Meta-analysis using RevMan

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Contents

1 Introduction

This practical is in two parts. The first part will introduce you to using RevMan for diagnostic test accuracy reviews and basic meta-analyses. You will explore options provided for presenting and analyzing data. The second part focuses on meta-analysis in Stata by fitting the bivariate model using the user written program `metandi`. The third and final part shows how to use the results obtained in Stata to generate graphical output in RevMan.

2 Dataset

The example dataset used in all the practical sessions on this course is a subset of data from the Cochrane diagnostic test accuracy (DTA) review of rapid diagnostic tests (RDTs) for diagnosis of uncomplicated *Plasmodium falciparum* malaria in endemic countries (Abba et al 2011). Malaria is a life-threatening infectious disease caused by the parasitic protozoan *Plasmodium*. *Plasmodium falciparum* and *Plasmodium vivax* are the two most common species infecting humans. The 'gold standard' for diagnosing malaria is microscopic examination of thick and thin blood films. Parasitological confirmation of malaria enables selection of appropriate treatment. However, timely, high quality microscopy may be unavailable in resource-poor settings. Immunochromatographic rapid diagnostic tests (RDTs) are alternatives to microscopic diagnosis.

RDTs use different types of antibody or antibody combinations to detect *Plasmodium* antigens. Some antibodies aim to detect a particular species while others are panmalarial aiming to detect all *Plasmodium* species. Type 1 RDTs use antibodies which detect histidine-rich protein-2 (HRP-2) antigen expressed only by *P. falciparum*. Type 4 RDTs use antibodies which detect HRP-2 and also include pan-specific antibodies that detect plasmodium lactate dehydrogenase (pLDH) from all *Plasmodium* species.

The aim of the review was to assess the diagnostic accuracy of RDTs for detecting clinical *P. falciparum* malaria in people living in malaria endemic areas who present to ambulatory healthcare facilities with symptoms of malaria, and to identify which types and commercial brands best detect clinical *P. falciparum* malaria.

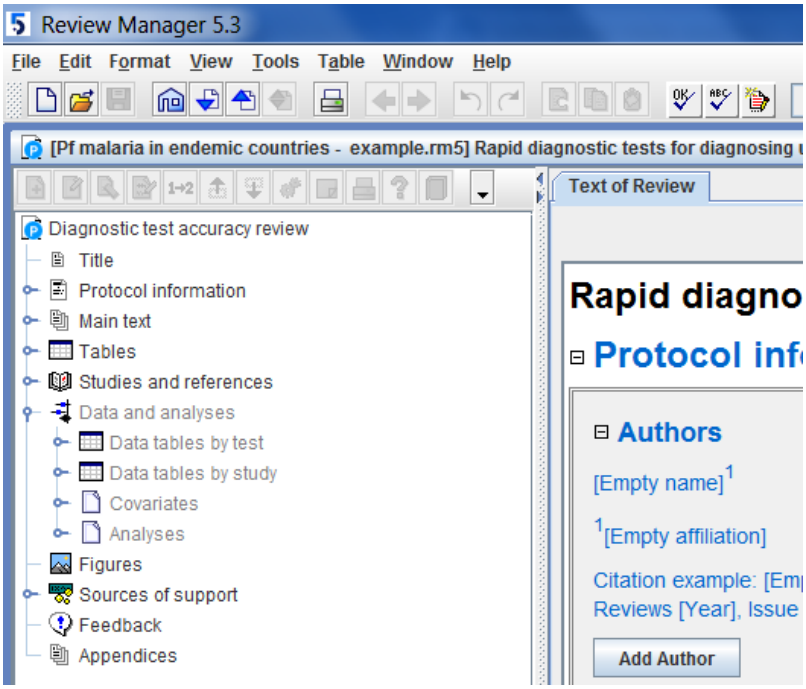
PART I

3 Starting RevMan

Launch Review Manager by double clicking on the RevMan file titled "Pf malaria in endemic countries - example". The file already contains studies and two tests—Type 1 RDTs and Type 4 RDTs. The file also contains some analyses. We will attempt to recreate analysis 1 which is the meta-analysis of type 1 RDTs.

4 Data and analyses in RevMan

Double click on ***Data and analyses*** or click on its node in the outline pane on the left to expand the tree to show data tables, covariates and analyses nodes.

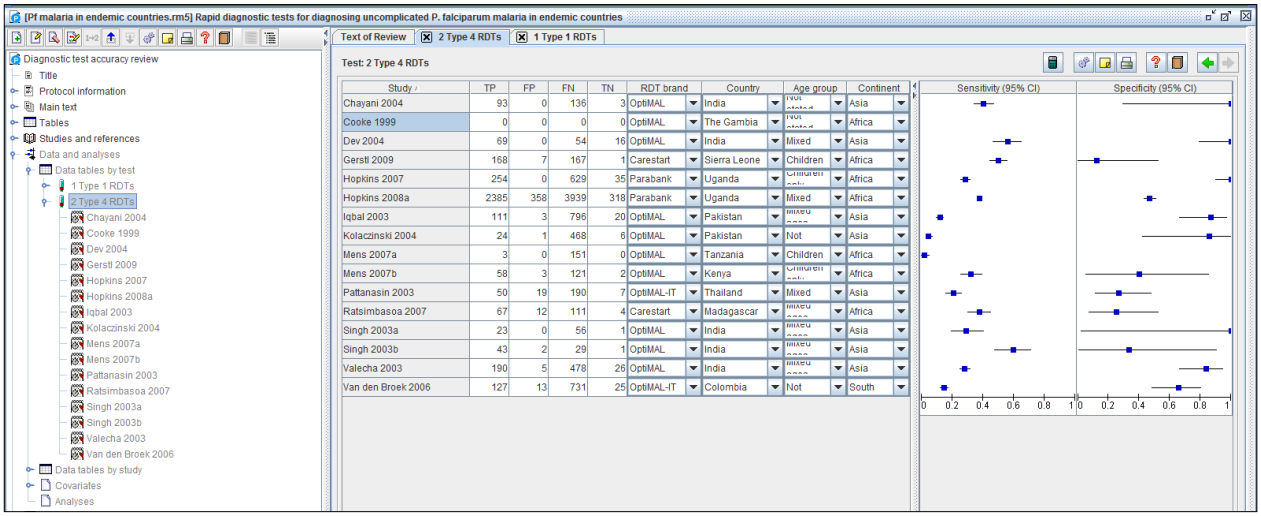


Double click on ***Data tables by test*** to view the list of tests. Double click on ***Type 4 RDTs*** to see the studies that have been added for this test.

5 RevMan calculator tool

With this tool, you can derive 2x2 data when only test accuracy measures such as sensitivity and specificity or LRs are reported in a primary study, as well as sample sizes for the 2 groups, or prevalence and total sample size.

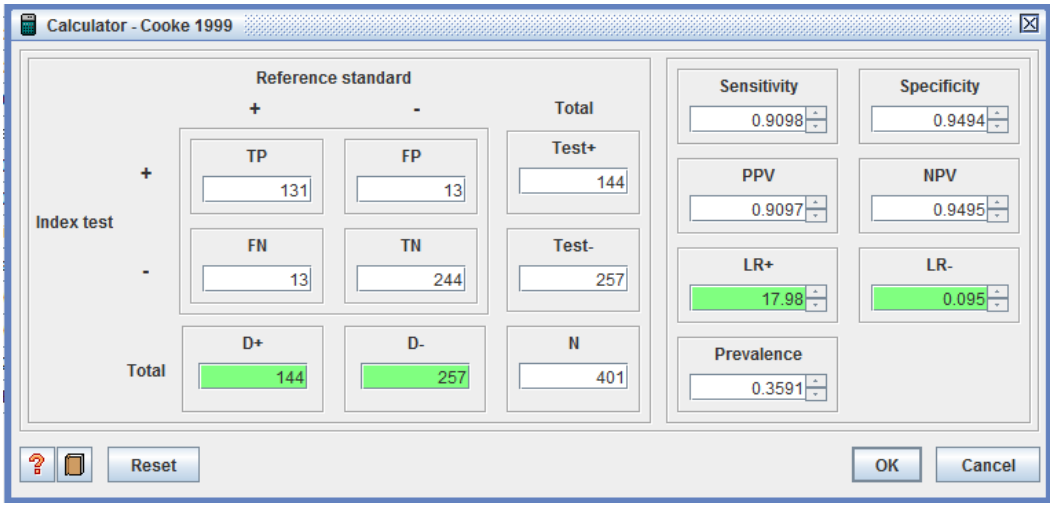
Click on the study **Cooke 1999**. Let's delete the study 2x2 data by entering 0 into the four cells for Cooke 1999. The data should look like that below.



Click the calculator button  in the top right hand corner (first icon) above the forest plots. Click reset. The calculator cells are now empty. Enter the information below in Table 1 into the calculator.

Table 1. Data for derivation of 2x2 table for Cooke 1999

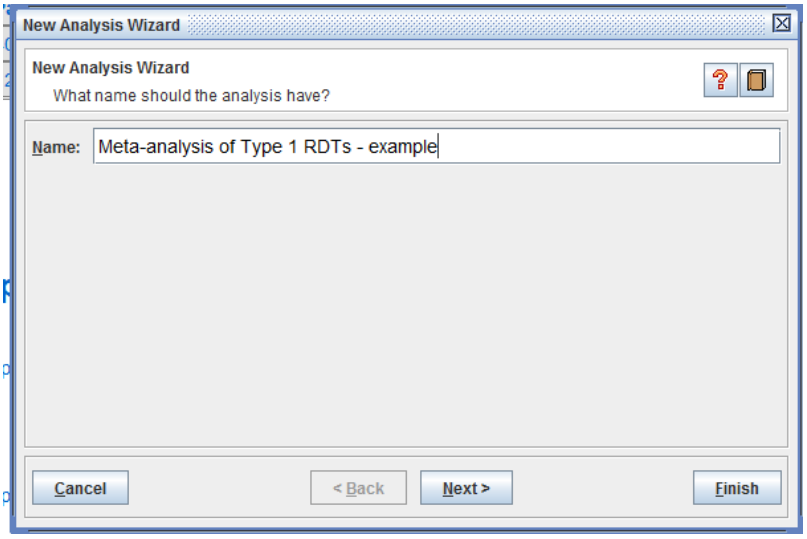
Study	Positive likelihood ratio	Negative likelihood ratio	Number of malaria cases	Number without malaria
Cooke 1999	17.98	0.095	144	257



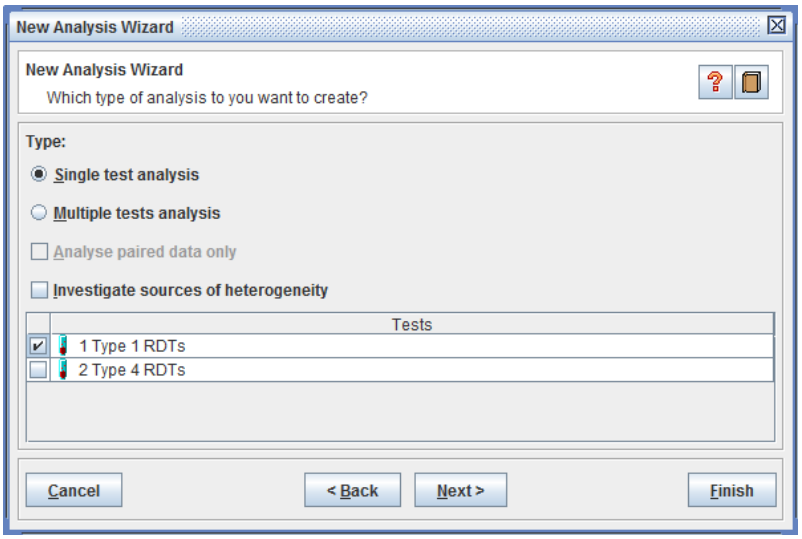
Click OK. The relevant fields in the 2x2 table for Cooke 1999 should be auto-populated with data. If using sensitivity and specificity or predictive values, note that they must be entered into the calculator in decimal form.

6 Add an analysis

To add an analysis right click on ***Analyses*** and click ***Add Analysis***. In the ***New Analysis Wizard***, enter "Meta-analysis of Type 1 RDTs - example" as the name of the analysis.

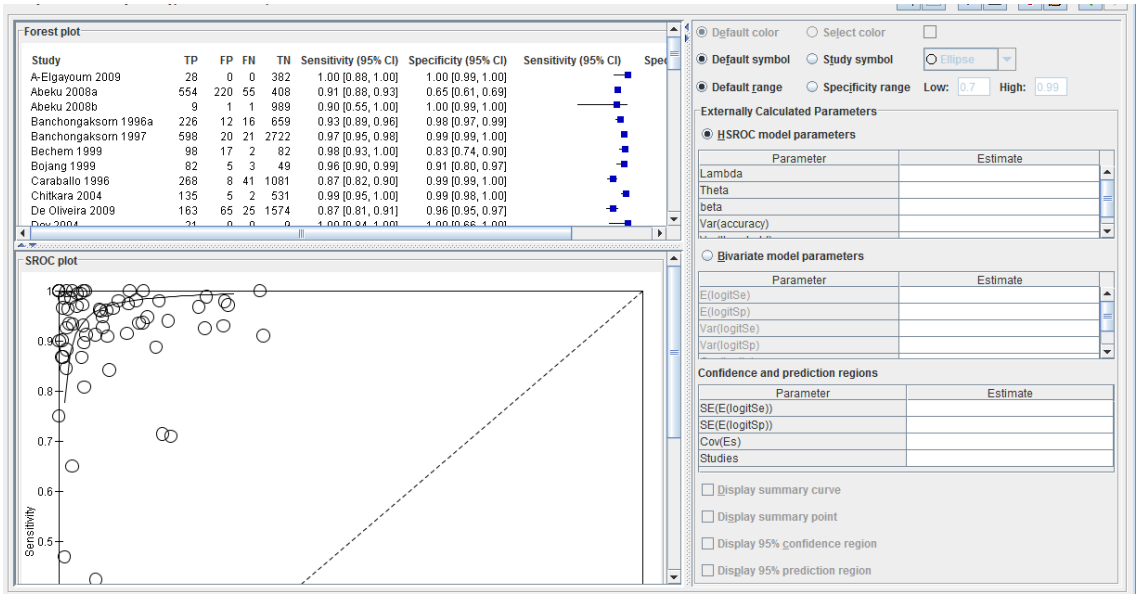


Next select the type of analysis. We want to analyse a single index test. Select Type 1 RDTs as the test.



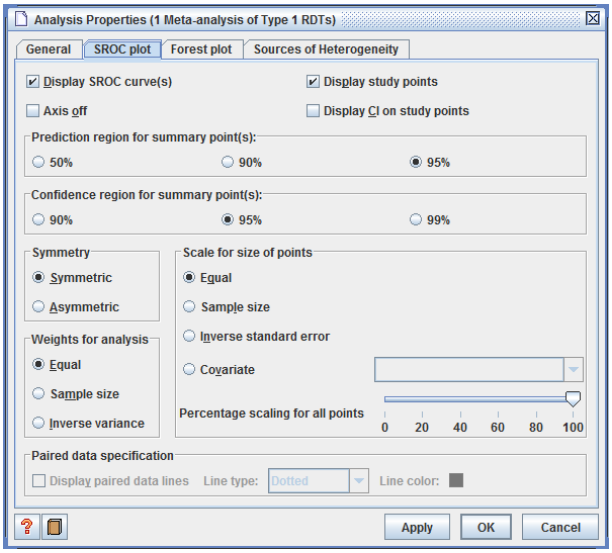
Multiple tests analysis enables test comparisons. Once selected the ***Analyse paired data only*** option will become enabled so that a direct comparison can be performed if required. The SROC plots for such analyses can show pairs of points from each study connected. If you select ***Investigate sources of heterogeneity*** then you can produce separate SROC curves for different categories of a chosen covariate or responses to a quality item.

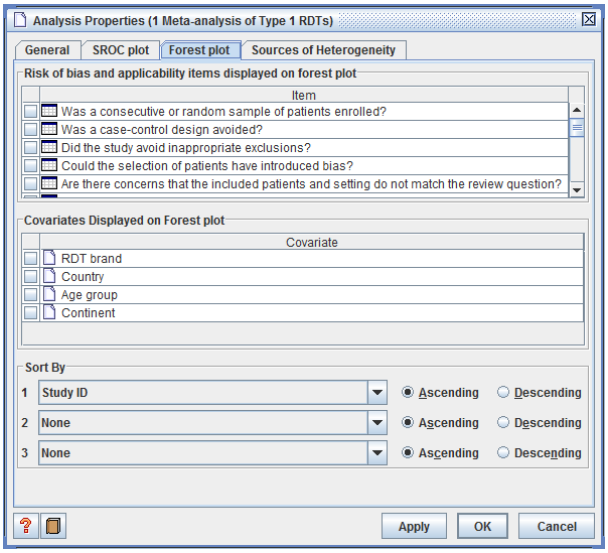
Complete the wizard to create the analysis shown below.



Adjust the ***Specificity range*** (on the analysis pane) so that the SROC curve is drawn within the range of the data. Do you know which method produced this curve?

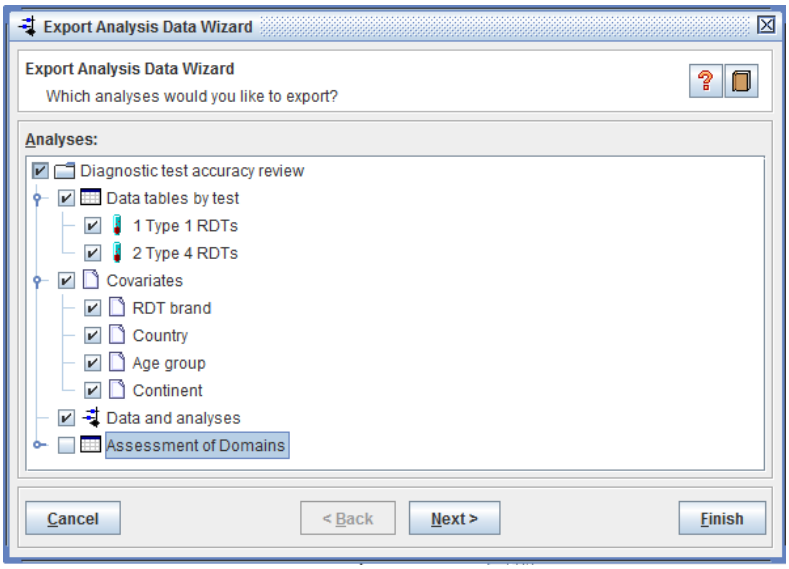
To edit the analysis, click on the properties button  (third icon in the right hand corner). If you are doing ok for time, have a go at changing the properties of the SROC plot using the options on the ***SROC plot*** tab, and properties of the forest plot using options on the ***Forest plot*** tab. If you are running out of time, do this later when you have time.





7 Exporting data

On the menu bar, click File>Export>Data and analyses to launch the ***Export Analysis Data Wizard***. Expand the various sections and deselect any test or covariate you do not wish to export. Select everything except ***Assessment of Domains***.



On the subsequent pages accept the default fields selected and also the .csv (comma separated values) file format. Finish and save the file as "pf malaria.csv". Ensure the .csv extension is included in the name of the file as RevMan will not automatically add it on if you delete it. Open the file and examine the data you exported.

PART II (if you have time)

8 Entering results from external analyses into RevMan

For those authoring a diagnostic test accuracy review in RevMan or using it to simply generate forest plots and SROC plots, the parameter estimates for the bivariate model or HSROC model can be copied from the output of the analyses done in a statistical package and pasted into the relevant boxes in the ***Externally Calculated Parameters*** window of the corresponding analysis in RevMan as shown below using a Stata output for the bivariate model. To save time, rather than copying each parameter estimate for the bivariate model that I fitted in Stata and pasting into RevMan one at a time, you can highlight the column of estimates in Table 2 and Table 3, copy and paste into RevMan. For Table 2 only highlight and copy the first 4 parameter estimates to avoid pasting the correlation parameter estimate in the Cov(logits) box. See further explanation in the box below.

Table 2. Estimates of bivariate model parameters

Parameter	Estimate
E(logitSe)	2.907366
E(logitSp)	2.96643
Var(logitSe)	1.288736
Var(logitSp)	1.886708
Cov(logits)	-0.1300819

Table 3. Estimates of parameters for confidence and prediction regions

Parameter	Estimate
SE(E(logitSe))	0.1659276
SE(E(logitSp))	0.183056
Cov(ES)	-0.0031803
Studies	65

Meta-analysis of diagnostic accuracy

Log likelihood = -445.63948 Number of studies = 65

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	2.907366	.1659276			2.582154	3.232578
E(logitSp)	2.96643	.183056			2.607647	3.325214
Var(logitSe)	1.288736	.3130033			.8006215	2.074438
Var(logitSp)	1.886708	.3931091			1.254154	2.838302
Corr(logits)	-.1300819	.1559903			-.4151528	.1782501
HSROC						
Lambda	5.894849	.2344721			5.435292	6.354405
Theta	.2506229	.2479344			-.2353195	.7365654
beta	.1905859	.1591698	1.20	0.231	-.1213811	.5025529
s2alpha	2.712956	.6489215			1.697621	4.335554
s2theta	.8810777	.1880231			.5799181	1.338634
Summary pt.						
Se	.9482094	.0081484			.9297041	.962042
Sp	.9510343	.0085246			.9313521	.9652837
DOR	355.5963	83.15242			224.8603	562.3435
LR+	19.36477	3.35792			13.78514	27.20281
LR-	.0544572	.0085307			.0400604	.0740279
1/LR-	18.36305	2.876562			13.50842	24.96233

Covariance between estimates of E(logitSe) & E(logitSp) -.0031803

Externally Calculated Parameters

○ HSROC model parameters

Parameter	Estimate
Lambda	
Theta	
beta	
Var(accuracy)	
Var(threshold)	

◉ Bivariate model parameters

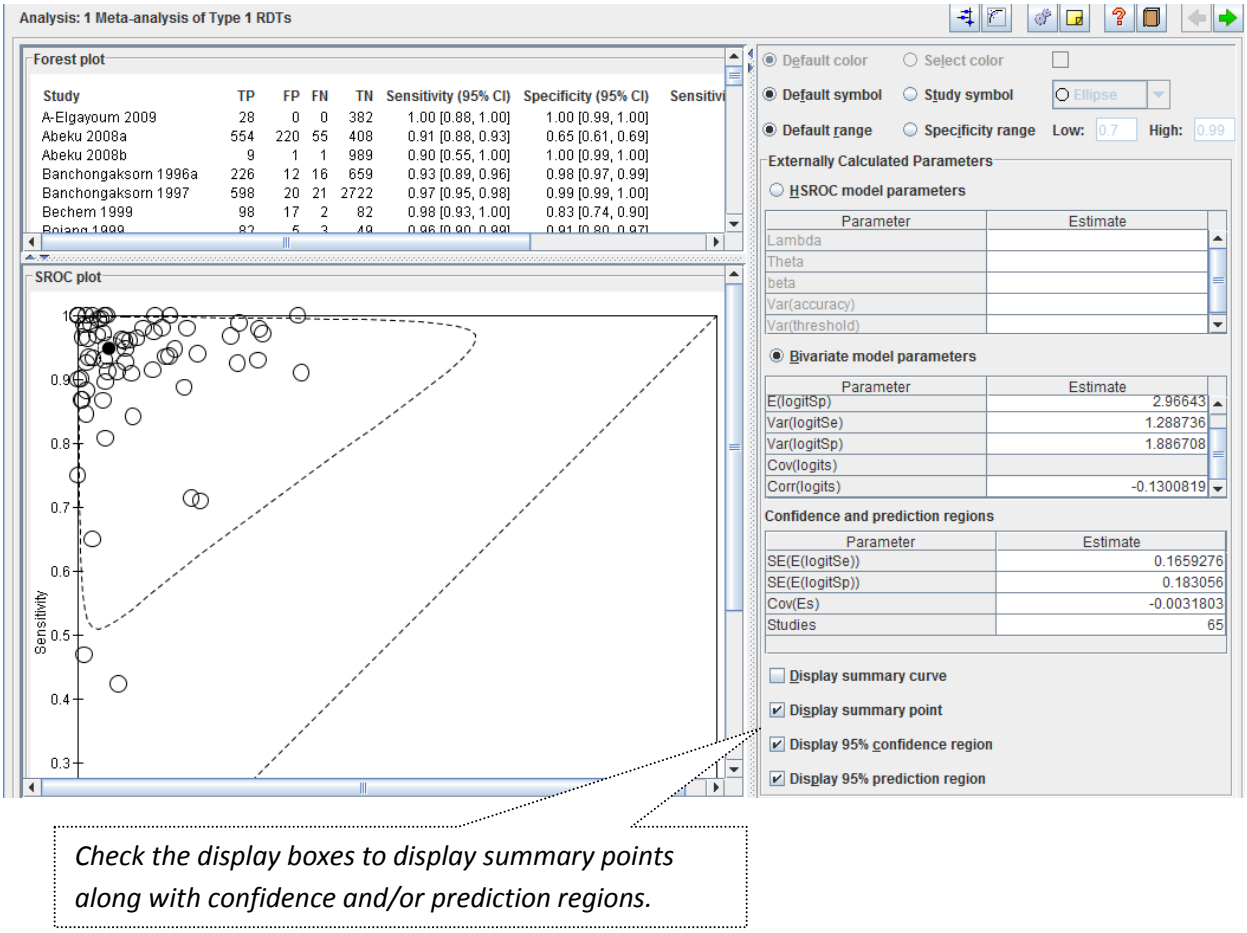
Parameter	Estimate
E(logitSe)	2.907366
E(logitSp)	2.96643
Var(logitSe)	1.288736
Var(logitSp)	1.886708
Cov(logits)	

Confidence and prediction regions

Parameter	Estimate
SE(E(logitSe))	0.1659276
SE(E(logitSp))	0.183056
Cov(Es)	-0.0031803
Studies	65

You need either the correlation or the covariance between the variances of the random effects for logit sensitivity and logit specificity. RevMan will disable one of the textboxes when one of them has been filled in. ***metandi*** *outputs the correlation of the logits (-0.1300819 above) so scroll down to use Corr(logits) instead of using Cov(logits). See screen shot below.*

Display summary point, confidence region and prediction region to obtain the SROC plot shown below.



Check the display boxes to display summary points along with confidence and/or prediction regions.

Remember to remove the SROC curve (based on the Moses-Littenberg method) generated by RevMan (see the ***SROC plot*** tab on the ***Properties*** dialogue box).

9 Additional information

`metandi` does not have an option for including a covariate in the bivariate model and so cannot be used for investigations of heterogeneity or test comparisons. You are also limited in what you can do to facilitate model convergence if there are model fitting problems (e.g. due to sparse data). Therefore it is useful to know how to fit the bivariate model using the command `xtmelogit` directly (for Stata 13 users, you can use `meqrlogit` instead of `xtmelogit` if you wish)—essentially doing what `metandi` does. A tutorial is available at http://dta.cochrane.org/software-meta-analysis-dta-studies. The aim of the tutorial is to guide both novice and experienced Stata users on how to perform meta-analysis of test accuracy studies by fitting the bivariate model using either the user written program `metandi` or the built in command `xtmelogit`.

References

Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane Database Syst Rev 2011;7:CD008122.

Chu H, Cole SR. Bivariate meta-analysis for sensitivity and specificity with sparse data: a generalized linear mixed model approach (letter to the Editor). J Clin Epidemiol. 2006;59:1331-1331.

Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors). 2010; http://srdta.cochrane.org/, Version 1.0. The Cochrane Collaboration.