRCI, ORCI, HRCI, RDCI, RDSE, WMD, Cohen, Hedges, Glass, ContCI, ContSE, Prev, NumRate, RateSE, RateRatio, RateDif, NumCorr (see notes below).
Method	text	One of: IV, RE, IVhet, QE, MH, Peto (see notes below).
Table	range	An Excel range, containing the study results for the meta-analysis (see notes below).

Notes:

1. The MAInputTable function either returns its 'Name' parameter (indicating that no errors were encountered) or an error message. See the section on Error messages. Please note that you can have multiple MAInputTable functions in an Excel workbook, but that each must have a unique name (and this requirement extends to MAIndirect functions, see below).
2. Table 1 defines the parameters of the MAInputTable function. Please note that the parameters of type text need to be entered between double quotes.
3. Table 2 gives the values the IOType parameter can take.

Table 2: values of the IOType parameter

Value	Description
NumRR	Binary analysis, input in numbers, output in risk ratios
NumOR	Binary analysis, input in numbers, output in odds ratios
NumRD	Binary analysis, input in numbers, output in risk differences
RRCI	Binary analysis, input in risk ratios and confidence intervals, output in risk ratios
ORCI	Binary analysis, input in odds ratios and confidence intervals, output in odds ratios

Value	Description
HRCI	Binary analysis, input in hazard ratios and confidence intervals, output in hazard ratios
RDCI	Binary analysis, input in risk differences and confidence intervals, output in risk differences
RDSE	Binary analysis, input in risk differences and standard errors, output in risk differences
WMD	Continuous analysis, input population size, mean, and standard deviation, output weighted mean difference
Cohen	Continuous analysis, input population size, mean, and standard deviation, output standardised mean difference (Cohen's *d*)
Hedges	Continuous analysis, input population size, mean, and standard deviation, output standardised mean difference (Hedges' adjusted *g*)
Glass	Continuous analysis, input population size, mean, and standard deviation, output standardised mean difference (Glass's Δ)
ContCI	Continuous analysis, input either WMD, Cohen's *d*, Hedges' adjusted *g*, or Glass's Δ with confidence intervals, output same as input
ContSE	Continuous analysis, input either WMD, Cohen's *d*, Hedges' adjusted *g*, or Glass's Δ with standard errors, output same as input
Prev	Pooling prevalences, input population size and number of cases, output proportion
NumRate	Pooling rates, input person time at risk and number of cases, output rate.
RateSE	Pooling rates, input rate and standard error, output rate
Rateratio	Pooling rate ratios, input person-time and event numbers, output rate ratio
Ratedif	Pooling differences in rates, input person-time and event numbers, output rate difference
NumCorr	Pooling correlation coefficients, input sample size and correlation coefficient, output correlation coefficient

4. The Method parameter stands for the following meta-analysis methods (see the section on Meta-analysis methods below):

Table 3: values of the Method parameter

Value	Description
IV	Inverse variance (fixed effects)
RE	Random effects (DerSimonian & Laird)
IVhet	Inverse variance heterogeneity (Doi *et al*)
QE	Quality effects (Doi & Thalib)
MH	Mantel Haenszel (fixed effects)
Peto	Peto method for odds ratios (fixed effects)

5. Not every IOType is compatible with every Method parameter (and combining incompatible ones will result in an error message to that effect):

Table 4: compatible values of the IOType and Method parameters

IOType\method	IV, IVhet, RE, QE	MH	Peto
NumRR	✔	✔	
NumOR	✔	✔	✔
NumRD	✔	✔	
RRCI, ORCI, RDCI, RDSE	✔		
WMD, Cohen,Hedges, Glass	✔		
ContCI, ContSE	✔		
Prev, NumRate, RateSE, RateRatio, RateDif, NumCorr	✔		

6. The number of columns of the Table parameter, and the kind of information in it, depends on the IOType and the Method parameters. Table 5 below specifies the columns the MAInputTable function expects for the various IOType and Method combinations.
   Please be aware that the MAInputTable function is very particular about order and content of the columns. Only when the layout is strictly adhered to will MetaXL function correctly or at all. For this reason, the precise columns are also obtainable through the MetaXL menu 'Input templates' item, see the section on the Menu below).
   In the table below N1 and N2 stand for population numbers in active and control arms respectively, each with their Cases and Non-cases (binary) or Mean and Standard deviation (continuous), and Qi stands for a quality rank derived from a univariate quality score (see section Meta-analysis methods). MetaXL however permits Qi column entry either as the total score, or as a rescaled score between 0..1 as detailed in the section on meta-analysis methods below. It does not matter what scale is used or what the maximum for that scale is so long as all studies are scored in the same way and with the same scale. For further information also consult the example spreadsheets.
   Lo and Hi CI stand respectively for the lower and higher limit of the confidence interval as input for the IOType parameters that take a confidence interval as input. The size of the input confidence interval can be set in the Options menu (see the section on the MetaXL menu below) and is independent of the size of the output confidence interval.
7. Please note that within an input Table each study name must be unique: it is an error when there are duplicate study names.

Table 5: columns of the Table parameter

IOTypes / Methods	Table Columns							
NumRR, NumOR, NumRD / IV, Ivhet, RE, MH, Peto	Study name	N1	Cases	Non-cases	N2	Cases	Non-cases	
NumRR, NumOR, NumRD / QE	Study name	N1	Cases	Non-cases	N2	Cases	Non-cases	Qi
ORCI, RRCI,	Study	RR/OR	Lo CI	Hi CI				

IOTypes / Methods	Table Columns							
RDCI / IV, Ivhet, RE	name	/RD						
ORCI, RRCI, RDCI / QE	Study name	RR/OR /RD	Lo CI	Hi CI	Qi			
RDSE / IV, IVhet, RE	Study name	RD	Standard error					
RDSE / QE	Study name	RD	Standard error	Qi				
WMD, Cohen, Hedges, Glass / IV, IVhet, RE	Study name	N1	Mean	StDev	N2	Mean	StDev	
WMD, Cohen, Hedges, Glass / QE	Study name	N1	Mean	StDev	N2	Mean	StDev	Qi
ContCI / IV, IVhet, RE	Study name	Effect size	Lo CI	Hi CI				
ContCI / QE	Study name	Effect size	Lo CI	Hi CI	Qi			
ContSE / IV, IVhet, RE	Study name	Effect size	Standard error					
ContSE / QE	Study name	Effect size	Standard error	Qi				
Prev / IV, IVhet, RE	Study name	N	Cases*					
Prev / QE	Study name	N	Cases*	Qi				
NumRate / IV, IVhet, RE	Study name	Person time	Cases					
NumRate / QE	Study name	Person time	Cases	Qi				
RateSE / IV, IVhet, RE	Study name	Rate	Standard error					
RateSE / QE	Study name	Rate	Standard error	Qi				
Rateratio / IV, IVhet, RE	Study name	Person time1	Cases1	Person time2	Cases2			
Rateratio / QE	Study name	Person time1	Cases1	Person time2	Cases2	Qi		
Ratedif / IV, IVhet, RE	Study name	Person time1	Cases1	Person time2	Cases2			
Ratedif / QE	Study name	Person time1	Cases1	Person time2	Cases2	Qi		
NumCorr / IV, IVhet, RE	Study name	Sample size	Correlation coefficient					
NumCorr / QE	Study name	Sample size	Correlation coefficient	Qi				

* The number of Cases fields depends on the number of categories.

MACumulative

MACumulative(Name,IOType,Method,Table): returns the Name parameter (if all is well) or an error message (if not). See the section on Error messages. Please note that you can have multiple MACumulative functions in an Excel workbook, but that each must have a unique name (and this requirement extends to MAInputTable function names).

Notes:

1. This function runs a cumulative meta-analysis. Please note that the user is responsible for entering the studies in the input table in the correct ascending order. See the MagnesiumCumulative example spreadsheet.
2. MACumulative has the same input parameters as MAInputTable (see tables 1 – 5 above).
3. Output is limited to the cumulative meta-analysis of the included studies and the cumulative weights associated with each step in the final (overall) meta-analysis. No heterogeneity statistics are included.
4. MACumulative allows only single category prevalence, and does not allow sub-groups and use in indirect comparisons. It will return an error if used in these circumstances.

MAIndirect

MAIndirect(Name,TableName1,TableName2): returns the Name parameter (if all is well) or an error message (if not). See the section on Error messages. Please note that you can have multiple MAIndirect functions in an Excel workbook, but that each must have a unique name (and this requirement extends to MAInputTable function names).

Notes:

1. This function implements adjusted indirect comparisons according to the Bucher method (Bucher, Guyatt et al. 1997). See the section on Indirect Comparisons and the discussion of the IndirectAF example spreadsheet in the Documentation section below for more information on indirect comparisons.
2. The Tablename1 & 2 parameters should be links to MAInputTable functions that contain the two meta-analyses for the indirect comparison. If one or both of the inputs consist of a single study, you must wrap the single study in a MAInputTable function in order for MAIndirect to accept it.
3. MAIndirect requires the input meta-analyses to have identical Methods and matching IOTypes. IOTypes match when the effect size is identical, for example NumOR and ORCI match, but NumOR and NumRR do not. MAIndirect returns an error when this requirement is not met.
4. Results from MAIndirect are available only through the MAPooledEffect and MAPooledEffectLCI, MAPooledEffectHCI, and MAPooledSE functions, for central estimate, CI, and standard error respectively. Other MetaXL spreadsheet output functions, such as MAIsquare, will return the #NUM! error when linked to MAIndirect. No graphical output is available from this function.
5. The MAIndirect function can only be used with effect measures that are based on separate estimates in each comparison group. This means that it cannot be

used for the single-arm IOTypes Prev, NumCorr, RateSE and NumRate. For these four IOtypes, MAIndirect returns an error.

MAMixed

MAMixed(Name,TableName1,TableName2): returns the Name parameter (if all is well) or an error message (if not). See the section on Error messages. Please note that you can have multiple MAMixed functions in an Excel workbook, but that each must have a unique name (and this requirement extends to MAInputTable function names).

Notes:

1. This function implements a meta-analysis of a direct meta-analytic estimate and an adjusted indirect estimate using the same statistical model as in the direct meta-analysis
2. The Tablename1 & 2 parameters should be links to MAInputTable and MAIndirect functions respectively. If the direct input consist of a single study, you must wrap the single study in a MAInputTable function in order for MAIndirect to accept it.
3. The MAMixed function can only be used with effect measures that are based on separate estimates in each comparison group. This means that it cannot be used for single-arm IOTypes Prev, NumCorr, RateSE and NumRate. For these four IOtypes, MAMixed returns an error.

MANetwork

MANetwork(Name,control,Table): returns the Name parameter appended with the name of the control (if all is well) or an error message (if not). See the section on Error messages. Please note that you can have multiple MANetwork functions in an Excel workbook, but that each must have a unique name or a different control.

Notes:

1. This function implements the Generalized Pairwise Modelling (GPM) method of network meta-analysis. It consists of multiple adjusted indirect comparisons according to the Bucher method (Bucher, Guyatt et al. 1997) by creating multiple 3-intervention closed loops. This procedure only allows those closed loops that have one common node selected via the “control” parameter. See the section on network meta-analysis in the documentation section below for more information on network meta-analyses and GPM.
2. The Table should be a cell range that links to three columns: First a column of MAInputTable functions or links to MAInputTable functions, second a column of active intervention names and third a column of control intervention names for each meta-analysis. If an input consists of a single study, you must wrap the single study in a MAInputTable function in order for MANetwork to accept it. The intervention names in columns two & three must be unique for each type of intervention. MANetwork uses these names to match actives and controls, and any difference in spelling of identical treatments will scupper this. It is therefore strongly recommended to make a list of treatment names, and populate columns 2 & 3 with links to this treatment list, see the example files ThrombolyticsNetwork and OralGlucoseNetwork.

3. MANetwork requires the input meta-analyses to have identical methods and matching IOTypes. IOTypes match when the effect size is identical, for example NumOR and ORCI match, but NumOR and NumRR do not. MANetwork returns an error when this requirement is not met.
4. The MANetwork function can only be used with effect measures that are based on separate estimates in each comparison group. This means that it cannot be used for single-arm IOTypes Prev, NumCorr, RateSE and NumRate. For these four IOtypes, MANetwork returns an error.

Important note

The remaining MetaXL functions mostly take a "TableName" parameter. In order for these functions to be associated with the correct MAInputTable (or other MetaXL input) function, the"TableName" parameter should be provided by linking it to the output of the corresponding MAInputTable function.

MASubGroups

MASubGroups(Name,TableName, Table): returns the Name parameter (if all is well) or an error message (if not).

Notes:

1. This function allows doing a subgroup analysis of the studies in the MAInputTable function with name TableName. The result will appear in the Results list (see below) as 'TableName by Name'.
2. The Table parameter is an Excel range that groups the names of the studies in the TableName analysis under appropriate headings. Table 6 shows an example layout with two subgroups, however, there is no limit to the number of subgroups.

Table 6: Layout of the MASubGroups function Table parameter

Subgroup 1 Label	Subgroup 2 Label
Study 1 Name	Study 2 Name
Study 4 Name	Study 3 Name
	Study 5 Name
	Study 6 Name

3. MetaXL uses the study names to compile the subgroups. Any differences in spelling between the study names in the MAInputTable and MASubGroups functions will scupper this. It is therefore strongly recommended to use links to the study names in the MAInputTable function to set up the subgroups in the MASubGroups function.
4. Subgroup results are reported in the forest plot and tabled outcomes (see below).
5. Examples of the use of this function are in the SchizophreniaPrev and MagnesiumSubGroups example files, see the section on the examples below.

MAMetaRegresData

MAMetaRegresData(TableName, Table): returns the TableName parameter with "MR Data" appended (if all is well) or an error message (if not).

Notes:

1. This function allows creation of a dataset that can be used for meta-regression analysis of the studies in the MAInputTable function with name TableName. The result will appear in the MAInputTable results as an additional table (in a "Meta-Regression data" tab) whose data can be copied and pasted into Stata.
2. The Table parameter is an Excel range that provides a range for the moderator variables. These variable values must appear in the same order as the studies in the meta-analysis data. The table range must include a first row with the headers for the moderator variables.
3. When there is missing data in a moderator table range ensure that a "." (period) is entered as blank cells may generate spurious values. The period is recognized as "missing value" in Stata.
4. An example of the use of this function is in the ThyCancerMetaRegress example file. For a discussion of the use of the dataset in Stata, see the section "Meta-regression using MetaXL to create the dataset and Stata to run the regression analysis" below.

MAPooledEffect

MAPooledEffect(TableName): returns the pooled effect size of the studies associated with the MAInputTable function called 'TableName'.

Note:

1. When the meta-analysis is of prevalence with 2 or more categories, this function takes as a second parameter the category number (1,2...). For more information on the meta-analysis of prevalence, see the section on this below.

MAPooledEffectLCI & MAPooledEffectHCI

MAPooledEffectLCI(TableName): returns the lower confidence interval of the pooled effect size of the studies associated with the MAInputTable function called 'TableName'.
MAPooledEffectHCI(TableName): returns the higher confidence interval of the pooled effect size of the studies associated with the MAInputTable function called 'TableName'.

Notes:

1. The size of the confidence interval can be set through the MetaXL menu item 'Options'. Default is 95%.
2. When the meta-analysis is of prevalence with 2 or more categories, these functions take as a second parameter the category number (1,2...). For more information on the meta-analysis of prevalence, see the section on this below.

MAPooledSE

MAPooledSE (TableName): returns the standard error of the pooled effect size of the studies associated with the MAInputTable function called 'TableName'.

Note:

1. The standard error is returned in the transformed scale of the effect size, e.g natural log scale for odds ratio and relative risk.
2. When the meta-analysis is of prevalence with 2 or more categories, this function takes as a second parameter the category number (1,2...). For more information on the meta-analysis of prevalence, see the section on this below.

MAForestName

MAForestName(TableName, Forest plot title): returns the Forest plot title parameter of the forest plot associated with the MAInputTable function called 'TableName'.

Notes:

1. This function can be used to override the default title of the forest plot. Default is the TableName of the linked MAInputTable function. To override the default is particularly useful for multiple category prevalence output, where by default all forest plots get the same name.
2. When the meta-analysis is of prevalence with 2 or more categories, this function takes as a second parameter the category number (1,2...). For more information on the meta-analysis of prevalence, see the section on this below.

MACochranQ

MACochranQ(TableName): returns Cochran's Q statistic for heterogeneity of the studies associated with the MAInputTable function called 'TableName'.

MAISquare

MAISquare(TableName): returns the I^2 statistic for heterogeneity of the studies associated with the MAInputTable function called 'TableName'.

MALFKIndex

MALFKIndex(TableName): returns the LFK-index statistic of asymmetry of the studies associated with the MAInputTable function called 'TableName'.

MATauSquare

MATauSquare(TableName): returns the τ^2 statistic for heterogeneity of the studies associated with the MAInputTable function called 'TableName'.

MANetworkH

MANetworkH(NetworkName): returns the weighted average $\bar{H}$ statistic for overall network (in)consistency within the final estimates associated with the MANetwork function called 'NetworkName'.

Notes:

1. This function will only return the $\bar{H}$ statistic for overall network (in)consistency if it is linked to a MANetwork function. In all other cases, the $\bar{H}$ statistic is undefined, and this function will return #NUM!.
2. See the section on Network Meta-analysis below for more information on this function and the interpretation of its result.

MAQIndex

MAQIndex(TableName): returns Q-index statistic of the Quality Effects model of the studies associated with the MAInputTable function called 'TableName'.

Notes:

1. This function will only return the Q-index of the meta-analysis associated with the MAInputTable function if this meta-analysis uses the Quality Effects model. In all other cases, the Q-index is undefined, and this function will return #NUM!.
2. See the section on Meta-analysis methods below for more information on the Quality Effects model and the Q-index.

MANumStudies

MANumStudies(TableName): returns the number of studies associated with the MAInputTable function called 'TableName'.

MApConsMixed

MApConsMixed(MixedName) returns the p-value of a test for consistency between the direct and indirect estimates that are inputs into a MAMixed function.

Notes:

1. The MixedName parameter should be a link to a MAMixed function. Links to other MetaXL functions will generate an error.
2. The test is based on the so-called Bucher method, see the section on Indirect estimates and Network meta-analysis below.
3. If the function returns a value of <0.05, there is statistically significant inconsistency between the direct and indirect input estimates.

MApOverallEffect

MApOverallEffect(TableName) returns the p-value of a test for the overall difference between active and control that are inputs into a MAInputTable function.

Notes:

1. The TableName parameter should be a link to a MAInputTable function, but is not defined for single arm meta-analyses such as prevalence. Links to these or to other MetaXL functions than MAInputTable will generate an error.
2. The test is two-sided, and when it returns a value of <0.05, there is a statistically significant difference at the 95% level between active and control.
3. This function was added in version 5.1 for the only reason that we wanted to pre-empt further emails from users that asked how to obtain this p-value. We think it is useless: once you have the pooled estimate and its CI, this p-value does not add any information. Moreover, it propagates the flawed idea that doing a meta-analysis is about testing a hypothesis. It is not, meta-analysis is about estimating a pooled effect size.

MetaXL menu and features

Introduction

In this section we will describe the MetaXL menu, and simultaneously explain the various features the menu gives access to. The MetaXL menu is located in the main Excel menu for Excel version 2003 and earlier, and in the MetaXL ribbon tab in version 2007 and later. It has the following entries.

Input templates

This menu item gives access to templates for the Table parameter of the MAInputTablefunction, see the description of this function above. As discussed there, this function requires a specific layout and content of its input Excel range in order to work correctly. When chosen, this menu item displays the following list of templates:

1. Binary numbers (IOType numOR, numRR, and numRD)
2. OR, RR, HR or RD and confidence interval (IOType RRCI, ORCI, HRCI, and RDCI)
3. RD and standard error (IOType RDSE)
4. Continuous numbers (IOType WMD, Cohen, Hedges, and Glass)
5. Continuous and confidence interval (IOType ContCI)
6. Continuous and standard error (IOType ContSE)
7. Prevalence numbers (IOType Prev)
8. Rate numbers (IOType NumRate)
9. Rate and standard error (IOType RateSE)
10. Rate ratio and rate difference (IOType RateRatio and RateDif)
11. Correlation (IOType NumCorr)
12. MANetwork function

The IOType parameters are described in Table 2 above. The user can choose the appropriate layout template and Copy it to the clipboard, which allows pasting it into Excel using the Paste button or Ctrl-V.
A checkbox determines whether the template will contain a field for a quality score (Qi), to be used with the Quality Effects model. Default is on, but it will not be included in the template for the MANetwork function. The template entry for Prevalence has an option to set the number of categories. Default is 1.

Results from MAInputTable and MASubgroups

While MetaXL has several functions to display selected results of the meta-analysis in Excel itself, full results are only available through this menu item. They are displayed in a pop-up window, with tabs to give access to tabled results, a forest, funnel and a Doi plot, the option to exclude one or more studies and recalculate results, and a sensitivity analysis. However, if the number of input studies is less than three, only the forest plot and tabled results will be available.
When more than one valid MAInputTable function is present in the workbook, choosing this menu item will present a Result list of available analyses. You can have as many results windows simultaneously open as you like.

Tabled results

The results table shows the list of input studies with their effect sizes, confidence intervals, and weight in the meta-analysis, together with the pooled result, the heterogeneity statistics I^2 (with CI) and Cochran's Q (with p-value), and, if the quality effects model is used, the Q-index (see the section on Meta-analysis methods below for an explanation of the Q-index).

The displayed number of decimals (3 is default) and the size of the confidence interval (95% is default) can be set in the Options menu item (see below). Results can be saved to comma-delimited file (*.csv, readable by Excel and many other programs) or copied to the clipboard (right-click, or choose Options) and pasted into Excel or Word. Note that you can adjust column widths and row heights using the mouse.

The table below shows the quality effects model results from the Omega3 example workbook.

Number	Name	MD	LCI 95%	HCI 95%	weight (%)
1	Alekseeva 2000	-0.400	-1.066	0.266	1.590
2	Borkman 1989	-0.150	-0.953	0.653	2.969
3	Connor 1993	-2.200	-9.749	5.349	2.024
4	Goh 1997	-0.860	-1.677	-0.043	4.479
5	Hendra 1990	-1.200	-1.851	-0.549	5.320
6	Jain 2002	-0.390	-0.709	-0.071	8.081
7	Luo 1998	-0.150	-1.066	0.766	5.614
8	McGrath 1996	-0.200	-0.680	0.280	7.252
9	McManus 1996	-0.620	-1.758	0.518	5.055
10	Morgan 1995	-2.250	-5.409	0.909	3.117
11	Mostad 2006	0.010	-0.733	0.753	8.098
12	Pelikanova 1992	0.070	-0.617	0.757	3.319
13	Petersen 2002	-0.500	-1.571	0.571	3.869
14	Puhakainen 1995	-0.580	-2.153	0.993	3.413
15	Schectman 1988	-0.600	-1.270	0.070	3.386
16	Silvis 1990	-0.360	-1.008	0.288	1.622
17	Sirtori 1997	-0.600	-0.824	-0.376	22.419
18	Woodman 2002	-0.170	-0.597	0.257	8.373
	Pooled	-0.525	-0.764	-0.285	100.000
	I-squared	0.542	0.000	50.239	
	Cochran's Q	17.093			
	Chi2, p	0.448			
	Q-Index	46.575			

Forest plot

The figure below shows the forest plot from a subgroup analysis by study size of the quality effects model in the Magnesium example workbook. It shows, in addition to the graph, for each study and the pooled effect the effect size and confidence interval, plus the weight of each study in the pooled effect size.

The forest plot can be saved to disk (as a Windows extended metafile, *.emf) or to the clipboard (right-click and choose 'Copy', or choose 'Copy' from the menu), and then pasted into other applications.

Forest plot options

Right-clicking the graph or choosing 'Options|Plot options' from the menu gives access to the Forest plot options form, where you can set many graph properties. Some of these properties can be saved to become your preferred defaults. Table 7 below displays the various options by section of the Forest plot options window, and indicates which ones can be saved.

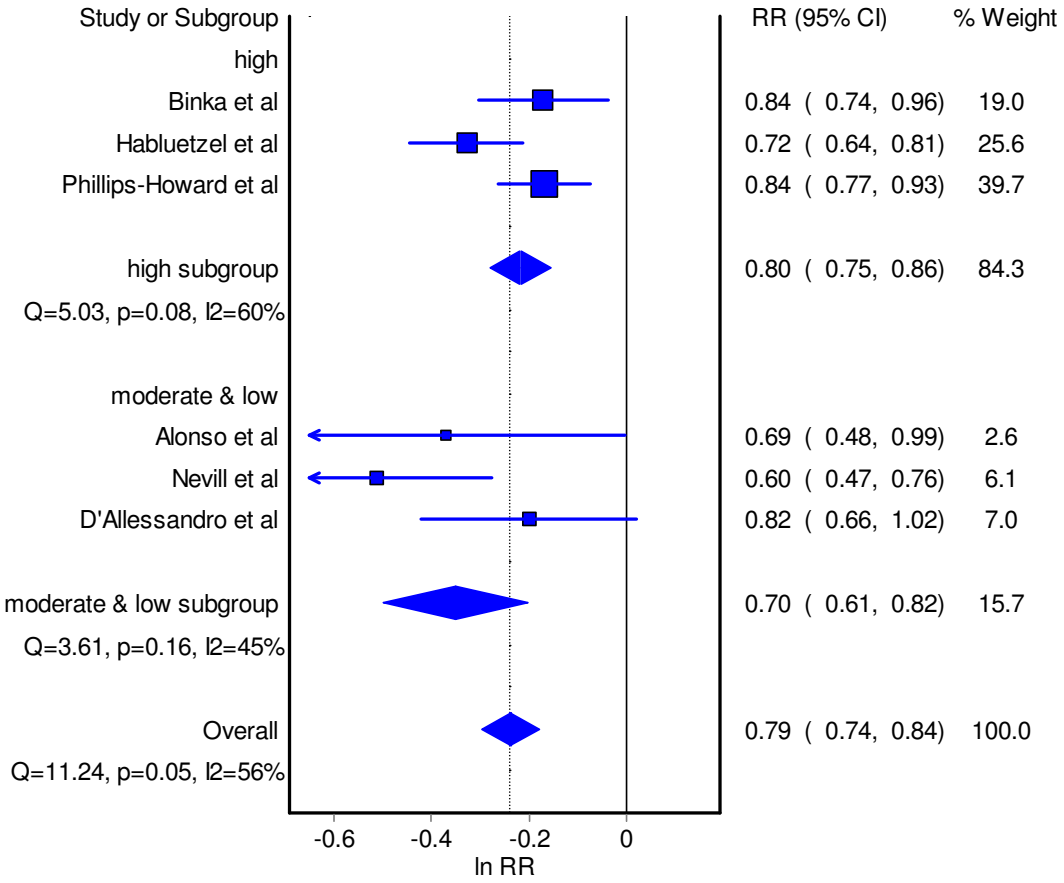


Table 7: Forest plot options

Section	Item	Comment	Saved
Colours	Panel	The panel of the graph is the graph area. Default is white.	✔
	Square	The studies' squares. Default is blue.	✔
	CI Line	The studies' confidence interval lines. Default is blue.	✔
X-axis	Auto	By default, the X-axis is scaled automatically. You need to uncheck this box in order to change the scaling.	
	Minimum, Maximum	By default, the minimum and maximum are set to the lowest and highest values of the confidence intervals of the included studies, respectively. When a confidence interval exceeds your chosen X-axis limit, it will display an arrow head. Error messages are	

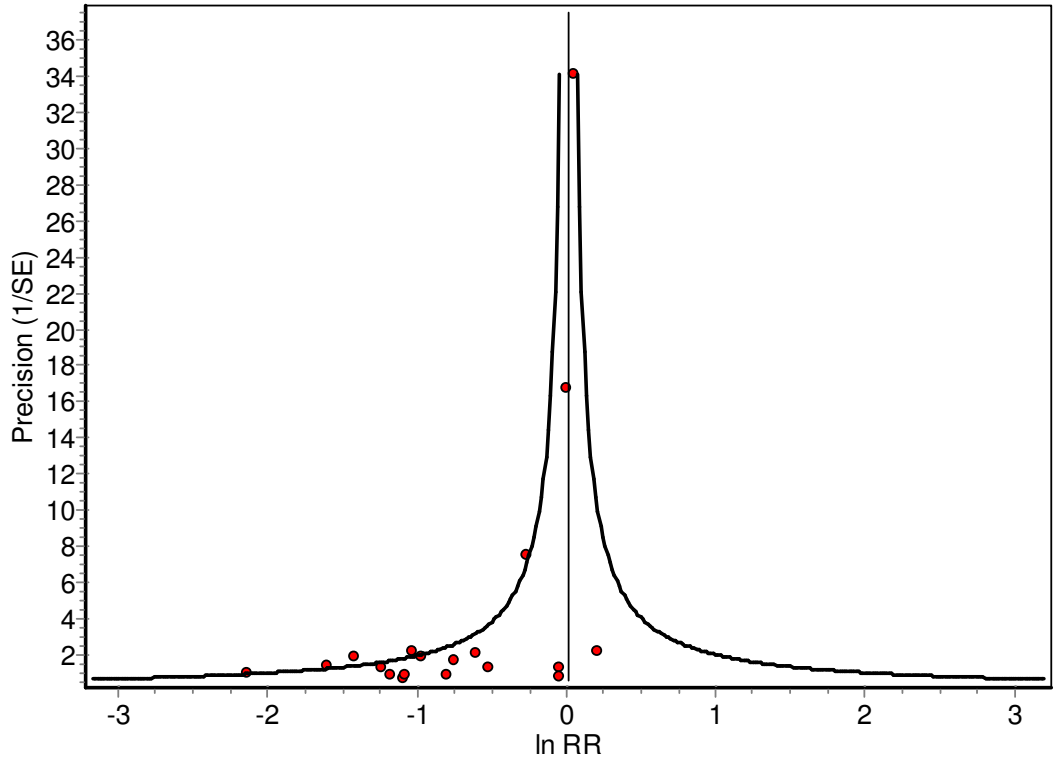
Section	Item	Comment	Saved
		displayed when your chosen limits are not correct, see the Section on error messages.	
	Ticks	This allows changing the number of ticks. Default is 5.	
	Rounding factor	The rounding of the numbers on the X-axis is mostly automatic, but you can override it if you wish so. Default is 0.1, meaning that a single decimal is displayed.	
Y-axis	Spacing	This allows changing the vertical spacing between the studies in the graph.	✔
	Right margin	The right margin of the plot shows by default the studies' effect size, confidence interval, and weight. This option allows changing the space for this information, which depends on whether you want to display the information, the font size, and your screen resolution.	✔
	Diamond height	The diamond in the graph displays the pooled effect size and confidence intervals. Its width is determined by the confidence intervals, but you can change its height.	✔
Fonts	Titles and labels	All text items in the plot can individually be set to any available font type, style, size, and colour.	
Miscellaneous	Show title	Determines whether the name of the meta-analysis will show as the title of the graph. Default is on.	
	Grid lines	Ticking this box will cause the graph to display grid lines. Default is off.	
	Filled diamond	When ticked, the overall effect diamond is solid, otherwise only the outline shows. Default is on.	✔
	Arrow size	Size of the arrow head that is displayed when confidence interval exceeds the X-axis scale.	✔
	Square size	Sets the size of the study squares (this retains the proportional differences)	✔
	Weights	Determines whether the right margin displays the weight of each study in the pooled effect size. Default is on.	
	Effect size and CI	Determines whether the right margin displays the effect size and confidence interval of each study. Default is on.	
	ES ln transform	With the Output option for OR and RR set to log scale (see below), this option determines whether the right margin effect size and confidence interval and tabled results are also on the log scale. Default is off.	✔
	CI line width	Determines the width of the studies' confidence interval line width. Default is 2.	✔

Section	Item	Comment	Saved
Effect size text		Allows setting the displayed effect size name in the graphs and associated tables. Primarily useful when MetaXL displays the generic ES (for effect size).	

When choosing 'File|Save settings' in this form the currently chosen options for which a check mark is in the 'saved' column of table 6 become the new defaults. This menu also allows restoring the original default values.

Funnel plot

The figure below shows the funnel plot from the Inverse Variance rate ratio method in the Magnesium example spreadsheet. Again, the funnel plot can be saved to disk or to the clipboard, see the discussion of the forest plot above.



Please note that the pooled estimate line is always based on fixed effects meta-analysis methods, which may differ from the pooled estimates obtained with quality and random effects methods.

Funnel plot options

Right-clicking the graph or choosing 'Options|Plot options' from the menu gives access to the Funnel plot options form. Table 8 below displays the various options by section of the Funnel plot options window, and indicates which ones can be saved.

Table 8: Funnel plot options

Section	Item	Comment	Saved
Colours	Panel	The panel of the graph is the graph area. Default is white.	✔

Section	Item	Comment	Saved
	Dot	The studies' dots. Default is red.	✔
X-axis	Ticks	This allows changing the number of ticks. Default is 5.	
Y-axis	Ticks	This allows changing the number of ticks. Default is 5.	
	Scale	There are three options for the Y-axis: Standard error (the default), Precision, and Inverse variance. For the relative merits of each, see Sterne & Egger (Sterne and Egger 2001).	✔
Fonts	Titles and labels	All text items in the plot can individually be set to any available font type, style, size, and colour.	
Miscellaneous	Show title	Determines whether the name of the meta-analysis will show as the title of the graph. Default is on.	
	Grid lines	Ticking this box will cause the graph to display grid lines. Default is off.	
	Tip labels	When ticked, study names are displayed in the graph. Default is off.	
	Dot size	Size of the study dots. Default is 3.	✔
Effect size text		Allows setting the displayed effect size name in the graphs and associated tables. Primarily useful when MetaXL displays the generic ES (for effect size).	

Again, some of the currently chosen options can be saved to become preferred defaults, and the original defaults can be restored.

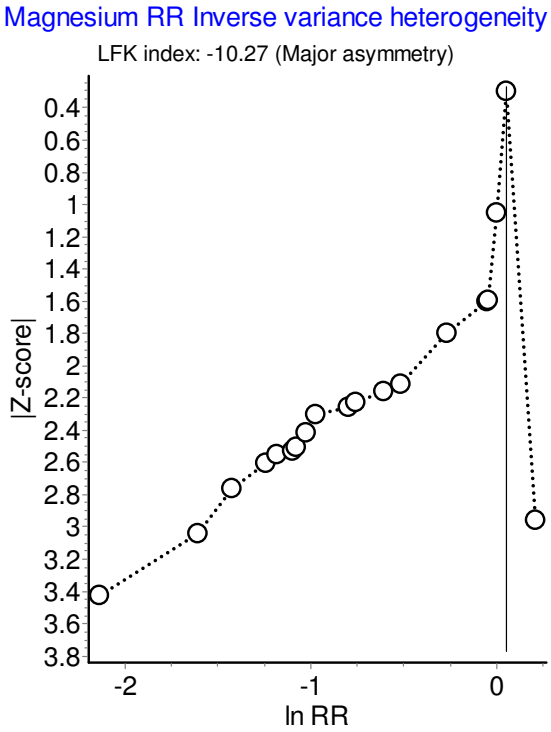
Doi plot

The figure below shows the Doi plot from the rate ratio effect size in the Magnesium example spreadsheet. Again, the Doi plot can be saved to disk or to the clipboard, see the discussion under forest plot above.

Like the funnel plot, the Doi plot is used to alert researchers to possible publication bias, but the Doi plot is more sensitive than the funnel plot. The interpretation, however, is much like that of the funnel plot: a symmetrical plot gives no reason to suspect publication bias, an asymmetrical one does. For a description of the calculation of the Doi plot, please refer to the Doi plot chapter in the Meta-analysis methods section below.

With symmetrical studies, the most precise trials will define the mid-point around which results should scatter, and thus they will be close to mid-rank and will be close to zero on the *Z*-score axis. Smaller less precise trials will produce an ES that scatters increasingly widely, and the absolute *Z*-score will gradually increase for both smaller and larger ES's on either side of that of the precise trials. Thus, a symmetrical triangle is created with a *Z*-score close to zero at its peak. If the trials are homogeneous and not affected by selection or other forms of bias, the plot will therefore resemble a symmetrical mountain with similar number of studies on each side and equal spread on each side. If either of the latter two is violated, then asymmetry exists.

The Doi plot also displays the LFK index of asymmetry, including an assessment of severity ('No', 'Minor', 'Major'). For details, please refer to the Doi plot chapter below.



Doi plot options

Right-clicking the graph or choosing 'Options|Plot options' from the menu gives access to the Doi plot options form. Table 9 below displays the various options by section of the Doi plot options window, and indicates which ones can be saved.

Table 9: Doi plot options

Section	Item	Comment	Saved
Axes	Ticks	This allows changing the number of ticks of the X- and Y axis. Default is 5.	
Dots	Size	Size of the study dots. Default is 5.	✔
	Colour	The studies' dots. Default is black.	✔
	Filled	Determines whether the study dots are open circle or not. Default is open circle.	✔
Main line	Width	The width of the main line. Default is 3.	✔
	Colour	Colour of the main line. Default is black.	✔
Mid-point line	Width	The width of the mid-point line. Default is 1.	✔
	Colour	Colour of the mid-point line. Default is black.	✔
Fonts	Titles and labels	All text items in the plot can individually be set to any available font type, style, size, and colour.	

Section	Item	Comment	Saved
Miscellaneous	Show title	Determines whether the name of the meta-analysis will show as the title of the graph. Default is on.	
	Show LFK	Determines whether the LFK index of asymmetry will be displayed. Default is on.	
	Grid lines	Ticking this box will cause the graph to display grid lines. Default is off.	
	Tip labels	When ticked, study absolute Z-values are displayed in the graph. Default is off.	
	Panel	The panel of the graph is the graph area. Default is white.	✔
Effect size text		Allows setting the displayed effect size name in the graphs and associated tables. Primarily useful when MetaXL displays the generic ES (for effect size).	

Again, some of the currently chosen options can be saved to become preferred defaults, and the original defaults can be restored.

Exclude
This tab shows the list of studies in the analysis, each with a check box next to it. When the check box is checked, the study is included in the analysis. You can uncheck studies and recalculate results by clicking the button. With this feature you can investigate which studies are the prime determinants of the pooled result, and which are the main source of heterogeneity.

Sensitivity
In this tab a table is displayed from a sensitivity analysis that excludes one by one each study in the analysis. The table shows the pooled effect sizes and the associated heterogeneity statistics. This feature gives a quick indication which study is the prime determinant of the pooled result, and which is the main source of heterogeneity. Note that you can adjust column widths and row heights using the mouse.

Meta-Regression data
This tab will show only when a MARegresData function is linked to the MAInputTable function. It shows a table with a number of standard study variables, plus user-defined moderator variables. The purpose is to copy this table and paste it into Stata as a dataset for meta-regression. For a full discussion of the dataset and the subsequent meta-regression analysis, see the section on "Meta-regression using MetaXL to create the dataset and Stata to run the regression analysis" below.

Results from MACumulative

After clicking the Results menu item, results from MACumulative functions are shown in the Result list by the MACumulative function names. Choosing this will display a pop-up window, with tabs to give access to a plot, tabled results, and a tab that allows excluding one or more studies and recalculate results.

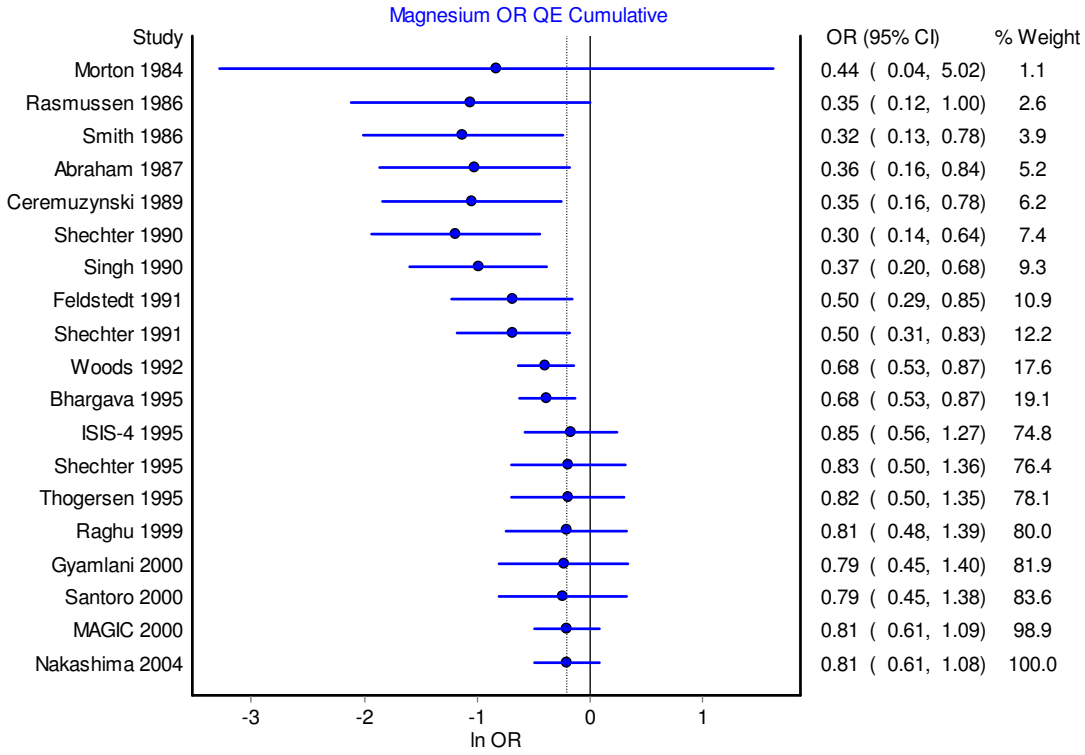
Tabled results

The results table shows the list of input studies with their effect sizes, confidence intervals, and the cumulative weight in the meta-analysis. Options apply as with the MAInputTable tabled results. The table below shows the quality effects model results from the MagnesiumCumulative example workbook.

Study	OR	LCI 95%	HCI 95%	Cumulative Weight (%)
Morton 1984	0.436	0.038	5.022	1.1
Rasmussen 1986	0.346	0.120	0.995	2.6
Smith 1986	0.323	0.134	0.781	3.9
Abraham 1987	0.360	0.155	0.836	5.2
Ceremuzynski 1989	0.352	0.159	0.778	6.2
Shechter 1990	0.304	0.145	0.639	7.4
Singh 1990	0.372	0.202	0.684	9.3
Feldstedt 1991	0.501	0.294	0.852	10.9
Shechter 1991	0.504	0.307	0.829	12.2
Woods 1992	0.675	0.526	0.866	17.6
Bhargava 1995	0.681	0.532	0.871	19.1
ISIS-4 1995	0.847	0.563	1.275	74.8
Shechter 1995	0.825	0.500	1.362	76.4
Thogersen 1995	0.823	0.500	1.354	78.1
Raghu 1999	0.812	0.476	1.385	80.0
Gyamlani 2000	0.792	0.447	1.401	81.9
Santoro 2000	0.787	0.447	1.384	83.6
MAGIC 2000	0.814	0.611	1.086	98.9
Nakashima 2004	0.811	0.609	1.080	100.0

Cumulative forest plot

The figure below shows the cumulative forest plot from of the quality effects model in the MagnesiumCumulative example workbook. It shows, in addition to the graph, for each study the effect size and confidence interval, plus the cumulative weight of each study in the pooled effect size. Again, options are available, similar to the standard forest plot described above.



Exclude

This tab shows the list of studies in the analysis, each with a check box next to it. When the check box is checked, the study is included in the analysis. You can uncheck studies and recalculate results by clicking the button. With this feature you can investigate the effect of specific studies on the result of the cumulative analysis.

Results from MAMixed

The Results menu item also gives access to results from the MAMixed function. However, since the number of input studies to MAMixed is two, the popup window only shows the forest plot and the table: the other outputs make no sense when the input number is two.

Results from MANetwork

After clicking the Results menu item, results from MANetwork functions are shown in the Result list as "MANetwork name vs control". Choosing this will display a pop-up window, with tabs to give access to a plot, tabled results, and an "All comparisons" table.

Tabled results

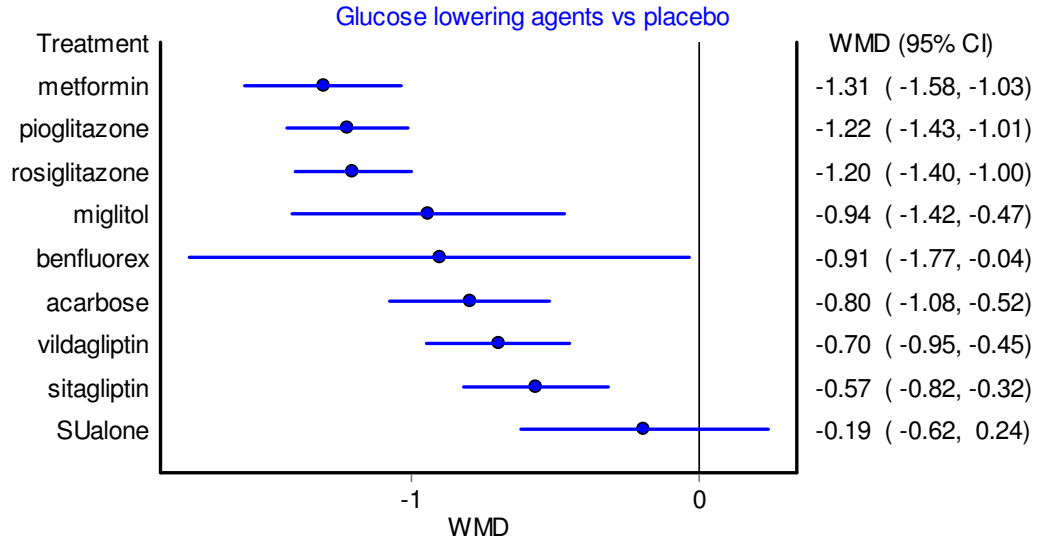
The results table shows the list of treatments (in this case from a network meta-analysis of oral glucose lowering agents versus a placebo control) with their effect sizes and confidence intervals. The table also shows a measure of consistency across the network as the average H statistic, see the section on Network Meta-analysis below for its interpretation.

Comparison	Active	Control	WMD	LCI 95%	HCI 95%
acarbose	acarbose	placebo	-0.800	-1.081	-0.519
SUalone	SUalone	placebo	-0.193	-0.624	0.237
benfluorex	benfluorex	placebo	-0.905	-1.774	-0.037
metformin	metformin	placebo	-1.308	-1.582	-1.035
miglitol	miglitol	placebo	-0.944	-1.418	-0.470
pioglitazone	pioglitazone	placebo	-1.224	-1.434	-1.015
rosiglitazone	rosiglitazone	placebo	-1.204	-1.404	-1.004
sitagliptin	sitagliptin	placebo	-0.570	-0.823	-0.317
vildagliptin	vildagliptin	placebo	-0.700	-0.949	-0.451
Consistency H	1.109				

Network forest plot

The figure below shows the forest plot from the network meta-analysis of oral glucose lowering agents versus a placebo control. Usually, network forest plots based on Bayesian methods rank treatments by the surface under the cumulative ranking curve (called SUCRA).

From a frequentist perspective, treatment effects are thought as fixed parameters and thus, strictly speaking, a concept like SUCRA does not make sense. A frequentist alternative called the P-score has been proposed but SUCRA or P-scores have no major advantage compared to ranking treatments by their point estimates (Rucker and Schwarzer 2015).



Treatments are therefore ranked by effect size in the network forest plot, with a dot giving the central estimate, and a line the confidence interval. In addition to the graph, for each treatment the effect size and confidence interval are shown. Again, the network forest plot can be saved to disk or to the clipboard, see the discussion of the forest plot above.

Network forest plot options

Right-clicking the graph or choosing 'Options|Plot options' from the menu gives access to the network forest plot options form, where you can set many graph

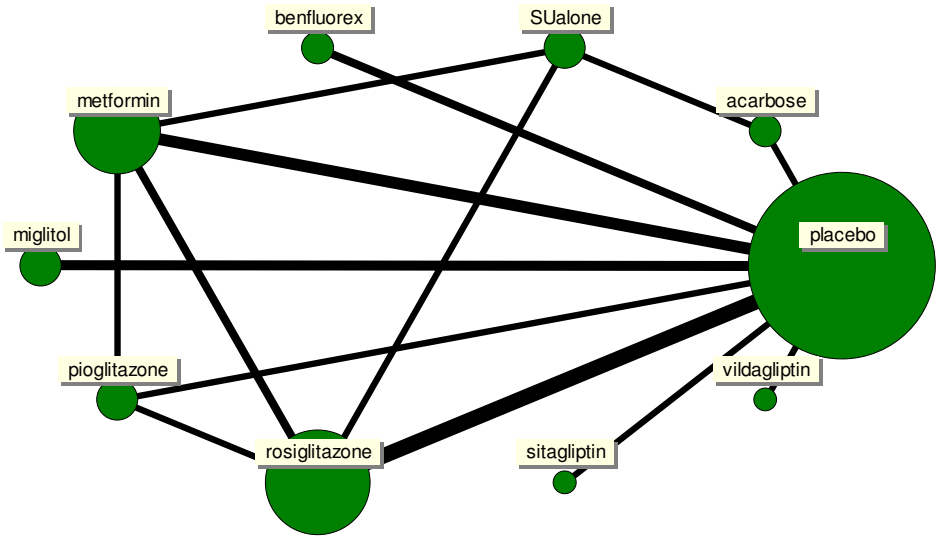
properties. Many of these properties are similar to the forest plot options, and as with the forest plot, some of these properties can be saved to become your preferred defaults. Please consult the discussion of the forest plot options and Table 7 above. The Network plot options also allows to manually exclude specific treatments from the plot.

All comparisons table

This table shows the list of direct estimates (the inputs of the analysis), indirect estimates, and result estimates, all with their effect sizes and confidence intervals. Direct and indirect estimates are given an ID number, which is used to identify on which comparisons the indirect and result estimates are based.

ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	aca-pla	acarbose	placebo	-0.800	-1.081	-0.519
2	aca-SUa	acarbose	SUalone	-0.400	-0.704	-0.096
3	ben-pla	benfluore	placebo	-0.905	-1.774	-0.037
4	met-pla	metformi	placebo	-1.152	-2.085	-0.219
5	met-SUa	metformi	SUalone	-0.370	-0.602	-0.138
6	mig-pla	miglitol	placebo	-0.944	-1.418	-0.470
7	pio-met	pioglitazo	metformi	0.160	-0.006	0.326
8	pio-pla	pioglitazo	placebo	-1.300	-1.549	-1.051
9	pio-ros	pioglitazo	rosiglitazc	0.100	-0.259	0.459
10	ros-met	rosiglitazc	metformi	-0.073	-0.390	0.244
11	ros-pla	rosiglitazc	placebo	-1.148	-1.379	-0.917
12	ros-SUa	rosiglitazc	SUalone	-1.200	-1.481	-0.919
13	sit-pla	sitagliptin	placebo	-0.570	-0.823	-0.317
14	vil-pla	vildaglipti	placebo	-0.700	-0.949	-0.451
	Indirect estimates (source IDs)					
15	Indirect pioglitazone vs placebo (7, 4)	pioglitazo	placebo	-0.992	-1.940	-0.044
16	Indirect pioglitazone vs placebo (9, 11)	pioglitazo	placebo	-1.048	-1.475	-0.622
17	Indirect rosiglitazone vs placebo (10, 4)	rosiglitazc	placebo	-1.225	-2.211	-0.240
18	Indirect metformin vs placebo (7, 8)	metformi	placebo	-1.460	-1.759	-1.161
19	Indirect metformin vs placebo (10, 11)	metformi	placebo	-1.075	-1.468	-0.683
20	Indirect SUalone vs placebo (2, 1)	SUalone	placebo	-0.400	-0.813	0.013
21	Indirect SUalone vs placebo (5, 4)	SUalone	placebo	-0.782	-1.744	0.179
22	Indirect rosiglitazone vs placebo (9, 8)	rosiglitazc	placebo	-1.400	-1.836	-0.964
23	Indirect SUalone vs placebo (12, 11)	SUalone	placebo	0.052	-0.312	0.416
	Result estimates (source IDs)					
	acarbose (1)	acarbose	placebo	-0.800	-1.081	-0.519
	SUalone (20, 21, 23)	SUalone	placebo	-0.193	-0.624	0.237
	benfluorex (3)	benfluore	placebo	-0.905	-1.774	-0.037
	metformin (4, 18, 19)	metformi	placebo	-1.308	-1.582	-1.035
	miglitol (6)	miglitol	placebo	-0.944	-1.418	-0.470
	pioglitazone (8, 15, 16)	pioglitazo	placebo	-1.224	-1.434	-1.015
	rosiglitazone (11, 17, 22)	rosiglitazc	placebo	-1.204	-1.404	-1.004
	sitagliptin (13)	sitagliptin	placebo	-0.570	-0.823	-0.317
	vildagliptin (14)	vildaglipti	placebo	-0.700	-0.949	-0.451

Network plot
The network plot shows the input data for the network meta-analysis. Each intervention, including the comparator, is represented by a circle. Interventions that have been directly compared in the input studies are connected with a line. The width of that line is proportional to the number of studies that compared the two interventions. The size of the intervention circle is proportional to the number of arms that intervention occurs across all input studies.
The figure below shows the network plot of the oral glucose lowering agents.



Network plot options
Right-clicking the graph or choosing 'Options|Plot options' from the menu gives access to the Network plot options form. Table 10 below displays the various options by section of the Network plot options window, and indicates which ones can be saved.

Table 10: Network plot options

Section	Item	Comment	Saved
Circles	Colour	The studies' circles. Default is green.	✔
	Minimum size	Size of the circle if intervention is just present in one arm. Default is 5.	✔
	Size increase	Determines the proportional increase in circle size with each additional arm it is in. Default is 5.	✔
Lines	Width	The width of the lines. Default is 5.	✔
	Colour	Colour of the lines. Default is black.	✔
Labels	Frame visible	The background frame visibility	✔
	Frame colour	The background colour of the intervention name labels. Default is yellow.	✔
	Font	Set the label font, its size and colour.	✔ size only

Section	Item	Comment	Saved
General	Panel colour	The background colour of the graph. Default is white.	✔
	Margin size	Determines the size of the graph margins, which, depending on the size of the circles, may cause circles to be clipped. Default is 5.	✔

Options

The Options menu item is organised in two tabs: Calculation and Output. The Calculation tab lets you set the following values:

1. Size of the confidence interval of the output. Size can range from 50-99%. Default is 95%.
2. Size of the confidence interval of the input for the IOTypes that take a confidence interval as input. Size can range from 50-99%. Default is 95%.
3. The value for the continuity correction (default is 0.5). Choices are, in addition to 0.5, 0.0, 0.25, 0.75, and 1. See the section on Continuity correction below for details.
4. The transformation used when meta-analysing prevalences. Options are 1) no transformation, 2) the logit transformation, and 3) the double arcsine transformation. For more on these transformations, see the section on Meta-analysis of Prevalence below. Default is double arcsine, and users are strongly advised to keep that option.
5. Normalise prevalence. The prevalence transformations may cause a multi-category prevalence pooled result to not add to 1. This option normalises the pooled prevalences such that they do. See the section on Meta-analysis of Prevalence below for more information. Default is on.

The Output tab gives access to the following features:

1. The number of decimals in the results table (default is 3) and the forest plot (default is 2).
2. The size of the font used in the results tables and other output. Default is 8, range is 2-16.
3. The forest plot output for relative risks (RR), odds ratios (OR), hazard ratios (HR), prevalences, rate ratios, and correlations can be set to be on the natural scale or transformed scale. Default is the transformed scale.
4. Graph titles: you can set whether the forest, funnel and Doi plots will show the meta-analysis name as the graph title. Default is on. You can override the choice made here through the Options of an individual plot.

All chosen options can be saved to become the preferred defaults by choosing File|Save settings. You can also restore the original defaults through this menu.

MetaXL User Guide

Choosing this item displays this document in a window. You can also consult this document through the Windows start menu MetaXL entry.

Examples

This item displays an Open file dialog where you can choose from the example workbooks that come with the MetaXL installation. You can also open these examples through the Windows start menu MetaXL entry. Please note that the example workbooks are not protected: any changes you make can be saved. The example workbooks are discussed in the Documentation section below.

Reset

Clicking this entry makes MetaXL to delete and recalculate all results in the current workbook. This is useful in at least two circumstances:

1. When you rename a worksheet with a MAInputTable function in it, the function will display the "Duplicate MAInputTable function names" error. Clicking "Reset" makes the error go away. Similarly for MAIndirect, MAMixed, and MANetwork functions.
2. After closing a workbook with MAInputTable functions in it, the calculated results remain present in memory and are listed when choosing "Show Results". Clicking "Reset" deletes the results from memory.

Please note that normally the MetaXL functions recalculate results just like any native Excel function: when Excel's Recalculation option is in the default "automatic" position, any change in the input data range will immediately be reflected in the results.

About MetaXL

This menu item displays the About box, with details of the MetaXL version and a link to the Epigear website (www.epigear.com).

Meta-analysis methods

Introduction

The aim of this section is to give some background to the special features of MetaXL, including references to the literature, and help the user to make full and appropriate use of these features. We first discuss ways to deal with heterogeneity between studies, and in particular the IVhet and quality effects models (which are unique to MetaXL) and why we think they are superior to the random effects model. Next we discuss the meta-analysis of prevalence, where (as far as we know) MetaXL is unique in that it provides methods for meta-analysing multiple-category prevalences. And in a third sub-section we discuss the way MetaXL deals with zero counts, the so-called continuity corrections.

One of the first things to realise is that, from a statistical point of view, meta-analysis is a very simple procedure: nothing more then taking the weighted average of a number of study results. The various methods differ in the way they assign individual study weights and how they apply them, but once that is settled, the pooled result is simply the weighted average.

This observation is certainly not meant to belittle meta-analysis: it is an invaluable and increasingly important tool, and a prime source of information for evidence based medicine and health economic evaluation. But the hard work in meta-analysis is in the validly collecting, digesting, and rating of often very heterogeneous studies. Once that is done, the statistical pooling of the results is almost a breeze.

Various models

While meta-analysis is essentially taking a weighted average of study results, there are different ways to take a weighted average. In the literature the main distinction is between fixed-effects and random-effects models (Deeks, Altman et al. 2001). The fixed-effects model is sub-divided into three methods: inverse variance, Mantel-Haenszel, and Peto's method for odd ratios. The random-effects model (see below) is a modification of the inverse variance fixed-effects model. For these methods and models, MetaXL implements the equations as outlined in the chapter by (Deeks, Altman et al. 2001).

MetaXL is unique in that it also implements a IVhet and a quality-effects model. The reason for this is that the random-effects model is an unsatisfactory answer to the problem it tries to address. We therefore propose the IVhet model as an interim replacement for the random effects model and quality-effects model as a better alternative to the IVhet model. As is the case with the random-effects model, both the IVhet and quality-effects model are a modification of the fixed-effects inverse variance method. Below we first describe the random-effects model and the way it tries to address the heterogeneity problem, next discuss the IVhet and then finally the quality-effects model.

Conventional meta-analysis: The fixed and random effects models

In conducting a meta-analysis, you must conventionally choose between a fixed- (FE) or random-effects (RE) model. The two models make very different assumptions about the data. The FE model assumes that all of the studies are estimating a common population effect-size and that the differences between the studies are simply a

function of sampling error (Lipsey and Wilson 2001, Senn 2007). This is rarely plausible with the possible exception of a meta-analysis of pure replications.
The weight in the 'inverse variance method' FE model is based on Woolf (Woolf 1955). The average effect size across all studies is computed, whereby the weights are equal to the inverse variance of each study's effect estimator. Larger studies and studies with less random variation are given greater weight than smaller studies. The weights (w) allocated to each of the studies are then inversely proportional to the square of the standard error (se), thus for the jth study

$$w_j = \frac{1}{se_j^{\,2}}$$

which gives greater weight to those studies with smaller standard errors.
As can be seen above the variability within each study is used to weight each studies effect in the current approach to combining them into a weighted average as this minimizes the variance (assuming each study is estimating the same target). So if a study reports a higher variance for its effect size estimate it would get lesser weight in the final combined estimate and vice versa. The problem with this sort of weighting in meta-analysis is that as heterogeneity (varying effects across studies) increases the model exhibits overdispersion (theoretical variance derived from the model underestimates the true estimator variance).

Weighting within the random-effects model assumes two sources of variability in effects, one from sampling error and one from study level differences. However the latter are based on the variability in effect sizes across the group of studies and it has been taken to imply that the random-effects model assumes a distribution of true population effects from which the observed studies are sampled (Lipsey and Wilson 2001, Senn 2007). The RE model generates a constant from the homogeneity statistic Cochran's Q and using this and other study parameters a random effects variance component (τ^2) is generated. The inverse of the sampling variance plus this constant that represents the variability across the population effects is then used as the weight

$$w_j^* = \frac{1}{se_j^2 + \tau^2}$$

where w_j^* is the random effects weight for the ith study.
However, because the weights equalize with increasing heterogeneity, this estimator in fact has when heterogeneity is present a greater variance and mean squared error (MSE) when compared to the FE estimator, especially if the number of meta-analysed studies is small. While the specification of the RE model results in a wider CI around the pooled estimate than the FE model, the widening is inadequate because the true variance is larger than the (computed) RE model variance, and substantial overdispersion remains. As a consequence, coverage of the RE model declines below the intended nominal level (usually 95%) with heterogeneity, and increasingly so (Brockwell and Gordon 2007, Cornell, Mulrow et al. 2014). We then have an RE estimator that produces over-confident results because of an underestimated statistical error and no satisfactory solution has been found despite attempts by Brockwell (Brockwell and Gordon 2007) and Noma (Noma 2011), among others.

The key problem with the random effects model is that a more likely cause of differences in effect size between trials is systematic error, and such sources of bias are not addressed appropriately by the random effects meta-analysis model (Conn and

Rantz 2003). Obviously, if a random variable is inserted to inflate the variance based on heterogeneity, it is not clear what aspect of between-trial differences is being assessed and fails to take into account meaningful differences between the individual studies. Also, because of this limitation of the random effects model, when used in a meta-analysis of badly designed studies, it will still result in bad statistics even though there is some statistical adjustment for heterogeneity. Furthermore, if we look critically at computational aspects of the random model, we immediately realize that the random effects meta-analysis is simply a process whereby the inverse variance weighting of the fixed model is reversed (to a variable extent) thus moving the weighted mean effect size back towards an unweighted mean. The extent of this reversal is solely dependent on two factors (Al Khalaf, Thalib et al. 2011):

1. Heterogeneity of precision (study size): The extent of the spread of precision of the studies involved as indicated by the maximum minus minimum inverse variance weights
2. Heterogeneity of effect size (τ^2): How many times bigger than the average variance of studies within the meta-analysis is the value of τ^2. (τ^2 alone is not comparable across different meta-analyses).

This model reduces the extreme diminution of the effect size of the smaller studies so that the pooled effect size now moves towards an intermediate value between trials with extremes of precision (Helfenstein 2002).This movement backwards towards an unweighted mean, however, is based on penalizing larger studies based on sample size and effect size (τ^2) heterogeneity. Is the random model analysis now any more valid than a fixed effects analysis when heterogeneity is present? Unfortunately the answer is *no* because there is no reason to automatically assume that a larger variability in study sizes or effect sizes (meta-analysis τ^2) automatically indicates a faulty larger study or more reliable smaller studies. Indeed, there is no reason why the conclusiveness of a meta-analysis should be associated with the random model method of reversal of the inverse variance weighting process of the included studies. As such the changes in weight introduced by this model to each study have no statistical or probabilistic interpretation and thus bear no relationship to what the studies actually have to offer.

Heterogeneity between trials can occur for a multitude of reasons some of which include chance, different definitions of treatment effects, credibility related heterogeneity (quality), and finally unexplainable and real differences (Bailey 1987). Credibility related heterogeneity (quality) is an important quantifiable difference and this refers to the likelihood of the trial design to generate unbiased results that are sufficiently precise and allow application in clinical practice (Verhagen, de Vet et al. 2001). Naturally, the flaws in the design of individual studies can be expected to create heterogeneity between trials as well as influence the magnitude of the meta-analysis results. If the quality of the primary material is inadequate, this may falsify the conclusions of the review, regardless of the presence or absence of effect size heterogeneity. This need for addressing heterogeneity in trials via study specific assessment has been obvious for a long time and the solution involves much more than the random model strategy of just inserting a random term based on effect size heterogeneity (Senn 2007). The unfortunate thing however is that the weight used in the RE model is an index of the variability of the effect sizes across trials and the same "situation specific" weight is applied to all studies. This creates two problems, first that these weights are meaningless (in the sense that they add no new information to the model), serving only to penalize big studies by transferring weight one way

from big to small studies. Second, they lead to underestimation of the statistical error and thus create over confident results because of poor coverage of the confidence interval. In order to rectify this situation, an alternative approach has been proposed in 2008 (Doi and Thalib 2008, Doi and Thalib 2009). In the QE model, both of the drawbacks of the random model type of re-distribution have been addressed. We have also developed a simpler IVhet model that is implemented in MetaXL as an interim solution when quality information is lacking. These models are discussed below.

More robust meta-analysis: The Inverse Variance Heterogeneity (IVhet) and Quality Effects (QE) models

This chapter has been published as two journal articles (Doi, Barendregt et al. 2015, Doi, Barendregt et al. 2015), and is for copyright reasons therefore removed from this *User Guide*. The subsection below on *The Quality Score* discusses the implementation of quality scores in MetaXL and under the *MetaXL functions* subsection above the selection of models is described. In the *Documentation* section below, several examples are described that are discussed in the articles, and come with the MetaXL download as example spreadsheets. Below are the two references and two abstracts.

The IVhet model

Advances in the Meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model

Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM.

Contemp Clin Trials 2015, 45:130-138 (Special 10th Anniversary issue).

This article examines an improved alternative to the random effects (RE) model for meta-analysis of heterogeneous studies. It is shown that the known issues of underestimation of the statistical error and spuriously overconfident estimates with the RE model can be resolved by the use of an estimator under the fixed effect model assumption with a quasi-likelihood based variance structure – the IVhet model. Extensive simulations confirm that this estimator retains a correct coverage probability and a lower observed variance than the RE model estimator, regardless of heterogeneity. When the proposed IVhet method is applied to the controversial meta-analysis of intravenous magnesium for the prevention of mortality after myocardial infarction, the pooled OR is 1.01 (95% CI 0.71 – 1.46) which favors the larger studies but also indicates more uncertainty around the point estimate. In comparison, under the RE model the pooled OR is 0.71 (95% CI 0.57 – 0.89) which, given the simulation results, probably reflects underestimation of the statistical error. Given the compelling evidence generated, we recommend that the IVhet model replace both the FE and RE models. To facilitate this, it has been implemented into a free meta-analysis software called MetaXL

The Quality Effects model

Advances in the Meta-analysis of heterogeneous clinical trials II: The quality effects model

Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM.

Contemp Clin Trials 2015, 45:123-129 (Special 10th Anniversary issue).

This article examines the performance of the updated quality effects (QE) estimator for meta-analysis of heterogeneous studies. It is shown that this approach leads to a decreased mean squared error (MSE) of the estimator while maintaining the nominal level of coverage probability of the confidence interval. Extensive simulation studies confirm that this approach leads to maintenance of the correct coverage probability of the confidence interval, regardless of the level of heterogeneity. It also retains a lower observed variance compared to the random effects (RE) model. The QE model is robust to subjectivity in quality assessment down to completely random entry, in which case its MSE equals that of the RE estimator. When the proposed QE method is applied to a meta-analysis of magnesium for myocardial infarction data, the pooled mortality odds ratio (OR) becomes 0.81 (95% CI 0.61 – 1.08) which favours the larger studies but also reflects the reduced uncertainty around the pooled estimate. In comparison, under the RE model, the pooled mortality OR is 0.71 (95% CI 0.57 – 0.89) which is less conservative than that of the QE results. The new estimation method has been implemented into the free meta-analysis software MetaXL which allows comparison of alternative estimators.

Q-index in the Quality Effects model

The extent of redistribution of the study weights due to non-credibility can be assessed via a Q-index ($\bar{Q}$) defined as follows:

$$\bar{Q} = \sum_{1}^{n} \left(\frac{(1-Q_j) \times w_j}{\sum_{1}^{n} w_j} \right)$$

The rationale for this index is that it tells us the extent to which (percent) redistribution of the IV weights have occurred through application of QE weights. The higher the Q-index, the more likely that the QE estimator variance has been reduced beyond that of the IVhet estimator. Thus, as the Q-index increases, the confidence interval width around the pooled estimate decreases beyond that of the IVhet estimator even though coverage remains at or above the nominal level.

The quality score

The quality score used with the QE model is essentially a safe-guards score. Thus if all studies are assessed against a list of predefined safeguards against bias (in other words a risk of bias assessment), a study with the maximum score simply has all safeguards in place and one with zero has none. This does not mean that the study with all the listed safeguards has no bias or that the magnitude of the score determines the magnitude of quantitative bias. This is because different quality components may influence bias in different directions and the magnitude or direction of the change in effect induced by a missing safeguard is an unknown. However, if the scores are converted into quality ranks between zero and 1 (by dividing each score by the score of highest scoring study in the group) then the best study will be ranked 1 and those with lower scores will be ranked lower. This rescaled quality rank (called Qi in MetaXL) then has a monotonic relationship to the bias ICC defined as between studies bias variance divided by the sum of within and between studies bias variance. The quality effects model redistribution of weights due to Qi would then help reduce estimator variance. It must be emphasized that this interpretation of quality requires neither the quantification of bias nor of any requirement that the quality parameters

exhaustively cover all possible sources of bias. An example of the computation of Qi for input into the quality effects model is given below (from the SchizophreniaPrev example spreadsheet). However, as noted in the section on MetaXL Functions, entry as a total score or a proportion of maximum score is also permitted as this will automatically be re-scaled by MetaXL as shown below.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Total score (max 11)	Max score in this group of studies = 10	Qi
Bondestam et al	*1*	*0*	*2*	*3*	*1*	*1*	*8*	*8/10=*	*0.8*
Shen et al	*1*	*0*	*1*	*2*	*0*	*1*	*5*	*5/10=*	*0.5*
Zharikov	*0*	*0*	*1*	*1*	*0*	*1*	*3*	*3/10=*	*0.3*
Babigian	*1*	*1*	*1*	*1*	*0*	*1*	*5*	*5/10=*	*0.5*
Fichter et al	*1*	*1*	*2*	*3*	*1*	*1*	*9*	*9/10=*	*0.9*
Keith et al	*1*	*1*	*2*	*3*	*2*	*1*	*10*	*10/10=*	*1*

Health states Quality scale variables

Q1 Were the target population and the observation period well defined?

Yes = 1
No = 0

Q2 Diagnostic criteria

Use of diagnostic system reported (DSM, ICD, RDC) = 1
Own system /symptoms described/no system/not specified = 0

Q3 Method of case ascertainment

Community survey/multiple institutions = 2
Inpatient/inpatients and outpatients/case registers = 1
Not specified = 0

Q4 Administration of measurement protocol

Administered interview = 3
Systematic casenote review = 2
Chart diagnosis/case records = 1
Not specified = 0

Q5 Catchment Area

Broadly representative (national or multi-site survey) = 2
Small area/not representative (single community, single university) = 1
Convenience sampling/ other (primary care sample/treatment group) = 0

Q6 Prevalence measure

Point prevalence (e.g. one month) = 2
12-month prevalence = 1
Lifetime prevalence = 0

General 'risk of bias' instruments, such as the Cochrane Collaboration tool, can also be used. In each domain, assign 3 points to 'low risk', 2 to 'medium', and 1 to 'high risk', for example, and the results can be transformed to Qi ranks using the method described above.

Burden of Disease studies

One final consideration is the type C trials, which usually deal with burden of disease, and where true differences across populations are expected. Here the overall effect

size should adequately reflect the fractional sub-population and the use of meta-analysis to pool such estimates is wrong and should be avoided when differences between subpopulations can be expected. Standard meta-analysis, if used to combine data for two or more countries, would over-represent smaller countries with larger datasets or under-represent larger ones with smaller datasets. Such weighting has been combined within meta-analysis previously (Batham, Gupta et al. 2009), but is incorrect in the absence of an appropriate model framework. In reality, a direct standardization procedure is needed for this purpose – not meta-analysis. Since, direct standardization is also a form of custom weighted meta-analysis, a modification of the quality effects model can be adapted to direct standardization using a population size weight given by $Psize_i/Psize_{max}$. These weights can then be applied using a modified quality effects procedure to achieve a standardized estimate (Doi, Barendregt et al. 2014). The underlying results would be equivalent to manually performed direct standardization in epidemiology. We are in the process of providing a software package where standardization can be applied to subpopulations of any effect size using sub-population weights.

Meta-analysis of Prevalence

This chapter has been published as (Barendregt, Doi et al. 2013), and is therefore for copyright reasons removed from this *User Guide*. The section above on *MetaXL menus and features* discusses under the *Options* subsection the three transformation methods described in the article (no transformation, logit, and double arcsine transformations) plus the normalisation option. In the *Documentation* section below, the multiple sclerosis example is described that is discussed in the article, and comes with the MetaXL download as an example spreadsheet.
Below is the reference and abstract.

Meta-analysis of prevalence.
Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T.
J Epidemiol Community Health.2013 67: 974-978.

Meta-analysis is a method to obtain a weighted average of results from various studies. In addition to pooling effect sizes, meta-analysis can also be used to estimate disease frequencies, such as incidence and prevalence. In this article we present methods for the meta-analysis of prevalence. We discuss the logit and double arcsine transformations to stabilise the variance. We note the special situation of multiple category prevalence, and propose solutions to the problems that arise. We describe the implementation of these methods in the MetaXL software, and present a simulation study and the example of multiple sclerosis from the Global Burden of Disease 2010 project. We conclude that the double arcsine transformation is preferred over the logit, and that the MetaXL implementation of multiple category prevalence is an improvement in the methodology of the meta-analysis of prevalence.

Meta-analysis of correlations, rate-ratios and rate difference

MetaXL uses the Fisher's z transformation to stabilize the variance of the correlation coefficient (r). Had this transformation not been applied then the variance of r would tend to grow smaller as r approaches 1. The transform is given by:

$$z = \frac{1}{2}\ln\left(\frac{1+r}{1-r}\right) = \text{arctanh}(r)$$

The standard error of z is given by:

$\frac{1}{\sqrt{N-3}}$ where N is the sample size

MetaXL reports results after back transformation and this is computed as:

$$r = \frac{\exp(2z)-1}{\exp(2z)+1} = \tanh(z)$$

With the MetaXL download there is an example spreadsheet that meta-analyses correlations (Medcompliance.xls, see discussion in the Documentation section below).

For rate-ratios, MetaXL does computations on the natural log scale with approximate variance given by:

$$Var(\ln rateratio) = \frac{1}{E_e} + \frac{1}{E_c}$$

For the rate difference, computations are done on the natural scale with variance given by:

$$Var(ratediff) = \frac{E_e}{Pt_e^2} + \frac{E_c}{Pt_c^2}$$

Given that the variances for rate-ratios and rate difference are approximate, caution should be exercised when event numbers are sparse.

An example workbook for rate ratios and differences is IPTcMalaria.xls, discussed in the Documentation section below.

Indirect comparisons and Network meta-analysis

Indirect comparison methods are used to measure the effect of two treatments that were each compared against a similar control group in a meta-analysis. For example, if treatment A and treatment B were directly compared vs placebo in separate meta-analyses, we can use these two pooled results to get an estimate of the effects of A vs B in an indirect comparison as effect A vs Placebo minus effect B vs Placebo.

Indirect comparison meta-analysis methods (also called network meta-analyses, in particular when multiple treatments are assessed simultaneously) generally use two main methodologies. First, (which is what is implemented in MetaXL) is the repeated comparison of a closed loop of three-treatments such that one of them is common to the two studies and forms the node where the loop begins and ends. Therefore multiple two-by-two comparisons (3-treatment loops) are needed to compare multiple treatments within MetaXL. Trials with more than two arms will need to have two arms only selected as MetaXL can only deal with independent pair-wise comparisons. The alternative methodology uses complex statistical modelling to include the multiple comparisons simultaneously between all competing treatments. These have been assessed using Bayesian methods, mixed linear models and meta-regression approaches.

Single closed loop: Transitivity and the MAIndirect function

Three treatment networks provide the basis for adjusted indirect comparisons (as implemented in MetaXL). In these comparisons two interventions are compared through their relative effect versus a common comparator. This is the three-treatment network in a closed loop with the common intervention forming a node and the loop starting and ending at this node. The discrepancy between the direct and adjusted indirect comparison has previously been assessed by the difference between the two estimates (Song, Altman et al. 2003). It was found that in most cases, results of adjusted indirect comparisons were not significantly different from those of direct comparisons. A significant discrepancy ($P<0.05$) was observed in only three out of the 44 comparisons the authors examined between the direct and the adjusted indirect estimates.

One important point is that the validity of the adjusted indirect comparisons depends on both the assumption of transitivity as well as on the robustness of meta-analytic methods. Transitivity refers to the validity of the indirect comparison and can only be evaluated conceptually within each closed loop. Transitivity is violated when the anchor node (i.e. the common intervention) differs systematically (not randomly) between trials. Such systematic differences may be due to effect modifiers that differ across the paired comparisons or if there is non-similar definition/implementation of the anchor treatment node across the compared trials. Transitivity must hold for indirect estimates to be valid.

In terms of the meta-analytic method, the literature recommends using the random effects instead of fixed effects model results for indirect comparisons, but only MetaXL enables use of more robust statistical approaches by way of the IVhet model and is expected to be extended to the quality effects model in the future. Therefore adjusted indirect comparisons, using a more robust model, can only be obtained through MetaXL, and the resulting indirect comparisons are likely to be more robust as well.

The calculations used by MetaXL for adjusted indirect comparison are quite straightforward. For example if we have two meta-analytic results, A vs placebo and B vs placebo. We can then note that

$r_A = r_o \times RR_A$

where *r* stands for risk and subscripts o, A & B denote placebo, active A and active B groups respectively. Similarly for the second meta-analysis

$r_B = r_o \times RR_B$

The indirect effect of A compared with B is then

$$RR_{A/B} = \frac{r_A}{r_B} = \frac{r_o RR_A}{r_o RR_B} = \frac{RR_A}{RR_B} = \exp\left(\ln(RR_A) - \ln(RR_B)\right)$$

And, because these are independent observations:

$\text{var}(\ln RR_{A/B}) = \text{var}(\ln RR_A) + \text{var}(\ln RR_B)$

This then justifies the adjusted indirect comparison. It should be pointed out that the user is left to decide whether to compute A vs B or B vs A and all relative effect sizes are symmetrical when exposure is interchanged – i.e.

$RR_{A/B} = 1 / RR_{B/A}$.

For example, if we have the following meta-analytic results:

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Direct estimates					
1	t-PA-PTCA	t-PA	PTCA	0.68	0.11	4.29
2	SK-t-PA	SK	t-PA	1.00	0.94	1.07
3	SK-PTCA	SK	PTCA	1.84	1.17	2.90

Then we can create a 3-treatment closed loop from estimates 2 & 3 and compute an indirect estimate as follows:

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Indirect estimates (source IDs)					
4	Indirect t-PA vs PTCA (2, 3)	t-PA	PTCA	1.84	1.16	2.91

Combining a pair of direct and indirect estimates: The MAMixed function

A pair of a direct estimate of effect and a single closed loop generated estimate of the same effect indirectly is synthesized using MAMixed in MetaXL. The synthesis method defaults to the method used in the synthesis of the direct estimates. For example when we combine 1 & 4 above using MAMixed we get:

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Mixed estimate (source IDs)					
5	t-PA (1, 4)	t-PA	PTCA	1.73	1.03	2.92

Multiple closed loops: the MANetwork function

In MetaXL, the closed loop of three treatments (forming nodes of the triangular loop) and the resulting indirect estimates can automatically be calculated if the comparator is fixed. In other words, MANetwork creates multiple 3-treatment closed loops with one node, the control, fixed and this control is a parameter to the MANetwork function. What is allowed to change is the anchor node (i.e. the treatment node common to both studies) and the active intervention node. Thus all indirect and result estimates have the same control comparator.

The algorithm is as follows:

1. First the direct comparisons space is explored for all indirect comparisons with the fixed control comparator.
2. Next it checks whether there are any "orphan" treatment comparisons: treatments without a comparison to the control. If this is the case, which can happen in (locally) sparse networks, the algorithm looks for further indirect comparisons by combining each direct and each indirect comparison to look for a combination that delivers an indirect comparison of an orphan with the control. If found, such an indirect comparison is labelled as "extended indirect" in the "All comparisons" table.
3. Step 2 is repeated until all orphans have been estimated, or no progress can be made anymore.
4. In the final step, MetaXL then pools the direct and indirect estimates (or multiple indirect estimates) using a standard meta-analysis to arrive at the final network estimate for each intervention versus the fixed comparator. The model used for the primary meta-analysis is also the default for the synthesis of direct and indirect estimates while single estimates are reported as such.

The algorithm makes sure that the same source information is never used more than once to obtain a specific indirect estimate. In the All comparisons table, study IDs are used to trace on what studies indirect and final results estimates are based.

For example, if we have 9 meta-analytic results (direct estimates) as follows:

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Direct estimates					
1	SK-t-PA	SK	t-PA	1.00	0.94	1.07
2	SK-at-PA	SK	at-PA	1.17	1.06	1.29
3	SK-SK+t-PA	SK	SK+t-PA	0.67	0.18	2.43
4	SK-r-PA	SK	r-PA	1.06	0.89	1.26
5	SK-PTCA	SK	PTCA	1.84	1.17	2.90
6	t-PA-PTCA	t-PA	PTCA	0.68	0.11	4.29
7	at-PA-r-PA	at-PA	r-PA	0.98	0.42	2.29
8	at-PA-TNK	at-PA	TNK	0.99	0.88	1.13
9	at-PA-PTCA	at-PA	PTCA	1.25	0.99	1.58

Then fixing PTCA as the control generates eight possible 3-treatment loops that include the fixed comparator node and thus eight indirect estimates versus this comparator:

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Indirect estimates (source IDs)					
10	Indirect SK vs PTCA (1, 6)	SK	PTCA	0.68	0.11	4.31
11	Indirect SK vs PTCA (2, 9)	SK	PTCA	1.46	1.14	1.88
12	Indirect t-PA vs PTCA (1, 5)	t-PA	PTCA	1.84	1.16	2.91
13	Indirect at-PA vs PTCA (2, 5)	at-PA	PTCA	1.57	0.99	2.50
14	Indirect SK+t-PA vs PTCA (3, 5)	SK+t-PA	PTCA	2.76	0.70	10.89
15	Indirect r-PA vs PTCA (4, 5)	r-PA	PTCA	1.73	1.06	2.82
16	Indirect r-PA vs PTCA (7, 9)	r-PA	PTCA	1.27	0.53	3.07
17	Indirect TNK vs PTCA (8, 9)	TNK	PTCA	1.26	0.96	1.64

The final network meta-analysis estimates are generated by pooling the various direct/indirect estimates (total 17) above into six final estimates for intervention versus the fixed comparator. This uses the same meta-analysis model used for generating the direct estimates above.

ID	Comparison	Active	Control	OR	LCI 95%	HCI 95%
	Result estimates (source IDs)					
	SK (5, 10, 11)	SK	PTCA	1.53	1.23	1.90
	t-PA (6, 12)	t-PA	PTCA	1.73	1.03	2.92
	at-PA (9, 13)	at-PA	PTCA	1.31	1.06	1.61
	SK+t-PA (14)	SK+t-PA	PTCA	2.76	0.70	10.89
	r-PA (15, 16)	r-PA	PTCA	1.61	1.05	2.47
	TNK (17)	TNK	PTCA	1.26	0.96	1.64

Inconsistency in a single loop or across the multiple loop network

A simple three-treatment triangular loop that assumes transitivity for the anchor node can still result in inconsistency between this indirect estimate and any available direct estimate. Consistency thus becomes important for mixed treatment comparisons. The terms consistency and heterogeneity both describe disagreement between direct estimates of the same comparison across studies while the term inconsistency applies to the same disagreement but this time between estimates coming from different *pooled* sources of the same comparison (e.g. direct and indirect evidence, or different routes of indirect evidence) (Salanti, Del Giovane et al. 2014). The two terms are thus very closely connected and inconsistency can be viewed as the extension of heterogeneity across different forms of pooled studies evaluating the same comparison.

Since inconsistency, like heterogeneity, is a statistical consequence of between-study differences, a statistically significant difference between μ_{BC}^{d} and μ_{BC}^{i} has been used to test for statistical inconsistency. Comparing μ_{BC}^{d} and μ_{BC}^{i} in a simple z-test (often called the Bucher method), has been implemented in the MApConsMixed function for a single closed loop analysis that uses the MAMixed function in MetaXL. An alternative for judging consistency is the simple observation of non-overlapping confidence intervals for μ_{BC}^{d} and μ_{BC}^{i}. However a non-significant inconsistency test result should not be taken as proof for the absence of inconsistency and the

methodological and clinical plausibility of the consistency assumption should also be considered.

The evaluation becomes a bit more complicated when we move from a single closed loop to multiple loops in a network. An alternative therefore for statistical evaluation of consistency that applies to the entire network would be for authors to report inconsistency in a similar fashion to heterogeneity in direct estimates. One measure of heterogeneity in direct estimates is H^2, which is derived from Cochran's Q (Higgins and Thompson 2002). For each network result estimate, authors can compute the H^2 value (or its square root, H) which would then represent the inconsistency per comparison made. For the overall network authors can compute the weighted average H^2 or H over all final comparisons reported as a measure of inconsistency across the entire network. Network result estimates based on single studies by default get an H^2 or H value of 1. H^2 is computed as Q divided by one less than the number of final point estimates being pooled, $Q/(k-1)$, and describes the relative excess in Q over its degrees of freedom. A second interpretation of H^2 is as the estimated residual variance from the regression of the standardized treatment effect estimates against the inverse standard error in each synthesis (Higgins and Thompson 2002). Since H^2 is a variance, its square root (H) would have a more direct interpretation in terms of the fold-increase in heterogeneity or inconsistency. In MetaXL, the weighted average ($\bar{H}$) over the network is computed as:

$$\bar{H} = \sqrt{\frac{\max\left[\max(1, n-1), \sum_{j=1}^{k} Q_j\right]}{\left(\sum_{j=1}^{k} n\right) - k + s}}$$

Where the max operator returns the highest value of the two elements, Q_j is the Cochran Q statistic value for final estimate j, k is the number of final estimates within the GPM network analysis, n is the number of data-points pooled across each final estimate and s is the number of non-pooled (single data-point) final estimates. This statistic can be obtained using the MANetworkH function from within MetaXL, and is also reported in the tabled output.

The interpretation is that $\bar{H}$ <3 indicates minimal inconsistency of treatment effects (the minimum possible $\bar{H}$ is 1). Values between 3 and 6 indicate modest network inconsistency and values > 6 suggest gross network inconsistency. The problem however with $\bar{H}$ is that it tends to become larger as synthesized data points become more precise and this means that in a network meta-analysis with high precision, high values of $\bar{H}$ may not be clinically meaningful in terms of network inconsistency.

If inconsistency is minimal to modest, then it is reasonable to pool effects from different routes. If inconsistency is found to be gross then it is useful to:

a) Check the data for errors
b) Use a different effect measure although empirical evidence suggests that different effect measures of dichotomous outcomes does not impact on statistical inconsistency (Veroniki, Vasiliadis et al. 2013).
c) Use synthesis models that allow for the heterogeneity induced by systematic differences. Both the IVhet and quality effects models do this. The latter however requires a quality assessment across the point estimates that make up the mixed results and this is not yet implemented in MetaXL. The quality effects model can still be used as the primary synthesis model but it should be

noted that then the mixed estimates are generated using the IVhet synthesis model. The IVhet synthesis model is currently the default for MAMixed when the primary models are other than IV and RE models.

Advantages of this approach to network meta-analysis

MetaXL implements what we call the Generalized Pairwise Modelling (GPM) framework for network meta-analysis. This framework is based on the repeated application of adjusted indirect comparisons, also known as the Bucher method (Bucher, Guyatt et al. 1997, Glenny, Altman et al. 2005). The validity of this method hinges on the sufficient similarity of the common control node (transitivity), and for the application in the GPM framework this requirement extends to all common nodes used to make an indirect comparison estimate. This, needless to say, is a pretty tall order.

But if we can reasonably assume that this requirement has been met, the remainder of the method is true mostly by definition. The indirect point estimate is equal to the difference of the two input point estimates, and the indirect variance equals the sum of the input variances (because these are independent observations). So apart from the assumption of sufficient similarity the GPM framework assumes only standard arithmetic and statistical rules.

The alternatives to the GPM method are multivariate frequentist and Bayesian Monte Carlo Markov Chain methods. Both alternatives need to make exactly the same assumption of sufficient similarity as the GPM framework. But on top of that, they need additional assumptions. In terms of the Bayesian approaches, this involves writing a directed acyclic graph (DAG) model for general-purpose Markov chain Monte Carlo (MCMC) software such as WinBUGS (van Valkenhoef, Lu et al. 2012). In addition, prior distributions have to be specified for a number of the parameters, (the choices being arbitrary, more so for priors on heterogeneity in random-effects models) and the data have to be supplied in a specific format (van Valkenhoef, Lu et al. 2012). Together, the DAG, priors, and data form a Bayesian hierarchical model. To complicate matters further, because of the nature of MCMC estimation, overdispersed starting values have to be chosen for a number of independent chains so that convergence can be assessed (Brooks and Gelman 1998). Currently, there is no software that automatically generates such models, although there are some tools to aid in the process and indeed the only attempt at automation requires that arm-level outcome data are available, and this is usually unavailable (van Valkenhoef, Lu et al. 2012). The frequentist multivariate meta-analysis method involve approximations and assumptions that are not stated explicitly or verified when the methods are applied (see discussion on meta-analysis above). In addition, if there is no common comparator in the network, then this has to be handled by augmenting the dataset with fictional arms with high variance, which is not very objective and requires a decision as to what constitutes a sufficiently high variance (van Valkenhoef, Lu et al. 2012). Other methods such as the iteratively re-weighted least squares used by Senn can lead to impossible results, such as when Senn applied a random effects model to their network meta-analysis, the confidence interval of a comparison based on a single study (sitagliptin vs placebo) greatly increased, moving from significance to non-significance (Senn, Gavini et al. 2013). “Is this reasonable?”, Senn then asks. Of course not. It is also impossible: the sitagliptin estimate should be impervious to changes in assumptions on heterogeneity since, being based on a single study,

heterogeneity simply does not apply. It is worth to note that with the GPM method this impossible effect does not occur (see the OralGlucoseNetwork example, which is based on the data from (Senn, Gavini et al. 2013).
We encourage researchers to compare the output from MetaXL to both results from a Bayesian analysis and a multivariate frequentist analysis. We think the MetaXL GPM framework is superior to the multivariate methods, be they Bayesian or frequentist, because it needs fewer assumptions. The limitation is that it can use only pairwise comparisons, and therefore is not able to include all data from trials with more than two arms. But since such trials are pretty rare, we think it is a price well worth paying.

The Doi plot

This chapter describes the calculations that underpin the Doi plot for the detection of publication bias. Essentially, the Doi plot is created by each subject in every trial within the meta-analysis being assigned the ES of their trial and ranked serially. As all subjects in a trial have the same ES, they will have the same rank and thus each trial has a single final rank based on the number of subjects in the study. However, because the actual number of subjects does not capture the trials' information content completely (the number of observed events in each arm of a study is often more important in driving the precision of the estimate than the study size per se), a synthetic number derived from the standard error (designated N_i) is used in lieu of study size. The final ranking is then converted to a percentile and then a Z-score and these steps are as follows:

First, N_i is generated as follows:

$$N_i = \text{int}\left(100 \times \frac{\max(SE_i^2)}{SE_i^2}\right)$$

Where SE is the standard error of the effect size (ES) and 100 is an arbitrarily selected starting point for study sample size. If i indexes studies in a meta-analysis such that there are i=1,…,k studies each with an ES, $\hat{\delta}_i$, and "patient-information" size, N_i, the k trials can then be ranked by increasing ES and serially numbering the N_i subjects across these k trials consecutively. The last subject number in each study (A_i) is determined by summing the N_i across trials with $\hat{\delta} \le \hat{\delta}_i$. Using indicator functions, if the list of studies is a set with a typical element $\hat{\delta}$, then in a subset defined by $\hat{\delta} \le \hat{\delta}_i$ the indicator function is defined by:

$$I_{\hat{\delta} \le \hat{\delta}_i}(\hat{\delta}) = \begin{cases} 1 & \text{if } \hat{\delta} \le \hat{\delta}_i \\ 0 & \text{if } \hat{\delta} > \hat{\delta}_i \end{cases}$$

and therefore

$$A_i = \sum_{i=1}^{k} [N_k \times I_{\hat{\delta} \le \hat{\delta}_i}(\hat{\delta}_k)]$$

If all subjects in a trial are assigned an equal rank, the final rank (R_i) of each trial based on the subjects can be computed again using indicator functions. This time the subset is defined by $\hat{\delta} < \delta_i$, and the indicator function is given as:

$$I_{\hat{\delta} < \hat{\delta}_i}(\hat{\delta}) = \begin{cases} 1 & \text{if } \hat{\delta} < \hat{\delta}_i \\ 0 & \text{if } \hat{\delta} \ge \hat{\delta}_i \end{cases}$$

and therefore

$$R_i = \frac{\max\left\{A_1 \times I_{\hat{\delta} < \hat{\delta}_i}(\hat{\delta}_1), \ldots, A_k \times I_{\hat{\delta} < \hat{\delta}_i}(\hat{\delta}_k)\right\} + A_i}{2}$$

R_i is then converted into a percentile (P_i) as follows:

$$P_i = \frac{(R_i - 0.5)}{\sum_{i=1}^{k} N_i}$$

Finally the percentile is converted into a Z-score using the inverse standard Normal distribution. This new measure of precision is now the absolute value of the Z-score

and the ES is then plotted against this absolute value of the *Z*-score to create the new mountain plot. With symmetrical studies, the most precise trials will define the mid-point around which results should scatter, and thus they will be close to mid-rank and will be close to zero on the *Z*-score axis. Smaller less precise trials will produce an ES that scatters increasingly widely, and the absolute *Z*-score will gradually increase for both smaller and larger ES's on either side of that of the precise trials. Thus, a symmetrical triangle is created with a *Z*-score close to zero at its peak. If the trials are homogeneous and not affected by selection or other forms of bias, the plot will therefore resemble a symmetrical mountain with similar number of studies on each side and equal spread on each side. If either of the latter two is violated, then asymmetry exists.

A quantitative measure of Doi plot asymmetry called the LFK index (because it was developed by a graduate student, Luis Furuya-Kanamori) is implemented in MetaXL. This index is given by:

$$LFK_{index} = \frac{5}{2n}\sum_{i=1}^{n}\left[Z_i + r(ES_i - ES_k)\right]$$

Where

$Z_i = Z_{score}$ of each study included in the meta-analysis

$ES_i = ES$ of each study included in the meta-analysis

$ES_k = ES$ of the study with the lowest $|Z_{score}|$ *

$n =$ number of studies included in the meta-analysis

* Note: $|Z_{score}|$ refers to the absolute values; whereas, Z_{score} refers to real numbers.

Interpretation of the index in terms of asymmetry:

No asymmetry: LFK index within ± 1

Minor asymmetry: LFK index exceeds ± 1 but within ± 2

Major asymmetry: LFK index exceeds ± 2

Continuity corrections

Binary studies

In some instances the outcome of interest may be very rare (or in some circumstances very common) leading to zero events occurring in either or both arms of a study. In such cases, the log-odds ratio and the log risk ratio become undefined (as are their variances) and hence this causes problems with the meta-analysis computations. To overcome this problem, a so called 'continuity correction factor, of 0.5, is often added to each cell of the 2×2 table for the studies with zero events in either arm. Using a continuity correction for studies with zero counts allows the log-odds ratio or log-risk ratio to be estimated, and hence allows synthesis via the meta-analysis methods used in MetaXL.

Yates first used the term correction for continuity in 1934 (Yates 1934). The premise for the use of 0.5 as a continuity correction is through the approximation of a discrete distribution by a continuous one (Sweeting, Sutton et al. 2004). In standard 2×2 tables, it has been argued that the use of 0.5 makes the average approximation of the error equal to zero (Cox 1970).

The default continuity correction for binary studies in MetaXL is 0.5. This correction is only applied to studies with 0 counts, other studies in the analysis are not affected. A continuity correction is not applied to Peto's method: a zero count poses no problem in that method, except when both arms of the study have a zero count. In that case you will get an error message, and you will have to apply a continuity correction manually.

The options menu of MetaXL lets you choose the size of the continuity correction, including setting it to 0 (see the Options section above). If you do that and MetaXL encounters a study with zero counts, the MAInputTable function gives an error message, see the section on Error messages below.

Pooled prevalence

When pooling prevalences (IOTypePrev) without transformation or with the logistic transformation, a continuity correction is applied automatically for studies where the observed prevalence is either 0 (adjusted to 0.0005) or 1 (adjusted to 0.9995). The setting of the continuity correction option has no bearing on the correction used when pooling prevalences. When using the default double arcsine transformation, no continuity correction is applied because this transformation does not need one.

Meta-regression using MetaXL to create the dataset and Stata[2] to run the regression analysis

Preliminaries

Sub-group analysis versus meta-regression

Heterogeneity between study results is an important issue in determining the conclusiveness of a meta-analysis. When there is substantial heterogeneity, the conclusiveness becomes doubtful: the basic assumption in meta-analysis is that all studies attempted to measure the same "net" treatment effect. When the studies end up with very different results, this means that systematic error is substantial. The studies may have been measuring the same effect in different ways, or using very heterogeneous methods or populations. The situation calls for an examination of the causes of the heterogeneity.

Two main methods to examine heterogeneity in meta-analysis exist: sub-group analysis and meta-regression. Of these, sub-group analysis is the simplest and most transparent, but also limited to categorical moderator variables, while meta-regression is more versatile and can also handle continuous moderator variables. In simple cases with a single categorical moderator variable, we strongly recommend using sub-group analysis, if only because it is simpler to do and results from a meta-regression will match. However, with multiple categorical moderator variables it may be simpler to use meta-regression, and if a moderator variable is continuous, meta-regression is the only option.

Meta-regression in Stata

In Stata, the metareg command is available for meta-regression. Yet the examples below do not use the metareg command but use the generic regress command instead. There is a good reason for this: the metareg command is based on the random effects model for meta-analysis, and, as we explain in the section on Meta-analysis methods above, we think the random effects model is seriously flawed and should be abandoned (in fact, providing alternatives to the random effects model is the *raison d'être* of MetaXL).

While we agree that with meta-regression it is not reasonable to assume that all of the heterogeneity is explained, and the possibility of 'residual heterogeneity' must be acknowledged in the statistical analysis, we disagree that the appropriate analysis is therefore 'random effects' rather than 'fixed effect' meta-regression (Thompson and Higgins 2002). There is a tendency in the literature to suggest that fixed effect meta-regression is likely to produce seriously misleading results in the presence of heterogeneity (Higgins and Thompson 2004). In reality, this is just an issue of quality of error estimation because with heterogeneity, the data is overdispersed relative to the model. Applying random effects weights does not fix the problem because in the face of gross heterogeneity these weights are all equal and therefore the regression defaults to an unweighted regression. We take the position that methods that allow for a multiplicative component of residual heterogeneity should be used which is in contrast to recommendations to use methods which allow for an additive component of residual heterogeneity (Thompson and Sharp 1999).

[2] We aimed to give a recipe for R too, however, we were not able to find equivalent R commands. If some R buffs are able to supply these, we will be happy to include them in our discussion.

Our alternatives to the random effects model, the IVhet and QE methods, have a multiplicative component of residual heterogeneity built in. We want to be able to use the study weights from our IVhet and QE models in the meta-regression. In order to get matching error variances, we use robust (Huber-Eicker-White-sandwich) error variances to account for the underestimated variance in such analyses under the regression model. Robust standard errors are meant to generate the correct standard errors for (heterogeneous) data that usually are heteroskedastic. These standard errors are usually bigger than the ordinary least squares (OLS) standard errors when ESs further from the mean are more variable. That is why we use the Stata regress command with the vce(robust) option.

The meta-regression dataset

The MARegresData function in MetaXL allows the creation of a regression dataset that can be directly pasted in Stata and used to run meta-regression analyses under this framework. The dataset appears in a table under the Meta-Regression data tab that will show in the MAInputTable output pop-up window when a MARegresData function is linked to the MAInputTable function. The MARegresData function creates all the necessary variables and weights required for the analysis.

The regression dataset table consists of nine fixed columns that describe each study's characteristics, and any number of user-defined columns that describe each study's moderator variables. The fixed columns are defined in the table below.

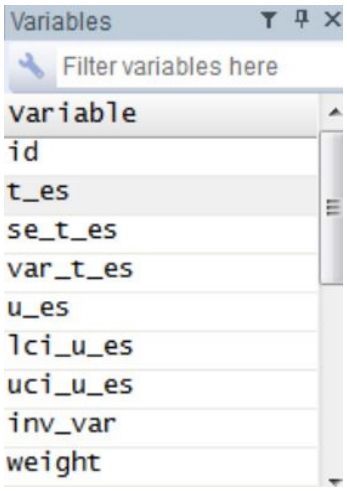
Variable name	Contents
ID	Study name
t_es	Transformed effect size
se_t_es	Standard error of the transformed effect size
var_t_es	Variance of the transformed effect size
u_es	Un-transformed effect size (ie natural scale)
lci_u_es	Lower CI of the un-transformed effect size
uci_u_es	Higher CI of the un-transformed effect size
inv_var	Inverse of the variance of the transformed effect size
weight	Weight of the study in the meta-analysis (normalized weights that sum to 1)

Please note that the regression is performed on the transformed variables: the transformed effect size called "t_es" as well as a weight under the model of interest called "weight". (The un-transformed variables u_es and its CI are there only for the convenience of the user, useful when back-transformed outputs are cumbersome to obtain, such as with the double arcsine transformation for prevalence). The variable t_es is the outcome variable and this is regressed against the user-defined moderator variables in the dataset. Analytical weights are applied in Stata and robust (Huber-Eicker-White-sandwich) standard errors are used to allow for correct error estimation.

Example: categorical moderator variables

We first illustrate categorical moderator variables using the **ThyCancerMetaRegres** example dataset in the MetaXL examples files list and which is also described below. This is a dataset of prevalence values for differentiated thyroid cancer and the moderator variable of interest is partial versus whole gland examination. (**Please note**:

all missing moderator values have been entered as a period: blank cells will produce spurious values in the meta-regression table, while the periods are recognized by Stata as missing values).We right-click on the "Meta-regression data" table in the results window and click copy.



In Stata, we click on the "Data Editor (Edit)" icon and then select edit → paste. Stata will ask if first row are variable names – select "yes". Now close the editor window.

The variable names will look like this in the "variables" window in Stata. The image on the left shows the computed variables and the moderators follow. In this example we are interested in the moderator called "whole" which is coded 0 for "partial" and 1 for whole.

We now proceed with meta-regression using this single moderator variable. The Stata code is:

```
Command
regress t_es ib0.whole [aweight=weight], vce(robust)
```

Type this in to the command area and press "enter"

The results window displays:

```
Linear regression                               Number of obs =        42
                                                F(  1,    40) =     16.11
                                                Prob > F      =    0.0003
                                                R-squared     =    0.3620
                                                Root MSE      =      .164

------------------------------------------------------------------------------
             |               Robust
        t_es |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      1.whole |   .2736751   .0681772     4.01   0.000     .1358839    .4114663
        _cons |   .4084489    .030226    13.51   0.000     .3473598     .469538
------------------------------------------------------------------------------
```

In the command "ib0" tells Stata that reference is "0" and to make the reference "1" this is changed to "ib1" with results as follows:

```
Linear regression                               Number of obs =        42
                                                F(  1,    40) =     16.11
                                                Prob > F      =    0.0003
                                                R-squared     =    0.3620
                                                Root MSE      =      .164

------------------------------------------------------------------------------
             |               Robust
       t_es |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    0.whole |   -.2736751   .0681772    -4.01   0.000    -.4114663   -.1358839
      _cons |    .682124   .0611107    11.16   0.000     .5586148    .8056333
------------------------------------------------------------------------------
```

We now have two constants (_cons) that represent the baseline in the reference subgroups which would be the subgroup results had we done a subgroup analysis using the IVhet model. To illustrate, below is part of the MAInputTable tabled output from a subgroup by "whole" using the IVhet model:

Study or subgroup	Double Arcsin Prevalence	LCI 95%	HCI 95%	weight (%)
Partial				
Hazard and Kaufman 1952	0.16	0.06	0.25	3.18
Hull 1955	0.25	0.12	0.38	1.72
…….	……	……	……	……
Bondeson et al. 1894	0.57	0.48	0.67	3.35
Yamamoto et al. 1990	0.69	0.59	0.78	3.18
Partial subgroup	**0.41**	**0.35**	**0.47**	**73.66**
Whole				
Komorowski and Hanson 1988	0.36	0.19	0.53	1.08
Fukunaga and Yatani 1975 (4)	0.48	0.40	0.56	4.73
……	……	……	……	……
Fukunaga and Yatani 1975 (2)	1.13	0.94	1.32	0.80
Harach et al. 1985	1.28	1.09	1.48	0.79
Whole subgroup	**0.68**	**0.53**	**0.83**	**26.34**
Pooled	**0.48**	**0.40**	**0.56**	**100.00**

The point estimates of the subgroups are the same as in the regression output, while the 95% CI's closely match. So in this simple example, subgroup analysis and meta-regression are equivalent.
However, the advantage with meta-regression is that we can easily add more moderator variables, for example:

```
Command
regress t_es ib1.whole ib2.year_cat i.age_cat [aweight=weight], vce(robust)
```

With results as follows:

```
Linear regression                               Number of obs =      42
                                                F(  7,    34) =    7.49
                                                Prob > F      =  0.0000
                                                R-squared     =  0.5305
                                                Root MSE      =  .15259
```

t_es	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
0.whole	-.2523504	.0664117	-3.80	0.001	-.3873153	-.1173855
year_cat						
1	-.2655245	.0928834	-2.86	0.007	-.4542864	-.0767627
3	.004001	.1131056	0.04	0.972	-.2258572	.2338593
4	-.0119669	.0966101	-0.12	0.902	-.2083023	.1843685
5	-.1035811	.1031274	-1.00	0.322	-.3131613	.1059991
6	-.0572841	.0982162	-0.58	0.564	-.2568834	.1423152
2.age_cat	.1006818	.0545572	1.85	0.074	-.0101919	.2115554
_cons	.6760018	.10354	6.53	0.000	.4655833	.8864203

This sort of analysis becomes very difficult to execute as a subgroup analysis despite the fact that all moderators are categorical. The results in the table above tell us that at baseline (whole examination with year_cat not the second period and the younger age category) the prevalence is $[\sin(0.676/2)]^2$ =0.11=11%. When gland examination is partial this drops to $[\sin((0.676-0.252)/2)]^2$ = 0.044 = 4.4%
While this example uses IVhet weights on the double arcsine square root transformed prevalence, it can also be done on the logit transformed prevalence for which weights would be somewhat different. The advantage with logit transformed prevalence is that odds ratios can also be computed (Warton and Hui 2011). We could of course have used QE or RE weights as analytical weights in Stata. While QE weights have certain additional benefits (Doi, Barendregt et al. 2015) over IVhet weights, we do not recommend random effects meta-regression as these weights serve no real purpose and do not have a meaningful interpretation.

Example: a continuous moderator variable

The **IHDCholMetaRegres** example uses 28 randomized trials of serum cholesterol reduction (by various interventions), and the risk of ischaemic heart disease (IHD) events observed. Both fatal IHD and non-fatal myocardial infarction were included as IHD events, and the analysis is based on the 28 trials reported by Law et al (Law, Wald et al. 1994). In these trials, cholesterol had been reduced by a variety of means, namely dietary intervention, drugs, and, in one case, surgery. The meta-regression looks at if increased benefit in terms of IHD risk reduction is associated with greater reduction in serum cholesterol, in order to lend support to the efficacy of these therapies and to predict the expected IHD risk reduction consequent upon a specified decrease in serum cholesterol.
The meta-regression uses the following command:

Command
```
regress t_es chol_reduc [aweight=weight], vce(robust)
```

In the previous example we mentioned that robust standard errors are often larger than OLS ones. However, the robust standard error can also be smaller than the usual

standard error: if the variance of the error terms tends to be lower when the ES is far from its mean, OLS standard errors will tend to be too large, and robust standard errors will tend to be smaller than OLS standard errors. In this case the robust standard errors are smaller than those reported without using vce(robust):

```
Linear regression                               Number of obs =        28
                                                F(  1,    26) =     30.23
                                                Prob > F      =    0.0000
                                                R-squared     =    0.2380
                                                Root MSE      =    .21453
```

t_es	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
chol_reduc	-.4752451	.0864316	-5.50	0.000	-.6529078	-.2975823
_cons	.1207613	.0677936	1.78	0.087	-.0185904	.2601129

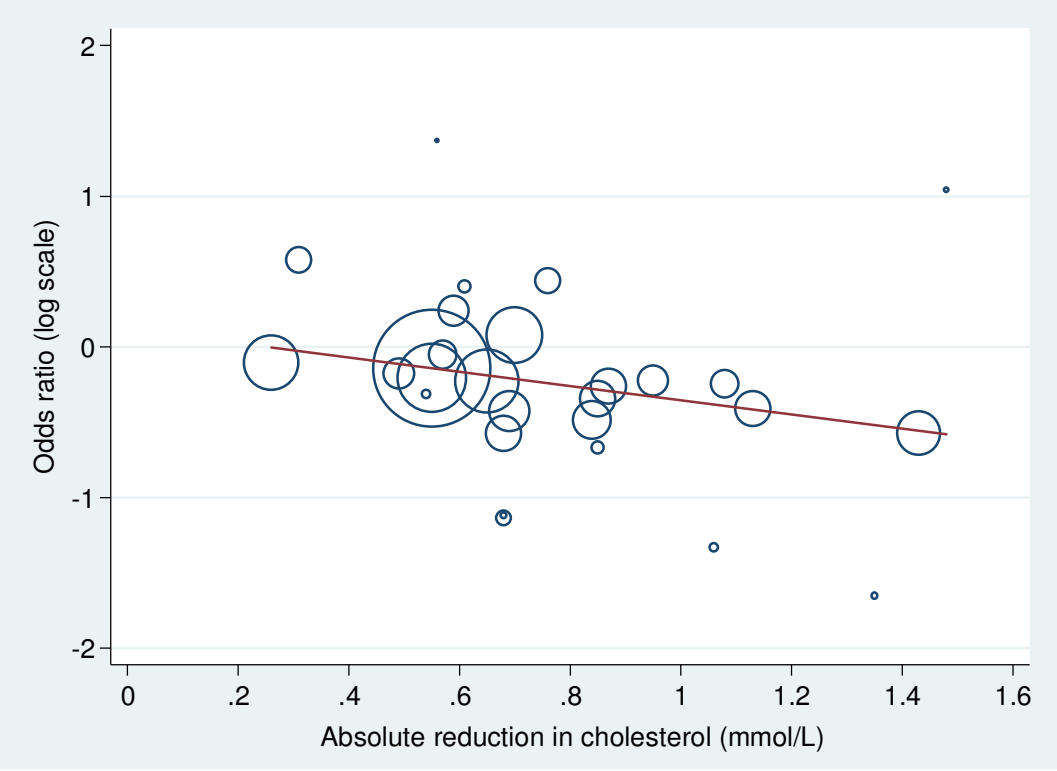
Without robust standard errors, the command and results would be:

Command

```
regress t_es chol_reduc [aweight=weight]
```

t_es	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
chol_reduc	-.4752451	.1667915	-2.85	0.008	-.8180899	-.1324002
_cons	.1207613	.1173062	1.03	0.313	-.120365	.3618875

From these analyses, each 1 mmol/L cholesterol reduction is estimated to reduce the odds ratio of IHD by 37 percent, that is 1-exp(-0.475); this relation is depicted in the figure below.



The plot depicts the estimated odds ratios of IHD events in 28 randomized trials of serum cholesterol reduction according to the extent of cholesterol reduction achieved in each trial. The circle corresponding to each trial has area inversely proportional to the variance of the log-odds ratio. The superimposed line is obtained by IVhet weighted regression

This plot is generated using the following command in Stata:

```
Command
twoway (scatter t_es chol_reduc [w=weight], msymbol(circle_hollow)) (lfit t_es chol_reduc [w=weight])
```

Documentation

Examples

Introduction

The MetaXL installation comes with a number of example Excel workbooks. All example workbooks are accessible through the MetaXL menu and the MetaXL entry in the Windows Start menu. Where they are located on your hard disk is difficult to say: it depends on your Windows version, your privileges on the PC, and possible changes to the proposed default directories that you may have made during installation. Details on this can be found in the section Installation issues of the Technical appendix of this guide.
Please note that the example workbooks are not protected: any changes that you make can be saved. If you want to preserve the original example workbooks but also experiment with them, you should first make copies of them to experiment with, for example by using 'Save as' to copy them to your standard Excel workbook directory. Of course you can always revert to the original example workbooks by re-installing MetaXL. Below is a brief description of each of the example workbooks.

ThyroidCancerRR

This meta-analysis is about high dose radio-active iodine (^{131}I) versus low dose after thyroidectomy in patients with differentiated thyroid cancer. The study looked at the risk of non-ablation, and the outcome is that high-dose patients have a 20-30% lower risk of non-ablation.
File name: ThyroidCancerRR.xls.

ThyCancerMetaRegres

This is an example of the use of the MARegresData function to create a meta-regression dataset for analysis in Stata. The meta-analysis is about prevalence of incidental differentiated thyroid cancer in autopsy studies over several decades. The study looked at the prevalence over time (year_cat) and the outcome is the transformed prevalence. While the transformation used in this example is the double arc sine square root transformation, the original paper uses the logit transformation.
File name: ThyCancerMetaRegres.xls.

Magnesium

This binary numbers example gives all the methods available for this kind of data: odds ratios according to five different methods, and risk ratios and differences according to four methods each. In addition, there are sheets with the same studies but then taking effect sizes and their 95% confidence intervals as inputs, and for the risk difference effect sizes and standard error as inputs, all for the IV, RE and QE methods. Note that in the Options menu you can set the size of the input confidence interval independently from the output confidence interval. Default is 95%. Also note that the results are identical between the various input formats.
The workbook summarises results of a number of trials of intravenous magnesium after suspected acute myocardial infarction. There has been much controversy about this topic, with the smaller trials showing a beneficial effect, but the large ISIS trial

showing a small but not statistically significant detrimental effect (Nuesch and Juni 2009).
In fixed effects analyses the large ISIS trial weighs-in heavily, and as a consequence the pooled effect sizes are not significant. The IVhet model produces the same pooled estimate as the inverse variance model, but with a much wider confidence interval to reflect the between study heterogeneity. The random effects model assigns a smaller weight to large studies in case of heterogeneity, resulting in significant pooled effect sizes. Interestingly, the quality effects model finds a beneficial effect in terms of its point estimate, but it is non-significant, mainly because the ISIS trial does not score very well on quality.
The heterogeneity statistics Cochran's Q and I^2 indicate that there is considerable heterogeneity. In a subgroup analysis of large (ISIS and MAGIC) versus smaller (all the rest) studies the heterogeneity within the subgroups disappears. An interesting finding, but not so easy to interpret.
File names: Magnesium.xls and MagnesiumSubGroups.xls.

MagnesiumCumulative

This example contains the same studies as in the Magnesium example, but now ordered in ascending time to accommodate a cumulative meta-analysis. Shown are the OR results of the QE, IVhet, and RE models.
File name: MagnesiumCumulative.xls.

Omega3WMD

A weighted mean difference example. The workbook contains sheets with input in numbers (population sizes, means, and standard deviations for both arms), and with effects sizes and either confidence intervals or standard errors as inputs. In all cases results are calculated according to the IV, RE, and QE methods, and are identical across input formats (as should be).
File name: Omega3WMD.xls.

MarshallSMD

This example is taken from the chapter in Egger et al where most of the methods implemented in MetaXL are based on (Deeks, Altman et al. 2001). Three trials comparing assertive community treatment with standard care for severely mental ill. The trials used different scoring systems, and therefore a standardised mean difference was used to combine them. Note that the scale used by the Lehman study runs opposite to the other two, the mean is therefore entered as a negative number. Results are presented for all three methods for standardised mean difference: Cohen's *d*, Hedges' adjusted *g*, and Glass's Δ. For these studies, results are very similar across SMD methods.
The workbook gives results for the IV, RE, and QE methods, and for input formats with numbers, confidence intervals, and standard errors.
File name: MarshallSMD.xls.

SchizophreniaPrev

A pooled prevalence estimate of acute schizophrenia in the population with schizophrenia. This example also gives the example of a quality scoring list, that runs on a scale from 0 to 11, and how to convert the score to the 0..1 range expected by

MetaXL. There is also a subgroup analysis of the studies by the income status of the countries where they were carried out.
File name: SchizophreniaPrev.xls.

MSMultipleCategoryPrev

Also a pooled prevalence example, this time of three multiple sclerosis categories "mild", "moderate", and "severe". The three categories should always add up to 1, but in case of the logit and double arcsine transformations do so only when the "Normalize prevalence" option in the options menu is set.
This example illustrates the use of the MAForestName function to override the default forest plot title which would otherwise be the same for each category. And finally, it illustrates the use of an additional parameter for the MAPooledEffect, MAPooledEffectLCI, MAPooledEffectHCI, and MAForestName functions to designate the category number the function should refer to.
File name: MSMultipleCategoryPrev.xls.

DiureticsPreEc

This is a 1985 meta-analysis of randomized trials by Collins and colleagues (Collins, Yusuf et al. 1985) on the effects of administering diuretics to high risk pregnant women for the prevention of pre-eclampsia. The effect size in the published meta-analysis was the relative risk but here we use the odds ratio as a recent re-analysis by Cornell and colleagues (Cornell, Mulrow et al. 2014) used the odds ratio effect size. The latter authors depict the problem with the RE model clearly and the IVhet model results suggest that the statistical error is greater than what the RE model portrays.
File name: DiureticsPreEc.xls.

FruitsVeg

This is a 2014 meta-analysis by Wang et al (Wang, Ouyang et al. 2014) examining the potential dose-response relation between fruit and vegetable consumption and risk of all cause mortality. The effect size (ES) is the hazard ratio and the IVhet model results suggest again that the statistical error is greater than what the RE model portrays.
File name: FruitsVeg.xls.

PulsesLDL

A meta-analysis of randomized controlled trials by Ha and colleagues (Ha, Sievenpiper et al. 2014) was undertaken to assess the effect of dietary pulse intake on established therapeutic lipid targets for cardiovascular risk reduction. The authors undertook a comprehensive quality assessment that we have used to compute results under the quality effects model. The effect size was the WMD and there was a more conservative effect under the QE model while under the RE model there was a larger effect with a narrower confidence interval. Application of the random effects model, as the authors did, underestimates the statistical error without justification.
File name: PulsesLDL.xls.

MedCompliance

This is a meta-analysis of controlled studies of voucher based reinforcement therapy (VBRT) in the treatment of substance use disorders (SUDs) undertaken by Lussier and colleagues (Lussier, Heil et al. 2006). One of the outcomes was medication compliance and this was the focus of this MetaXL sheet. The effect size was the Pearson's product moment correlation coefficient (r) and positive values of r correspond to superior outcomes for VBRT relative to the control treatment. Cohen (Cohen 1994) defines $r = 0.10$, $r = 0.30$ and $r = 0.50$ to represent small, medium and large effect sizes, respectively. There was a more conservative effect under the QE and IVhet models while under the RE model there was a larger effect with a narrower confidence interval (and equal weights as expected under heterogeneity for this model).
File name: MedCompliance.xls.

IPTcMalaria

This is a meta-analysis of intermittent preventive treatment of malaria in children less than five years of age (IPTc) as a measure to control the burden of malaria in the Sahel and sub-Sahelian areas of Africa where malaria transmission is markedly seasonal (Wilson and Taskforce 2011). One of the outcomes was effect of IPTc on clinical malaria during the intervention period and this was the focus of this MetaXL sheet. We however excluded studies without quality assessment as well as used only a single arm from multi-arm studies to avoid a unit of analysis problem. The effect size was the rate ratio and values less than 1 correspond to a superior outcome for IPTc relative to the control treatment. There was a more conservative confidence interval with our newer models while under the RE model there was a narrower confidence interval (and more or less similar weights as expected under heterogeneity for this model). We also computed the rate difference for the same data for comparison.
File name: IPTcMalaria.xls.

IndirectAF

This is a comparison of antithrombotic therapy, warfarin and aspirin, for patients with atrial fibrillation from Hart et al (Hart, Benavente et al. 1999). The data allow both an indirect comparison of meta-analyses of warfarin and aspirin vs placebo plus a direct comparison. Estimates are made using the MAIndirect and MAMixed functions. The studies comparing active to placebo are homogenous, hence the various statistical models provide similar results. However, there is some heterogeneity for the direct comparison of warfarin and aspirin and the results vary across models. The indirect results for warfarin vs aspirin have narrower confidence intervals and a stronger point estimate but are consistent with the direct results given the uncertainty around the direct result (especially IVhet results).
The paper by Hart et al states "To estimate the relative risk reduction, the combined odds ratio was computed by using the modified Mantel–Haenszel (Peto) method", which seems to confuse several things simultaneously. Therefore this example sheet uses the dynamic data (person time) from the paper and thus reports rate ratios. The authors' reported relative risks have been noted in the example sheet.

This example also contains an analysis of the same data using the MANetwork function instead of MAIndirect and MAMixed. As can be seen, the results are identical.
File name: IndirectAF.xls.

ThrombolyticsNetwork

Two recent overviews of treatment for acute myocardial infarction were combined and published as an example in the BMJ (Caldwell, Ades et al. 2005) and this combined data as reported in the BMJ are utilized in this example. The two overviews were those of Boland and colleagues (Boland, Dundar et al. 2003) who reviewed 14 randomised controlled trials making two or three way comparisons of six thrombolytic treatments and Keeley and colleagues (Keeley, Boura et al. 2003) who looked at 23 randomised controlled trials that compared primary percutaneous transluminal coronary angioplasty (PTCA) with thrombolytic treatment (streptokinase, alteplase, or accelerated alteplase). We subjected 9 direct estimates to a network meta-analysis using multiple 3-intervention loops and fixing one intervention node (control) to PTCA. The results from MANetwork match those reported in the BMJ paper that had used a Bayesian Markov chain Monte Carlo method.
File name: ThrombolyticsNetwork.xls.

OralGlucoseNetwork

Senn (Senn, Gavini et al. 2013) reports data on a network meta-analysis where patients with type 2 diabetes were treated with sulfonylurea alone or sulphonylurea plus either of acarbose, benfluorex, metformin, miglitol, pioglitazone, placebo, rosiglitazone, sitagliptin or vildagliptin making 10 treatment groups. Our GPM analysis utilizes all 26 studies reported but uses only 52 of the 53 reported arms. One arm of a study with 3 arms was excluded. This three arm trial (metformin-acarbose-placebo) was limited to analysis of the metformin and placebo arms only. The trials included in the analysis were open or double-blind randomised controlled trials with parallel groups, a minimum of 50 randomised patients and measurements of HbA1c after a follow-up ranging from 3 to 12 months. HbA1c was the endpoint and the mean HbA1c change from baseline was used. Where this change was not available but the value at outcome of the raw (unadjusted by baseline) value was available, this was used instead. The example sheet depicts results from our GPM analysis as well as a multivariate frequentist and Bayesian analysis of the same data presented by Rucker and Schwarzer (Rucker and Schwarzer 2015).
File name: OralGlucoseNetwork.xls.

IHDCholMetaRegres

This is an example of the use of the MARegresData function to create a meta-regression dataset for analysis in Stata. The example uses 28 randomized trials of serum cholesterol reduction (by various interventions), and the risk of ischaemic heart disease (IHD) events observed. Both fatal IHD and non-fatal myocardial infarction were included as IHD events, and the analysis is based on the 28 trials reported by Law et al (Law, Wald et al. 1994). In these trials, cholesterol had been reduced by a

variety of means, namely dietary intervention, drugs, and, in one case, surgery. The meta-regression looks at if increased benefit in terms of IHD risk reduction is associated with greater reduction in serum cholesterol, in order to lend support to the efficacy of these therapies and to predict the expected IHD risk reduction consequent upon a specified decrease in serum cholesterol.
File name: IHDCholMetaRegres.xls.

Error messages

Introduction

Generally in software, there are two types of error messages: planned ones and un-planned ones. The former kind anticipates user mistakes and tries to give an informative message, pointing the user in the right direction. The latter kind pops-up when un-anticipated circumstances occur, and the error messages of the compiler used (in this case Delphi), host application (Microsoft's Excel), or operating system (Microsoft's Windows) kick in. This kind of error "message" includes crashing of the application, for an Excel add-in like MetaXL this usually means crashing of Excel itself as well. Software developers refer to this kind of error messages as "bugs". While we have tried to anticipate all user mistakes, experience learns that software users are far more creative in making mistakes than software developers will ever fathom. So it is likely that you will encounter both kinds of error messages. Below we first give the messages for the mistakes we anticipated, and then for the ones we did not. The former will be returned by the MAInputTable and MAIndirect functions and when you try to get results from an analysis that shows such an error message.

MAInputTable error messages

Error: unknown IOType parameter
The MAInputTable function did not recognise the IOType parameter name you specified. Please check your spelling, and table 2 above for the IOType parameters that are defined. Note that the parameter name has to be enclosed in double quotes (ie "NumOR"). The parameter name is not case-sensitive.

Error: unknown Method parameter
The MAInputTable function did not recognise the Method parameter name you specified. Please check your spelling, and table 3 above for the Method parameters that are defined. Note that the parameter name has to be enclosed in double quotes (ie "IV"). The parameter name is not case-sensitive.

Error: incompatible input and method parameters
Both the IOType and Method parameters are recognised, but not all combinations of them are valid. Please consult table 4 above to see which combinations of parameter values are compatible.

Error: too many (few) columns in table
Given the IOType and the Method parameters you specified, the MAInputTable function expects a defined number of columns in the input range parameter. This error occurs when there are too many (few) columns in this table. Please consult table 5 above to see which columns MAInputTable expects, and what should be in each. Use the Input Templates entry from the MetaXL Excel menu to set up a correct input table.

Error: duplicate MAInputTable function names
This error occurs when two or more MAInputTable or MAIndirect functions are present with the same Name parameter. The Name parameter needs to be unique, so the remedy is simple: rename the duplicate. Please note that this error will also occur

when the MAInputTable functions with the same name are in different Excel workbooks that are open simultaneously.
This error also occurs when you rename a worksheet with MAInputTable functions in it, or when you move the cells with the function in it. Remedy: go to the MetaXL menu and click 'Reset'.

Error: duplicate study names
Each study included in the MAInputTable range parameter needs to have a unique name, and this error is reported when there is at least one duplicate study name. The remedy is to make sure study names are different.

Error: invalid or missing study name
MetaXL expects studies included in the MAInputTable range parameter to have valid names. A missing name means the cell that should contain the name is empty, an invalid name is one with at least one character that offends. This error can occur when the range parameter includes an empty row. Remedy: make sure your range parameter refers to the correct range, fill empty Name cells, and do not use characters outside the alphanumeric range.

Error: continuity correction needed
This error can only occur (with the exception of the Peto model) when you have changed the default MetaXL setting of the continuity correction. See the discussion of the continuity correction option setting above.
The error also occurs in the Peto model when there are no events in both arms. In that case you can either decide to exclude those studies, or put in a continuity correction manually in the input table.

Error: invalid negative or 0 values in input table
This error can occur with the IOType parameters ORCI and RRCI. With these IOType parameters, the MAInputTable function expects either RR or OR effect sizes with their confidence intervals (see table 5 above and the Input Templates entry from the MeataXL Excel menu for the correct inputs for this IOType). By definition, all these input fields must be >0, and this error occurs when one of them is not.
This error also occurs when in a continuous analysis population size numbers or standard deviations are less than or equal to 0. And when an IOType with standard error input is used with a standard error that is not more than 0.

Error: invalid negative values in input table
This error is returned by the pooled prevalence IOTypePrev method when either the population number or number of cases entered is less than 0. And the binary methods (IOType NumRR, NumOR, and NumRD) return this error when the numbers entered are less than 0.

Error: quality weights cannot be negative
The quality weights input MetaXL expects to be positive: negative quality scores are not allowed.

An unknown error occurred
An error occurred, and MetaXL did catch it, but it is at a loss what caused it. It should not be one of the errors listed above, but that is of little help. If you get this error and it is reproducible (i.e. if it occurs predictably with some workbook or action), we are very interested in receiving a description of the problem, if possible with a copy of the offending workbook. Please send email to info@epigear.com.

MAIndirect error messages

Error: duplicate MAIndirect function names
This error occurs when two or more MAIndirect or MAInputTable functions are present with the same Name parameter. The Name parameter needs to be unique, so the remedy is simple: rename the duplicate. Please note that this error will also occur when the MAIndirect functions with the same name are in different Excel workbooks that are open simultaneously.
This error also occurs when you rename a worksheet with MAIndirect functions in it, or when you move the cells with the function in it. Remedy: go to the MetaXL menu and click 'Reset'.

Error: input MAs do not exist, IOTypes are unsuited, or have incompatible methods or IOTypes
A number of issues can cause this error message:

1. *Input MAs do not exist:* MAIndirect requires the two input meta-analyses to be provided by links to their MAInputTable functions.
2. *IOTypes are unsuited:* the IOTypes of single arm meta-analyses (Prev, NumCorr, RateSE and NumRate) cannot be used for indirect comparisons.
3. *Incompatible methods:* the methods parameters of the input meta-analyses must be identical.
4. *Incompatible IOTypes:* the effect sizes of the input meta-analyses must be identical.

MANetwork error messages

Error: duplicate MANetwork function names
This error occurs when two or more MANetwork functions are present with the same Name and Control parameter. The combination of the Name and Control parameters needs to be unique, so the remedy is simple: rename the duplicate. Please note that this error will also occur when the MANetwork functions with the same name and control are in different Excel workbooks that are open simultaneously.
This error also occurs when you rename a worksheet with MANetwork functions in it, or when you move the cells with the function in it. Remedy: go to the MetaXL menu and click 'Reset'.

Error: IOTypes are unsuited, or have incompatible methods or IOTypes
A number of issues can cause this error message:

1. *IOTypes are unsuited:* the IOTypes of single arm meta-analyses (Prev, NumCorr, RateSE and NumRate) cannot be used for indirect comparisons.
2. *Incompatible methods:* the methods parameters of the input meta-analyses must be identical.
3. *Incompatible IOTypes:* the effect sizes of the input meta-analyses must be identical.

Error: unattached nodes in dataset
This error occurs when one (or more than one) study does not share either an active or control arm with any of the other studies. In other words: it is not part of the network, and a network meta-analysis is impossible.
Note that this error can occur because of typos in the names of the interventions of the input table: users are strongly advised to use a single list of interventions and set up the MANetwork input table using links from that list, see the network example spreadsheets.

Error: a MANetwork function error occurred
Error in input table
These are not very specific error messages, and it is not clear at this point what may cause these errors. We hope to provide more informative advice in a future release.

MARegresData error messages

Error: meta-regression data not supported for cumulative meta-analysis
You have linked the MARegresData function to a MACumulative function instead of a MAInputTable function.

Error: meta-regression data not supported for network meta-analysis
You have linked the MARegresData function to a MANetwork function instead of a MAInputTable function.

Error: input MAInputTable does not exist
The MARegresData function could not find the MAInputTable function it was linked to, so probably the link is faulty.

Error: Moderator table has too few (many) rows
The Moderator table of the MARegresData function must have a number of rows equal to 1+ the number of studies in the MAInputTable function it was linked to. The additional row is the header row.

Error in Moderator table
There is something wrong with the Moderator table of the MARegresData function, but it is not clear to MetaXL what.

Forest and network plot options error messages

These error messages occur when you are manually changing the scaling of the X-axis. They either are displayed at the bottom of the Plot options window, or as a pop-up message.

Error: not a number
MetaXL tried to convert what is in the Minimum and Maximum text edit boxes to numbers, but it failed to do so because of inappropriate formatting or the presence of non-numeric characters.

Error: minimum must be less than maximum
The Minimum value specified must always be less than the Maximum value.

Error: Maximum X-axis value is less than highest study point estimate
Error: Minimum X-axis value is greater than lowest study point estimate
MetaXL requires that the Minimum and Maximum values specified are such that the central point estimates of all studies in the meta-analysis are between these two values.

Bugs

No software is without bugs, and that is undoubtedly true for MetaXL (and for Excel, for that matter). Things can go wrong, and once they have done so, the software may have become unstable and start to produce error messages whatever you do. In such cases it is often advisable to quit Excel altogether and start anew.
In particular, when MetaXL has given incomprehensible error messages like 'Access violation', 'Invalid floating point operation', or 'Range check error', or when Excel crashes, things have seriously gone wrong and a restart is often required. If the problem is reproducible (i.e. if it occurs predictably with some workbook or action), we are very interested in receiving a description of the problem, if possible with a copy of the offending workbook. Please send email to info@epigear.com.

Trouble shooting

Sometimes the combination of MetaXL and Excel will not behave as the user expects, with a frustrated user as a consequence. In this section we try to pre-empt some of the situations where this might occur by explaining what is going on and offering a solution. Most of this is based on user experiences in our own work environment (including ourselves). We are happy to hear of any other potential conundrums: if you have any, please email them to info@epigear.com and we will either try to solve the issue or add them to this list.

1. The MetaXL functions are not recognised by Excel (they show the #NAME? error).

   If you see this error on just a single or a few MetaXL functions, while other MetaXL functions are fine, you most likely made a typo in the function name. If you are unsure how a particular function name is spelled, use the Excel Function Wizard: all MetaXL functions are available in the category 'MetaXL'.
   If all MetaXL functions show this error, and you are confident that they are spelled correctly, most likely MetaXL is not properly (or not at all) installed. Check whether the MetaXL add-in is listed and active (Excel 2003 and earlier: Tools|Add-ins; Excel 2007 and later: Office Button|ExcelOptions|Add-ins|Go). Make sure the add-in is listed and the checkbox next to its name is checked. If the add-in is not listed, you can try to use the 'Browse' button of the Excel Add-in Manager to add it to the list, but most likely something went wrong during installation (e.g. you had Excel running while installing MetaXL). Remedy: quit Excel, and install MetaXL.

2. The MetaXL functions are recognised by Excel, but not correctly (they show the #VALUE! error).

   If you see this error on just a single or a few MetaXL functions, while other MetaXL functions are fine, you most likely made an error in the number of parameters the function takes. If you are unsure about the parameters of a particular function, use the Excel function wizard: all MetaXL functions are available in the category 'MetaXL'.
   This error also occurs when you forgot to put double quotes around the text input parameters of the MAInputTable function.
   Another occasion this error occurs (but this is an Excel and not a MetaXL issue) is when you use the wrong parameter separator in Excel functions: when your system or Excel is configured to have a comma as the decimal separator (as in many European countries), the parameter separator is a semicolon (;), when the decimal separator is a period, the parameter separator is a comma.

3. A MetaXL function returns #NUM!.

   When the MAInputTable or MAIndirect function returns an error, all MetaXL function linked to it will return this error. Remedy: fix the problem with the

MAInputTable or MAIndirect function.
If this is not the case, you most likely made an error in the value of the parameters the function takes. If you are unsure about the values the parameters of a particular function can take, use the Excel function wizard: all MetaXL functions are available in the category ‘MetaXL’, and help is given on the parameter values they can take. Or look up the function in the MetaXL Functions section above.

Known issues

1. When you rename a worksheet with MAInputTable functions in it, the functions report the “duplicate MAInputTable function names” error. Remedy: go to the MetaXL menu, and click ‘Reset’.

MetaXl versions

A list of the updates of MetaXL, most recent first.

Version 5.3

September, 2016.
An important update: addition of a MARegresData function to facilitate using MetaXL results in meta-regression analysis using Stata. See the section on Meta-regression using MetaXL to create the dataset and Stata to run the regression analysis above.

Version 5.2

July, 2016.
An important update:

1. Addition of a Network plot for the Network meta-analysis. See the section on the output from the MAnetwork function above.
2. Changes to the spacing of the tabled output, and to how the pop-up forms and fonts scale across screen resolutions and sizes.

Version 5.1

May, 2016.
An important update:

1. Addition of a measure for inconsistency in Network meta-analysis through the MANetworkH function. See the section on this function above.
2. Added the MApOverallEffect function, see its description above.

Version 5.0

April, 2016.
A major update:

1. Addition of cumulative meta-analysis through the MACumulative function. See the section on this function above.
2. Added error message for MANetwork: unattached nodes in dataset. See the MANetwork error messages above.

Version 4.01

March, 2016.
A minor update: improved user control of the X-axis scaling for the forest and network forest plots.

Version 4.0

February, 2016.
A major update:

1. Addition of Network meta-analysis through the MANetwork function. See the section on Indirect Comparisons and Network meta-analysis above.
2. Added functions: MAMixed and MApConsMixed. See the section on Indirect Comparisons and Network meta-analysis above.

Version 3.1

November, 2015.

An important update:

1. Addition of the MAIndirect function, which allows doing indirect comparisons. See the section on Indirect Comparisons and Network meta-analysis above.
2. Added function: MAPooledSE.

Version 3.0

October, 2015.
A major update:

1. Addition of the Doi plot and LFK index for the detection of publication bias. See the section on this above.
2. Added IOTypes: hazard ratio, rate ratio, rate difference, and correlations.
3. A limitation that the funnel plot would not be shown when doing quality or random effects meta-analysis has been lifted.
4. Bug fix: printing of the graphs did not work. Resolved.
5. Bug fix: the IOTypes with CI input would bomb when the output CI differed from the input. Resolved.

Version 2.2

September, 2014.
A bug fix: subgroup analysis could not handle manual exclude of studies. Resolved.

Version 2.1

July, 2014.
An important update: the input format for the quality score of the Quality Effects model has been relaxed. See the sections on the MAInputTable function and on the Quality score for details.

Version 2.0

April, 2014.
A major update: addition of the Inverse Variance heterogeneity (IVhet) model, as a second alternative to the random effects model. Details are in the section on Meta-analysis methods.
A bug fix: MetaXL would crash when in the Peto model both arms would have 0 events. Now an error message occurs: Continuity correction needed.

Version 1.4

December, 2013.
An update of the Quality Effects model: the variance of the pooled effect size is now calculated using an exact expression instead of an approximation. Details are in the section on Meta-analysis methods.

Version 1.34

October, 2013.
A bug fix: when using more than one MASubgroups function linked to the same MAInputTable function, MetaXL got confused. Resolved.

Version 1.33

August, 2013.
A minor update: the Journal of Epidemiology and Community Health has published our article on the Meta analysis of prevalence, and for copyright reasons the corresponding section in the *User Guide* has been removed.

Version 1.32

April, 2013.
A minor update: a bug that in case of multiple category prevalence reset a category outcomes to the last one when 'plot options' was chosen has been resolved.

Version 1.31

March, 2013.
A minor update.

1. A few equations in this *User Guide* were corrected.
2. The forest plot now supports asymmetric diamonds, useful when the option of a natural scale X-axis is chosen.
3. A bug in the forest plot when multiple category prevalence and subgroup analysis were combined has been resolved.

Version 1.3

November, 2012.
A major update: support for 64-bit Excel is added.

Version 1.2

May, 2012.
A minor update.

1. This version introduces full support for the Excel 2007+ ribbon user interface, with a MetaXL tab in the ribbon.
2. The MetaXL menu in Excel 2003 and earlier is now positioned at the end, in an attempt to accommodate non-English versions of Excel.

Version 1.11

April, 2012.
A minor update.

1. An additional function: MAForestName, to override the default title of the forest plot.
2. With multiple category prevalence output the various output windows now cascade instead of overlap.
3. An additional example: MSMultipleCategoryPrev.
4. The installation detects whether Excel is running, and quits after announcing it should not.
5. The installation detects whether Excel 64-bit is installed, and quits after announcing that this version of MetaXL is not compatible with 64-bit Excel.

Version 1.1

February, 2012.
A major update, with several enhancements.

1. Subgroup analysis: MASubGroups function and the ability of the forest plot to display subgroups.
2. Other enhancements of the forest plot, such as options to determine the width of the confidence interval lines.
3. Additional functions to display outcomes in the Excel spreadsheet: MATauSquare and MAQIndex.
4. More options can now be saved to become user-preferred defaults.
5. Several enhancements to the meta-analysis of prevalence:
    a. Introduction of three different options for transformations: none, logit, and double arcsine.
    b. Introduction of multi-category prevalence meta-analysis.
    c. A 'normalise' option to make sure multiple category pooled results sum to 1.
    d. An additional parameter for the MaPooledEffect, MaPooledEffectLCI, and MAPooledEffectHCI functions to determine the category number.
    e. Multiple output windows in case of multiple category prevalence.
    f. Addition of a section to this *User Guide* on the *Meta-analysis of Prevalence*.
6. A complete rewrite of the methods used to exchange data with Excel, in preparation of planned support for 64-bit Excel.

Version 1.0

January, 2011.
The first public release.

Technical appendix

Installation issues

Where are your files?

Installation is usually painless, the most important thing to remember is that Excel should not be running when you install MetaXL. If Excel is running, you will get an error message during installation that the add-in could not be installed. Remedy: quit Excel and try again.

Once you've installed MetaXL, where are the files? This depends. For one thing, the installation program gives you a choice. But even if you go with the defaults, it still depends, in particular on the user rights you have on the PC. If you have administrator rights, the MetaXL xll add-in will go into Program Files, while the example spreadsheets and such go into a subdirectory of Documents and Setting\All Users (Windows XP) or Program data (Windows 7 and later).

If you do not have the rights to install software on your PC, you nevertheless can install MetaXL. MetaXL will then install all files under Documents and Setting\Your User Name\MetaXL (Windows XP) or Users\Your User Name\MetaXL (Windows 7 and later). In this case you may get the message during installation that "You may have to install the add-in manually". In practice this usually turns out to be not the case: if you open one of the example spreadsheets and do not get #NAME? errors, you're fine. If you do get those errors, you will have to go to Tools|Add-ins (Excel 2003 and earlier) or Office Button|Excel|Options|Add-ins|Go (Excel 2007 and later) and browse where the file 'MetaXL.xll' is located (now you know why it is important to know where your files are).

The Excel development team at Microsoft seriously dropped the ball with respect to support for the 2007+ ribbon interface in the C application programming interface (C-API): there is none whatsoever. This forced us to take the messy route of XLM and VBA to support the ribbon interface. Yuck! The Excel 2007 and later installation therefore has a second add-in (called MetaXLRibbon.xlam) installed that takes care of the ribbon issues.

To minimise the pain of finding the MetaXL files, all supplementary files (documentation and examples) are accessible through the Start|Programs|MetaXL menu that is created by the installation program.

A note to IT personnel

As described above, users can install MetaXL even when they have no administrator rights. What is more, when you install MetaXL as administrator, other users will not be able to use it. The reason is that the installation program writes to the Windows registry key HKEY_LOCAL_USER, not to HKEY_LOCAL_MACHINE. There are good reasons for that (which need not to be elaborated here), but the upshot is that IT should leave it to the users themselves to install the software, even on multiple user machines in computer labs.

An unhelpful Excel offer

Sometimes Excel will offer to move the add-in file 'MetaXL.xll' to its 'AddIns' folder. Never, repeat never, accept this. If you do, it will cause all kinds of mischief, in particular after upgrading to a newer version of MetaXL. It is one of those features of Excel where you really wonder what they were thinking at Microsoft.

If you have already accepted the offer, here are the steps to undo the harm:

1. Go to the AddIns directory (you can find where it is by going through the steps outlined in the *Where are your files?* section above to manually add the add-in: when you click the Browse button, Excel will start in the AddIn folder).
2. Delete the MetaXL.xll file. You cannot do so when Excel is running, so you have to quit Excel first.
3. Start Excel. It will complain that it cannot find the MetaXL add-in. When you go to the Excel add-ins list (see above), it will ask you whether the MetaXL add-in should be removed from its list. Click 'yes' to that.
4. Re-install MetaXL.

After having gone through this, you will probably remember to decline Excel's offer in the future ☺.

Statistical and other scientific sources

In the development of MetaXL, we have adopted the Stata™ implementation of meta-analysis as the gold standard. There are two reasons for this. The first is that we have access to Stata, and therefore it is easy to check the MetaXL results against those of Stata. But the second reason is more important: most of the statistical input for MetaXL is from the excellent book edited by Matthias Egger et al, in particular the chapter by Deeks, Altman, and Bradburn (Deeks, Altman et al. 2001). Various authors of the book's chapters, most of which were first published in the BMJ, were also involved in the implementation of Stata's metan command. If you find any discrepancies between Stata and MetaXL results, we are eager to hear them (info@epigear.com).

So if MetaXL is designed to reproduce the Stata results, then why produce it in the first place? Again for two reasons. The first is that not everybody has access to Stata, and buying a Stata license just for doing the odd meta-analysis is an expensive option. For the many people who have Excel installed, MetaXL offers free access to meta-analysis.

But again the second reason is more important. The overarching issue in meta-analysis is how to deal with heterogeneity between studies. Currently the standard approach is to reach for the random effects model when the heterogeneity statistics (Cochran's Q and I^2) indicate that heterogeneity exceeds a certain threshold, making the various fixed effects models inappropriate.

We think the random effects model is a poor solution to the problem of heterogeneity. The assumption of the random effects model is that the observed heterogeneity is due to real differences in effect sizes: the different effect sizes themselves have a Normal distribution, and thus the meta-analysis aims to estimate the mean underlying true effect.

It is debatable whether the variation in underlying true effect is more common than variations due to systematic errors between studies. The latter is certainly more likely for the bulk of studies in Medicine and thus the random effects model is not an adequate solution, unless you accept its basic premise, which we think results in a random effects summary that lacks interpretation. Indeed, Peto even called use of random-effects meta-analysis "wrong" because it answers a question that is "abstruse and uninteresting"(Peto 1987).

While we are prepared to accept that the real effect size might have a Normal distribution, we are convinced that the studies in a meta-analysis are neither

exchangeable nor that their observed heterogeneity is overwhelmingly driven by differences in the underlying effect size. We are also convinced that we are correct in our assumption that sources of bias are the main drivers of heterogeneity, and thus it is much better to deal with heterogeneity by explicitly assessing and weighting for study quality. If for some reason you cannot or don't want to weigh for quality, you can use the IVhet model that produces a wider confidence interval around the pooled estimate but retains the individual study weights of the inverse variance model.
So that is where MetaXL comes in: no other meta-analysis software offers the quality effects or the inverse variance heterogeneity models that are implemented in MetaXL[3]. By making MetaXL freely available, we hope and expect that explicitly dealing with study quality in meta-analysis will be encouraged, and that the inappropriate use of the random effects model to deal with between study heterogeneity will become obsolete.

Software

MetaXL was developed in Object Pascal, using Embarcadero's Delphi XE2. While many people seem to think C++ is essential for this kind of project, Object Pascal is actually just as powerful, easier to use, and beats all C++ compilers by its blazing speed.
Writing xll add-ins for Excel has been described as a black art. While we would hesitate to call it that, it certainly requires lots of stamina. The main reasons are that the Microsoft Excel xll software development kits are rather short on detail, and that Excel proves to be a wilful environment to program for, with a tendency to either crash or sulk if anything is wrong rather than be explicit about it.
Fortunately, where Microsoft left a lot to be desired, some people have stepped in. We are indebted to David Bolton whose article "Writing (Non Com) Excel Add-ins in Delphi" (which originally appeared in Delphi Magazine but is now floating around on the Web), despite some strange errors, gave the necessary heads up in our first steps on this road. An invaluable resource is also Steve Dalton's "Financial applications using Excel add-in development in C/C++"(Dalton 2007). But as the title suggests, you need to be able to understand C(++) code to get the most out of this book.
Excel 2007 was a major upgrade from previous versions. Among other things, it sports a 'big grid', i.e. many more rows and columns than previous versions. This required a change in its basic data type, the XLOPER, to the XLOPER12. These special data types have the flexibility to describe the different things Excel works with: text, numbers, ranges, etc. Excel 2007 and later versions are largely backward compatible with add-ins written for earlier versions, but MetaXL actively supports the new features of Excel 2007 and higher by implementing a dual interface, and presenting the applicable one depending on which version of Excel is running.
Few people will at this point have the 64-bit version of Excel 2010 or later installed: the default installation of Office is 32-bit. Starting with version 1.3, MetaXL is compatible with both 32- and 64-bit Excel. The installation program contains two versions of the add-in, and installs the correct one depending on the Excel version.
The MetaXL installation program was written using Inno Setup 5 (www.jrsoftware.org). This is one of those amazing things: it is freeware, but beats commercial installation software such as InstallShield hands down on features as ease of use, power, and flexibility. Recommended.

[3] MIX version 1.7 implements the quality effects model, but it is no longer supported, and MIX version 2 has dropped the quality effects model.

About the authors

Jan Barendregt is the founder and owner of EpiGear International Pty Ltd (www.epigear.com), which makes free and low-cost software. He is also Honorary Associate Professor at the School of Public Health, University of Queensland, Brisbane, Australia.
Email: jan@epigear.com or j.barendregt@sph.uq.edu.au.
Suhail Doi is Associate Professor of Clinical Epidemiology at the Research School of Population Health, Australian National University, Canberra, Australia.
Email: suhail.doi@anu.edu.au or sardoi@gmx.net.

References

Al Khalaf, M. M., L. Thalib and S. A. Doi (2011). "Combining heterogeneous studies using the random-effects model is a mistake and leads to inconclusive meta-analyses." J Clin Epidemiol **64**: 119-123.

Bailey, K. R. (1987). "Inter-study differences: how should they influence the interpretation and analysis of results?" Stat Med **6**(3): 351-360.

Barendregt, J. J., S. A. Doi, Y. Y. Lee, R. Norman and T. Vos (2013). "Meta-analysis of prevalence." Journal of Epidemiology and Community Health **67**: 974-978.

Batham, A., M. A. Gupta, P. Rastogi, S. Garg, V. Sreenivas and J. M. Puliyel (2009). "Calculating prevalence of hepatitis B in India: using population weights to look for publication bias in conventional meta-analysis." Indian J Pediatr **76**(12): 1247-1257.

Boland, A., Y. Dundar, A. Bagust, A. Haycox, R. Hill, R. Mujica Mota, T. Walley and R. Dickson (2003). "Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation." Health Technol Assess **7**(15): 1-136.

Brockwell, S. E. and I. R. Gordon (2007). "A simple method for inference on an overall effect in meta-analysis." Stat Med **26**(25): 4531-4543.

Brooks, S. P. and A. E. Gelman (1998). "General methods for monitoring convergence of iterative simulations." Journal of Computational and Graphical Statistics **7**(4): 434–455.

Bucher, H. C., G. H. Guyatt, L. E. Griffith and S. D. Walter (1997). "The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials." J Clin Epidemiol **50**(6): 683-691.

Caldwell, D. M., A. E. Ades and J. P. Higgins (2005). "Simultaneous comparison of multiple treatments: combining direct and indirect evidence." BMJ **331**(7521): 897-900.

Cohen, J. (1994). "The earth is round ($p < 0.05$)." American Psychologist **49**: 997–1003.

Collins, R., S. Yusuf and R. Peto (1985). "Overview of randomised trials of diuretics in pregnancy." Br Med J (Clin Res Ed) **290**(6461): 17-23.

Conn, V. S. and M. J. Rantz (2003). "Research methods: managing primary study quality in meta-analyses." Res Nurs Health **26**(4): 322-333.

Cornell, J. E., C. D. Mulrow, R. Localio, C. B. Stack, A. R. Meibohm, E. Guallar and S. N. Goodman (2014). "Random-effects meta-analysis of inconsistent effects: a time for change." Ann Intern Med **160**(4): 267-270.

Cox, D. R. (1970). "The continuity correction." Biometrika **57**: 217-219.

Dalton, S. (2007). Financial Applications Using Excel Add-in Development in C/C++. Chichester, Wiley.

Deeks, J. J., D. G. Altman and M. J. Bradburn (2001). Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. Systematic reviews in health care: Meta-analysis in context. M. Egger, G. Davey Smith and D. G. Altman. London, BMJ Publishing Group**:** 285-312.

Doi, S. A., J. J. Barendregt, S. Khan, L. Thalib and G. M. Williams (2015). "Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model." Contemp Clin Trials **45**: 130-138.

Doi, S. A., J. J. Barendregt, S. Khan, L. Thalib and G. M. Williams (2015). "Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model." Contemp Clin Trials **45**: 123-129.

Doi, S. A., J. J. Barendregt and C. Rao (2014). "An updated method for risk adjustment in outcomes research." Value Health **17**(5): 629-633.

Doi, S. A. and L. Thalib (2008). "A quality-effects model for meta-analysis." Epidemiology **19**(1): 94-100.

Doi, S. A. and L. Thalib (2009). "An alternative quality adjustor for the quality effects model for meta-analysis." Epidemiology **20**(2): 314.

Glenny, A. M., D. G. Altman, F. Song, C. Sakarovitch, J. J. Deeks, R. D'Amico, M. Bradburn, A. J. Eastwood and G. International Stroke Trial Collaborative (2005). "Indirect comparisons of competing interventions." Health Technol Assess **9**(26): 1-134, iii-iv.

Ha, V., J. L. Sievenpiper, R. J. de Souza, V. H. Jayalath, A. Mirrahimi, A. Agarwal, L. Chiavaroli, S. B. Mejia, F. M. Sacks, M. Di Buono, A. M. Bernstein, L. A. Leiter, P. M. Kris-Etherton, V. Vuksan, R. P. Bazinet, R. G. Josse, J. Beyene, C. W. Kendall and D. J. Jenkins (2014). "Effect of dietary pulse intake on established therapeutic lipid targets for cardiovascular risk reduction: a systematic review and meta-analysis of randomized controlled trials." CMAJ **186**(8): E252-262.

Hart, R. G., O. Benavente, R. McBride and L. A. Pearce (1999). "Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis." Ann Intern Med **131**(7): 492-501.

Helfenstein, U. (2002). "Data and models determine treatment proposals--an illustration from meta-analysis." Postgrad Med J **78**(917): 131-134.

Higgins, J. P. and S. G. Thompson (2004). "Controlling the risk of spurious findings from meta-regression." Stat Med **23**(11): 1663-1682.

Higgins, J. P. T. and S. G. Thompson (2002). "Quantifying heterogeneity in a meta-analysis." Stat Med **21**: 1539-1558.

Keeley, E. C., J. A. Boura and C. L. Grines (2003). "Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials." Lancet **361**(9351): 13-20.

Law, M. R., N. J. Wald and S. G. Thompson (1994). "By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?" BMJ **308**(6925): 367-372.

Lipsey, M. W. and D. B. Wilson (2001). "The way in which intervention studies have "personality" and why it is important to meta-analysis." Eval Health Prof **24**(3): 236-254.

Lussier, J. P., S. H. Heil, J. A. Mongeon, G. J. Badger and S. T. Higgins (2006). "A meta-analysis of voucher-based reinforcement therapy for substance use disorders." Addiction **101**(2): 192-203.

Noma, H. (2011). "Confidence intervals for a random-effects meta-analysis based on Bartlett-type corrections." Stat Med **30**(28): 3304-3312.

Nuesch, E. and P. Juni (2009). "Commentary: Which meta-analyses are conclusive?" Int J Epidemiol **38**(1): 298-303.

Peto, R. (1987). "Why do we need systematic overviews of randomized trials?" Stat Med **6**: 233-244.

Rucker, G. and G. Schwarzer (2015). "Ranking treatments in frequentist network meta-analysis works without resampling methods." BMC Med Res Methodol **15**: 58.

Salanti, G., C. Del Giovane, A. Chaimani, D. M. Caldwell and J. P. Higgins (2014). "Evaluating the quality of evidence from a network meta-analysis." PLoS One **9**(7): e99682.

Senn, S. (2007). "Trying to be precise about vagueness." Stat Med **26**(7): 1417-1430.

Senn, S., F. Gavini, D. Magrez and A. Scheen (2013). "Issues in performing a network meta-analysis." Stat Methods Med Res **22**(2): 169-189.

Song, F., D. G. Altman, A. M. Glenny and J. J. Deeks (2003). "Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses." BMJ **326**(7387): 472.

Sterne, J. A. C. and M. Egger (2001). "Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis." Journal of Clinical Epidemiology **54**: 1046–1055.

Sweeting, M. J., A. J. Sutton and P. C. Lambert (2004). "What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data." Stat Med **23**(9): 1351-1375.

Thompson, S. G. and J. P. Higgins (2002). "How should meta-regression analyses be undertaken and interpreted?" Stat Med **21**(11): 1559-1573.

Thompson, S. G. and S. J. Sharp (1999). "Explaining heterogeneity in meta-analysis: a comparison of methods." Stat Med **18**(20): 2693-2708.

van Valkenhoef, G., G. Lu, B. de Brock, H. Hillege, A. E. Ades and N. J. Welton (2012). "Automating network meta-analysis." Res Synth Methods **3**(4): 285-299.

Verhagen, A. P., H. C. de Vet, R. A. de Bie, M. Boers and P. A. van den Brandt (2001). "The art of quality assessment of RCTs included in systematic reviews." J Clin Epidemiol **54**(7): 651-654.

Veroniki, A. A., H. S. Vasiliadis, J. P. Higgins and G. Salanti (2013). "Evaluation of inconsistency in networks of interventions." Int J Epidemiol **42**(1): 332-345.

Wang, X., Y. Ouyang, J. Liu, M. Zhu, G. Zhao, W. Bao and F. B. Hu (2014). "Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies." BMJ **349**: g4490.

Warton, D. I. and F. K. Hui (2011). "The arcsine is asinine: the analysis of proportions in ecology." Ecology **92**(1): 3-10.

Wilson, A. L. and I. P. Taskforce (2011). "A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc)." PLoS One **6**(2): e16976.

Woolf, B. (1955). "On estimating the relation between blood group and disease." Ann Hum Genet **19**(4): 251-253.

Yates, F. (1934). "Contingency tables involving small numbers and the chi-squared test." Journal of the Royal Statistical Society **1**: 217-235.