MetaDTA User Guide Version 1.0

https://crsu.shinyapps.io/dta_ma/

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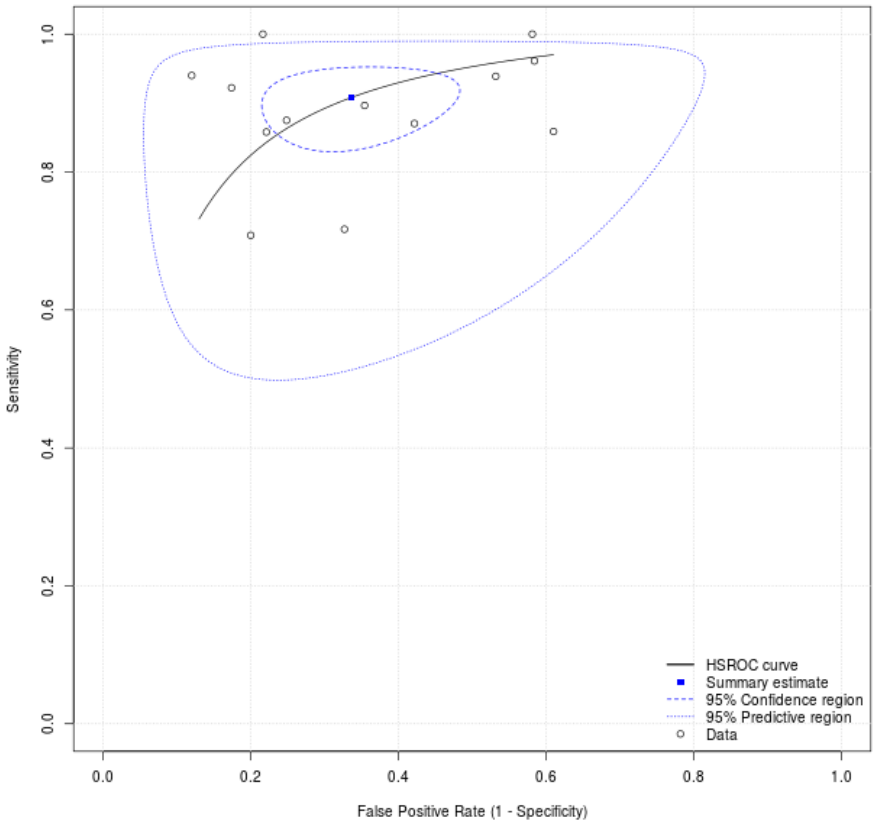

This User Guide uses MetaDTA Version 1.43

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Complex Reviews Support Unit

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Contents

1. Introduction

MetaDTA is an interactive web-based application for conducting meta-analysis of diagnostic test accuracy studies and was developed by the NIHR Complex Reviews Support Unit (CRSU). Diagnostic tests generally comprise of a measure which splits individuals into healthy or diseased. To assess accuracy, a diagnostic test is compared to the "gold standard" test which is assumed to provide the true diagnosis of individuals. There are two parameters which are often used to assess the accuracy of diagnostic tests. Sensitivity is the proportion of patients with the disease correctly diagnosed by the test. Specificity is the proportion of patients without the disease correctly diagnosed by the test. For those new to this topic, an interactive primer (also developed by the CRSU) on the evaluation of diagnostic test accuracy can be found here: https://crsu.shinyapps.io/diagprimer/.

A meta-analysis of diagnostic test accuracy (DTA) studies synthesises both sensitivity and specificity from multiple studies to evaluate the performance of a diagnostic test. The results are often presented either around a mean point or as a summary receiver operating characteristic (SROC) curve. MetaDTA produces SROC plots, and pooled estimates for sensitivity and specificity together with uncertainty in their estimation. MetaDTA has a wide range of graphical features allowing you to customise the SROC plots and consider the distribution of quality assessment results or other covariates. MetaDTA can also be used to aid sensitivity analyses by examining the impact on the results when excluding studies.

MetaDTA has been built using R software and primarily the existing R packages Shiny and lme4[1]. Shiny allows users to build interactive web applications and host them on a server. Although the app uses R, running on the server in the background, the user never interacts directly with it nor needs to know anything about R. The statistical analysis is conducted using the package lme4. A full list of all R packages used in the building of MetaDTA can be found on the References page of MetaDTA (see Section 7). MetaDTA is available to any user with an up-to-date web browser, without requiring any specialist software. MetaDTA is available at https://crsu.shinyapps.io/dta_ma/.

We kindly ask you to cite MetaDTA whenever its output is used. MetaDTA should be cited as: Freeman SC, Kerby CR, Patel A, Cooper NJ, Quinn T, Sutton AJ. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test accuracy studies: MetaDTA. BMC Medical Research Methodology 2019; 19: 81.

In this User Guide we will demonstrate the features available within MetaDTA version 1.43 (14th August 2019). We will start by showing you how you can upload your own dataset to MetaDTA and then demonstrate the features of MetaDTA using one of the inbuilt datasets. The MetaDTA home page is shown in Figure 1. MetaDTA consists of five pages (Load Data, Meta-Analysis, Sensitivity Analysis, Prevalence and References) which can be accessed by clicking on the appropriate page name in the grey bar at the top of the web page. This User Guide will guide you through each page in turn. Any feedback or queries about MetaDTA should be sent to ajs22@le.ac.uk.

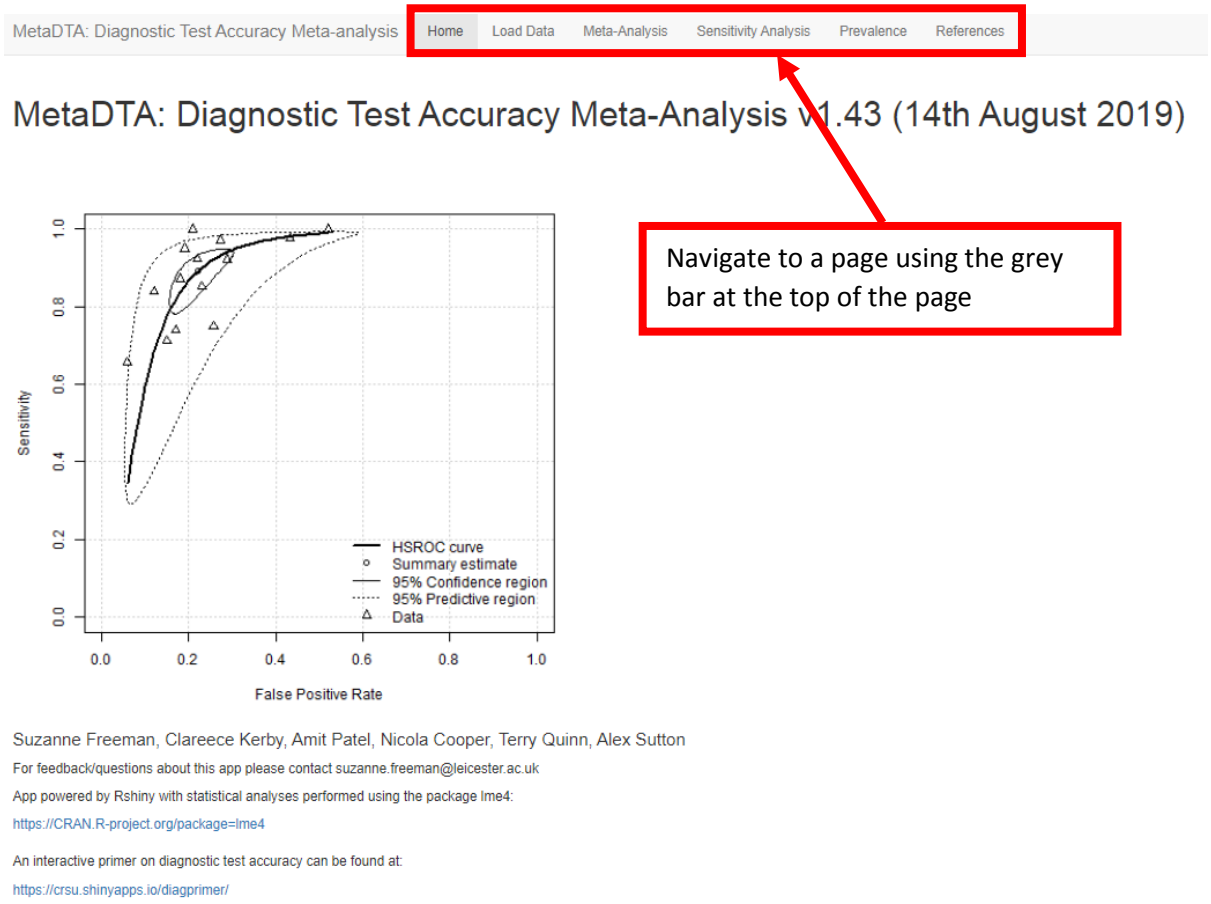


Figure 1: MetaDTA home page

2. Loading your own data

The Load Data page consists of a grey box on the left hand side of the page and three tabs: File Upload, Example Datasets and Data for Analysis (Figure 2). MetaDTA can upload data from delimited files. The files can be comma, semicolon, tab or space delimited. The first row of the data file should contain the column headings and these have to be labelled a specific way (explained in the app see Figure 2 and below). Column headings are specified on the `File Upload' tab (Figure 2). To assist with the labelling of column headings inbuilt datasets are available to download (see Section 3).

As a minimum there should be six columns containing the author, year, number of true positives, false negatives, false positives and true negatives. However, MetaDTA can also handle data relating to quality assessment using the QUADAS-2 tool[2] and covariates. QUADAS-2 consists of four key domains: patient selection, index test, reference standard, flow and timing. All four domains are assessed for risk of bias and the first three in terms of applicability concerns giving a total of seven domains. To include quality assessment results within MetaDTA all seven columns are required. Study-level covariates can be added by including an additional column per covariate.

To load your own dataset:

1. Select the correct `File delimiter' option from the list in the grey box (Figure 2)
2. Click the `Select' button at the top of the grey box (Figure 2)
3. A box will appear which will allow you to navigate through your computers file system until you find the file you wish to upload
4. Select the file you wish to upload and click open
5. Once the upload is completed a blue bar will appear showing `Upload complete' (Figure 3)
6. Click on the `Data for Analysis' tab if you want to check your dataset has uploaded in the format expected (Figure 3)

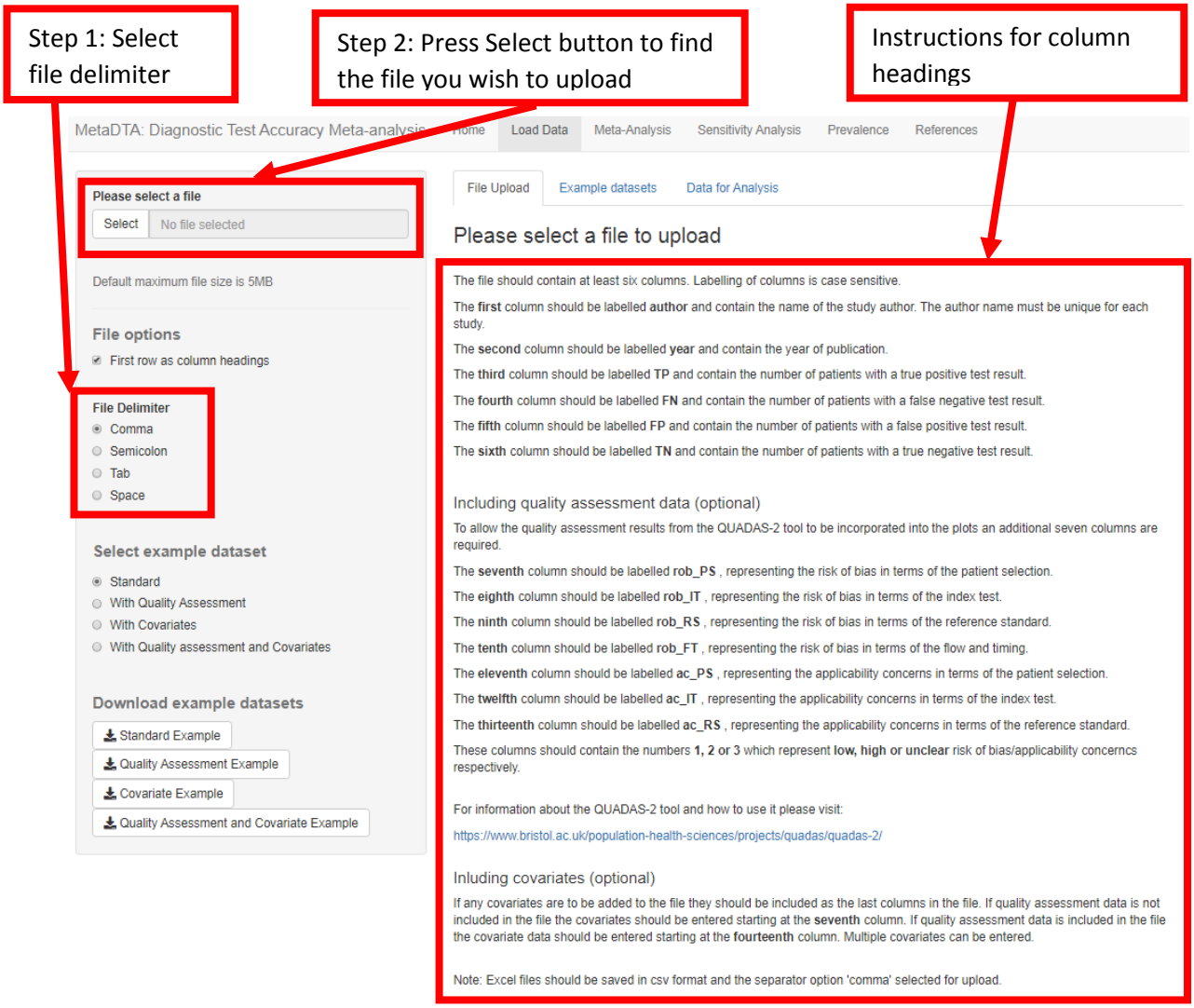


Figure 2: Load Data page showing the File Upload tab and highlighting steps 1 and 2 to upload your own dataset

MetaDTA also includes example datasets available for you to download (see Section 3). The `Data for Analysis' tab will always display the dataset that is currently loaded and used for analysis within MetaDTA. Prior to upload of your own dataset this tab will display the inbuilt default dataset.

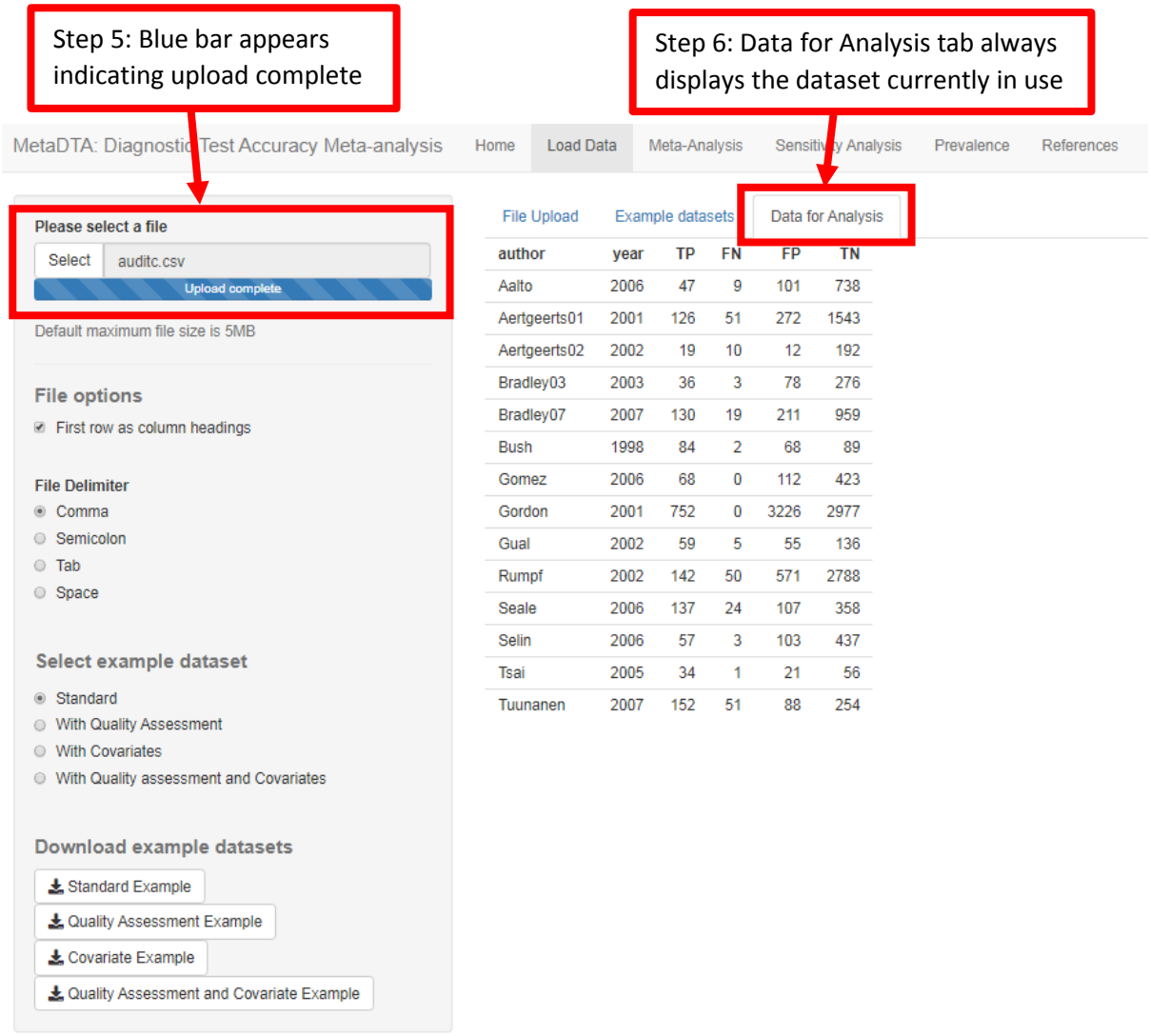


Figure 3: Load Data page showing the File Upload tab and highlighting steps 5 and 6 to upload your own dataset

Helpful Hints for uploading your own dataset to avoid error messages

- Excel spreadsheets must be saved in comma separated value (csv) format before uploading to MetaDTA
- The labelling of column headings is case sensitive
- The author field should be unique for every row of data
- At the time of upload, studies must be ordered by the `author' column alphabetically from A to Z (Excel can do this easily)

3. Using an inbuilt dataset

MetaDTA comes complete with four inbuilt datasets which can be used to familiarise yourself with the features of MetaDTA. The four datasets are also available to download in csv format and can be used to help ensure that your own data is in the correct format for upload to MetaDTA. These datasets can be accessed from the grey box on the Load Data page.

In the grey box under the heading `Select example dataset' there are four options (Figure 4):

- Standard: a dataset containing six columns for author, year, true positive, false negative, false positive and true negative, the default option.
- With Quality Assessment: contains the same six columns as the Standard dataset with an additional seven columns corresponding to the seven domains of QUADAS-2.
- With covariates: contains the same six columns as the Standard dataset with additional columns corresponding to covariates (one column per covariate).
- With Quality assessment and Covariates: contains the same six columns as the Standard dataset with an additional seven columns corresponding to the seven domains of QUADAS-2 and additional columns for covariates.

Under the heading `Download example datasets' the four inbuilt datasets can be downloaded by clicking on the corresponding button (Figure 4). The datasets will download as csv files.

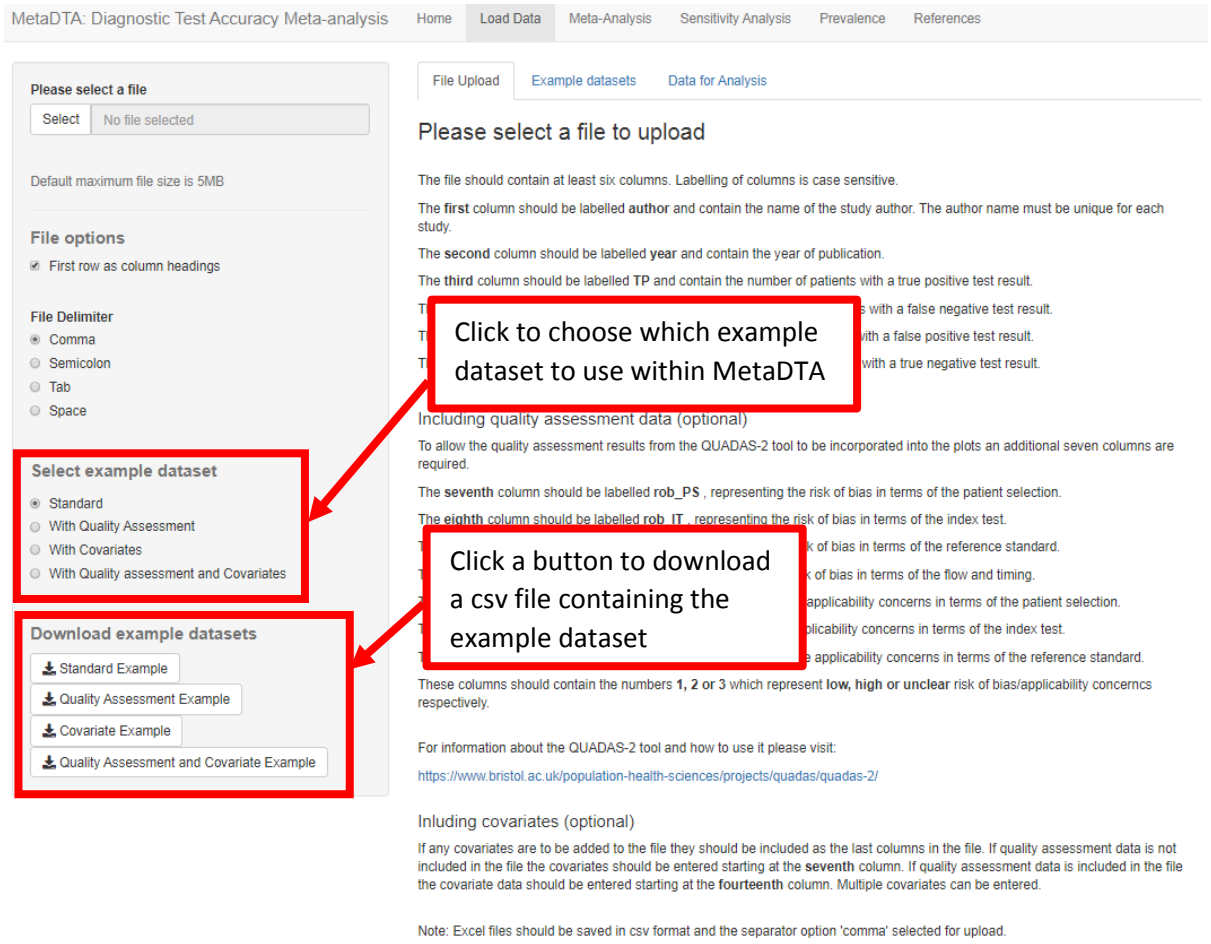


Figure 4: How to select an example dataset to use within MetaDTA and how to download an example dataset

Illustrative example

Throughout the remainder of this User Guide we will use the inbuilt dataset with quality assessment and covariates. This dataset is from a systematic review investigating the accuracy of an informant-based questionnaire, for detection of all cause dementia in adults[3]. The dataset consists of thirteen studies assessing the use of the IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) tool for identifying adults with dementia within a secondary care setting.

The IQCODE tool contains a number of questions which are scored on a five point scale. The IQCODE tool has a number of different variants, depending on how many questions are asked. The questions are based on the performance of everyday tasks related to cognitive function. These are then rated on a scale of 1-5. The final score is an average score for each question. The threshold used in each study is included as a covariate (see below). The IQCODE tool is only a screening tool and does not offer a definitive diagnosis of dementia.

The dataset contains quality assessment results and three covariates. Risk of bias and applicability were assessed in each of the thirteen studies using the QUADAS-2 tool[2]. The first covariate is the

country in which each individual study was conducted. The second covariate is the threshold used in each individual study. In this case if an individual's final score was higher than the threshold the individual was classified as having dementia and would require further diagnosis. The final covariate is labelled as 'IQCODE' and indicates which variant of the tool was used in each individual study. The variants are identified by the number of questions used in the questionnaire. There are three different variants the 16-item, 26-item and 32-item.

This dataset can be downloaded by clicking the `Quality Assessment and Covariate Example' button under `Download example datasets' as demonstrated in Figure 4. The resulting csv file is shown in Figure 5. The column headings from this file can be easily used when constructing your own dataset to upload to MetaDTA.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	author	year	TP	FN	FP	TN	rob_PS	rob_IT	rob_RS	rob_FT	ac_PS	ac_IT	ac_RS	Threshold	Country	IQCODE
2	Flicker	1997	188	28	35	48	2	2	2	3	1	3	1	3.6	Australia	26
3	Garcia	2002	83	7	4	19	2	1	1	1	1	1	1	3.6	Spain	16
4	Goncalves	2011	109	43	17	35	1	1	2	1	1	1	1	4.1	Australia	16
5	Hancock	2009	73	12	36	23	1	2	1	1	1	3	1	3.6	UK	16
6	Harwood	1997	43	0	29	105	1	2	3	1	1	2	1	3.3	UK	16
7	Jorm	1991	17	7	9	36	2	2	1	2	2	1	1	3.6	Australia	26
8	Knaefelc	2003	215	14	50	44	1	2	1	2	1	1	3	3.6	Australia	16
9	Mackinnor	1998	52	6	17	31	2	2	1	3	3	3	1	3.6	Switzerlan	16
10	Mulligan	1996	33	0	25	18	2	2	3	3	3	3	3	3.3	Switzerlan	26
11	Narasimha	2008	145	24	90	317	2	2	2	2	2	3	3	3.4	Singapore	16
12	Sikkes	2010	173	7	52	37	2	2	1	1	2	1	1	3.3	Netherlan	16
13	Siri	2006	94	6	12	88	2	2	1	2	3	2	3	3.3	Thailand	32
14	Tang	2003	21	3	41	124	1	2	1	2	2	2	1	3.4	Hong Kong	26

Figure 5: Screen shot of csv file resulting from downloading the `Quality Assessment and Covariate Example' dataset

4. Meta-Analysis

MetaDTA fits the random effects bivariate binomial model of Chu & Cole[4]. Sensitivity and specificity are jointly modelled with the estimates from each study assumed to vary but come from a common underlying distribution with an unstructured between-study covariance matrix[1]. The underlying R code to perform the meta-analysis is taken from Partlett & Takwoingi[5]. Without covariates the bivariate model is mathematically equivalent to the hierarchical summary receiver operating characteristic (HSROC) model[6]. Therefore the HSROC parameters are estimated using the bivariate model parameters and the equivalence equations of Harbord et al.[6] The HSROC parameters are used to draw the SROC plot. Percentage study weights are calculated using the methodology of Burke et al.[7]

On the Meta-Analysis page the `Study-level Outcomes' tab displays a table containing sensitivity and specificity for each study. Clicking on the grey up arrow next to `Sens' sorts the table into ascending order based on sensitivity. Figure 6 shows that across studies sensitivity ranges from 70.8% to 100%. In the same way we can identify that specificity ranges from 39% to 88%. Clicking on the `Download Table' button allows you to download a copy of this table as a csv file. At the top of the table is a search box allowing you to search within the table for specific studies, years or values which may be useful with larger datasets.

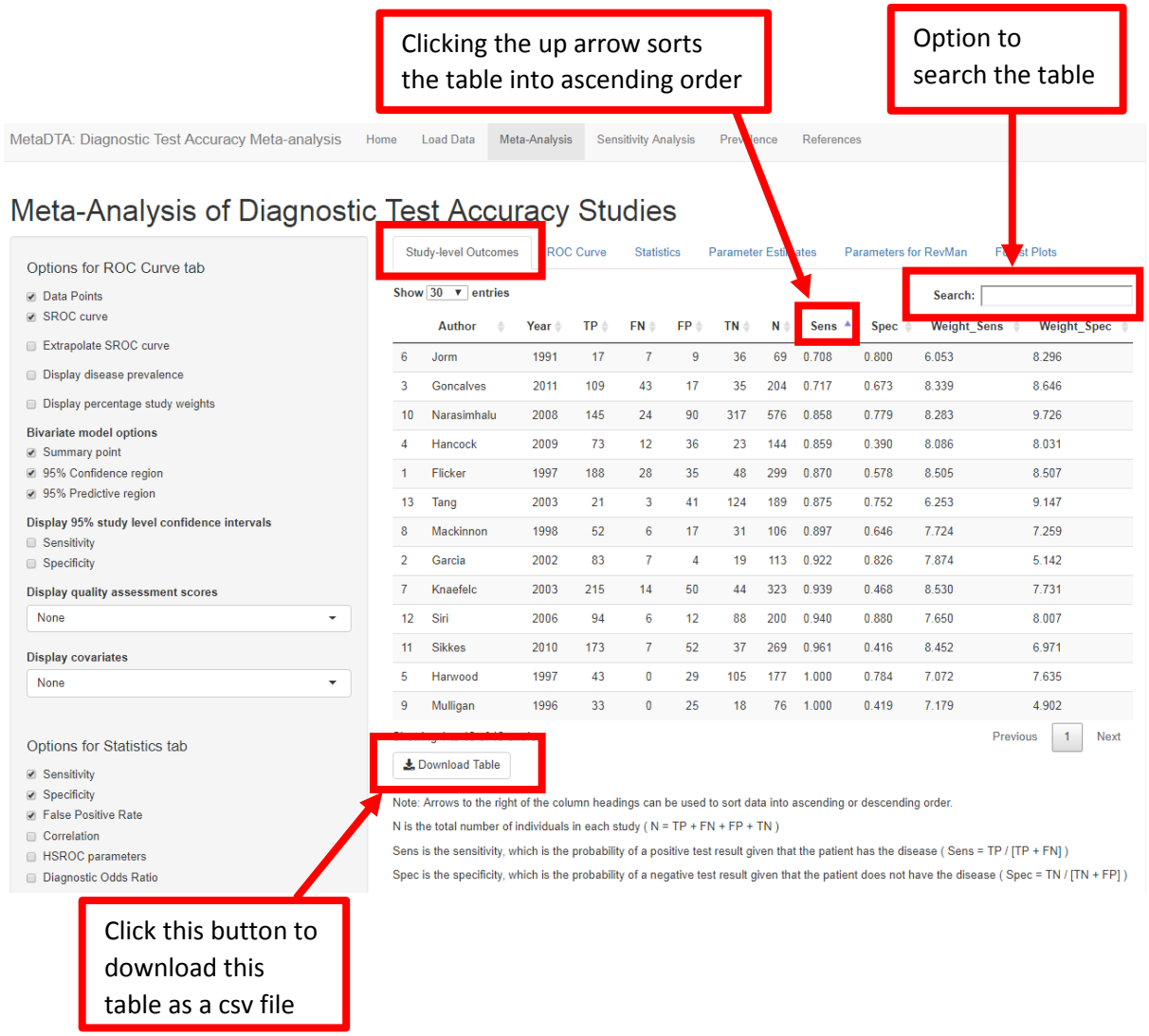


Figure 6: Meta-Analysis page showing the Study-level Outcomes tab and highlighting the options for sorting, searching and downloading the table

The `ROC Curve' tab displays the SROC for the dataset. Figure 7 shows the plot displayed by the default options. The default options are to display the individual study data points, the SROC curve, summary point, 95% confidence region and 95% predictive region. For more information on predictive regions see Riley et al.[8] The plot can be customised using the options within the grey box on the left hand side of the page.

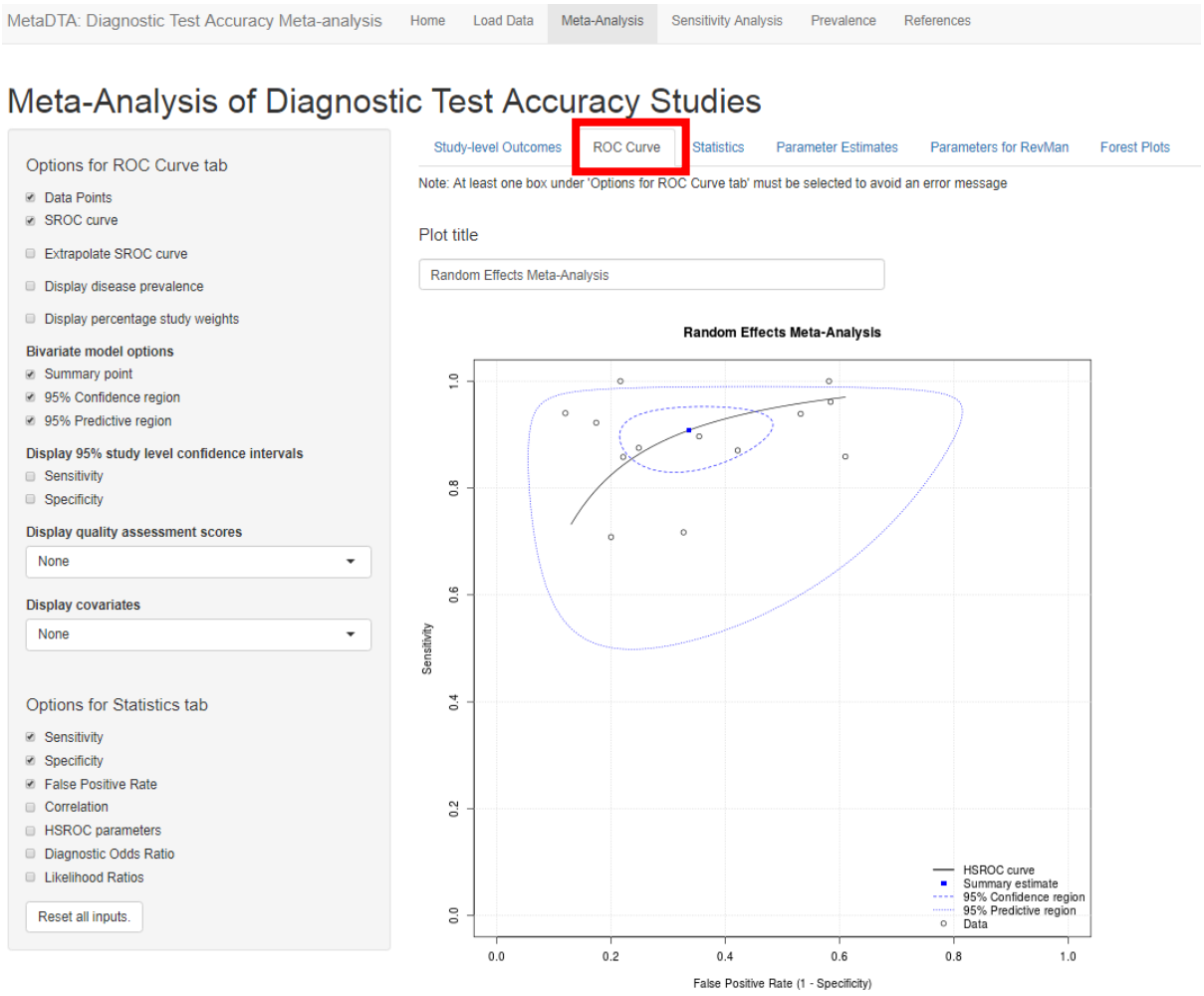


Figure 7: Screen shot of the default options displayed on the ROC Curve tab

Initially we may just want to consider the individual study estimates and their 95% confidence intervals for sensitivity and specificity. This can be achieved by de-selecting the bivariate model options and the SROC curve and selecting to display the study level confidence intervals, as in Figure 8. In both Figure 7 and Figure 8 we can clearly see the greater variation in specificity values across studies compared to sensitivity.

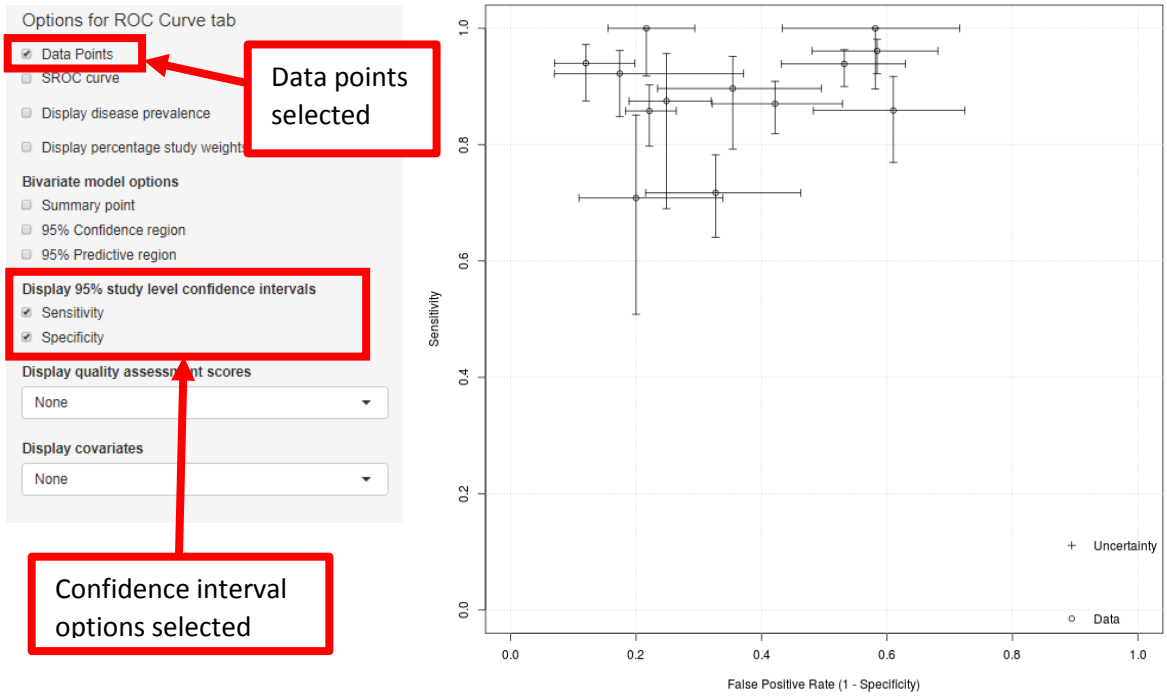


Figure 8: SROC plot displaying study estimates of sensitivity and specificity with 95% confidence intervals

Figure 9 is created by selecting the options `Display disease prevalence' and `Display percentage study weights'. The title of the plot is changed by typing into the box above the plot.

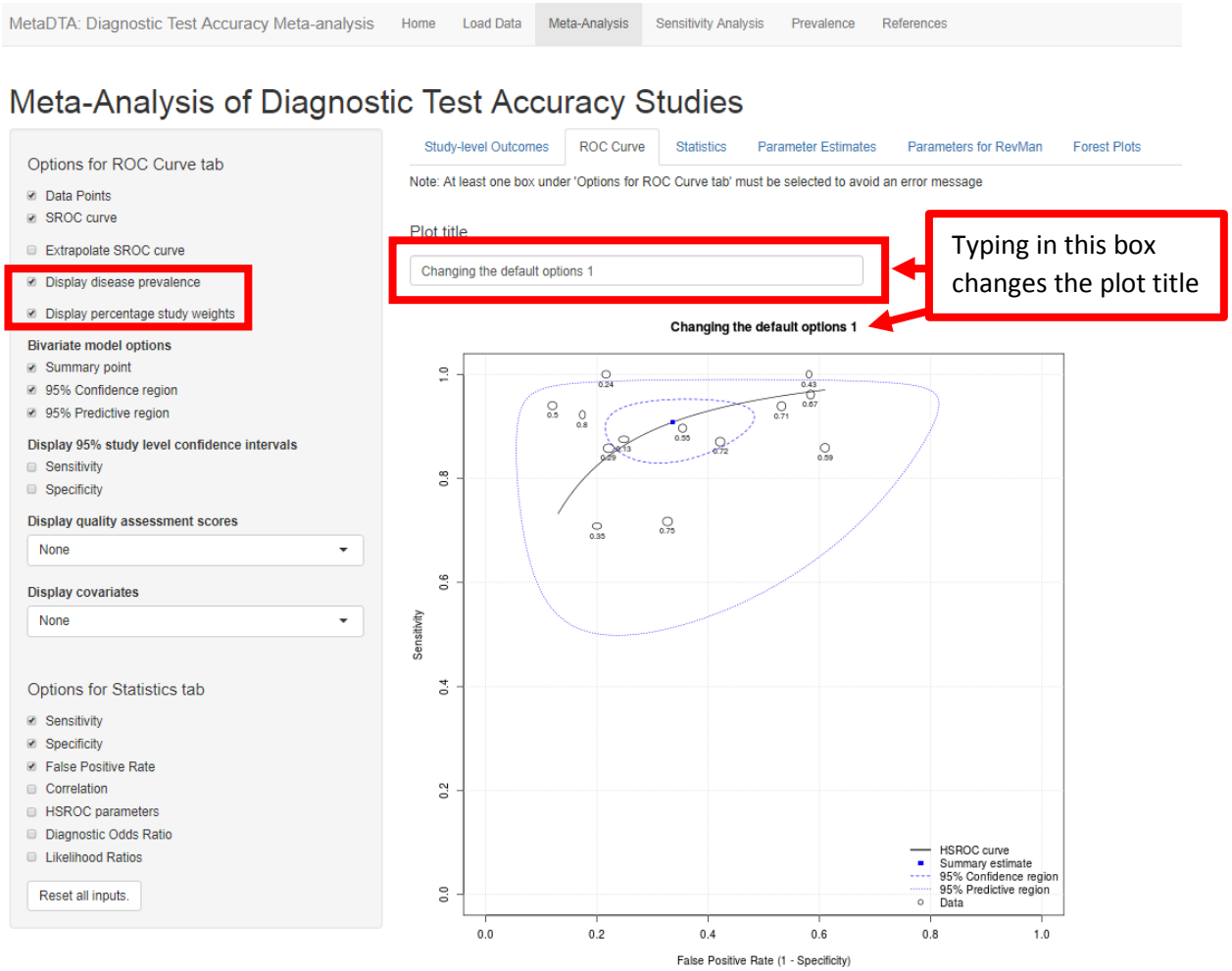


Figure 9: SROC plot displaying disease prevalence and percentage study weights and highlighting the option to change the plot title

Figure 10 is a zoomed in version of Figure 9. Here we can see that disease prevalence in the individual studies ranges from 13% to 80%. Displaying the percentage study weights shows that there is fairly equal weighting of sensitivity and specificity within each study.

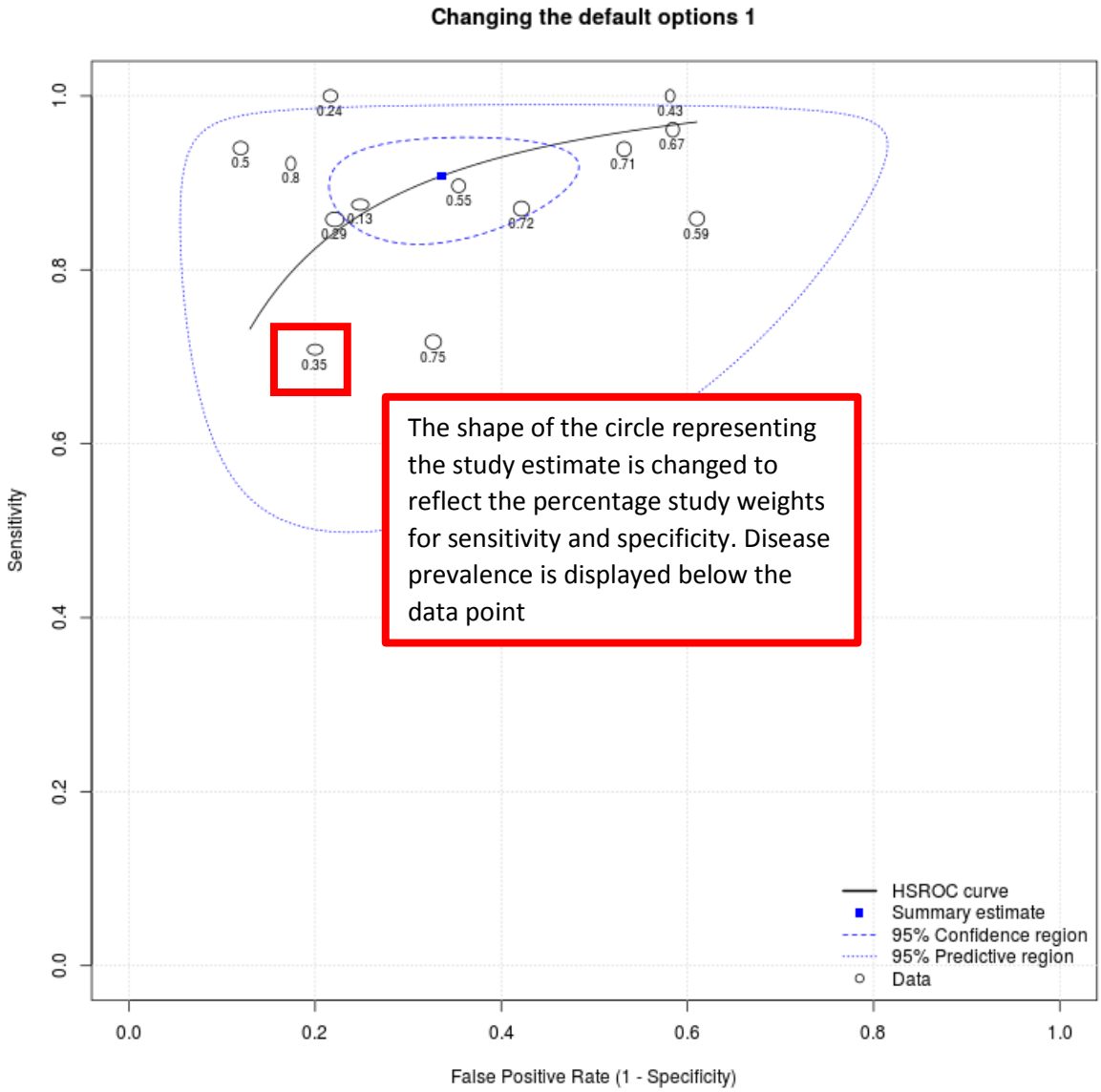


Figure 10: Zoomed in version of Figure 9 showing SROC plot with disease prevalence and percentage study weights

In the grey box on the left hand side under the heading `Display quality assessment scores' the drop down menu allows for the seven domains of QUADAS-2 to be incorporated into the SROC plot either individually or in combination. Selecting the options `Risk of bias (all)', `Applicability concerns (all)' or `Both risk of bias and applicability concerns' changes the data points into glyphs with four, three or seven segments respectively, representing the four risk of bias domains (Figure 11a), three applicability concerns domains (Figure 11b) or all seven QUADAS-2 domains (Figure 11c) respectively.

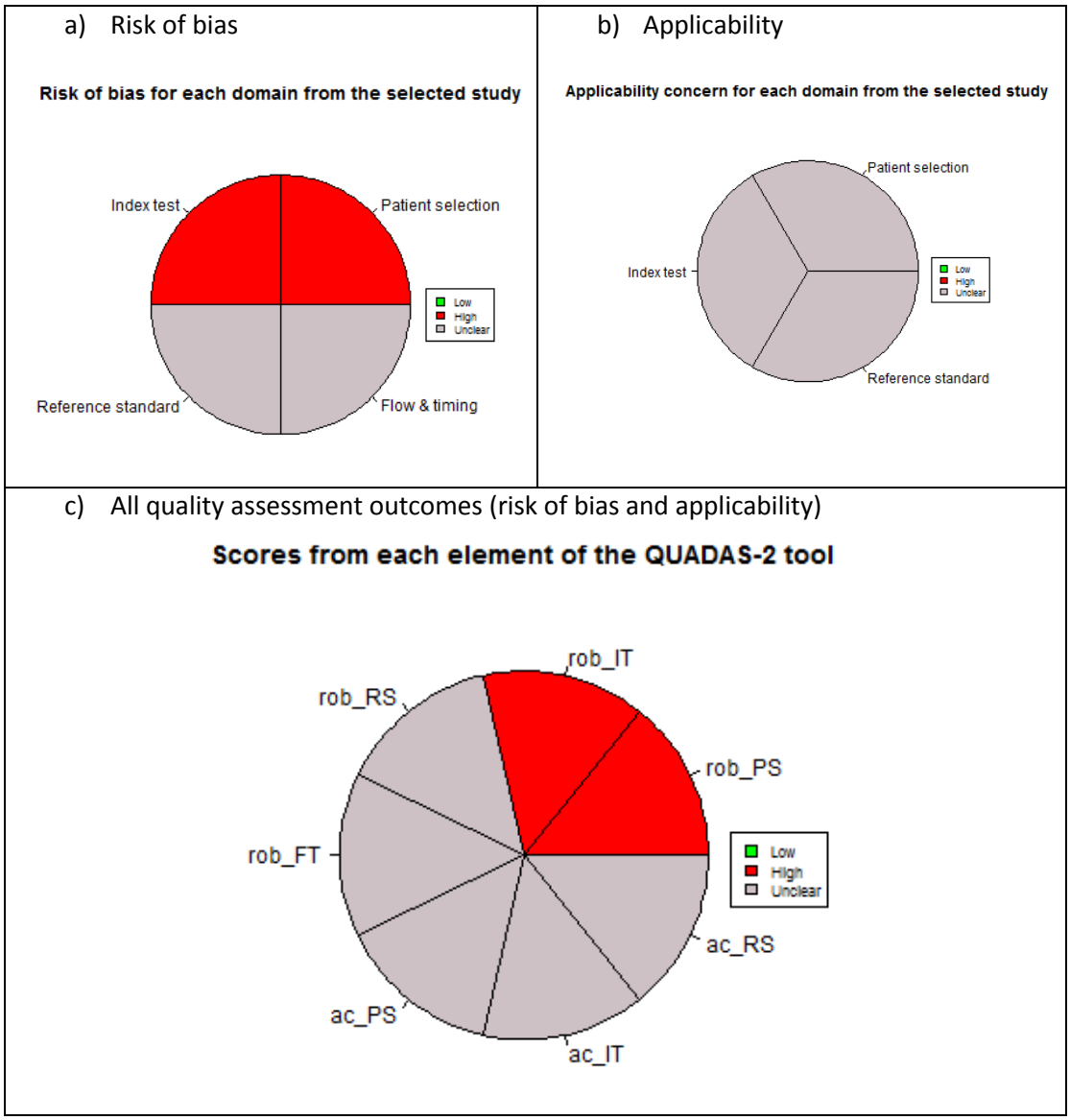


Figure 11: a) Glyph showing all four risk of bias domains for a specific study, b) Glyph displaying all three applicability concern domains for a specific study, c) Glyph displaying all seven QUADAS-2 domains for a specific study

In Figure 12 we can see that for the patient selection domain of the risk of bias assessment, five studies have low risk of bias, eight have high risk of bias and no studies have unclear risk of bias. By selecting `Both risk of bias and applicability concerns' we can see in Figure 13 that there are two studies for which all seven QUADAS-2 domains are either high or unclear risk of bias. We may choose to exclude these studies as a sensitivity analysis to assess their impact on the results.

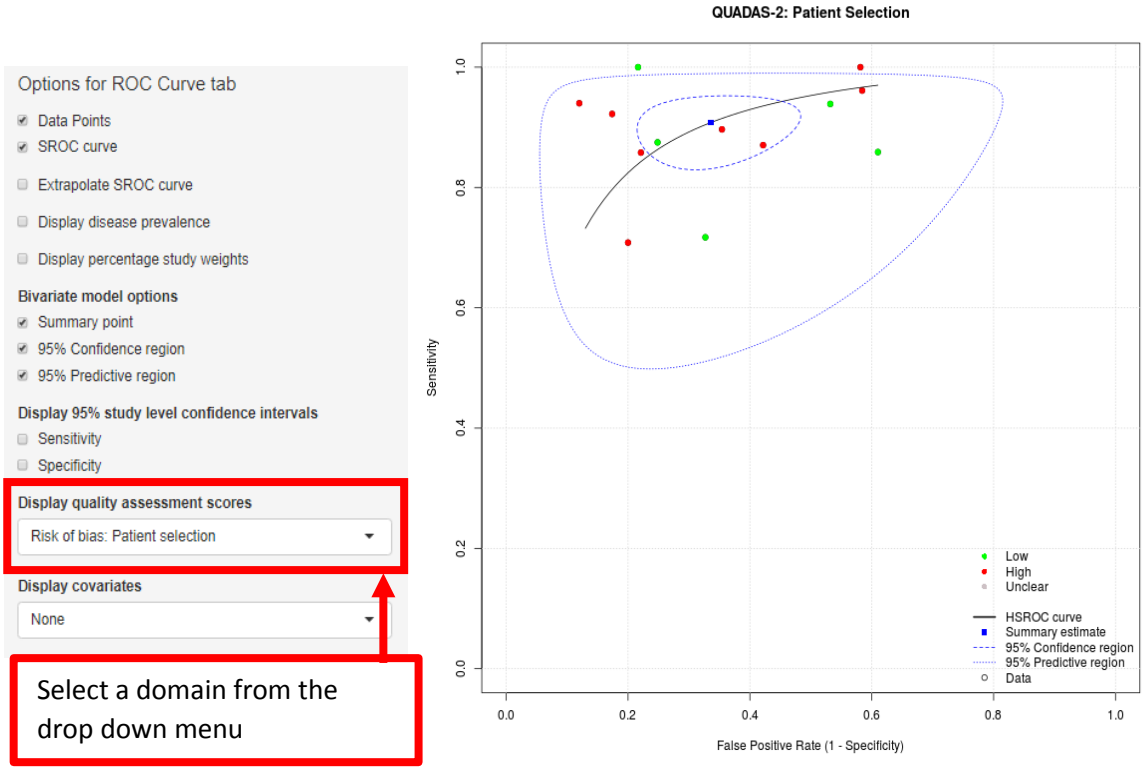


Figure 12: SROC plot displaying quality assessment results for the patient selection risk of bias domain from QUADAS-2

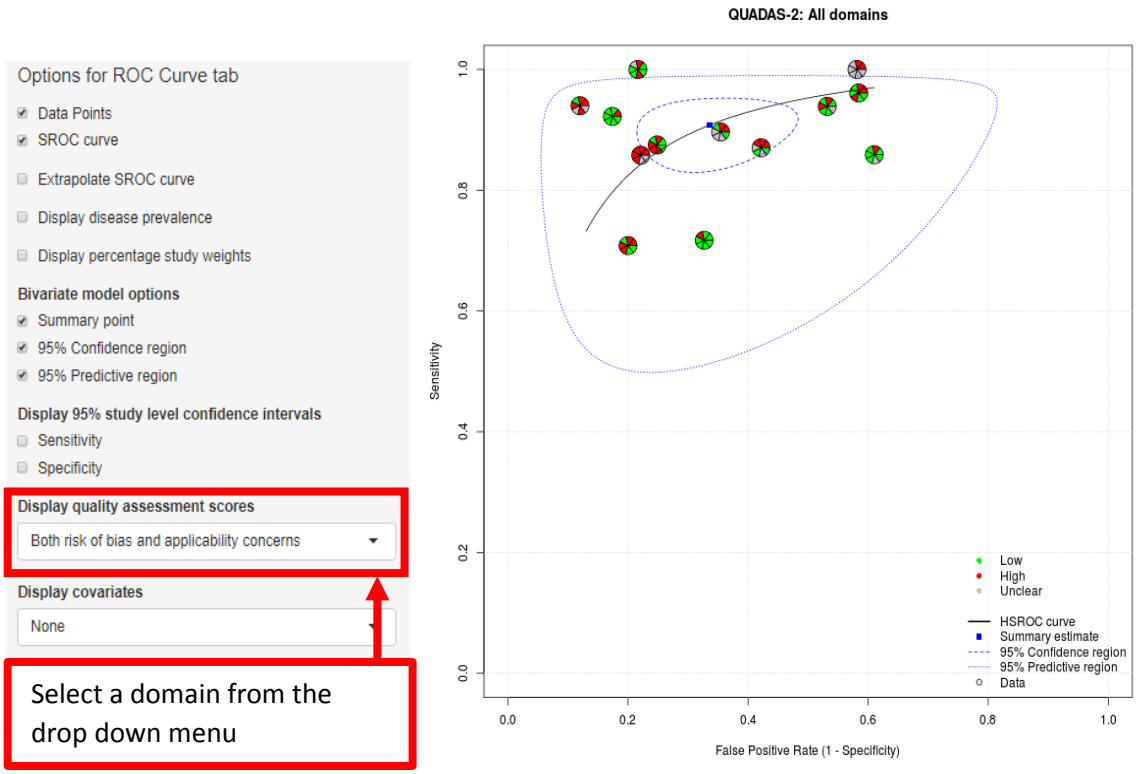


Figure 13: SROC plot displaying quality assessment results for all seven QUADAS-2 domains

Clicking on the middle of a data point displays the study name and estimates of sensitivity and specificity below the plot. If choosing the options `Risk of bias (all)', `Applicability concerns (all)' or `Both risk of bias and applicability concerns' from the display quality assessment scores menu then clicking on the middle of the glyph will display a larger version of the glyph below the plot alongside the study estimates of sensitivity and specificity (Figure 14).

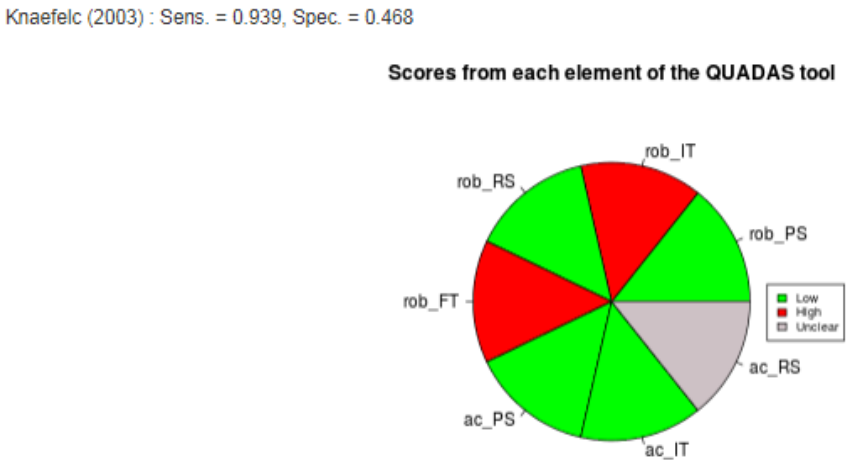


Figure 14: Glyph and study estimates of sensitivity and specificity which can be obtained by clicking the middle of a data point when the option `Both risk of bias and applicability concerns' is selected from the `Display quality assessment scores' menu

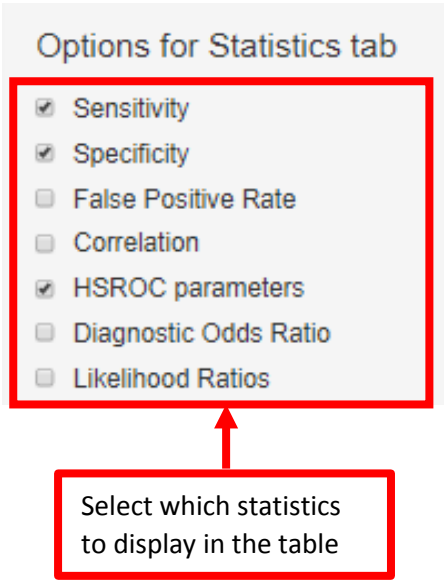
By clicking on the middle of the glyphs we can identify 'Mulligan' and 'Narasimhalu' as the two studies with high or unclear risk of bias for all seven QUADAS-2 domains.

The option `Display covariates' allows study-level covariate values to be displayed alongside the individual study estimate of sensitivity and specificity. The default option is to display this as text but alternative options include colouring the data points or doing both. In Figure 15 we have selected the covariate IQCODE from the drop down menu and chosen to display the values as both text and coloured points. In Figure 15 we can see that there is only one study with an IQCODE value of 32 so we may want to consider excluding this study in sensitivity analyses.

Figure 15: SROC plot displaying the IQCODE covariate with text next to the individual study data point and colouring the data points based on the IQCODE value

Additional options on this tab include the option, below the plot, to download the plots in png or pdf format. The examples shown above for customising SROC plots are not exhaustive and many permutations of options can be selected. We encourage the user to explore what is possible for themselves and their dataset.

The `Statistics' tab reports a number of different statistics which may be of interest when conducting a meta-analysis of diagnostic test accuracy studies. The statistics can be displayed by selecting the appropriate options in the grey box on the left hand side of the page. In Figure 16 we can see that the meta-analysis estimate of sensitivity is 90.8% (95% CI: 85.8%, 94.2%) and specificity is 66.4% (95% CI: 56.3%, 75.2%). Figure 16 also displays the HSROC parameters which are required to re-construct the SROC curve in software such as Cochrane Review Manager[9]. Other options include the false positive rate, correlation, diagnostic odds ratio and likelihood ratios.



Parameter	Estimate	2.5% CI	97.5% CI
Sensitivity	0.908	0.858	0.942
Specificity	0.664	0.563	0.752
θ	0.766		
λ	2.930		
β	-0.051		
σ_θ	0.350		
σ_α	0.877		
logit(sensitivity)	2.289	1.798	2.781
logit(specificity)	0.681	0.254	1.108

Figure 16: Selecting statistics to display on the Statistics tab

The `Parameter Estimates' tab displayed in Figure 17 shows parameter estimates from the bivariate normal distribution for mean sensitivity and specificity (on the logit scale) which may be useful for further modelling that requires an estimate of test performance with uncertainty.

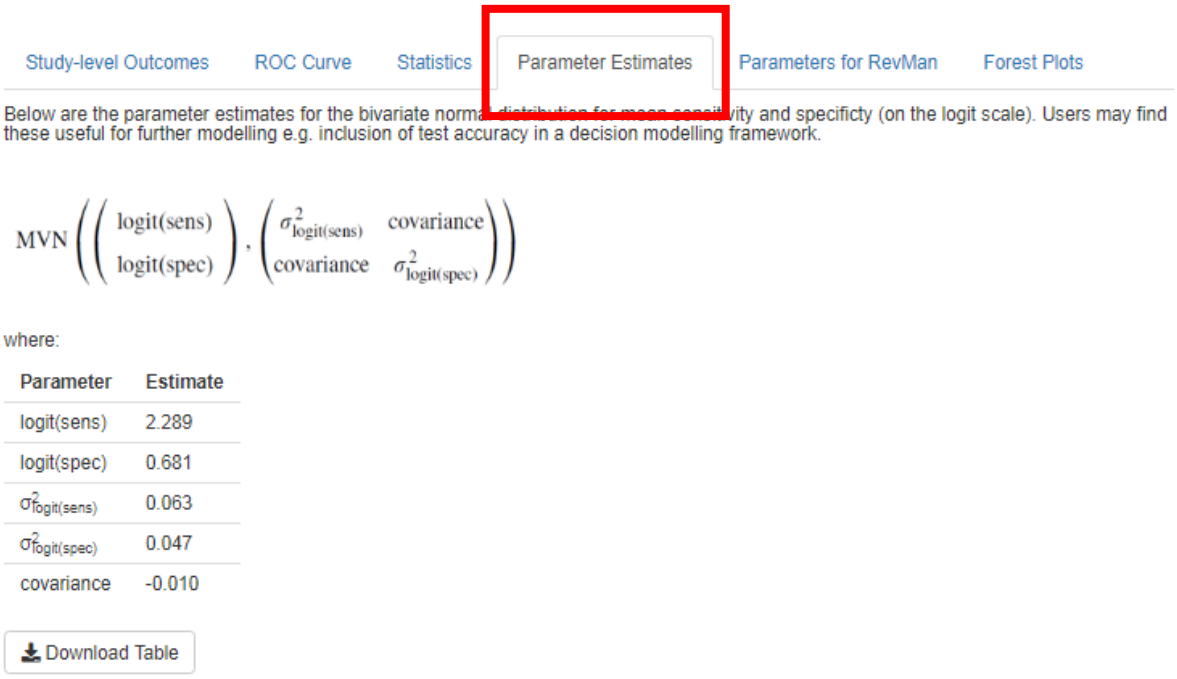


Figure 17: The parameter estimates tab

For users who wish to include the analysis results as part of a Cochrane review, the parameter values required by Cochrane's RevMan software to construct plots in the ROC space are presented in the `Parameters for RevMan' tab (Figure 18).

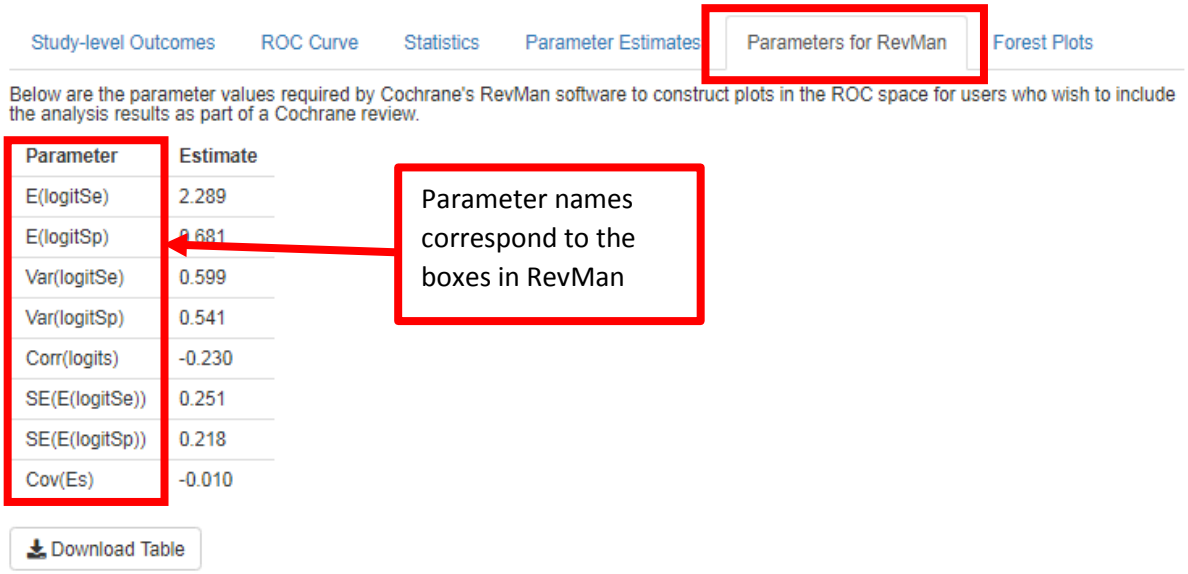


Figure 18: The parameters for RevMan tab

The `Forest Plots' tab displays separate forest plots of sensitivity and specificity estimates from individual studies (Figure 19). Each plot can be downloaded in png or pdf format.

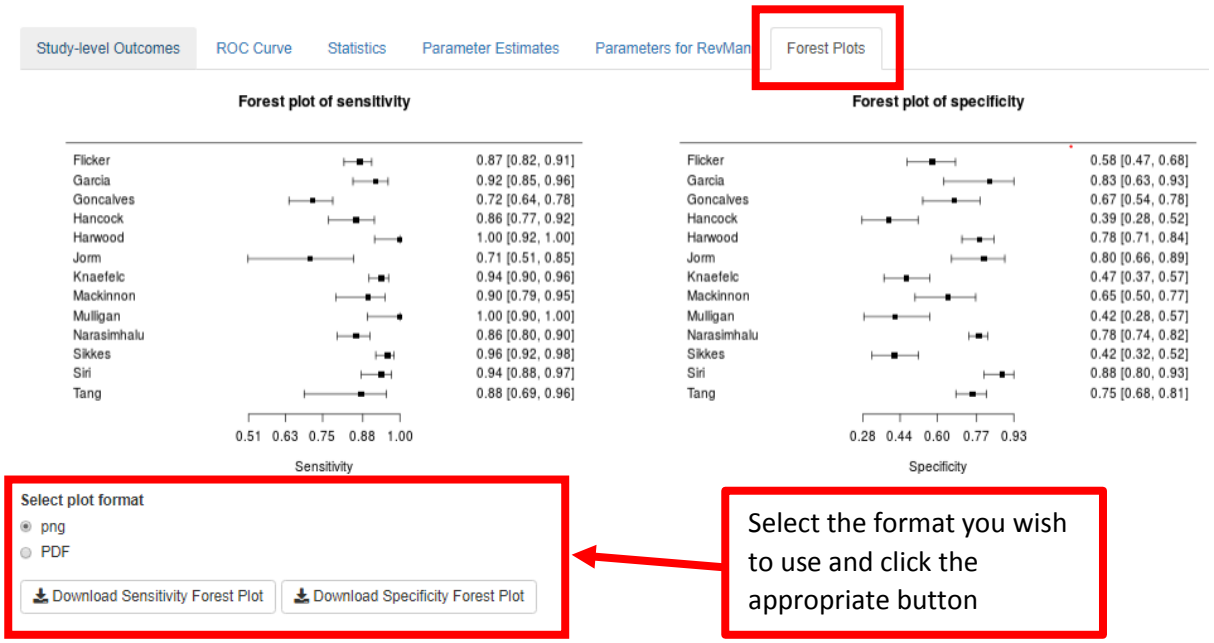


Figure 19: The forest plots tab highlighting the options for downloading the plots

5. Sensitivity Analysis

The purpose of sensitivity analysis is to explore the impact on results of assumptions you've made in the primary analysis. Earlier we identified two studies ('Mulligan' and 'Narasimhalu') which were at high or unclear risk of bias for all seven QUADAS-2 domains. In this section, we will conduct sensitivity analysis excluding these two studies to assess the impact of restricting the analysis to studies with better risk of bias ratings than these on our conclusions.

The Sensitivity Analysis page has the same layout as the Meta-Analysis page with one addition. At the bottom of the grey box on the left hand side you will find a list of all the studies included in the meta-analysis. To conduct sensitivity analyses by excluding studies click on the box next to the study name to exclude the study from the sensitivity analysis. For example, in Figure 20 we exclude the 'Mulligan' and 'Narasimhalu' studies which were identified to have high or unclear risk of bias for all 7 domains earlier.

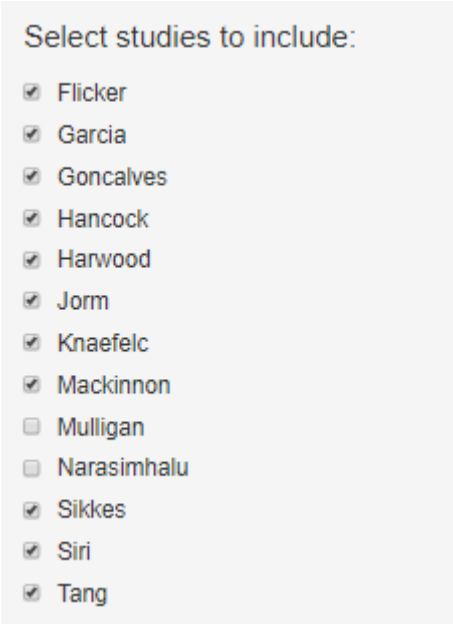


Figure 20: Selecting studies to include in sensitivity analyses

This grey box is important. Only the studies selected here will contribute to the analyses displayed within the five tabs on the Sensitivity Analysis page. For example, following the exclusion of the 'Mulligan' and 'Narasimhalu' studies, the table on the `Study-level Outcomes' tab now only includes 11 studies, Figure 21.

Show 30 entries Search:

	Author	Year	TP	FN	FP	TN	N	Sens	Spec	Weight_Sens	Weight_Spec
1	Flicker	1997	188	28	35	48	299	0.870	0.578	10.074	10.013
2	Garcia	2002	83	7	4	19	113	0.922	0.826	9.303	5.864
3	Goncalves	2011	109	43	17	35	204	0.717	0.673	9.880	10.177
4	Hancock	2009	73	12	36	23	144	0.859	0.390	9.568	9.466
5	Harwood	1997	43	0	29	105	177	1.000	0.784	8.340	8.872
6	Jorm	1991	17	7	9	36	69	0.708	0.800	7.177	9.710
7	Knaefelc	2003	215	14	50	44	323	0.939	0.468	10.103	9.086
8	Mackinnon	1998	52	6	17	31	106	0.897	0.646	9.135	8.486
9	Sikkes	2010	173	7	52	37	269	0.961	0.416	10.010	8.220
10	Siri	2006	94	6	12	88	200	0.940	0.880	9.033	9.313
11	Tang	2003	21	3	41	124	189	0.875	0.752	7.377	10.794

Showing 1 to 11 of 11 entries Previous 1 Next

Download Table

Note: This table only includes studies selected in the sidebar.

N is the total number of individuals in each study (N = TP + FN + FP + TN).

Sens is the sensitivity, which is the probability of a positive test result given that the patient has the disease (Sens = TP / [TP + FN]).

Spec is the specificity, which is the probability of a negative test result given that the patient does not have the disease (Spec = TN / [TN + FP]).

Weight_Sens is the precentage study weight of sensitvitiy, calculated using methods by Burke et al.

Weight_Spec is the percentage study weight of sensitivity, calculated using methods by Burke et al.

Figure 21: The Study-level outcomes table for the sensitivity analysis excluding the Mulligan and Narasimhalu studies

On the Sensitivity Analysis page there is an additional option in the grey box under `Options for ROC Curve tab' that asks you to select which model results to display. In Figure 22 both the original model and the sensitivity analysis model results are displayed. The sensitivity analysis is presented in black and blue in the foreground with the original model displayed in grey in the background. Here, we can see that excluding the two studies has had little effect on changing the meta-analysis estimates of sensitivity and specificity or the SROC curve itself. However, both the confidence and predictive regions are slightly larger reflecting the smaller amount of evidence in the analysis.

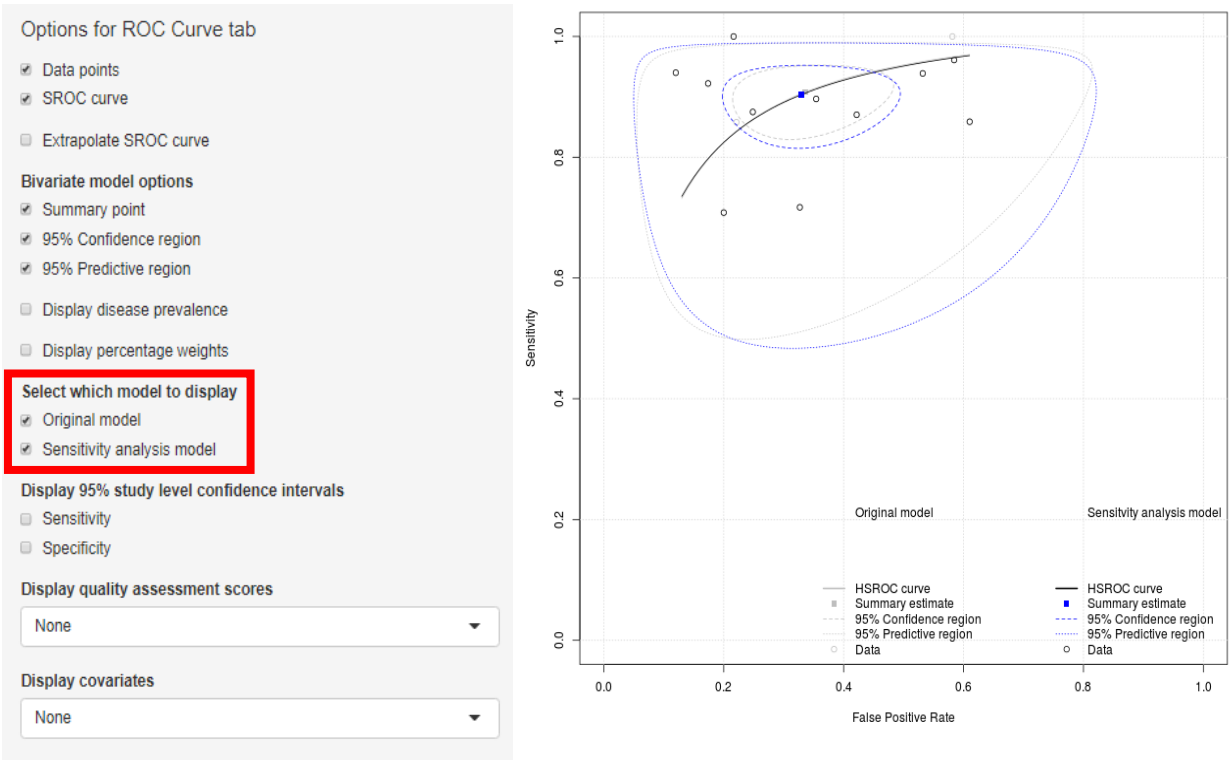


Figure 22: SROC plot displaying both the original model and the sensitivity analysis model

Alternatively, we may wish to only display the sensitivity analysis model, as in Figure 23.

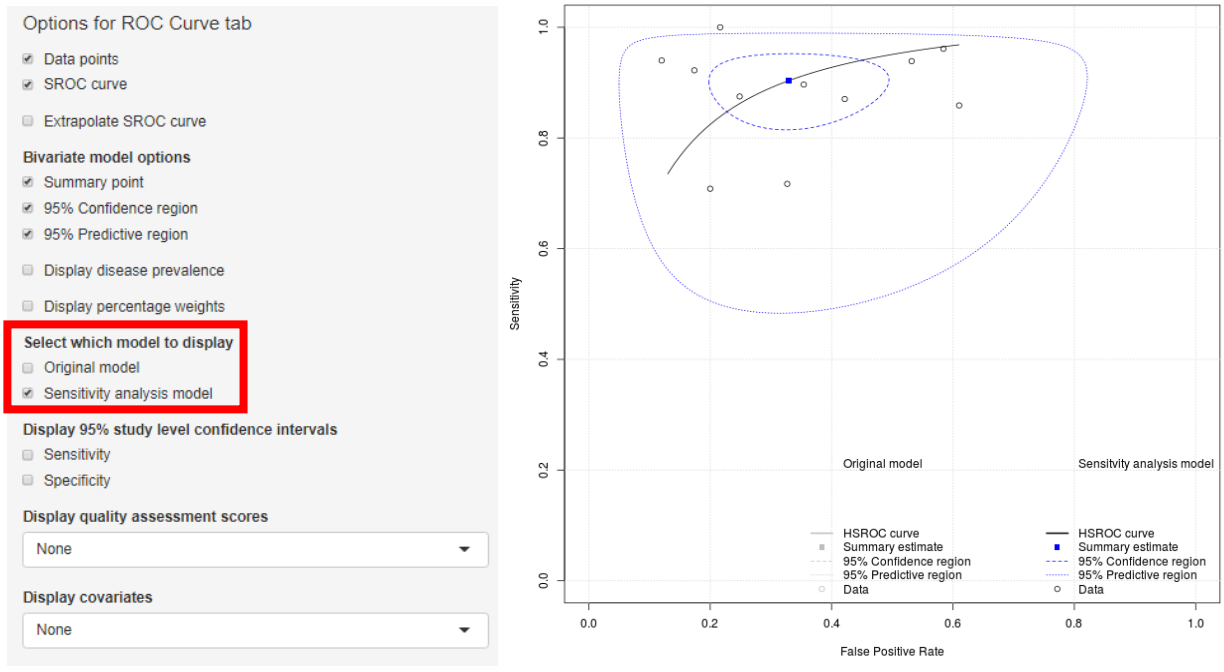


Figure 23: SROC plot displaying the sensitivity analysis model only

All the options available on the Meta-Analysis page for customising the SROC plot are also available on the Sensitivity Analysis page and work in the same way as described in Section 4.

The `Statistics' tab now contains two tables. The top table contains the meta-analysis results from all of the studies in the dataset whilst the bottom table contains the meta-analysis results from the sensitivity analysis model (Figure 24). Here we can see that the exclusion of the 'Mulligan' and 'Narasimhalu' studies has had very little effect on sensitivity and specificity, changing the mean sensitivity from 90.8% to 90.4% and the mean specificity from 66.4% to 67.1%.

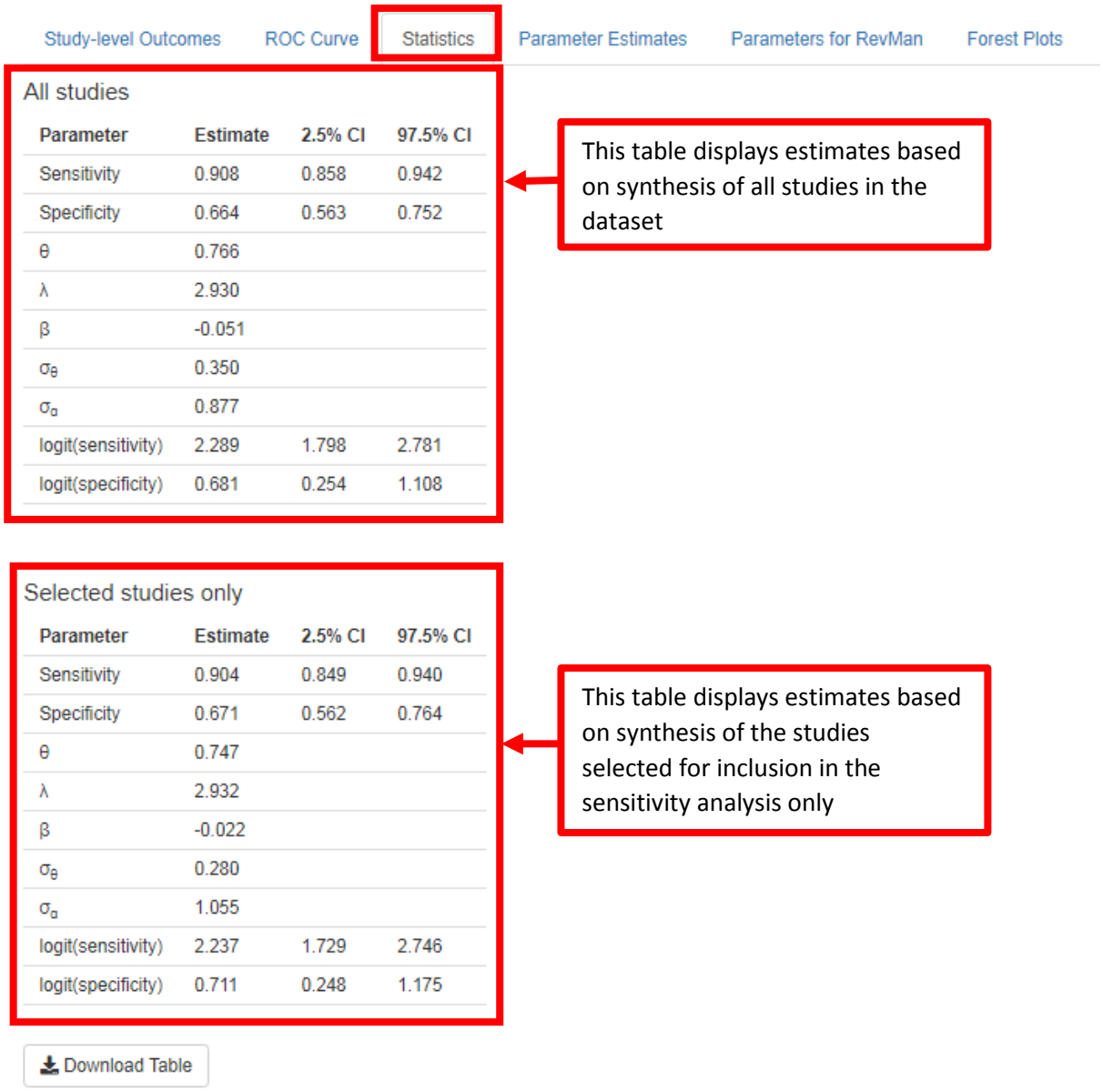


Figure 24: Statistics tab for sensitivity analysis

The `Parameter Estimates', `Parameters for RevMan' and `Forest Plot' tabs all work in the same way on the Sensitivity Analysis page as they do on the Meta-Analysis page.

6. Prevalence

The Prevalence page predicts how many patients in practice you would expect to have true positive, false positive, true negative and false negative results for a given disease prevalence based on the meta-analysis results and helps to give the results some clinical context. The page consists of two tabs: Meta-analysis and Sensitivity analysis. The Meta-analysis tab uses the meta-analysis results from synthesising all studies in the dataset. The Sensitivity analysis tab uses the meta-analysis results from the sensitivity analysis model including only selected studies. The default prevalence is set as the mean value of prevalence across all the studies in the meta-analysis. The default number of patients is set as 1000. Both of these options can be changed using the options in the grey box on the left hand side of the page (Figure 25).

In Figure 25 we can see that with 1000 patients and a disease prevalence of 52% we would expect 633 patients to test positive for the disease, 472 of these will be true positives and 161 false positives, and 367 patients to test negative for the disease, 319 of these will be true negatives and 48 false negatives. Figure 25 also displays the 95% confidence intervals around these estimates reflecting the uncertainty in the estimation of the diagnostic test in the meta-analysis.

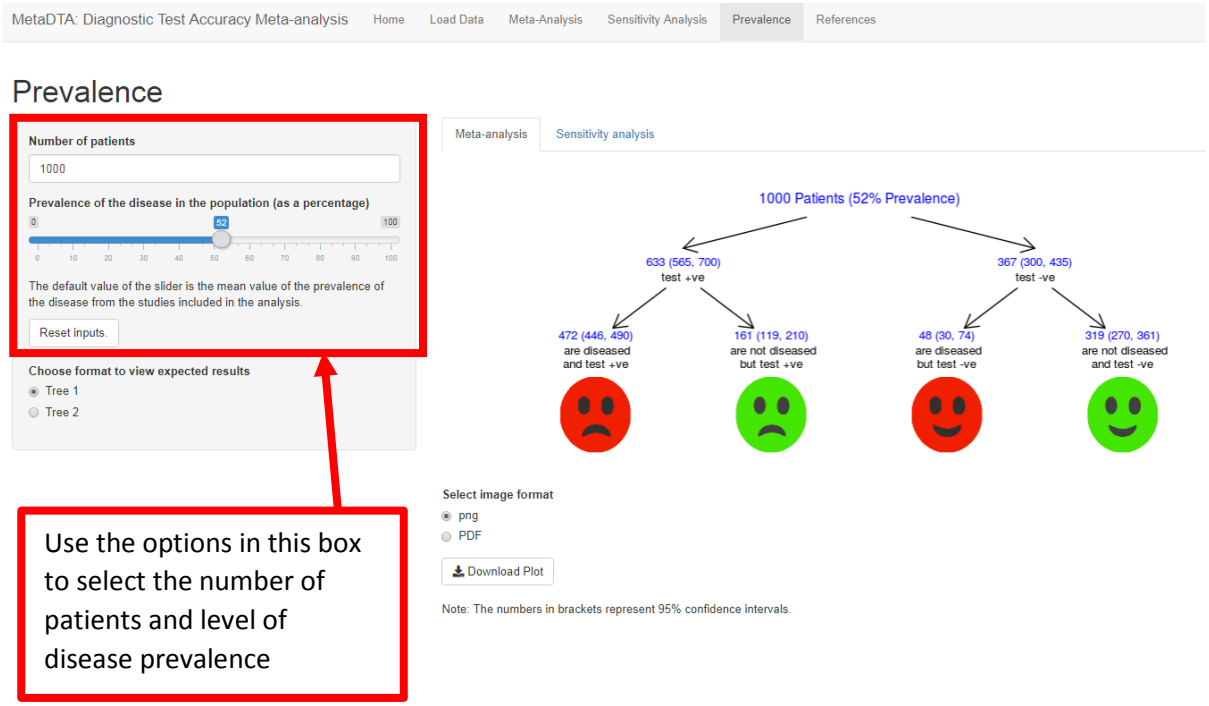


Figure 25: The Meta-analysis tab on the Prevalence page highlighting the options for changing the number of patients and prevalence in the plot

Figure 25 initially splits patients by test result followed by disease status. However if we select `Tree 2' in the grey box on the left hand side then we can divide patients by disease status first and then test result (Figure 26).

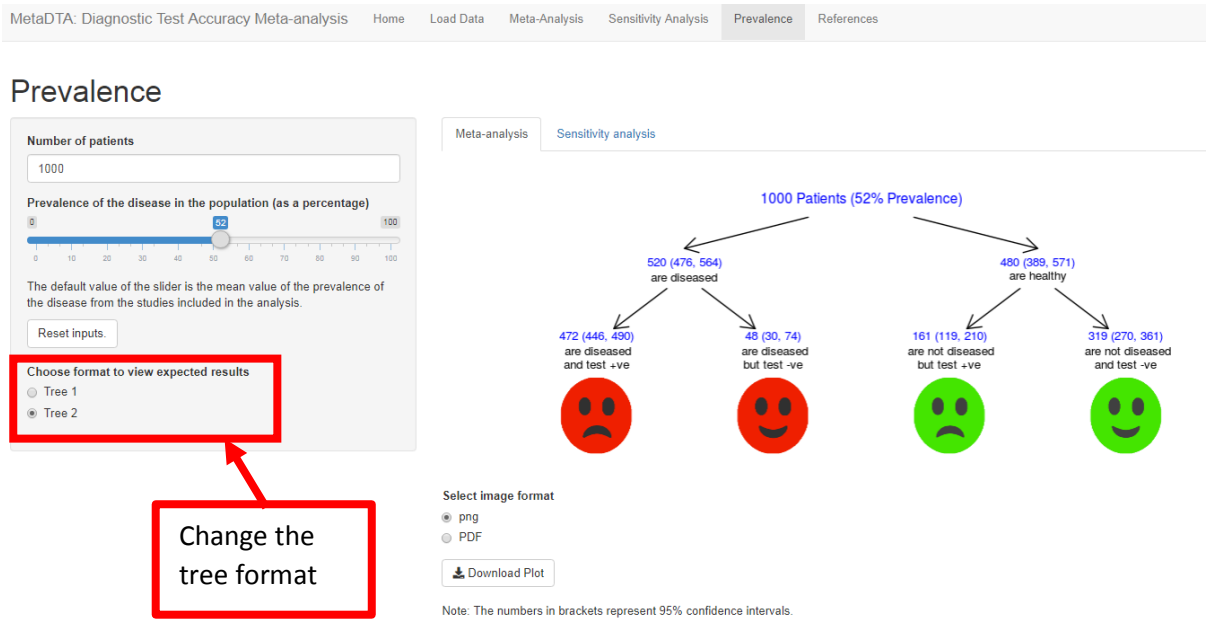


Figure 26: The Meta-analysis tab on the Prevalence page highlighting the option to change the plot format

The prevalence of disease can easily be changed using the slider in the grey box. For example, if we change the prevalence value to the median across all studies, 59%, then we see that the number of patients expected to test positive increases to 674, the number of true positive patients increase to 536 and the number of false negative patients reduces to 138 (Figure 27).

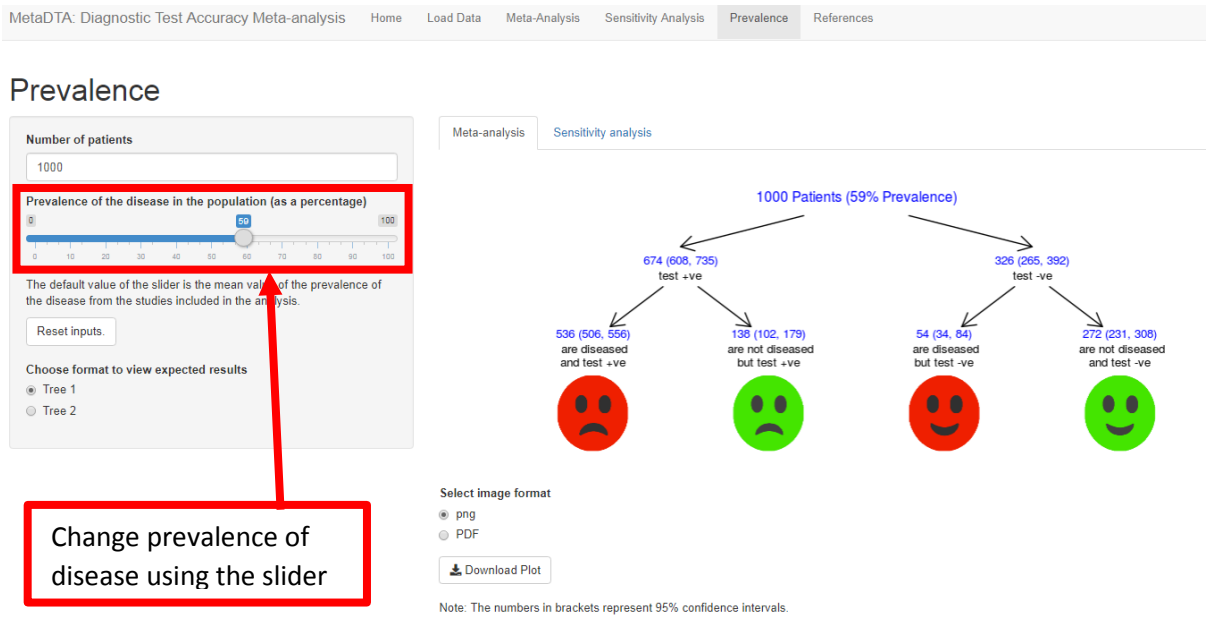


Figure 27: The Meta-analysis tab on the Prevalence page highlighting the option to change the disease prevalence

On the Prevalence page, the `Sensitivity analysis' tab works in the same way as the `Meta-analysis' tab. However, it only includes the studies selected in the grey box on the left hand side of the Sensitivity Analysis page (Section 5, Figure 20) to estimate the test performance. In Figure 28, we can see that after excluding the 'Mulligan' and 'Narasimhalu' studies there is little change in the prediction of the number of patients with true positive, false positive, true negative and false negative results.

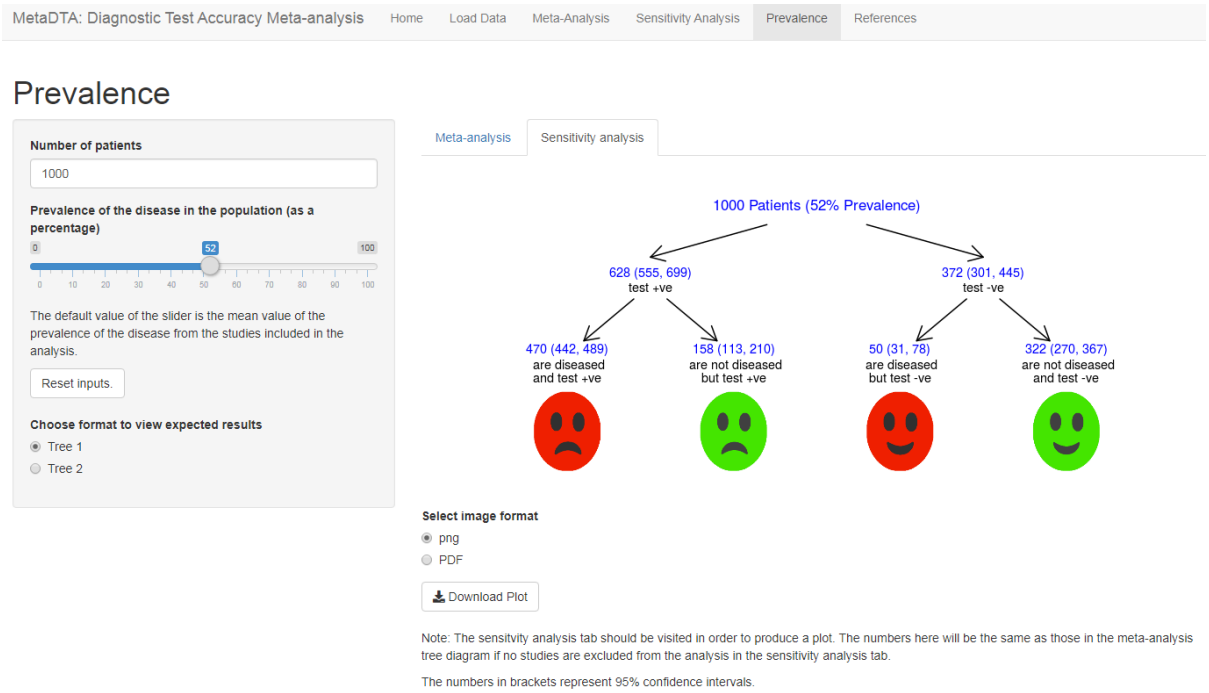


Figure 28: The Sensitivity analysis tab on the prevalence page

7. References

The References page contains a list of references for the methodology implemented in MetaDTA as well as the R software packages used to develop MetaDTA (Figure 29).

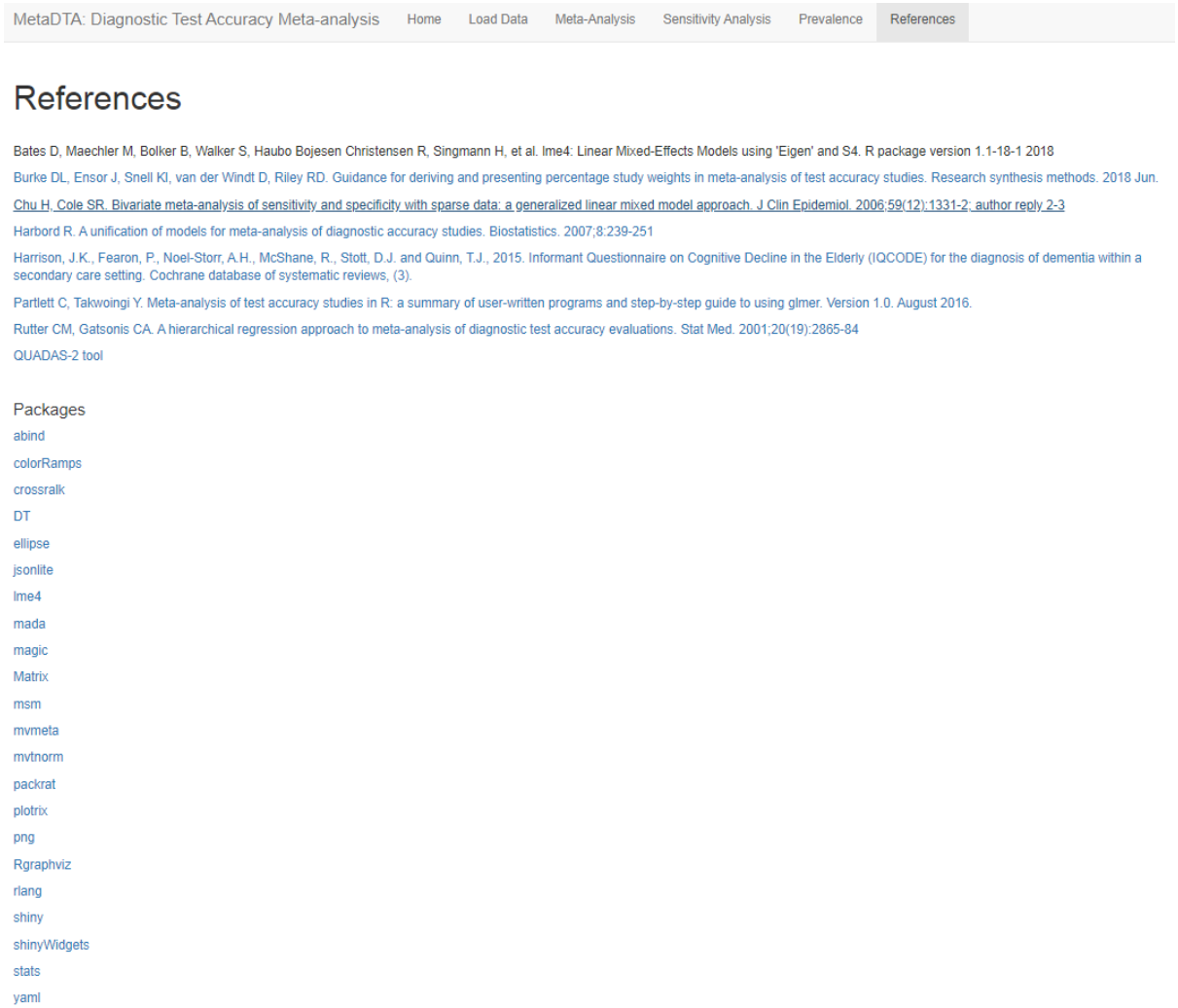


Figure 29: Screen shot of the References page

8. Bibliography

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