METAGRAPHITI BY STATA

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Ann Arbor, Michigan

METAGRAPHITI

Statistical Graphics For Interpretation, Exploration And Presentation Of Meta-analysis Data

METAGRAPHITI BY STATA

VISUOGRAPHIC FRAMEWORK FOR USING STATA FOR:

- Testing and correcting for publication bias
- Investigating heterogeneity
- Summary of Data and Sensitivity Analyses

METAGRAPHITI

- Avoid potential misrepresentation by faulty distributional and other statistical assumptions.

- Facilitates greater interaction between the researcher and the data by highlighting interesting and unusual aspects of the quantitative data.

METAGRAPHITI

- User-friendlier summaries of large, complicated quantitative data sets.
- Preliminary exploration before definite data synthesis.
- Effective emphasis of important features rather than details of data.

CONTINGENCY TABLE FOR EXTRACTION OF DATA

		Target condition (reference test result)		
		Present	Absent	Totals
Index test result	Abnormal	a	b	a+b
	Normal	c	d	c+d
	Totals	a+c	b+d	a+b+c+d

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive Predictive value= a/(a+b)
Negative predictive value =d/(c+d)
Likelihood ratio abnormal test= Sensitivity/(1-Specificity)
Likelihood ratio normal test = (1-Sensitivity)/Specificity
Diagnostic Odds Ratio =(a×d)/(c×b)

DIAGNOSTIC VS. TREATMENT TRIAL

- True Positives =Experimental Group With the Monitored Outcome Present (a).
- False Positives = Control Group With the Outcome Present (b).
- False Negatives=Experimental Group With the Outcome Absent (c).
- True Negatives= Control Group With the Outcome Absent (d).

DIAGNOSTIC VS. TREATMENT TRIAL

- The Expression for the Odds Ratio (OR) =(a x d)/(b x c).
- Relative risk in experimental group {[a/(a + c)]/[b/(b+ d)]} =Likelihood Ratio for a Positive Test.
- Relative Risk in Control Group = Likelihood Ratio for a Negative Test.

EXPLORING PUBLICATION BIAS

- Published studies do not represent all studies on a specific topic.
- Trend towards publishing statistically significant ($p < 0.05$) or clinically relevant results.
- Publication bias assessed by examining asymmetry of funnel plots of estimates of odds ratios vs. precision.

EXPLORING PUBLICATION BIAS

- Funnel plot
- Begg's rank correlation plot
- Egger's regression plot
- Harbord's modified radial plot

FUNNEL PLOT

- A funnel diagram (a.k.a. funnel plot, funnel graph, bias plot):

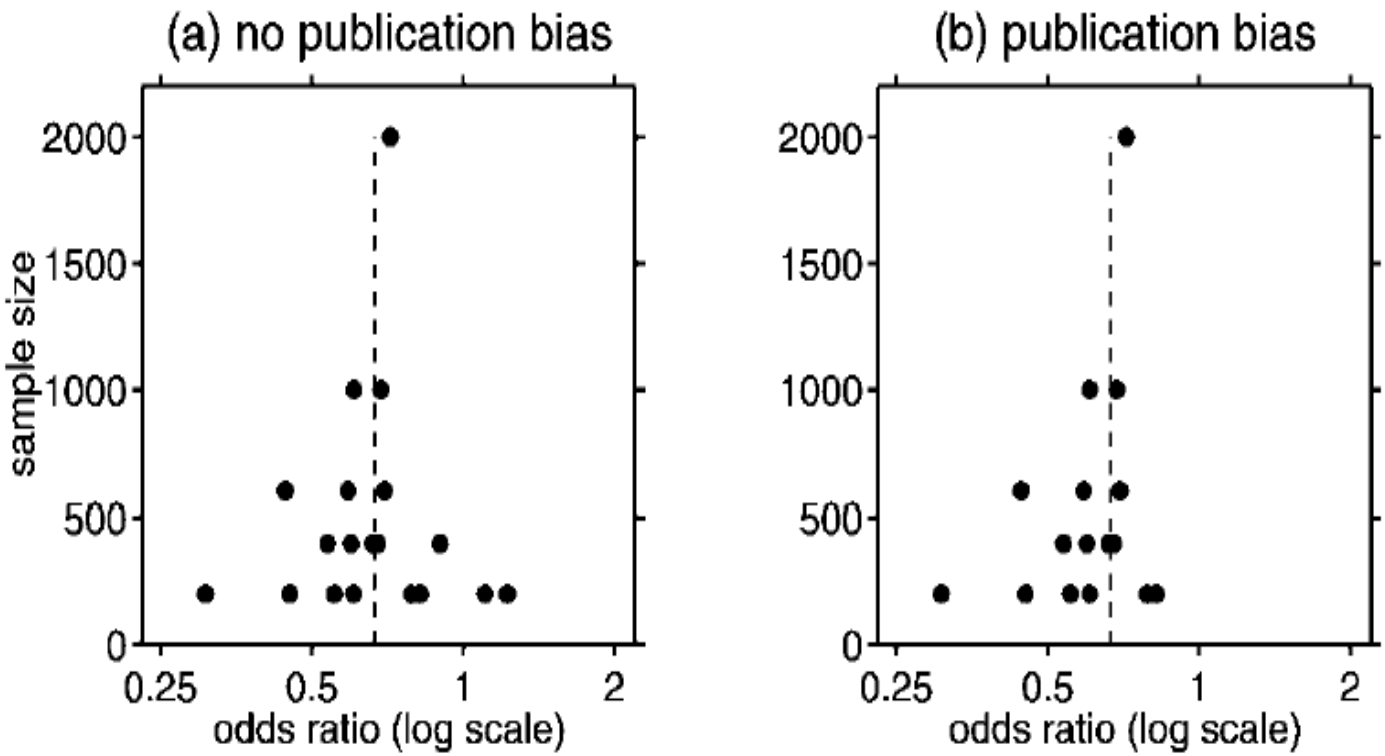
- Special type of scatter plot with an estimate of sample size on one axis vs. effect-size estimate on the other axis

FUNNEL PLOT

- Based on statistical principle that sampling error decreases as sample size increases

- Used to search for publication bias and to test whether all studies come from a single population

FUNNEL PLOTS

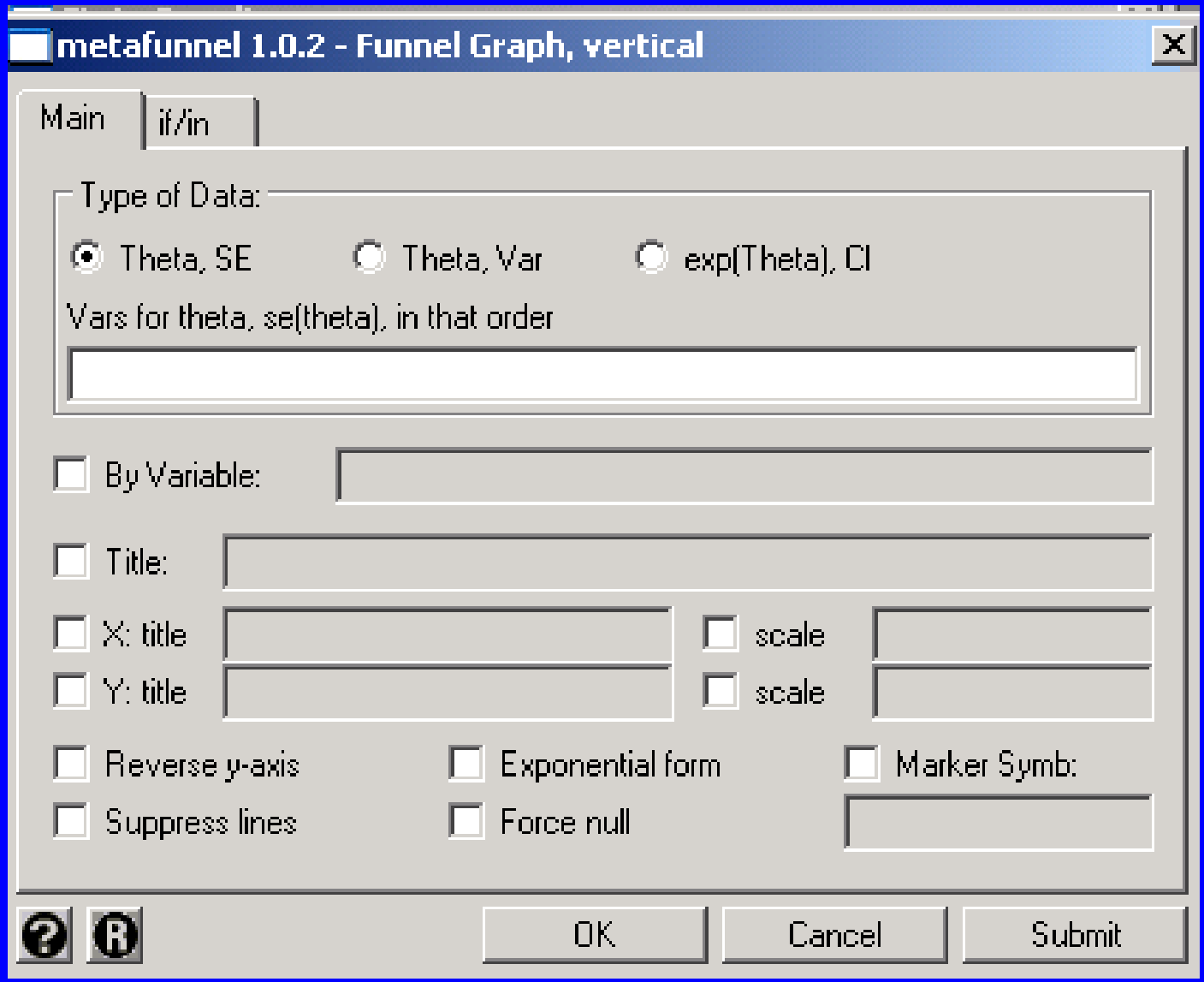


FUNNEL PLOTS

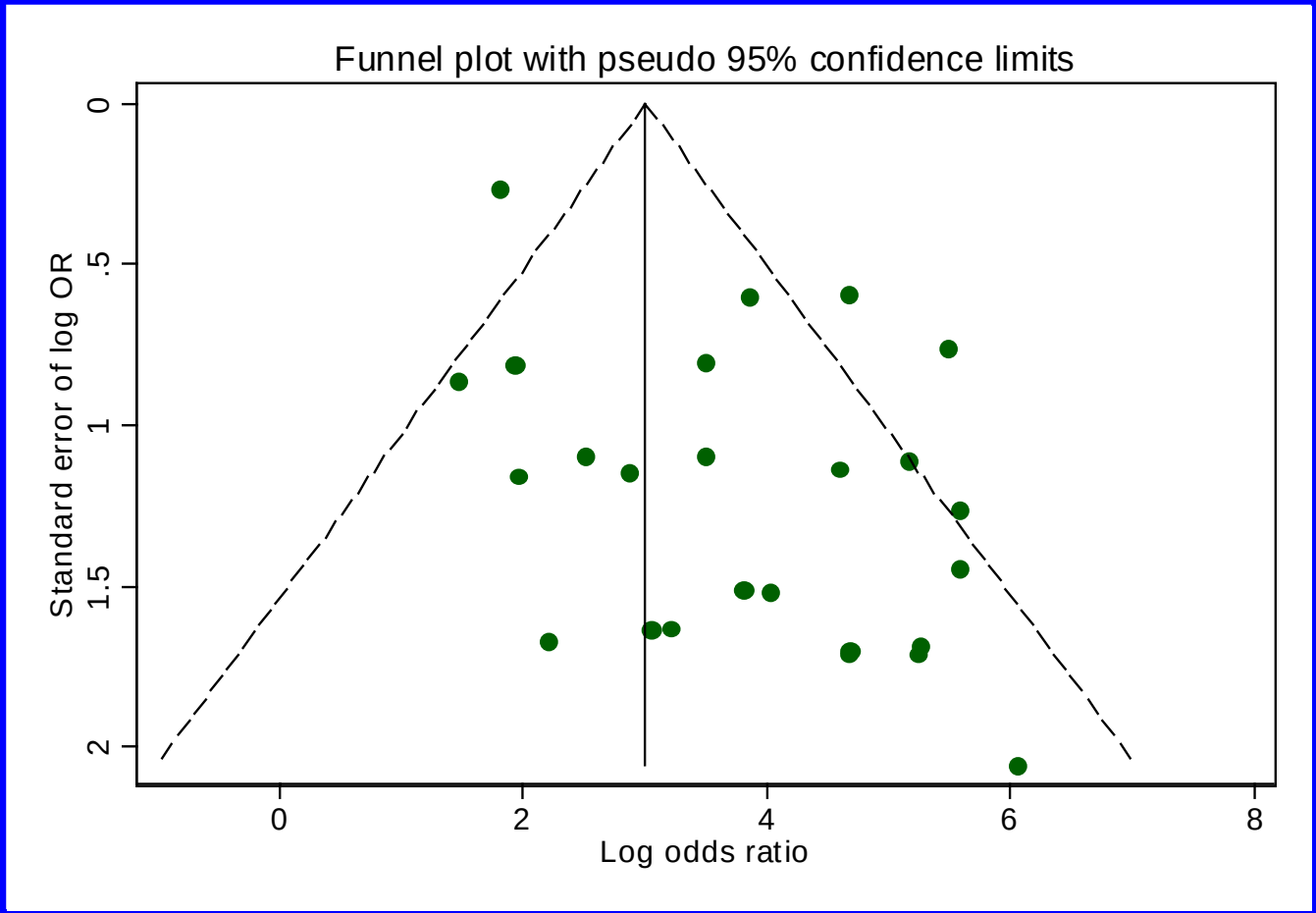
STATA SYNTAX/COMMAND

- metafunnel ldor seldor, xlab(0(2)8) xtitle (Log odds ratio) ytitle(Standard error of log OR) saving(zfunnel, replace)

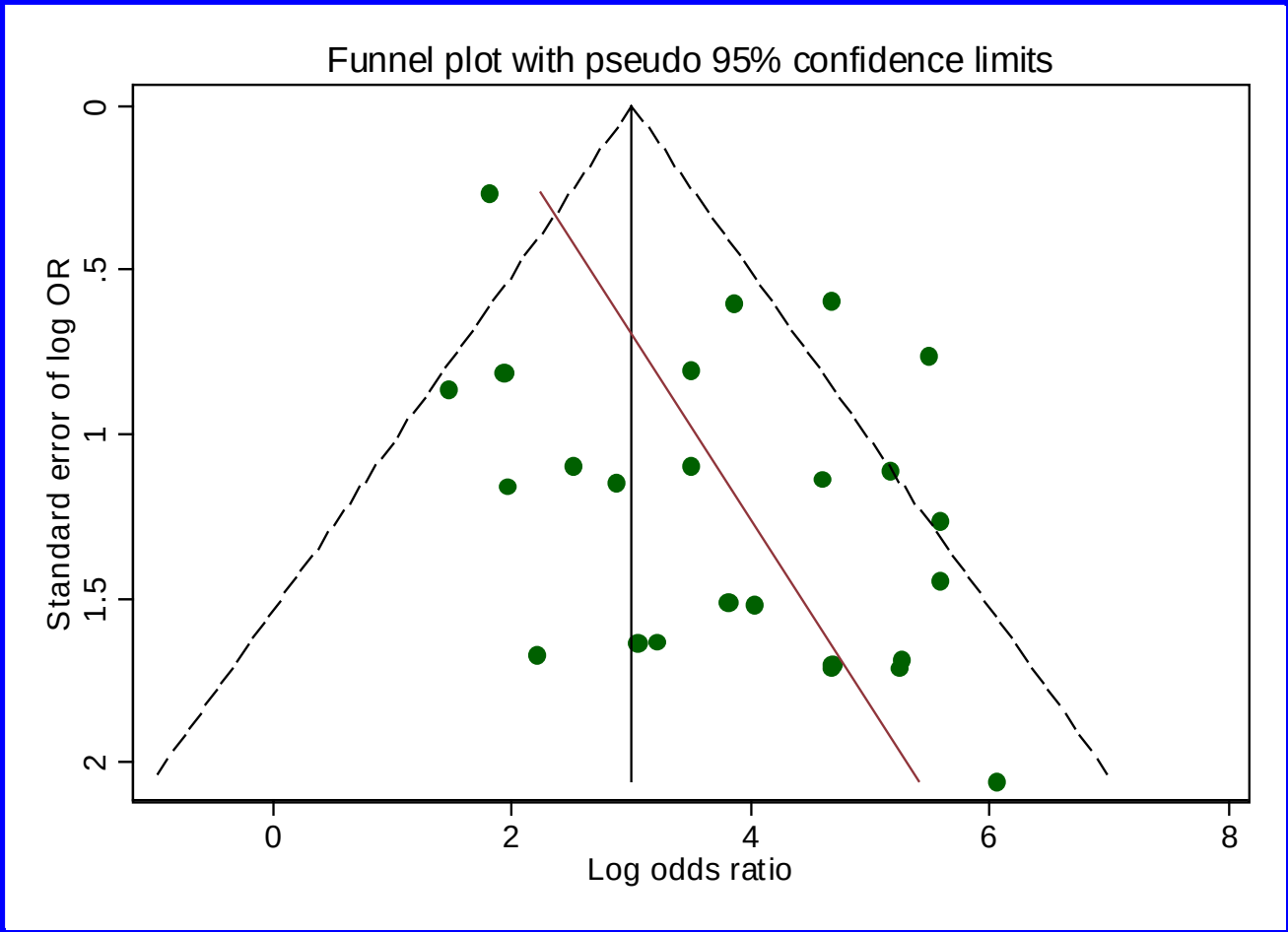
- metafunnel ldor seldor, xlab(0(2)8) xtitle(Log odds ratio) ytitle (Standard error of log OR) egger saving (eggerfunnel, replace)


metafunnel 1.0.2 - Funnel Graph, vertical
Main
if/in
Type of Data:
Theta, SE
Theta, Var
exp(Theta), CI
Vars for theta, se(theta), in that order
By Variable:
Title:
X: title
scale
Y: title
scale
Reverse y-axis
Exponential form
Marker Symb:
Suppress lines
Force null
OK
Cancel
Submit

FUNNEL PLOT


Funnel plot with pseudo 95% confidence limits
Standard error of log OR
0
.5
1
1.5
2
0
2
4
6
8
Log odds ratio

FUNNEL PLOT


Funnel plot with pseudo 95% confidence limits
Standard error of log OR
0
.5
1
1.5
2
0
2
4
6
8
Log odds ratio

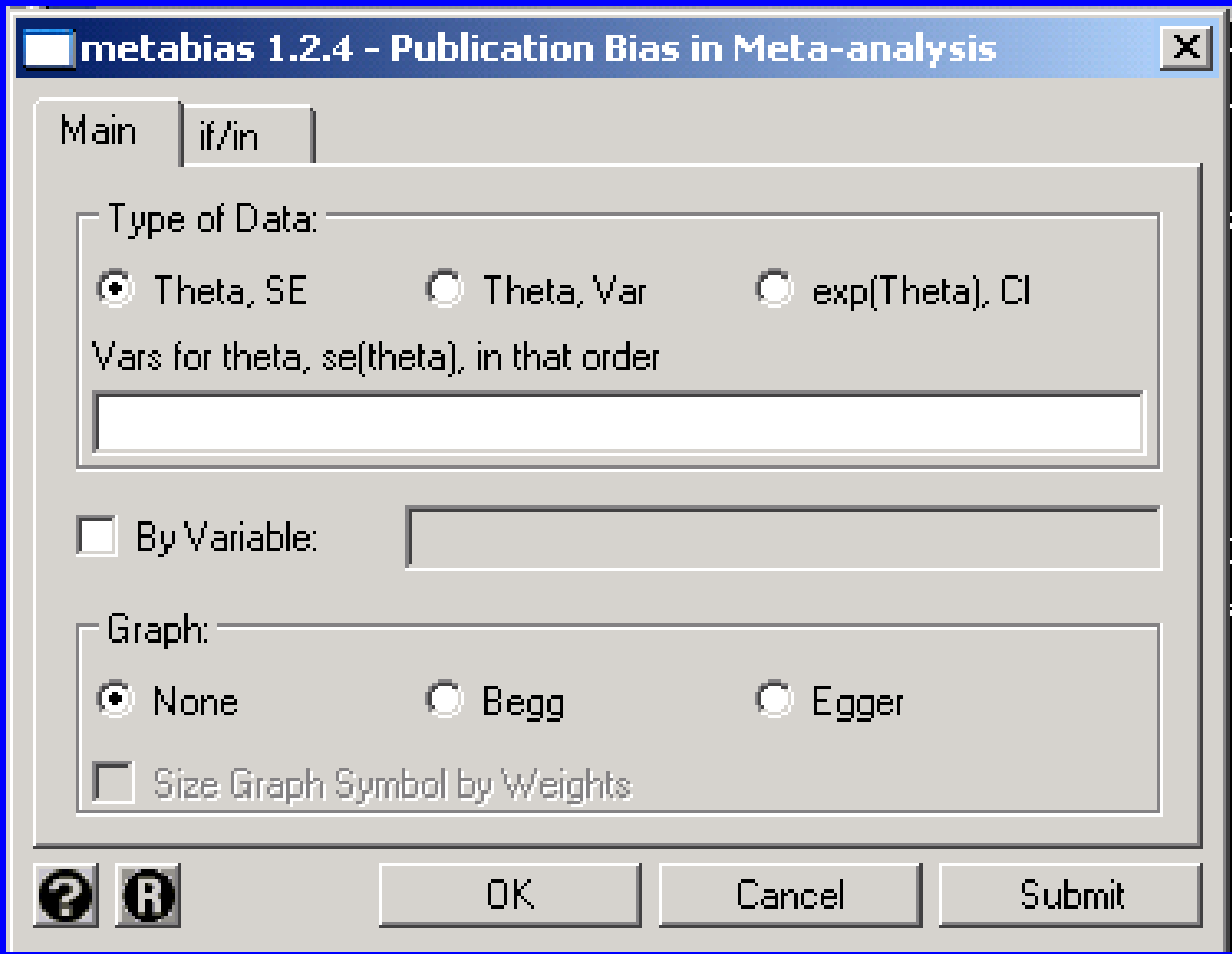
BEGG'S BIAS TEST

- An adjusted rank correlation method to assess the correlation between effect estimates and their variances.
- Deviation of Spearman's rho from zero=estimate of funnel plot asymmetry.
- Positive values=a trend towards higher levels of effect sizes in studies with smaller sample sizes

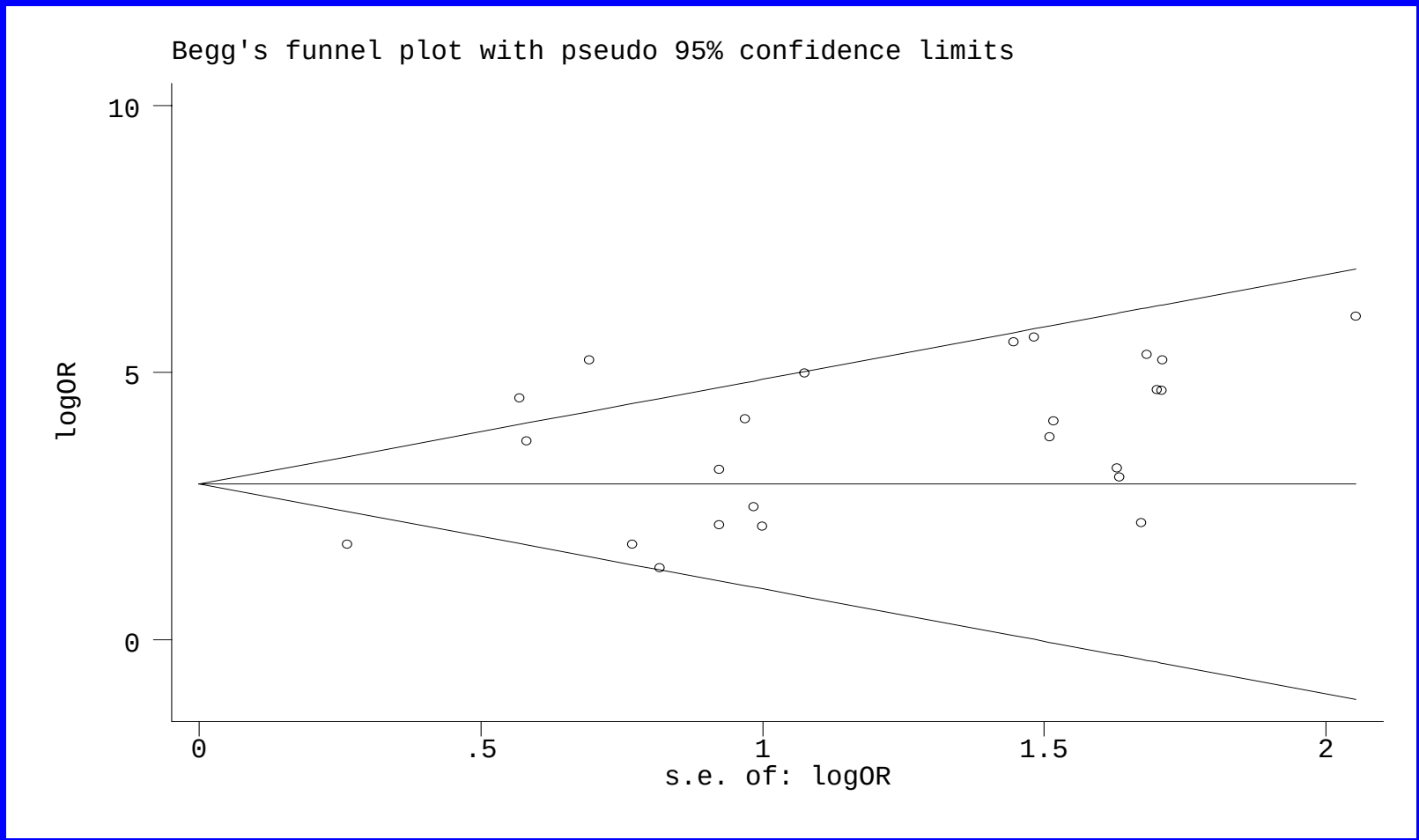
BEGG'S BIAS TEST

STATA SYNTAX/COMMAND

```
metabias LogOR seLogOR,
  graph(b) saving(beggplot,
  replace)
```


metabias 1.2.4 - Publication Bias in Meta-analysis
Main
if/in
Type of Data:
Theta, SE
Theta, Var
exp(Theta), CI
Vars for theta, se(theta), in that order
By Variable:
Graph:
None
Begg
Egger
Size Graph Symbol by Weights
OK
Cancel
Submit

BEGG'S BIAS PLOT



BEGG'S BIAS TEST

adj. Kendall's Score (P-Q) = 26
Std. Dev. of Score = 40.32
Number of Studies = 24
z = 0.64
Pr > |z| = 0.519
z = 0.62 (continuity corrected)
Pr > |z| = 0.535 (continuity corrected)

EGGER'S REGRESSION METHOD

- Assesses potential association b/n effect size and precision.
- Regression equation: SND = A + B x SE(d)-1. SND=standard normal deviate (effect, d divided by its standard error SE(d)); A =intercept and B=slope. .

EGGER'S REGRESSION METHOD

- The intercept value (A) = estimate of asymmetry of funnel plot
- Positive values (A > 0) indicate higher levels of effect size in studies with smaller sample sizes.

EGGER'S REGRESSION METHOD

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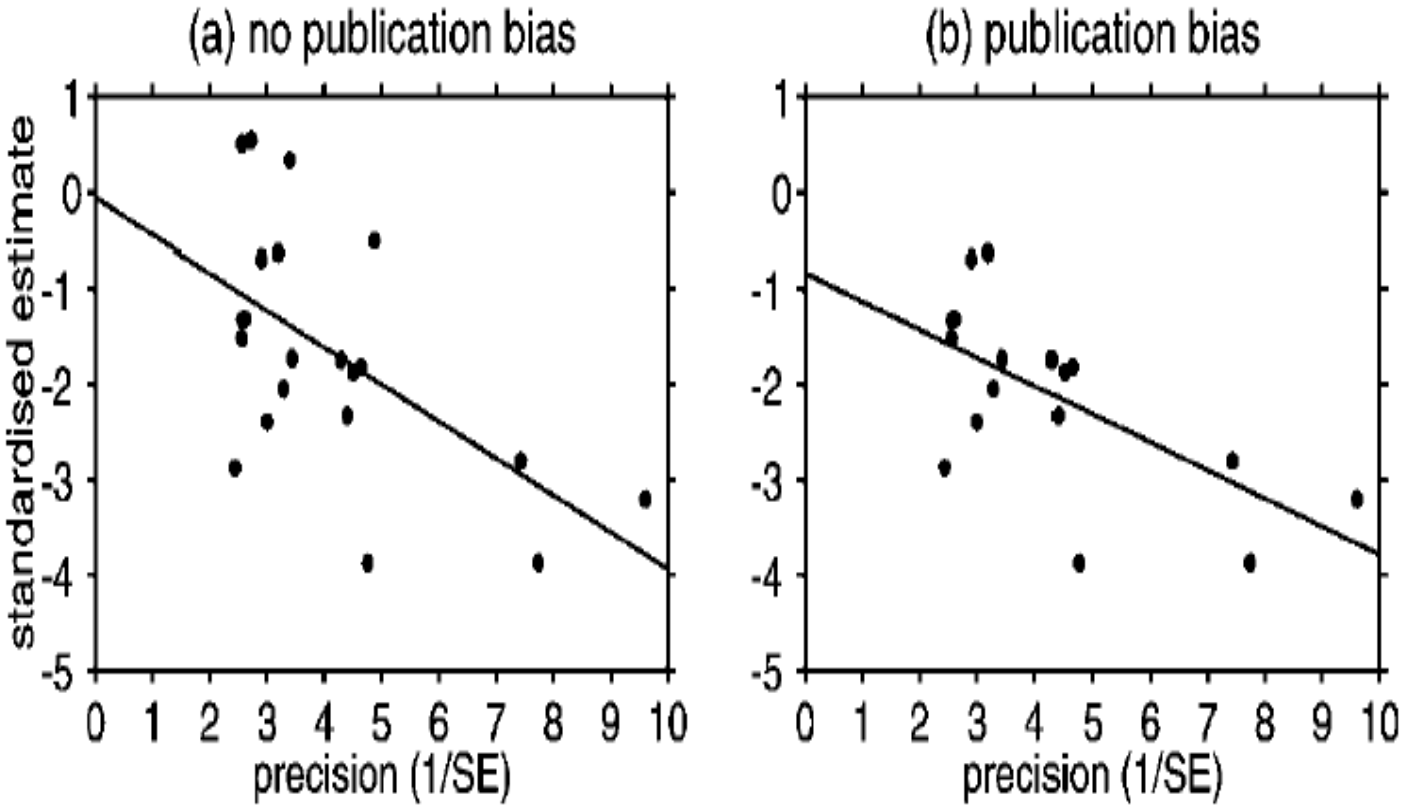
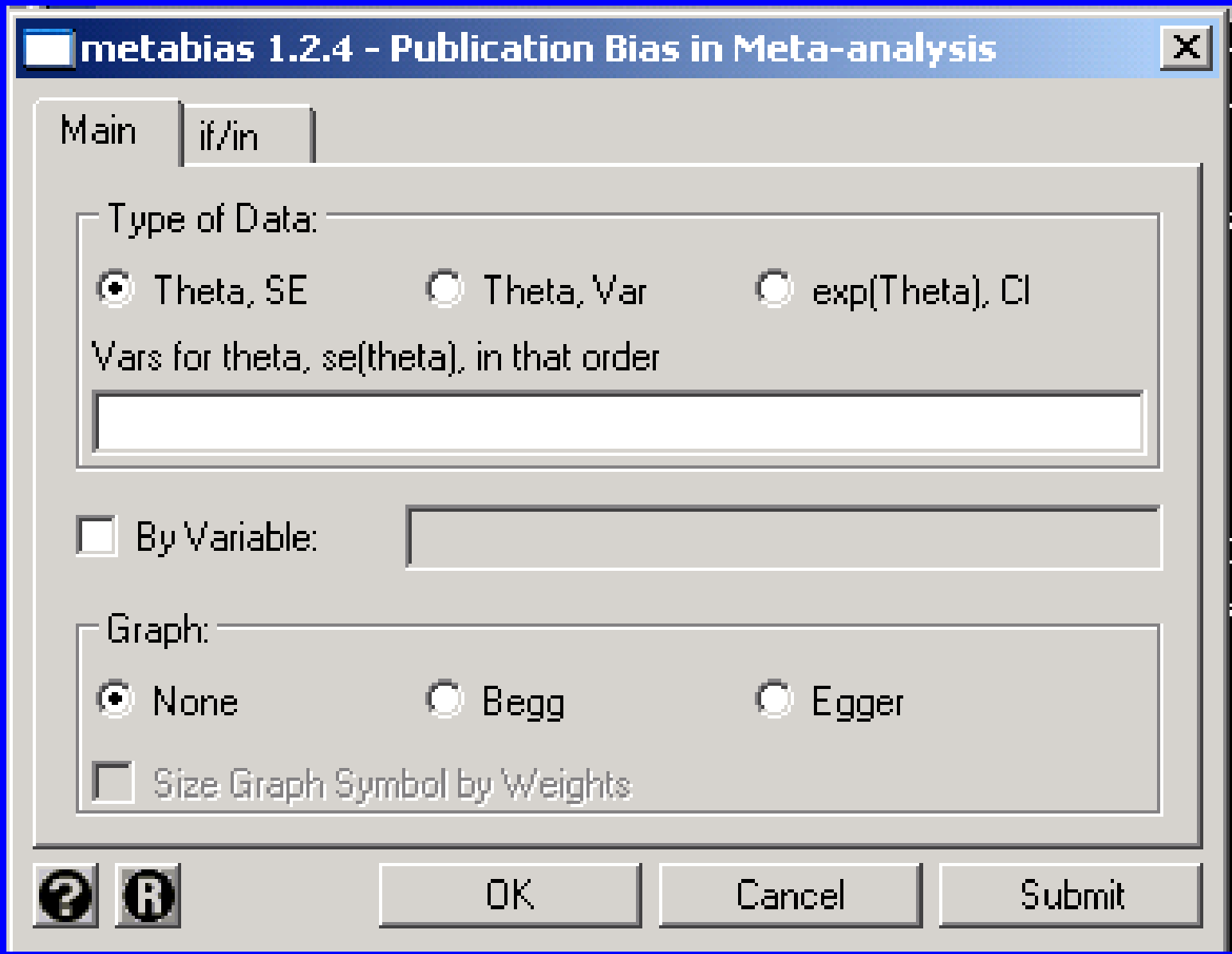
EGGER'S PLOT


(a) no publication bias
(b) publication bias
standardised estimate
precision (1/SE)
precision (1/SE)
1
0
-1
-2
-3
-4
-5
0 1 2 3 4 5 6 7 8 9 10

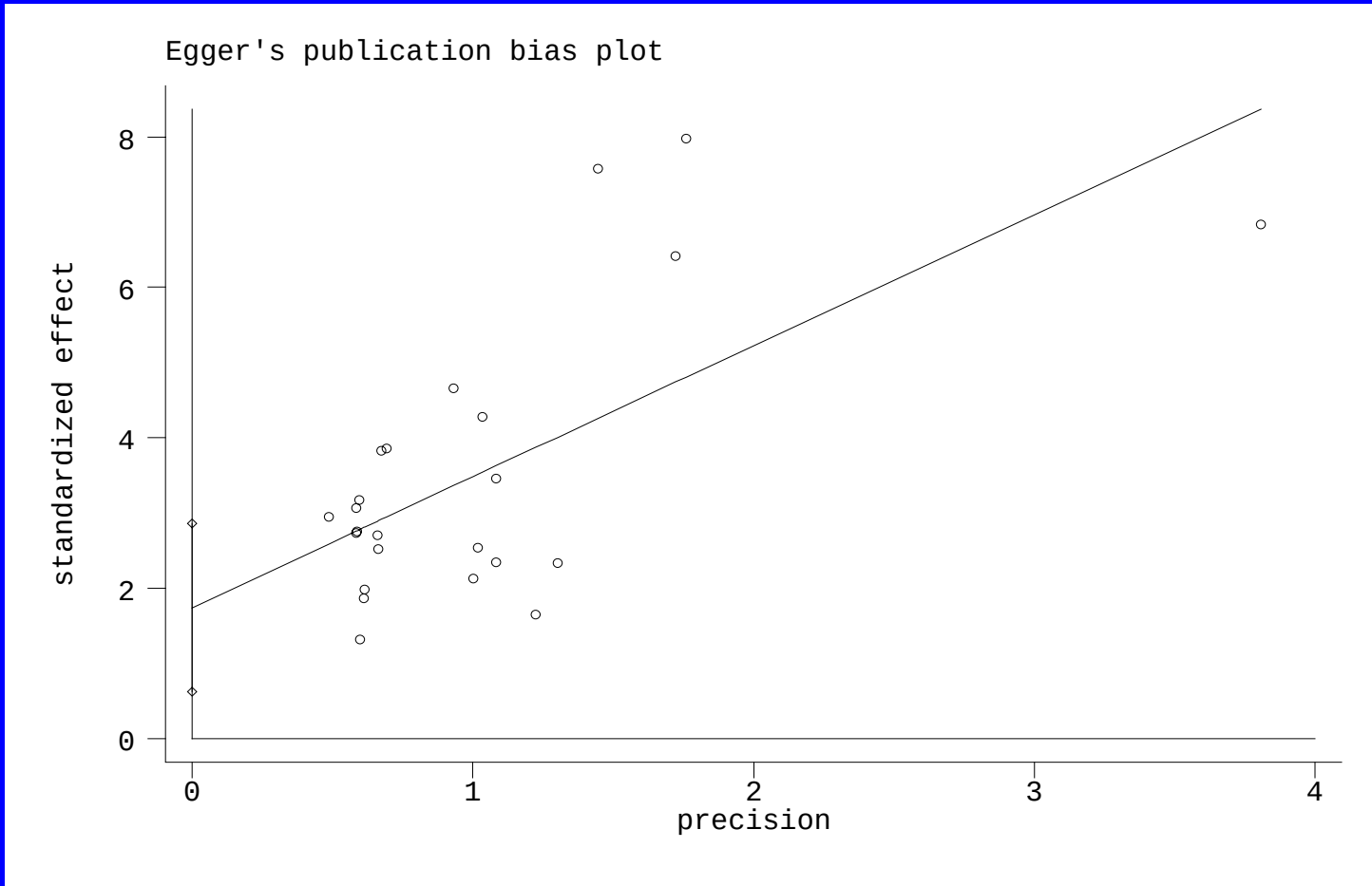
EGGER'S METHOD

STATA SYNTAX/COMMAND

```
metabias logOR selogOR,
  graph(e) saving(eggerplot,
  replace)
```


metabias 1.2.4 - Publication Bias in Meta-analysis
Main
if/in
Type of Data:
Theta, SE
Theta, Var
exp(Theta), CI
Vars for theta, se(theta), in that order
By Variable:
Graph:
None
Begg
Egger
Size Graph Symbol by Weights
OK
Cancel
Submit

EGGER'S PLOT


Egger's publication bias plot
standardized effect
0
2
4
6
8
0
1
2
3
4
precision

EGGER'S METHOD

Std_Eff	Coef.	P>|t|	[95% CI]	
slope	1.737492	0.001	.8528166	2.622168
bias	1.796411	0.002	.7487423	2.84408

HARBORD'S MODIFIED BIAS TEST

- Test for funnel-plot asymmetry Regresses Z/sqrt(V) vs. sqrt (V), where Z is the efficient score and V is Fisher's information (the variance of Z under the null hypothesis).

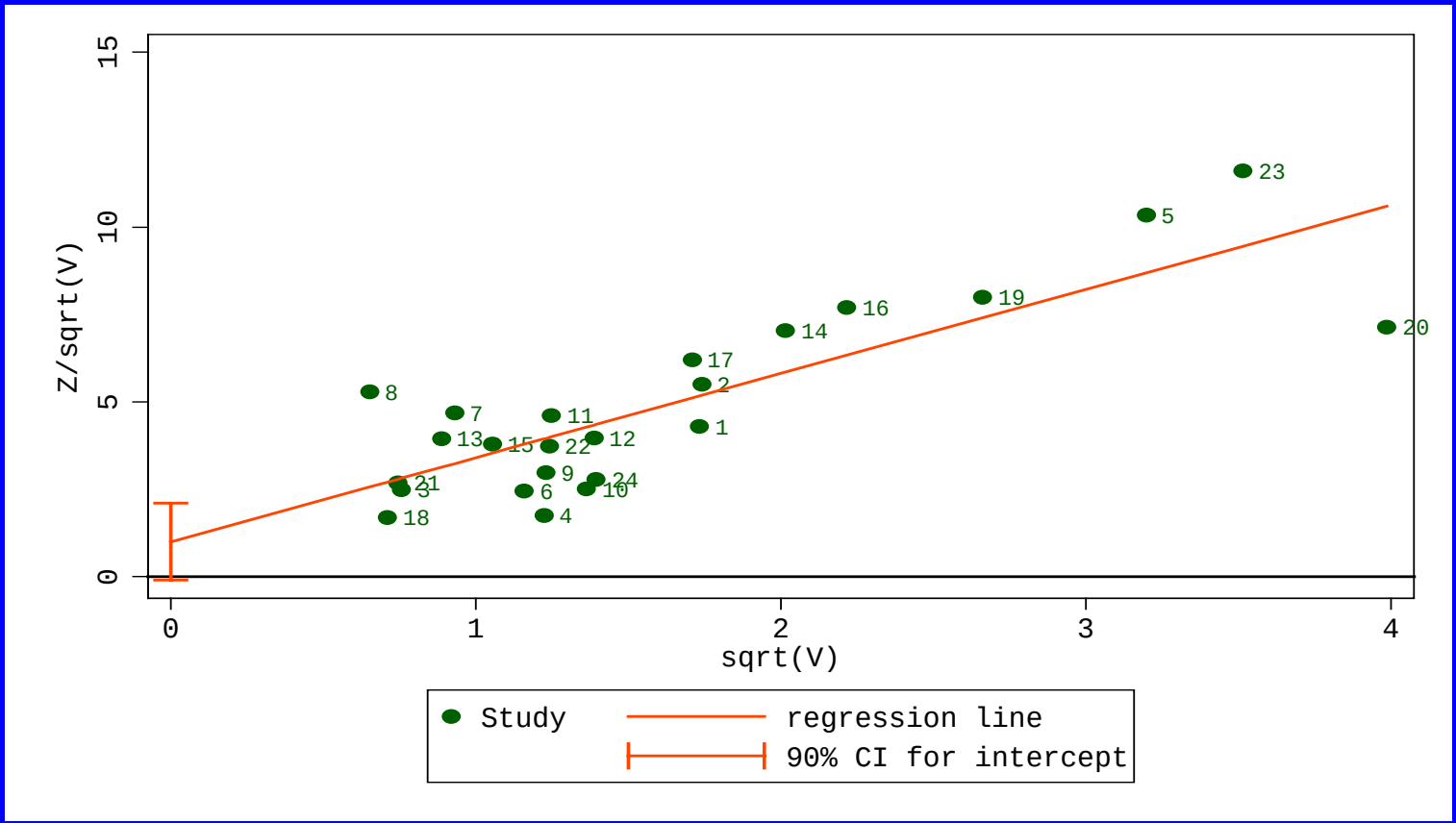
- Modified Galbraith plot of Z/sqrt(V) vs. sqrt(V) with the fitted regression line and a confidence interval around the intercept.

HARBORD'S MODIFIED BIAS TEST

STATA SYNTAX/COMMAND

```
metamodbias tp fn fp tn, graph
  z(Z) v(V) mlabel(index)
  saving(HarbordPlot, replace)
```

HARBORD'S MODIFIED BIAS TEST



HARBORD'S MODIFIED BIAS TEST

ZoversqrtV	Coef.	Std. Err.	P>|t|	[90% Conf.	Interval]
sqrtV	2.406756	.3464027	0.000	1.811933	3.00158
bias	.9965934	.6383554	0.133	-.0995549	2.092742

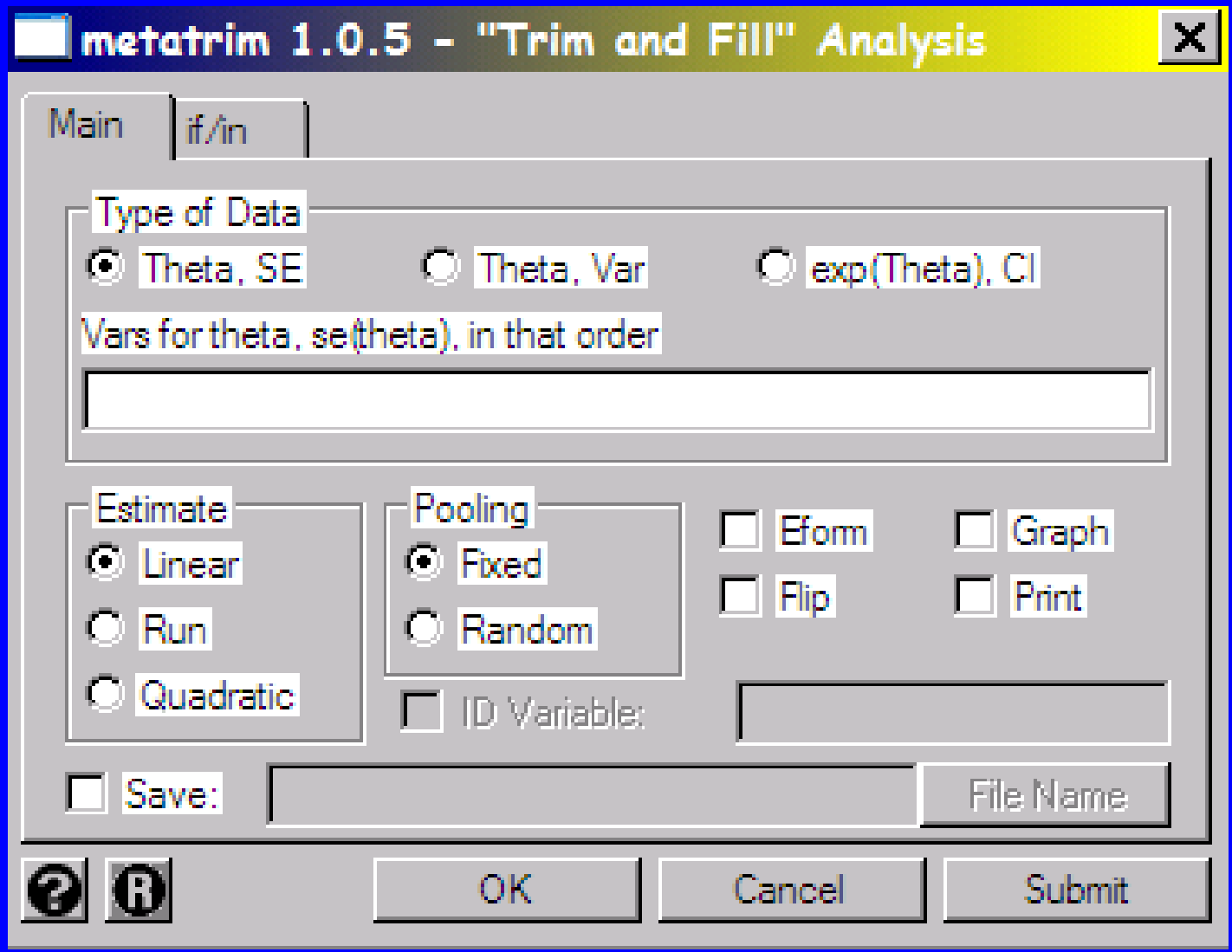
TRIM AND FILL

- A rank-based data augmentation technique used to estimate the number of missing studies and to produce an adjusted estimate of test accuracy by imputing suspected missing studies. Both random and fixed effect models may be used to assess the impact of model choice on publication bias.

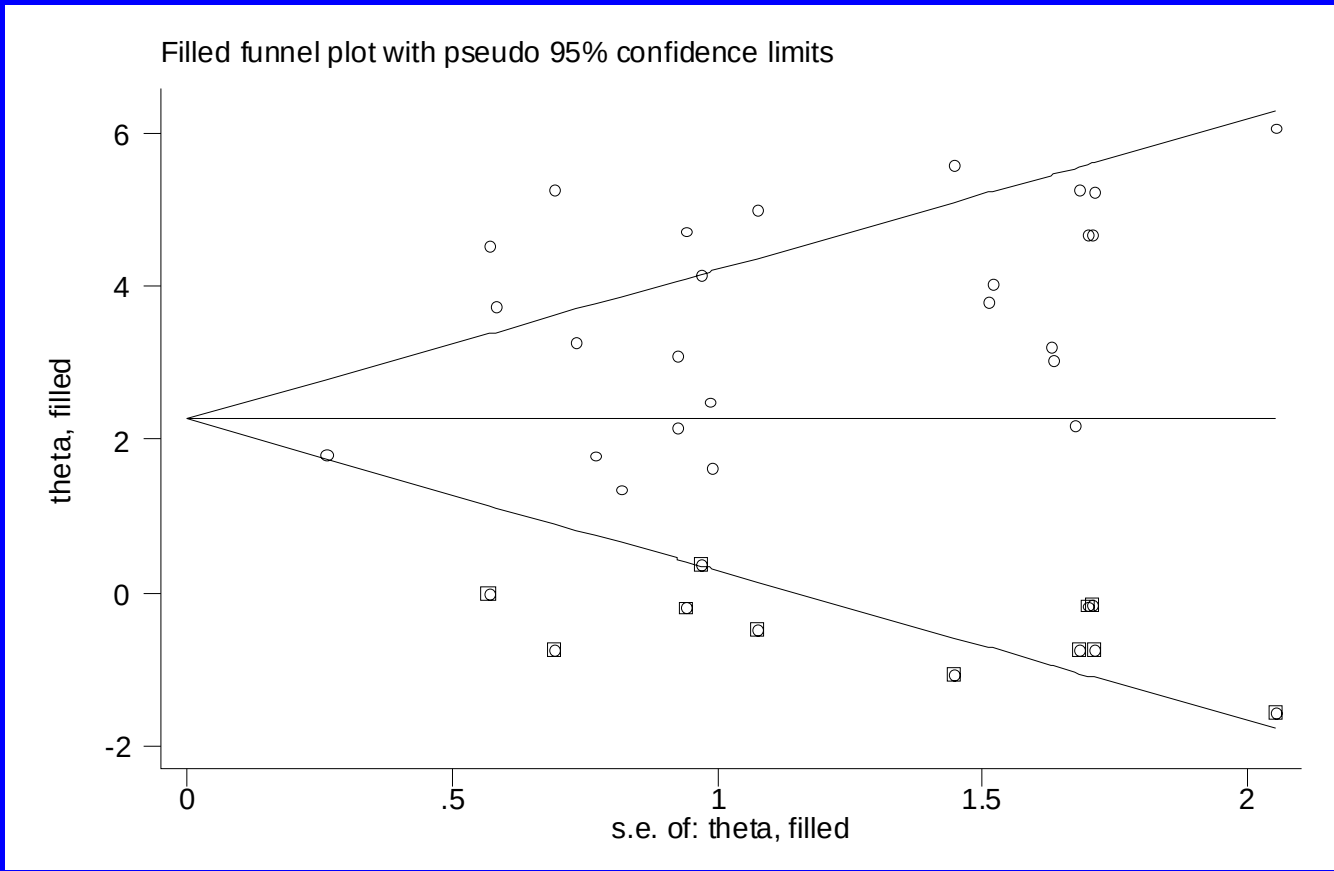
TRIM AND FILL

STATA SYNTAX/COMMAND

- metatrim LogOR seLogOR, eform funnel print graph id(author)saving(tweedieplot, replace)


metatrim 1.0.5 - "Trim and Fill" Analysis
Main
if/in
Type of Data
Theta, SE
Theta, Var
exp(Theta), CI
Vars for theta, se(theta), in that order
Estimate
Linear
Run
Quadratic
Pooling
Fixed
Random
Eform
Graph
Flip
Print
ID Variable:
Save:
File Name
OK
Cancel
Submit

TRIM AND FILL



INVESTIGATING HETEROGENEITY

- Heterogeneity means that there is between-study variation.
- Potential sources of heterogeneity:
  1. Study population
  2. Study design
  3. Statistical methods,
  4. Covariates adjusted for (if relevant).

GALBRAITH PLOT

- Standardized effect vs. reciprocal of the standard error.
- Small studies/less precise results appear on the left side and the largest trials on the right end .

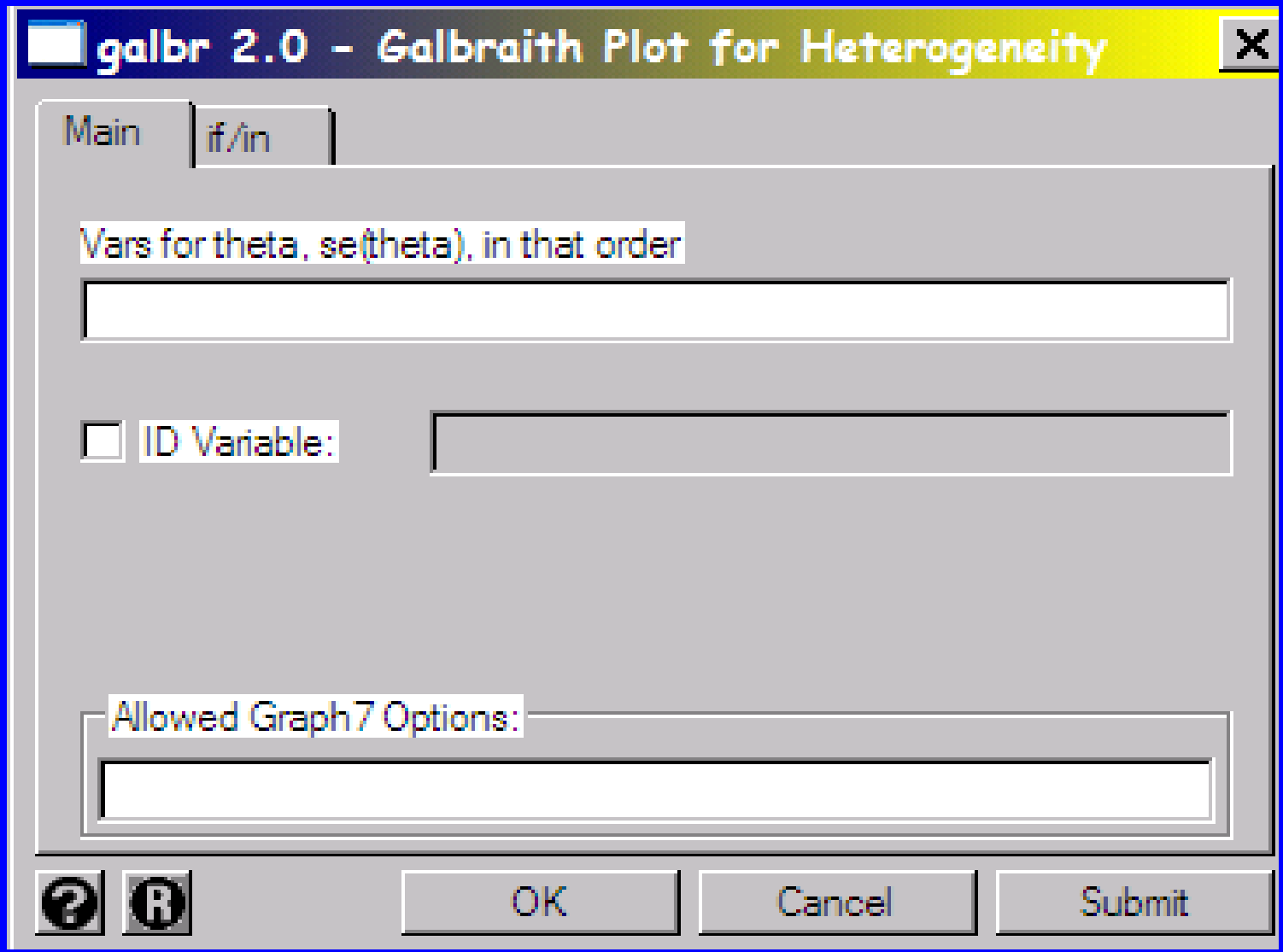
GALBRAITH PLOT

- A regression line , through the origin, represents the overall log-odds ratio.
- Lines +/- 2 above regression line =95 per cent boundaries of the overall log-odds ratio.
- The majority of within area of +/- 2 in the absence of heterogeneity.

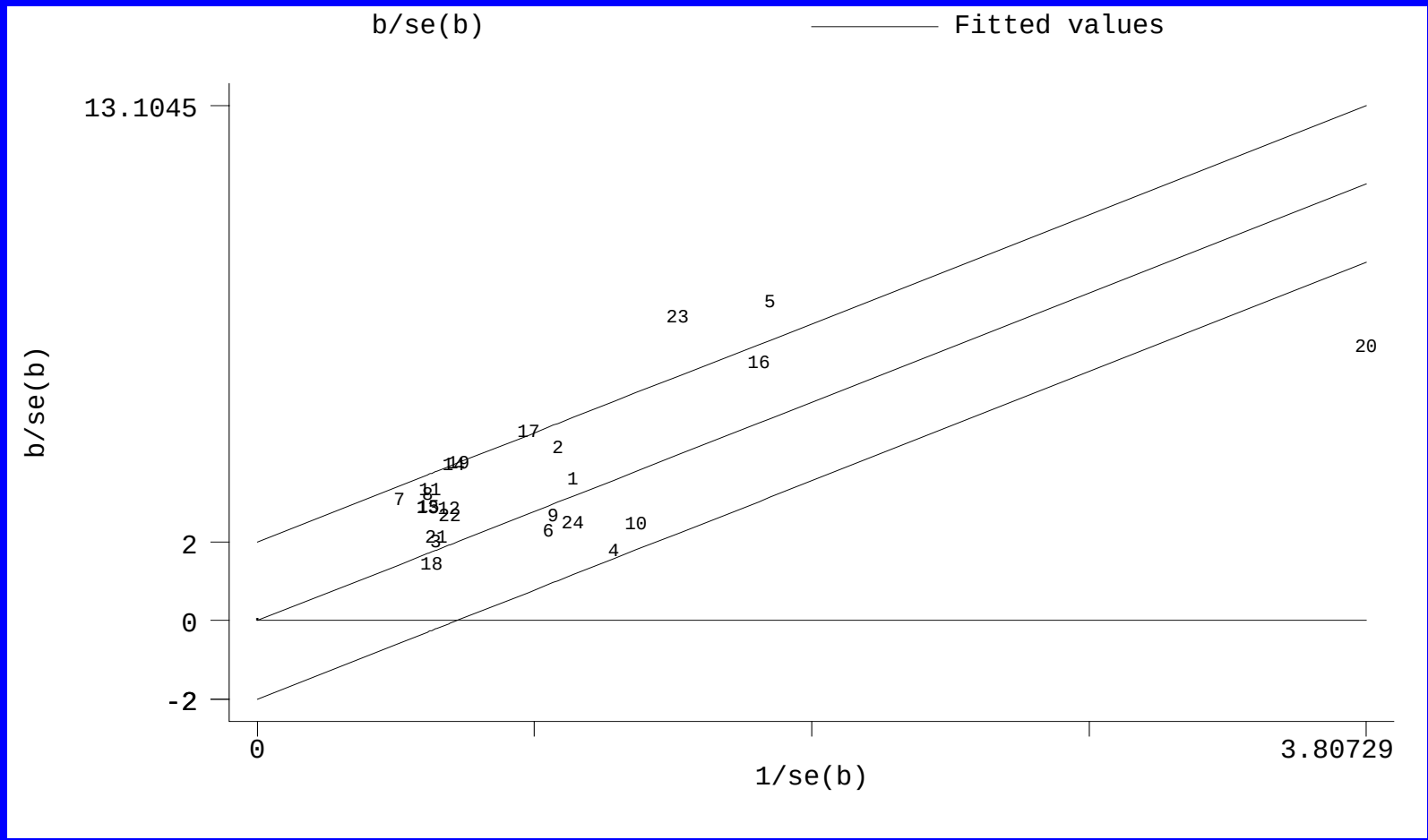
GALBRAITH PLOT

STATA SYNTAX/COMMAND

- galbr LogOR seLogOR, id(index) yline(0) saving(gallplot, replace)


galbr 2.0 - Galbraith Plot for Heterogeneity
Main
if/in
Vars for theta, se(theta), in that order
ID Variable:
Allowed Graph7 Options:
OK
Cancel
Submit

GALBRAITH PLOT



L'ABBE PLOT

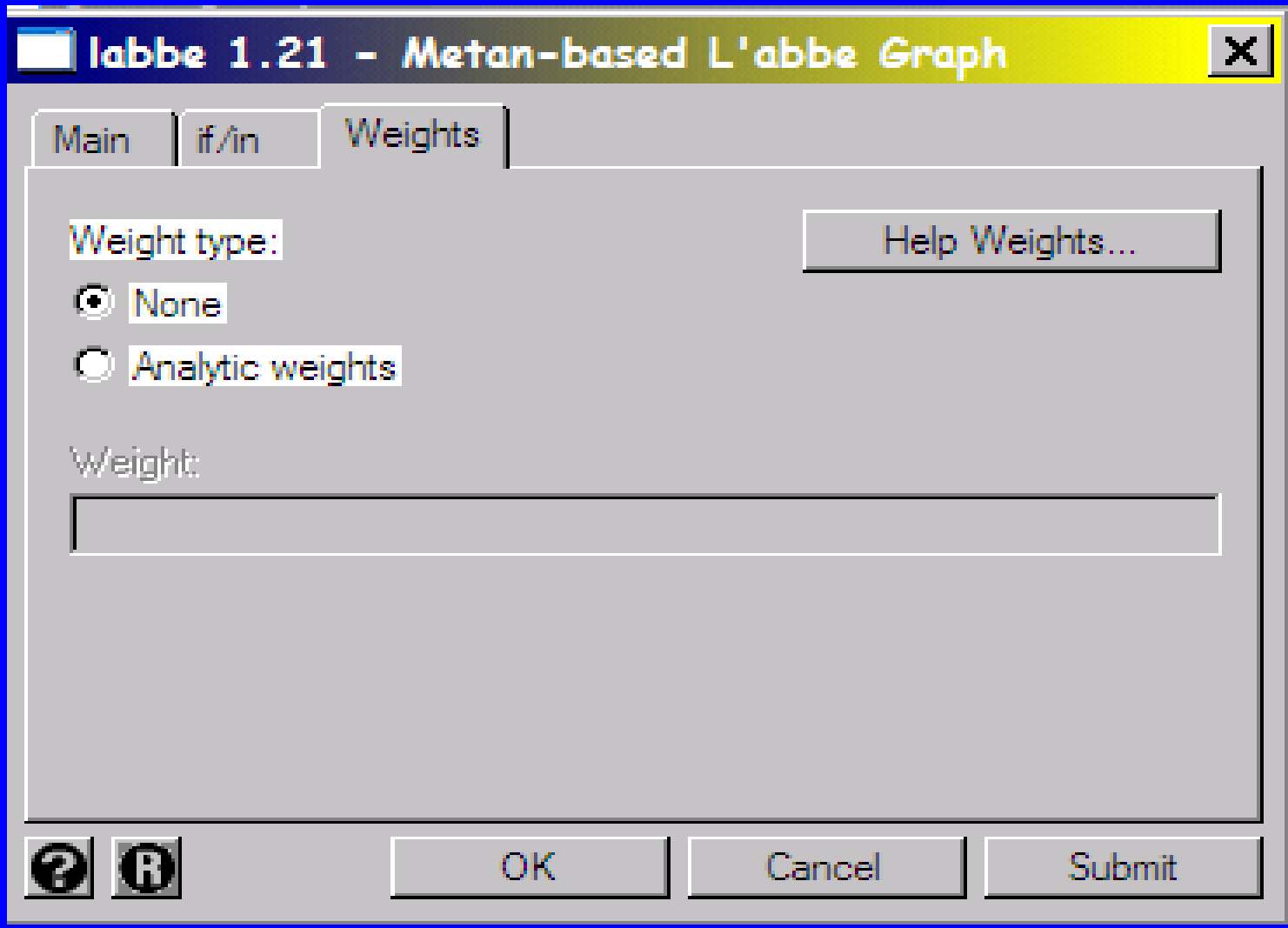
- This plots the event rate in the experimental (intervention) group against the event rate in the control group

- An aid to exploring the heterogeneity of effect estimates within a meta-analysis.

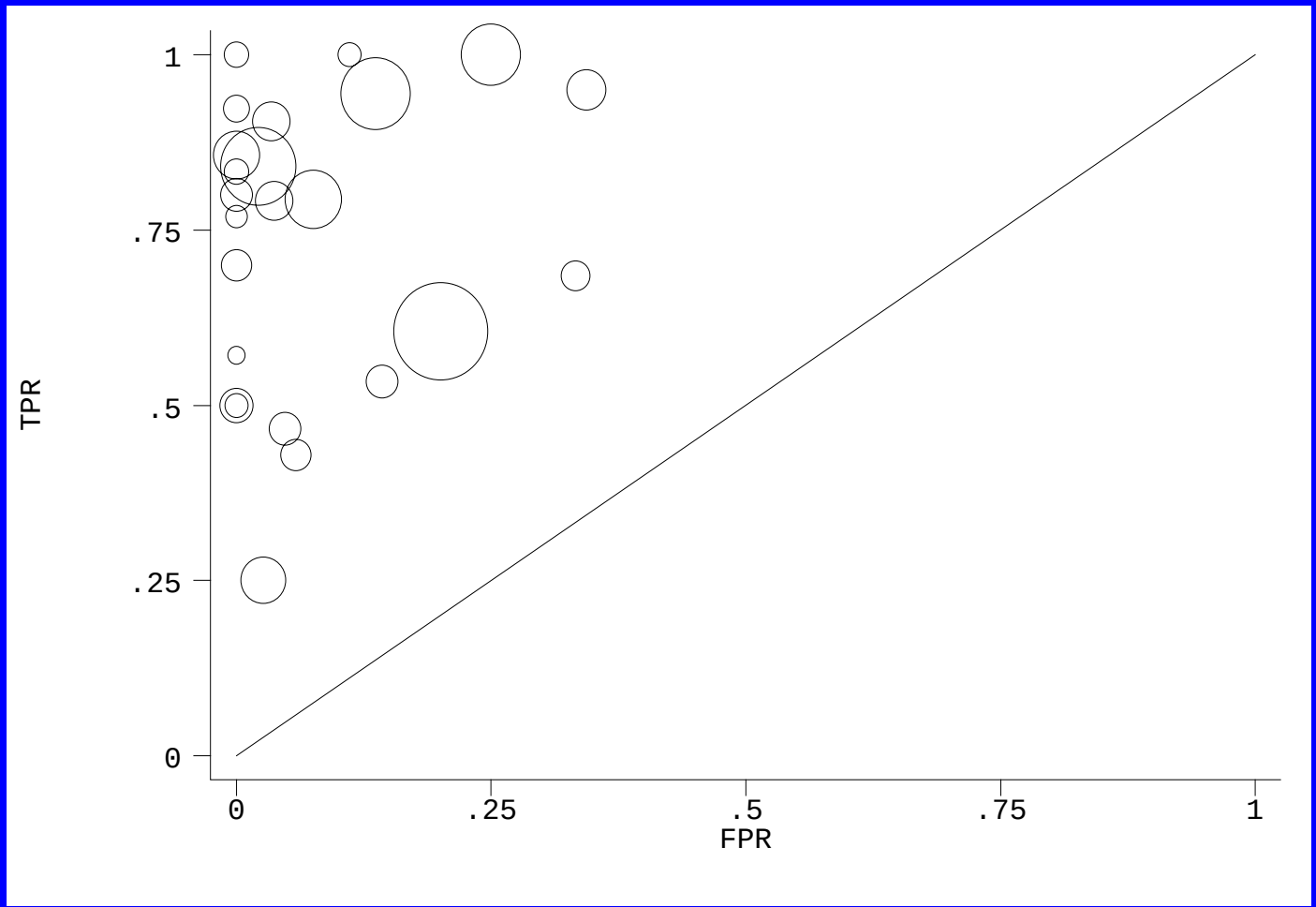
L'ABBE PLOT

STATA SYNTAX/COMMAND

```
labbe tp fn fp tn, s(O)
   xlab(0,0.25,0.50,0.75,1)
   ylab(0,0.25,0.50,0.75,1) l1("TPR)
   b2("FPR") saving(flabbeplot,
   replace)
```


labbe 1.21 - Metan-based L'abbe Graph
Main
if/in
Weights
Weight type:
Help Weights...
None
Analytic weights
Weight:
OK
Cancel
Submit

L'ABBE PLOT



DATA SUMMARY

STATA 8 SYNTAX

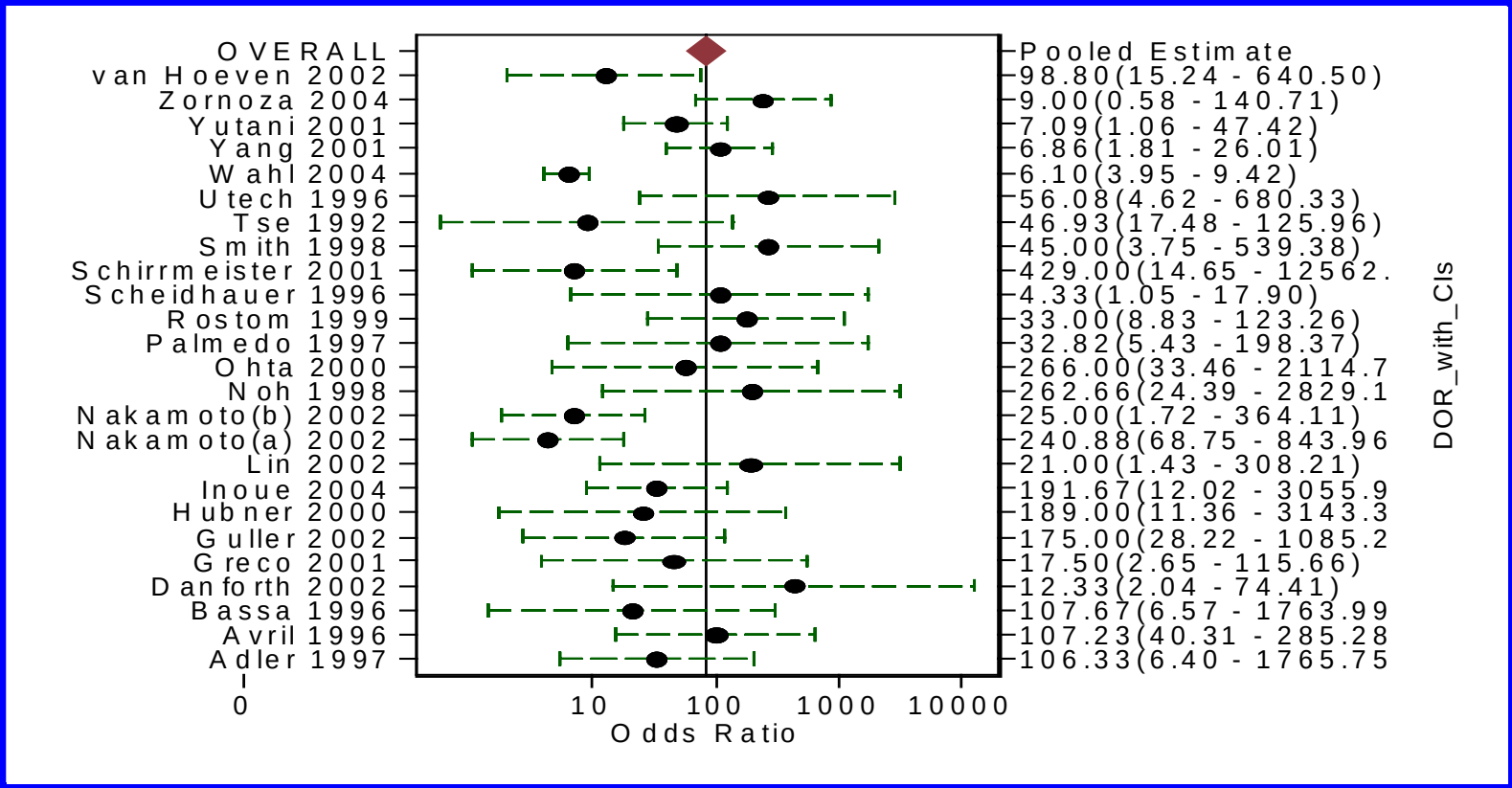
```
twoway (rcap dorlo dorhi Study, horizontal
blpattern(dash))(scatter Study dor, ms(O)msize(medium)
mcolor(black))(scatter DOR_with_CIs eb_dor, yaxis(2)
msymbol(i) msize(large) mcolor(black))(scatteri 26 83,
msymbol(diamond) msize(large)), ylabel(1(1)25 26
"OVERALL", valuelabels angle(horizontal)) xlabel(0 10
100 1000 10000)  xscale(log) ylabel(1(1)25 26 "Pooled
Estimate", valuelabels angle(horizontal) axis(2))
legend(off) xtitle(Odds Ratio) xline(83,
lstyle(foreground))  saving(OddsForest, replace)
```

DATA SUMMARY

- metan tp fn fp tn, or fixed nowt sortby(year) label(namevar=author, yearvar=year) t1(Summary DOR, Fixed Effects) b2(Diagnostic Odds Ratio) saving(SDORFE, replace) force xlabel(0,1,10,100,1000)

- metan tp fn fp tn, or random nowt sortby(year) label(namevar=author, yearvar=year) t1(Summary DOR, Random Effects) b2(Diagnostic Odds Ratio) saving(SDORRE, replace) force xlabel(0,1,10,100,1000)

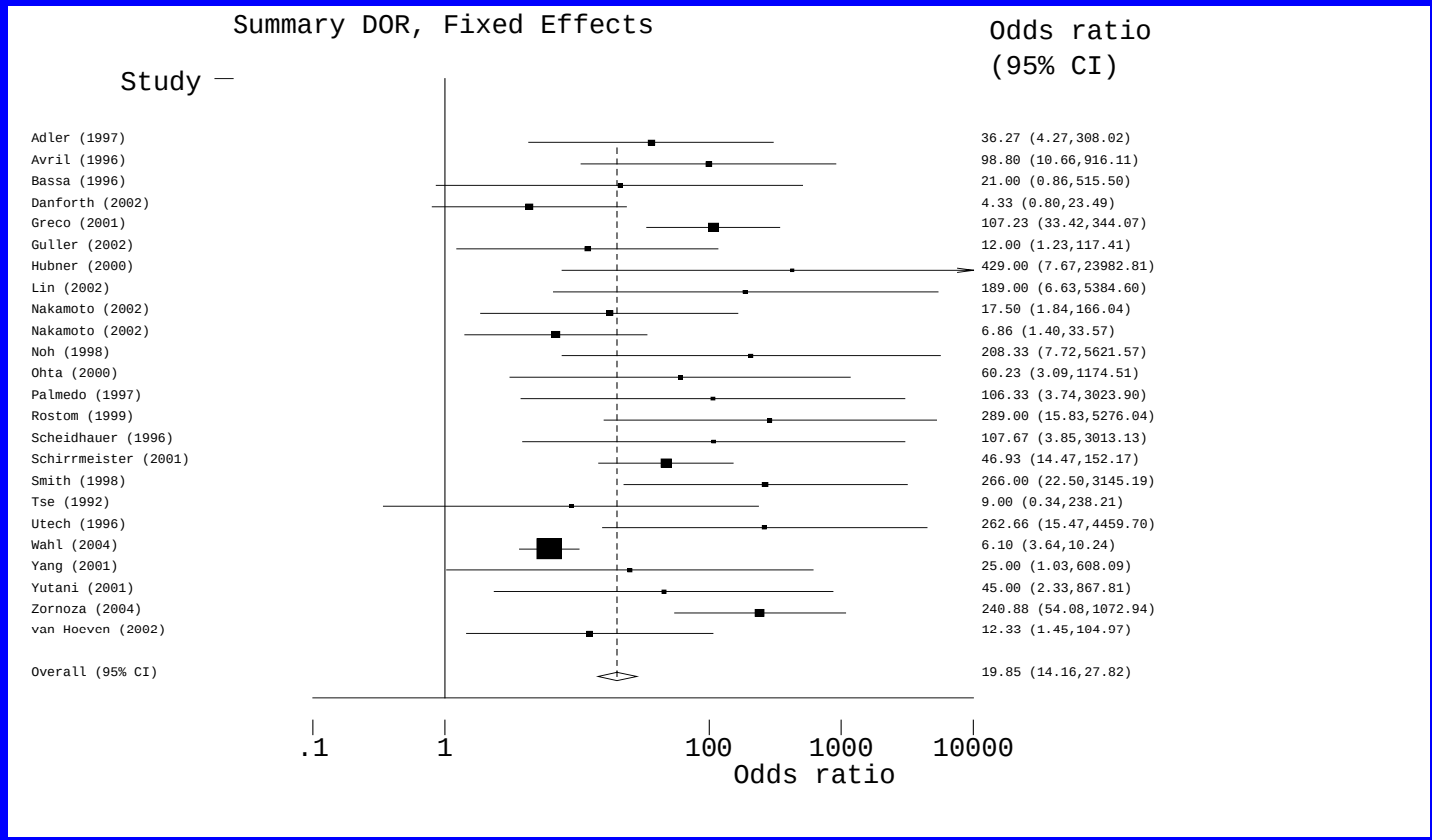
STATA 8 FOREST PLOT



FIXED EFFECTS META-ANALYSIS

- Assumes homogeneity of effects across the studies being combined the true effect size has a common true value for all studies.
- In the summary estimate only the variance of each study is taken into account.

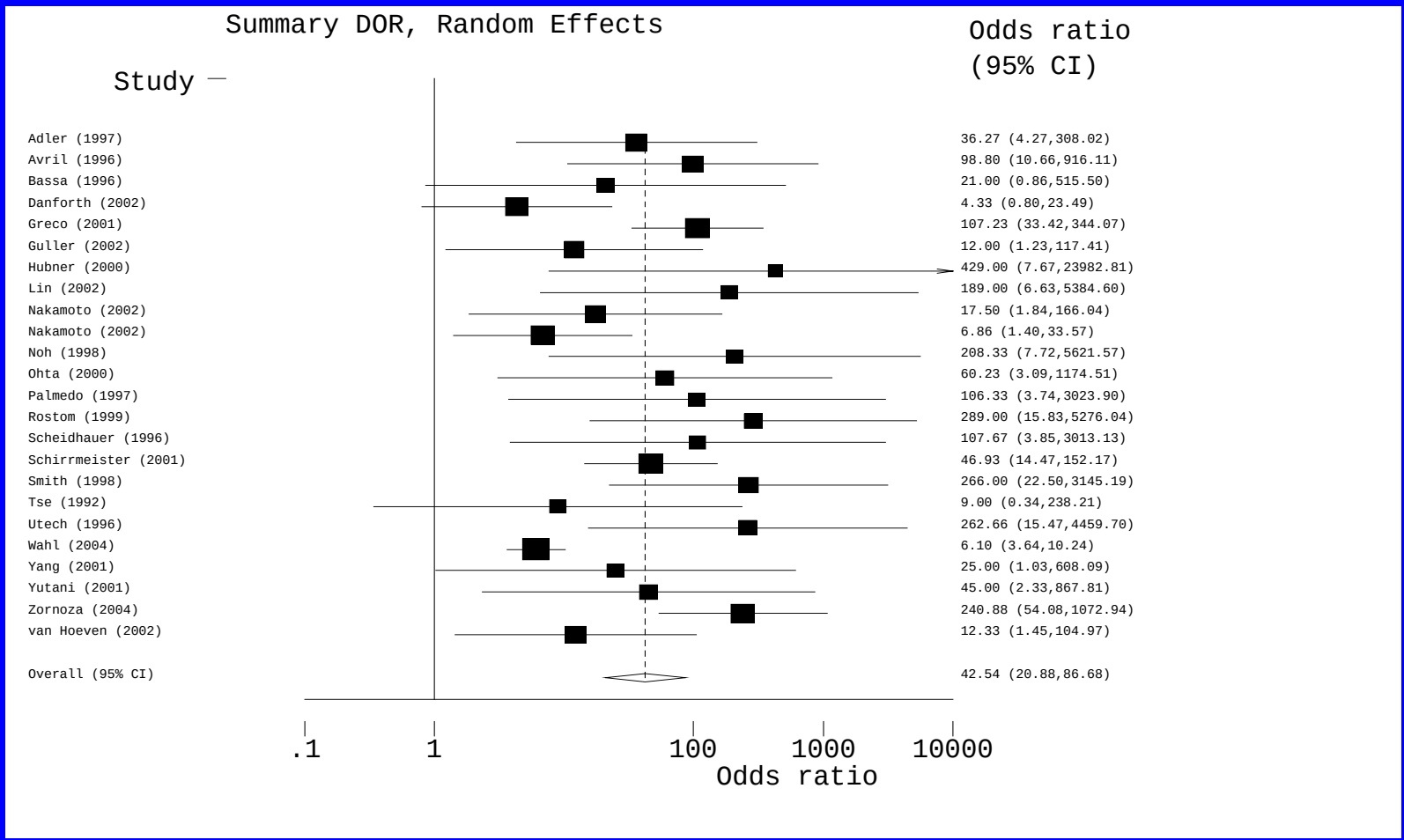
FIXED EFFECTS FOREST PLOT



RANDOM EFFECTS META-ANALYSIS

- Heterogeneity is incorporated into the pooled estimate by including a between study component of variance.
- Assumes sample of studies included in the analysis is drawn from a population of studies.
- Each sample of studies has a true effect size.

RANDOM EFFECTS FOREST PLOT

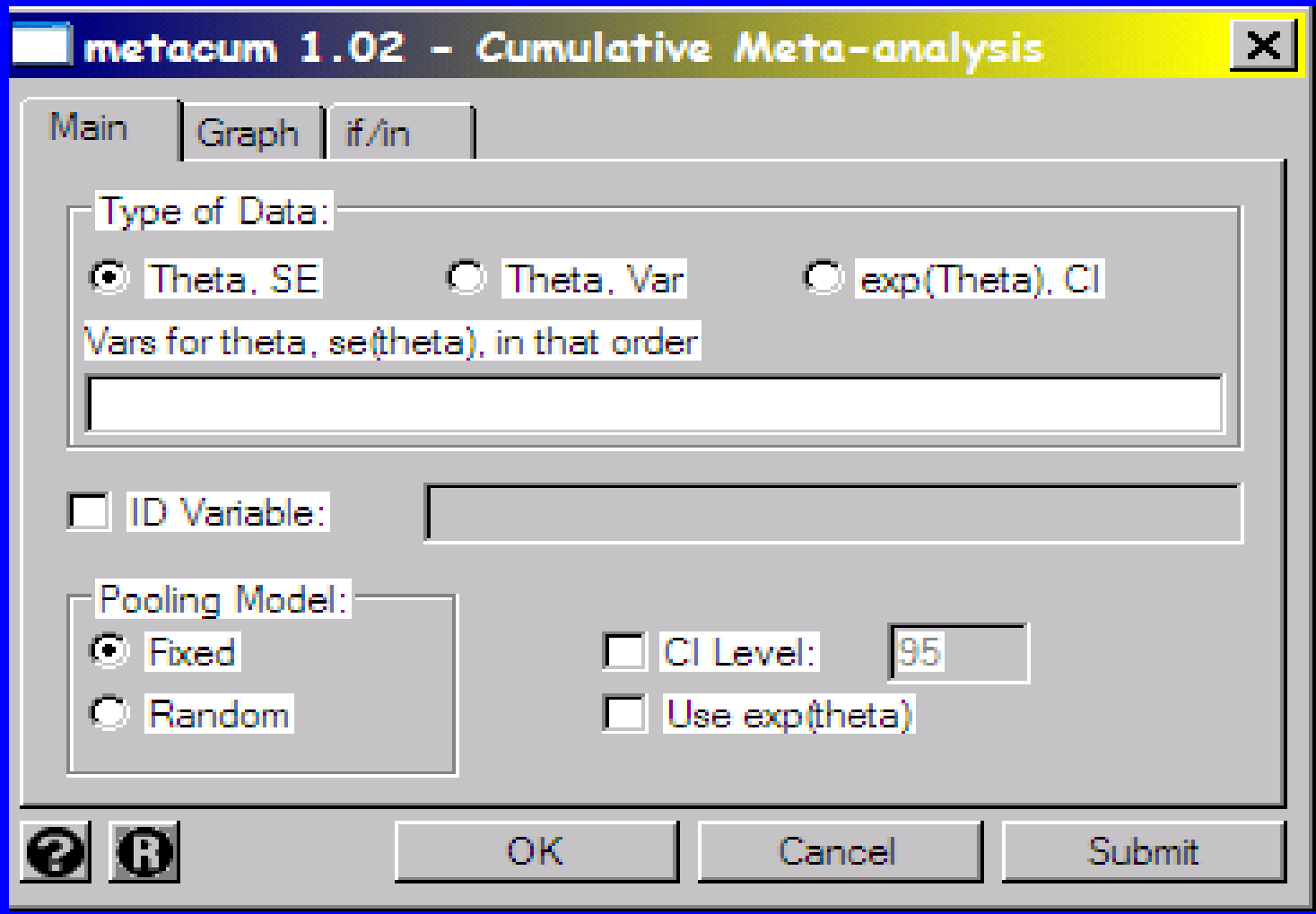


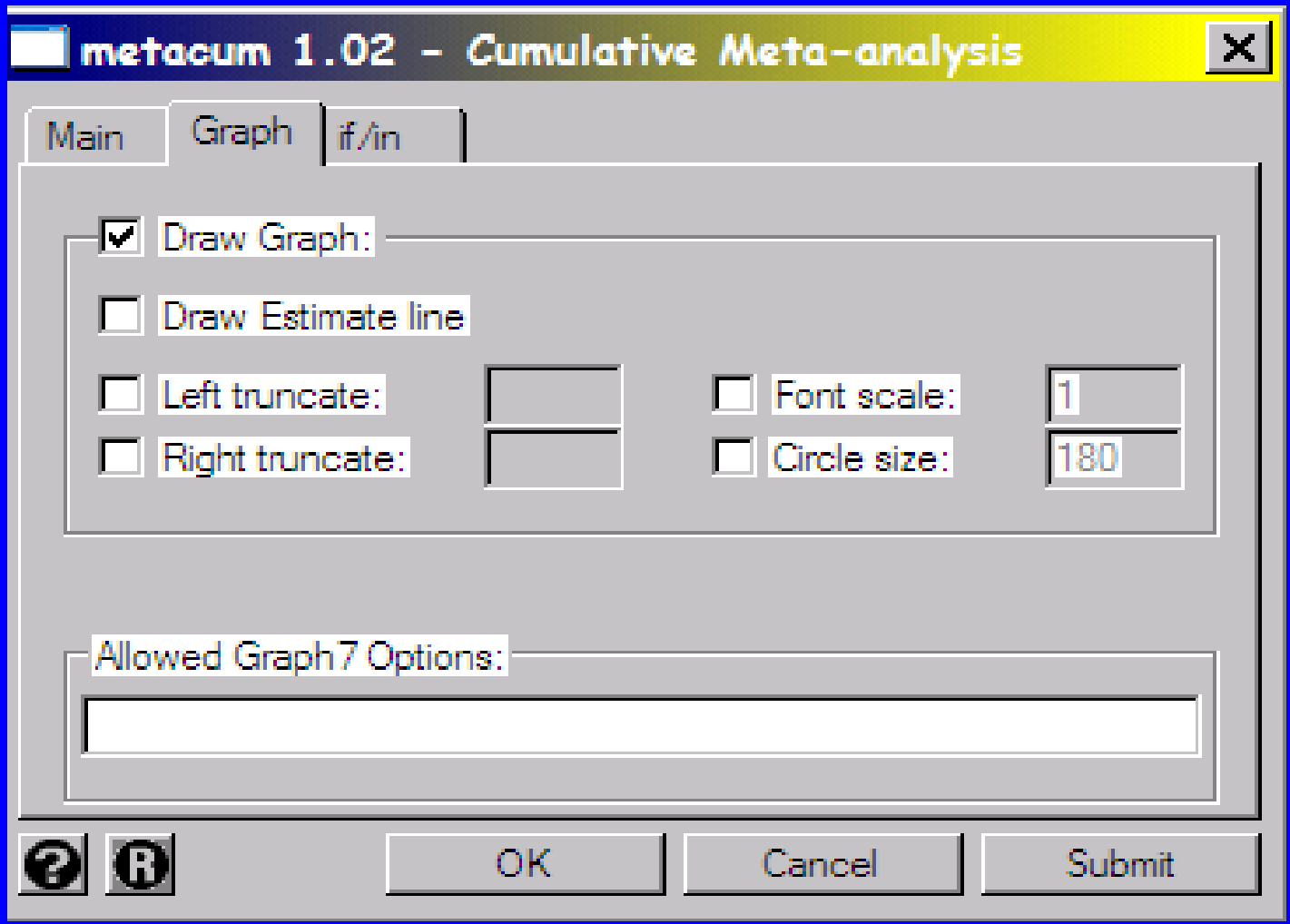
CUMULATIVE META-ANALYSIS

- studies are sequentially pooled by adding each time one new study according to an ordered variable. For instance, the year of publication; then, a pooling analysis will be done every time a new article appears.

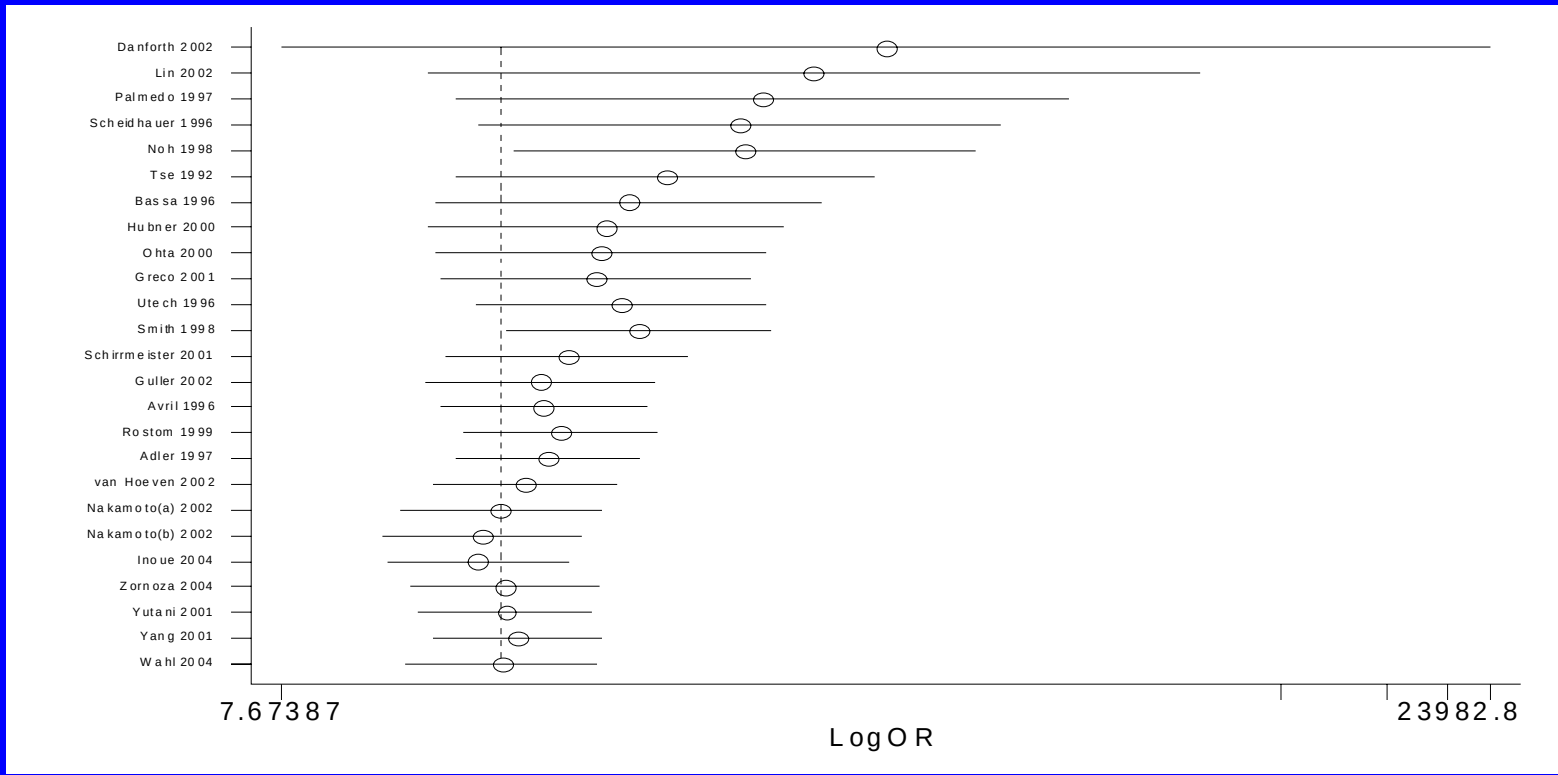
CUMULATIVE META-ANALYSIS

- metacum LogOR seLogOR, eform id(author) effect(f) graph cline saving(year_fcummplot, replace)


metacum 1.02 - Cumulative Meta-analysis
Main
Graph
if/in
Type of Data:
Theta, SE
Theta, Var
exp(Theta), CI
Vars for theta, se(theta), in that order
ID Variable:
Pooling Model:
Fixed
Random
CI Level:
95
Use exp(theta)
OK
Cancel
Submit


metacum 1.02 - Cumulative Meta-analysis
Main
Graph
if/in
Draw Graph:
Draw Estimate line
Left truncate:
Right truncate:
Font scale:
1
Circle size:
180
Allowed Graph7 Options:
OK
Cancel
Submit

CUMMULATIVE META-ANALYSIS

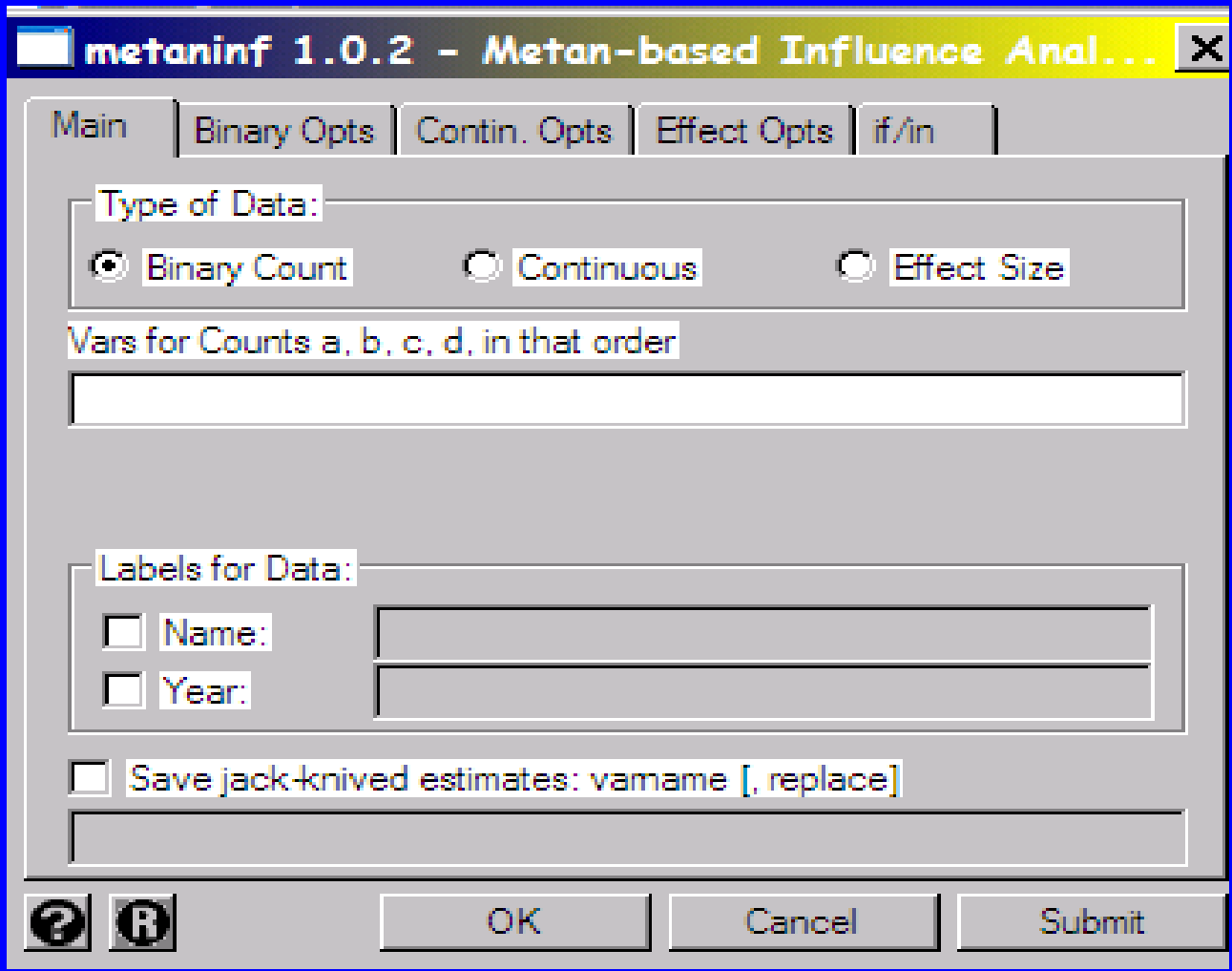


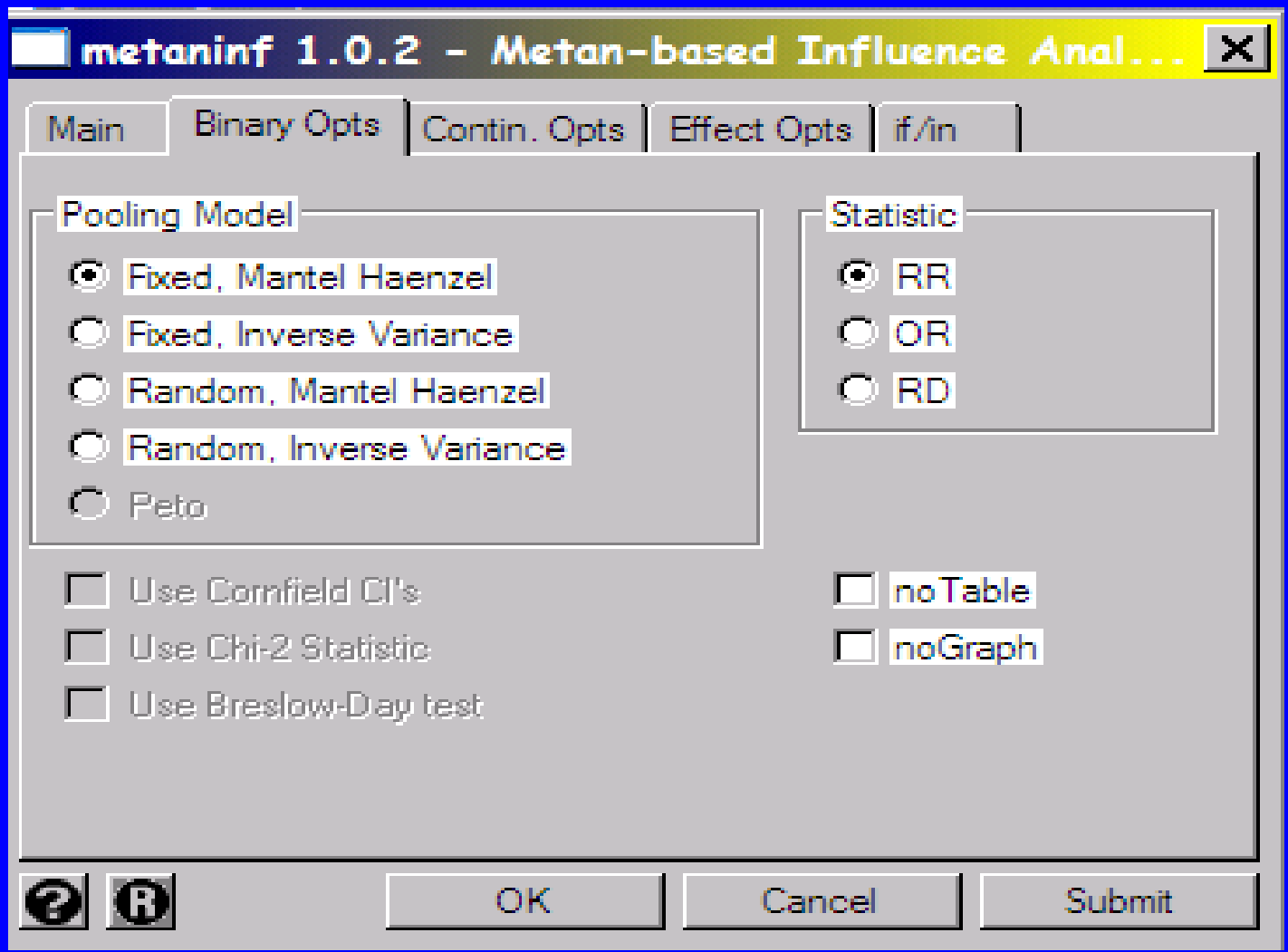
INFLUENCE ANALYSIS

- studies are pooled according influence of a trial on overall effect defined as the difference between the effect estimated with and without the trial

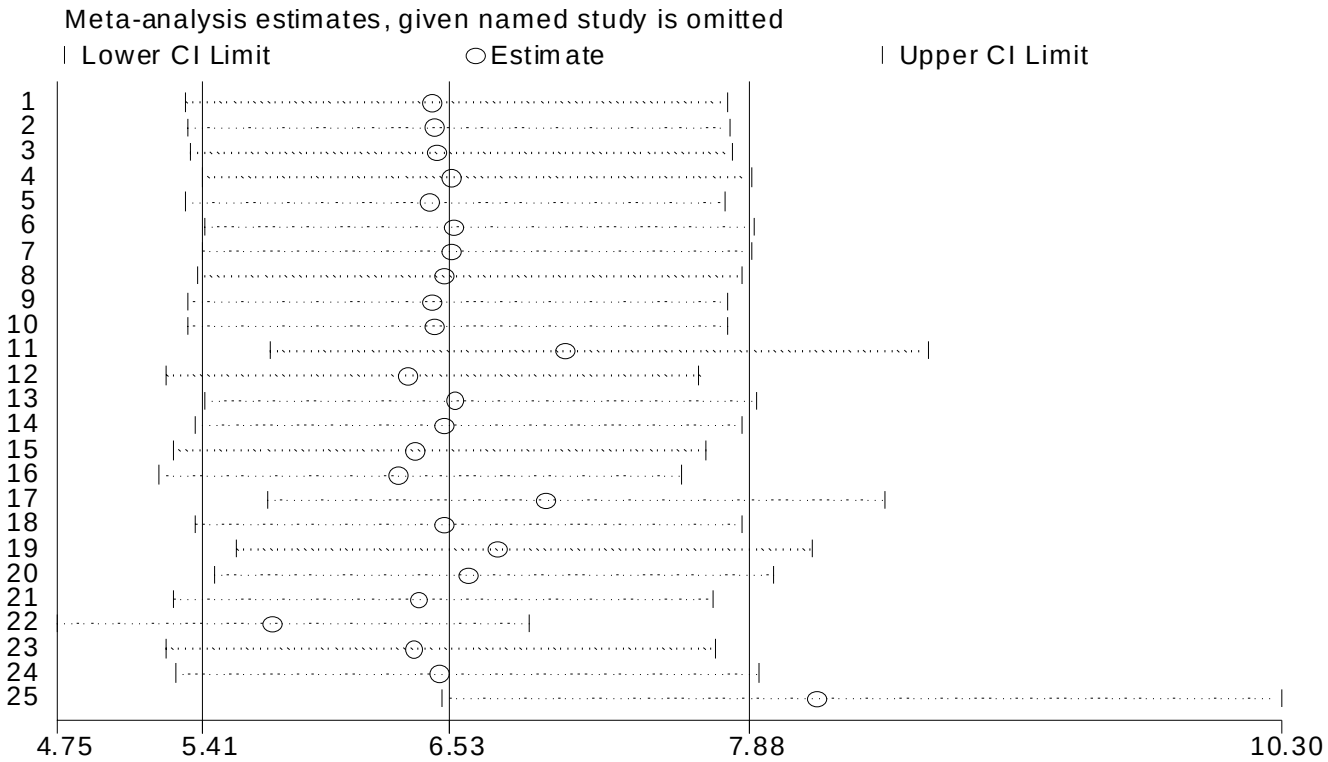
INFLUENCE ANALYSIS

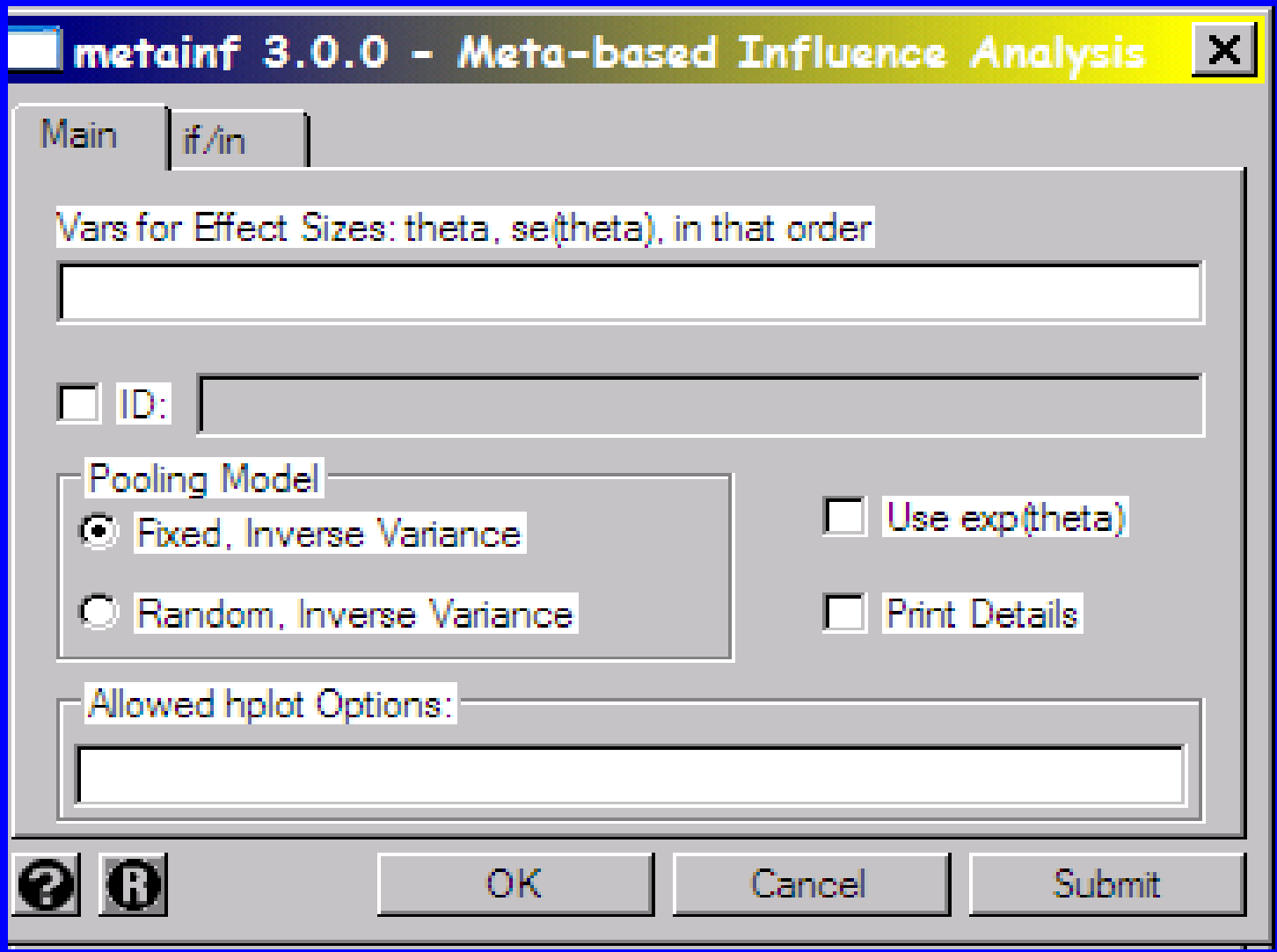
- metaninf tp fn fp tn, id(author)
  saving(influplot, replace)
  save(infcoeff, replace)


metaninf 1.0.2 - Meta-based Influence Anal...
Main
Binary Opts
Contin. Opts
Effect Opts
if/in
Type of Data:
Binary Count
Continuous
Effect Size
Vars for Counts a, b, c, d, in that order
Labels for Data:
Name:
Year:
Save jack-knived estimates: vamame [, replace]
OK
Cancel
Submit


metaninf 1.0.2 - Metan-based Influence Anal...
Main
Binary Opts
Contin. Opts
Effect Opts
if/in
Pooling Model
Fixed, Mantel Haenzel
Fixed, Inverse Variance
Random, Mantel Haenzel
Random, Inverse Variance
Peto
Statistic
RR
OR
RD
Use Cornfield CI's
Use Chi-2 Statistic
Use Breslow-Day test
noTable
noGraph
OK
Cancel
Submit

INFLUENCE ANALYSIS




metainf 3.0.0 - Meta-based Influence Analysis
Main
if/in
Vars for Effect Sizes: theta, se(theta), in that order
ID:
Pooling Model
Fixed, Inverse Variance
Random, Inverse Variance
Use exp(theta)
Print Details
Allowed hplot Options:
OK
Cancel
Submit

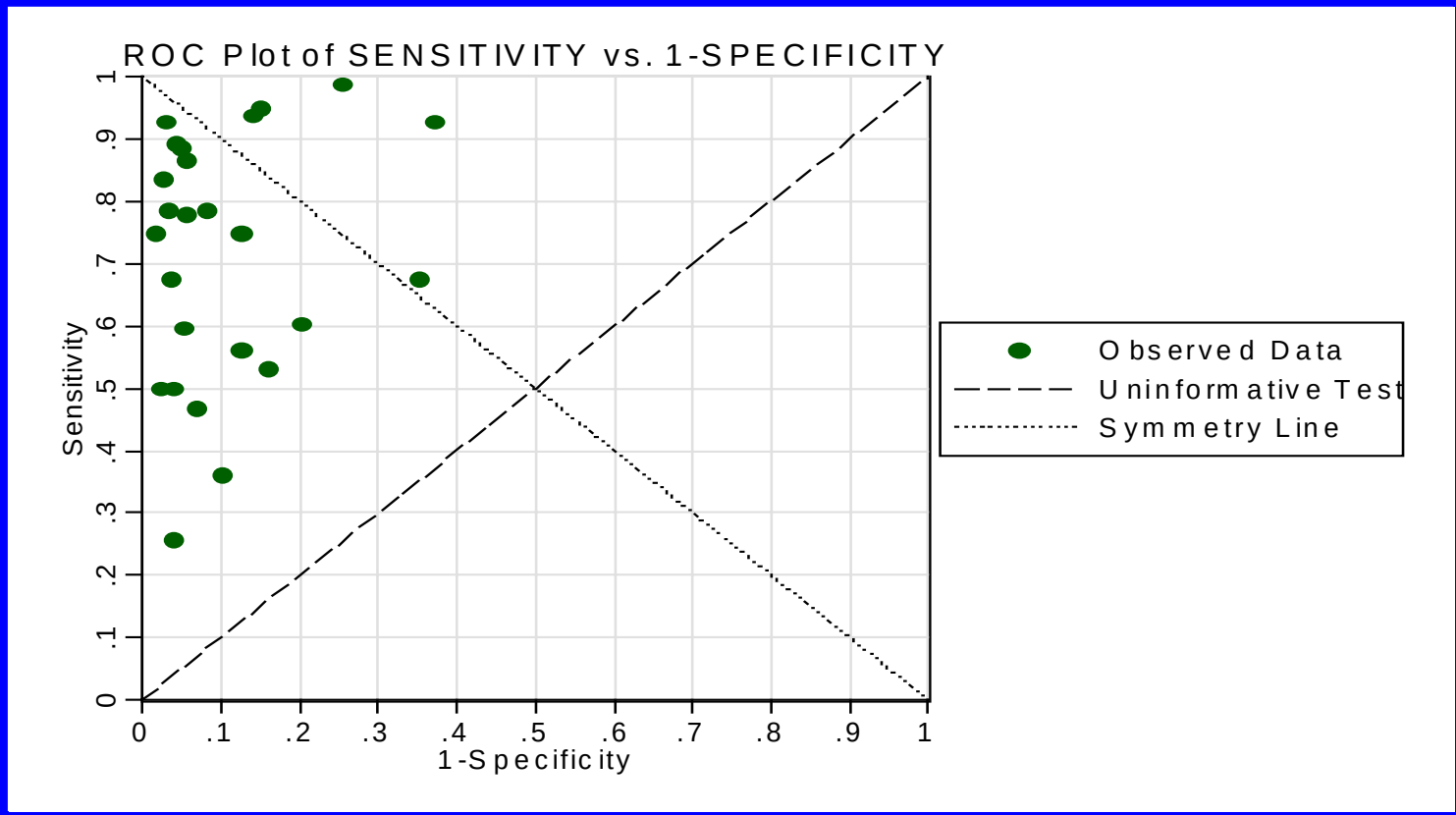
ROC PLOT

- A scatter plot true positive fraction (sensitivity) vs. false positive fraction (1-specificity)
- aids in visualization of range of results from primary studies

ROC PLOT

```
twoway (scatter TPF FPF, sort ) (lfit uTPR FPF, sort
range(0 1) clcolor(black) clpat(dash) clwidth(vthin)
connect(direct)) (lfit sTPR FPF, sort range(0 1)
clcolor(black) clpat(dot) clwidth(vthin)
connect(direct)),  ytitle(Sensitivity) ylabel(0(.1)1, grid)
xtitle(1-Specificity) xlabel(0(.1)1, grid) title(ROC Plot
of SENSITIVITY vs. 1-SPECIFICITY, size(medium))
legend(pos(3) col(1) lab(1 "Observed Data") lab(2
"Uninformative Test") lab(3 "Symmetry Line"))
saving(ROCplot, replace) plotregion(margin(zero))
```

ROC PLOT


ROC Plot of SENSITIVITY vs. 1-SPECIFICITY
Sensitivity
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
1-Specificity
Observed Data
Uninformative Test
Symmetry Line

LINEAR REGRESSION MODELS

ORDINARY LEAST SQUARES METHOD:

Studies are weighted equally

WEIGHTED LEAST SQUARES METHOD:

Weighted by the inverse variance weights of the odds ratio, or simply the sample size

ROBUST-RESISTANT METHOD:

Minimizes the influence of outliers

REGRESSION ANALYSIS

- Logit transformations of the TP rate (sensitivity) and FP rate (1 - specificity).

$$D=\ln(DOR) = \text{logit}(TPR) - \text{logit}(FPR)$$

- Differences in logit transformations, D, regressed on sums of logit transformations, S.

$$S=\text{logit}(TPR)+\text{logit}(FPR)$$

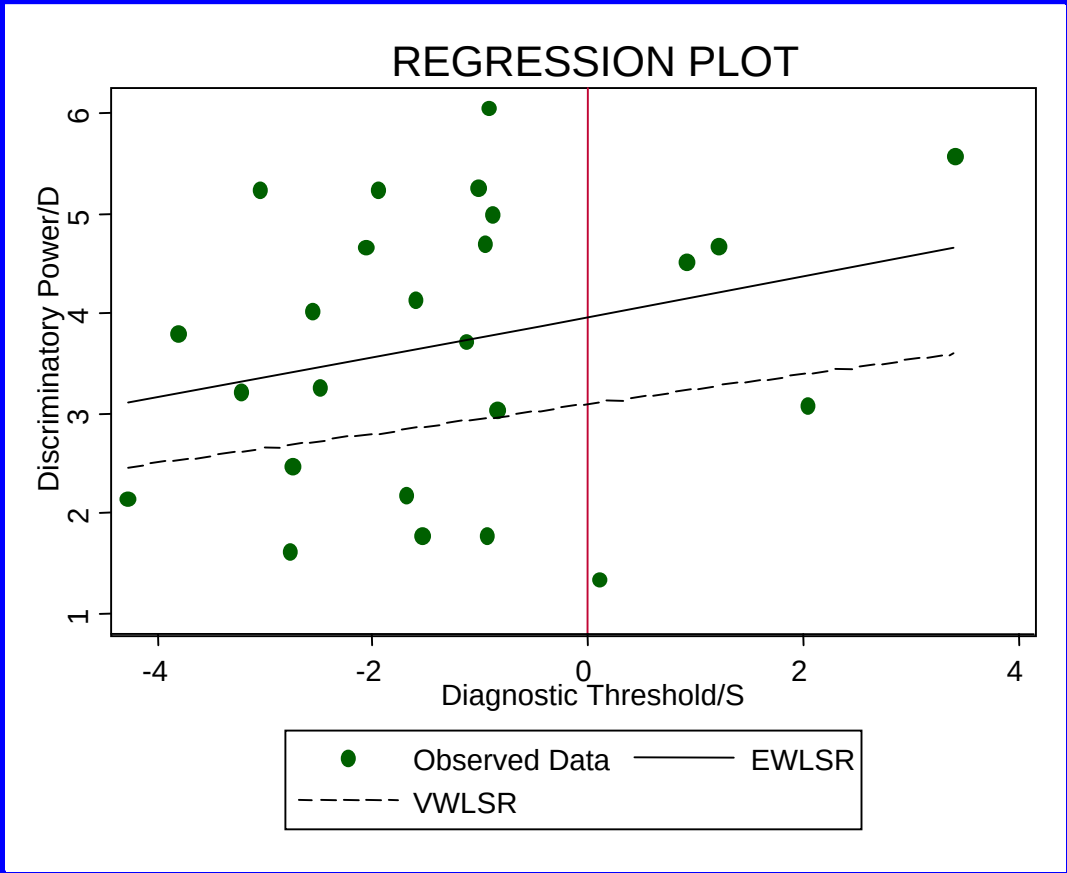
- Logit(TPR)=natural log odds of a TP result and logit(FPR) =natural log of the odds of a FP test result.

ACCURACY-THRESHOLD

STATA SYNTAX/COMMAND

- twoway (scatter D S, sort msymbol(circle)) (lfit tfitted S, clcolor(black) clpat(solid) clwidth(thin) connect(direct))(lfit wfitted S, clcolor(black) clpat(dash) clwidth(thin) connect(direct)), ytitle(Discriminatory Power/D) xtitle(Diagnostic Threshold/S) title(REGRESSION PLOT) legend(lab(1 "Observed Data")lab(2 "EWLSR")lab(3 "VWLSR"))saving(regplot, replace) xline(0) yscale(noline)

ACCURACY-THRESHOLD



SUMMARY ROC CURVE

- Back transformation of logistic regression to conventional axes of sensitivity [TPR] vs. (1 – specificity) [FPR]) with the equation
- $TPR = 1/\{1 + \exp[- a/(1 - b)]\}$ $[(1 - FPR)/(FPR)]^{(1 + b)/(1 - b)}$.
- Slope (b) and intercept (a) are obtained from the linear regression analyses

SUMMARY ROC CURVES

- STATA SYNTAX/COMMAND
- twoway (scatter TPF FPF, sort msymbol(circle) msize(medium) mcolor(black))(fpfit tTPR FPF, clpat(dash)clwidth(medium) connect(direct))(fpfit wTPR FPF, clpat(solid)clwidth(medium) connect(direct))(lfit uTPR FPF, sort range(0 1) clcolor(black) clpat(dash) clwidth(thin) connect(direct)) (lfit sTPR FPF, sort range(0 1) clcolor(black) clpat(dot) clwidth(medium) connect(direct)), ytitle(Sensitivity/TPF) yscale(range(0 1)) ylabel(0(.2)1,grid) xtitle(1-Specificity/FPF) xscale(range(0 1)) xlabel(0(.2)1, grid) legend(lab(1 "Observed Data")lab(2 "EWLSR")lab(3 "VWLSR")lab(4 "RRLSR")lab(5 "Uninformative Test") lab(6 "Symmetry Line") pos(3) col(1)) title(SUMMARY ROC CURVES) graphregion(margin(zero)) saving(aSROCplot, replace)

SUMMARY ROC CURVES