MIDAS RETOUCH REGARDING DIAGNOSTIC ACCURACY META-ANALYSIS

Ben A. Dwamena, MD
University of Michigan Radiology and VA Nuclear Medicine, Ann Arbor

2014 Stata Conference, Boston, MA - July 31, 2014

Medical Diagnostic Test

Any measurement aiming to identify individuals who could potentially benefit from preventative or therapeutic intervention

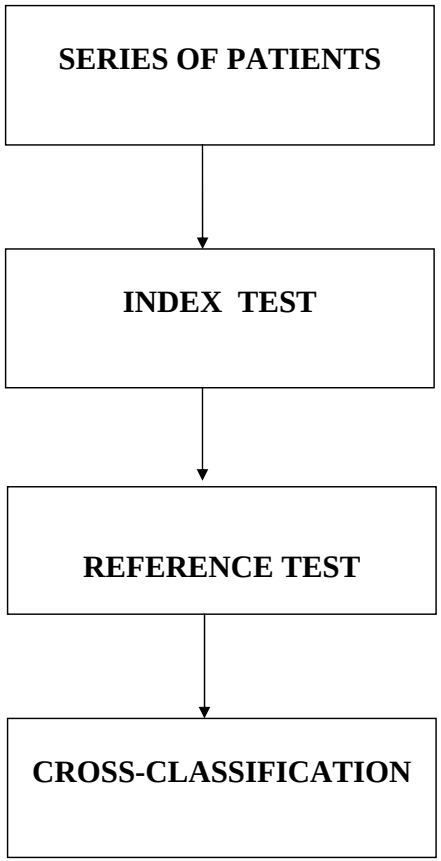
This includes:

1. Elements of medical history
2. Physical examination
3. Imaging procedures
4. Laboratory investigations
5. Clinical prediction rules

University of Michigan
Medical School

Diagnostic Accuracy Studies

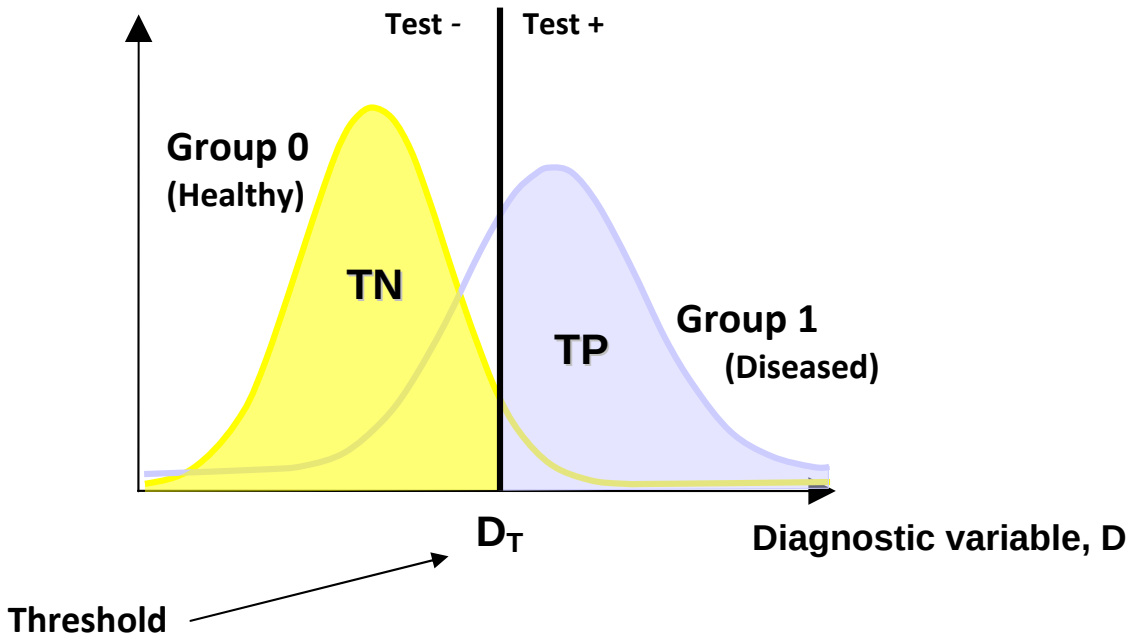
Figure: Basic Study Design



University of Michigan
Medical School

Diagnostic Accuracy Studies

Figure: Distributions of test result for diseased and non-diseased populations defined by threshold (DT)



University of Michigan
Medical School

Diagnostic Test Performance

1. The performance of a diagnostic test assessed by comparison of index and reference test results on a group of subjects
2. Ideally these should be patients suspected of the target condition that the test is designed to detect.

Binary test data often reported as 2×2 matrix

	Reference Test Positive	Reference Test Negative
Test Positive	True Positive	False Positive
Test Negative	False Negative	True Negative

University of Michigan Medical School

Measures of Diagnostic Performance

Sensitivity (true positive rate)	The proportion of subjects with disease who are correctly identified as such by test
Specificity (true negative rate)	The proportion of subjects without disease who are correctly identified as such by test
Positive predictive value	The proportion of test positive subjects who truly have disease
Negative predictive value	The proportion of test negative subjects who truly do not have disease

University of Michigan Medical School

Measures of Diagnostic Performance

Likelihood ratios (LR)	The ratio of the probability of a positive (or negative) test result in the patients with disease to the probability of the same test result in the patients without the disease
Diagnostic odds ratio	The ratio of the odds of a positive test result in patients with disease compared to the odds of the same test result in patients without disease.
ROC Curve	Plot of all pairs of (1-specificity, sensitivity) as positivity threshold varies

University of Michigan
Medical School

Meta-analysis

1. Glass(1976)
   Meta-analysis refers to the statistical analysis that combines the results of some collection of related studies to arrive at a single conclusion to the question at hand

2. Meta-analysis may be based on aggregate patient data (APD meta-analysis) or individual patient data (IPD meta-analysis)

University of Michigan
Medical School

Meta-analytical Methods

1. Meta-analysis of sensitivity and specificity separately by direct pooling or modeling using fixed-effects or random-efffects approaches

2. Meta-analysis of postive and negative likelihood ratios separately using fixed-effects or random-efffects approaches as applied to risk ratios in meta-analysis of therapeutic trials

3. Meta-analysis of diagnostic odds ratios using fixed-effects or random-efffects approaches as applied to meta-analysis of odds ratios in clinical treatment trials

4. Summary ROC Meta-analysis using fixed-effects or random-efffects approaches

Summary ROC methods provide the most general approach

University of Michigan Medical School

Summary ROC Meta-analysis of Diagnostic Test Accuracy

The most commonly used and easy to implement method

1. Linear regression analysis of the relationship
   D = **a** + **b**S where :
   D = (logit TPR) - (logit FPR) = ln DOR
   S = (logit TPR) + (logit FPR) = proxy for the threshold

2. **a** and **b** may be estimated by weighted or unweighted least squares or robust regression, back-transformed and plotted in ROC space

3. Differences between tests or subgroups may examined by adding covariates to model

University of Michigan
Medical School

Summary ROC Meta-analysis of Diagnostic Test Accuracy

1. Assumes variability in test performance due only to threshold effect and within-study variability
2. Does not provide average estimates of sensitivity and specificity
3. Continuity correction may introduce non-negligible downward bias to the estimated SROC curve
4. Does not account for measurement error in S
5. Ignores potential correlation between D and S
6. Confidence intervals and p-values are likely to be inaccurate

University of Michigan
Medical School

Threats to Validity of Diagnostic Meta-analysis Results

Valid meta-analyses of test accuracy must account for the following :

1. Threshold Effects
2. Unobserved heterogeneity
3. Methodological quality bias
4. Explainable Heterogeneity
5. Publication and other sample size-related bias

University of Michigan
Medical School

Extent of Heterogeneity

1. Assessed statistically using the quantity I^2 described by Higgins and colleagues
2. Defined as percentage of total variation across studies attributable to heterogeneity rather than chance
3. I^2 is alculated as:

$$I^2 = ((Q - df)/Q) \times 100.$$

Q is Cochran's heterogeneity statistic; **df** equals degrees of freedom.

University of Michigan
Medical School

Extent of Heterogeneity

1. I^2 lies between 0% and 100%
2. 0% indicates no observed heterogeneity
3. Greater than 50% considered substantial heterogeneity
4. Advantage of I^2 : does not inherently depend on the number of the studies

University of Michigan
Medical School

Explaining Heterogeneity: Meta-regression

Formal investigation of sources of heterogeneity is performed by meta-regression:
a collection of statistical procedures (weighted/unweighted linear, logistic regression) in which the study effect size is regressed on one or several covariates

University of Michigan
Medical School

Bivariate Random-Effects Model

Recommended hierarchical model for meta-analysis of binary test data (a generalized linear mixed model with **binomial** family and **logit** link function (commonly) but may use probit or complementary log-log)

1. Joint modeling of sensitivity(Se) and specificity (Sp)
   - Preserves bivariate data structure.
   - Estimates between-study heterogeneity and any existing correlation between these two measures (often due to threshold effects) via random effects.
2. Provides informative clinical results.
   - summary sensitivity, specificity, diagnostic odds ratio and likelihood ratios.
   - summary receiver operating curve (SROC)

University of Michigan
Medical School

Meta-analysis of sensitivity and specificity

Specification of Bivariate Model

$$\mathbf{TN}^i|\mu_i \sim \mathbf{Bin}(\mathbf{TN}^i + \mathbf{FP}^i, \mathbf{Sp}^i)$$

$$\mathbf{logit}(\mathbf{Sp}^i) = \mathbf{X}_i\alpha + \mu_i$$

$$\mathbf{TP}^i|\nu_i \sim \mathbf{Bin}(\mathbf{TP}^i + \mathbf{FN}^i, \mathbf{Se}^i)$$

$$\mathbf{logit}(\mathbf{Se}^i) = \mathbf{Z}_i\beta + \nu_i$$

$$\begin{pmatrix}\mu_i \\ \nu_i\end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix}0 \\ 0\end{pmatrix}, \begin{pmatrix}\sigma_\mu & \rho\sigma_\mu\sigma_\nu \\ \rho\sigma_\mu\sigma_\nu & \sigma_\nu\end{pmatrix}\right]$$

University of Michigan
Medical School

Meta-analysis of sensitivity and specificity

Bivariate Model

- The index i represents study i in the meta-analysis.
- TN, FP, TP and FN represent the number of true negatives, false positives, true positives, and false negatives.
- $\mathbf{Sp} = \frac{\mathbf{TN}}{\mathbf{TN}+\mathbf{FP}}$ and $\mathbf{Se} = \frac{\mathbf{TP}}{\mathbf{TP}+\mathbf{FN}}$.
- $\mathbf{X}_i, \mathbf{Z}_i$ represent possibly overlapping vectors of covariates related to **Sp** and **Se**
- The covariance matrix of the random effects μ and ν is parameterized in terms of the between-study variances σ^2_μ and σ^2_ν and the correlation ρ

University of Michigan
Medical School

Estimation

1. Maximizing an approximation to the likelihood integrated over the random effects.
2. Different integral approximations are available, with adaptive Gaussian quadrature as method of choice
3. Requires a number of quadrature points to be specified
4. Estimation accuracy increases as the number of points increases, but at the expense of an increased computational time.

University of Michigan
Medical School

Stata-native commands

1. Before Stata 10: **gllamm**

```
gllamm ttruth disgrp1 disgrp2, nocons i(study) nrf(2) eqs(disgrp1 disgrp2) ///
f(bin) l(logit) denom(num) adapt ip(m) nip(nip)
```

2. Stata 10: **xtmelogit**

```
xtmelogit (ttruth disgrp1 disgrp2, noc)(study: disgrp1 disgrp2, noc cov(unstr)), ///
bin(num) laplace var nofet noret nohead refineopts(iterate(4))
```

3. Stata 13: **meglm and company**

```
meglm (ttruth disgrp1 disgrp2, noconstant)(study: disgrp1 disgrp2, noconstant ///
cov(exch)), family(binomial _num) notab nohead nolr nogr dnumerical
```

```
meglm (ttruth disgrp1 disgrp2, noconstant)(study: disgrp1 disgrp2, noconstant ///
cov(exch)), family(binomial _num) link(probit) notab nohead nolr nogr
```

University of Michigan
Medical School

User-written dedicated commands

1. Before Stata 10: **midas** (v. 1.0, August 2007)
2. Stata 10: **midas** (v.2.0, December 2008) and **metandi** (March2008)
3. Stata 13: **midas** v.3.0

University of Michigan
Medical School

metandi

An estimation commmand by Roger Harbord, University of Bristol

1. Performs meta-analysis of diagnostic test accuracy studies in which both the index test under study and the reference test (gold standard) are dichotomous.

2. Fits two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives within each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies.

University of Michigan
Medical School

metandi

1. Estimates are displayed for the parameters of both the bivariate model and the Hierarchical Summary Receiver Operating Characteristic (HSROC) model
2. In Stata 8 or 9, makes use of the user-written command gllamm.
3. In Stata 10 metandi uses xtmelogit by default.
4. Limited analytic and graphic options

University of Michigan
Medical School

midas v.1.0, v2.0

A comprehensive and medically popular program for diagnostic test accuracy meta-analysis.

1. Implementation of some of the contemporary statistical methods for meta-analysis of binary diagnostic test accuracy.

2. Primary data synthesis is performed within the bivariate mixed-effects logistic regression modeling framework.

3. Likelihood-based estimation is by adaptive gaussian quadrature using gllamm(version 1.0) or xtmelogit (version 2.0)

University of Michigan
Medical School

midas v.1.0, v2.0

1. Average sensitivity and specificity (optionally depicted in SROC space with or without confidence and prediction regions), and their derivative likelihood and odds ratios are calculated from the maximum likelihood estimates.

2. facilitates exploratory analysis of heterogeneity, threshold-related variability, methodological quality bias, publication and other precision-related biases.

3. Bayes' nomograms, likelihood-ratio matrices, and probability modifying plots may be derived and used to guide patient-based diagnostic decision making.

University of Michigan
Medical School

midas v.1.0, v2.0

Relevant sources/documentation

1. midas from http://fmwww.bc.edu/RePEc/bocode/m
2. help file in pdf form. http://fmwww.bc.edu/repec/bocode/m/midas.pdf
3. Meta-analytical integration of diagnostic accuracy studies in Stata http://repec.org/nasug2007/BD-nasug2007.ppt
4. Meta-analytical integration of diagnostic accuracy studies in Stata http://repec.org/wcsug2007/Dwamena-wsug2007.pdf

University of Michigan
Medical School

midas v3.0

Updated for Stata 13

1. Estimation command and a wrapper for meglm in Stata 13.
2. Flexibility for specifying covariance structures.
3. Link functions other than logit (e.g. probit, cloglog).
4. Extensive post-estimation options and specification of starting values (especially with sparse data).
5. Univariate (independent) versus bivariate (correlated) modeling of sensitivity and specificity.

University of Michigan
Medical School

Data transformation

1. **Binomial or Bernoulli**

```
gen study = _n
gen ttruth1 = tn
gen ttruth2 = tp
gen num1 = tn+fp
gen num2 = tp+fn
reshape long num ttruth, i(study) j(dtruth) string
tabulate dtruth, generate(disgrp)
```

2. **Bernoulli**

```
gen freq=1
bin2bern ttruth, fw(freq) binomial(num)
```

University of Michigan
Medical School

midas 3.0

Flexible Covariance structures

1. **Independent**: one unique variance parameter per random effect, all covariances 0
2. **Exchangeable**: equal variances for random effects, and one common pairwise covariance
3. **Identity**: equal variances for random effects, all covariances 0
4. **Unstructured**: all variances and covariances to be distinctly estimated

University of Michigan
Medical School

midas 3.0

Alternative Link Functions

University of Michigan
Medical School

midas 3.0

Univariate (independent) versus bivariate (correlated) modeling

	Disparate Variances	Equal Variances
Bivariate	Unstructured	Exchangeable
Univariate	Independent	Identity

University of Michigan
Medical School

midas 3.0

Estimation Syntax

```
midas varlist(min=4 max=4) [if] [in] , [ID(varname) Link(string)
NIP(integer 20) VARiance(string) noNUMerical SORTby(varlist
min=1) LEVEL(integer 95) noESTimates FITstats noHEADer ]
```

University of Michigan
Medical School

midas 3.0

Replay/Post-estimation Syntax

```
midas [if] [in] , [Level(cilevel) FITstats noHEADer noESTimates
UPVstats(numlist min=2 max=2) FORest SROC(string) FAGAN(numlist
min=1 max=3) CONDIProb(string) LRMatrix(string) LINPred FITted
MODdiag XSIZE(passthru) YSIZE(passthru) TITLE(passthru) cc(real
0.5) MScale(real 0.90) TEXTScale(real 0.90) CSIZE(real 36)
SCHEME(passthru) GRSave(string) XTITLE(passthru)
YTITLE(passthru)]
```

University of Michigan
Medical School

parameter	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
thetaspe	2.06	0.40	5.15	0.00	1.28	2.85
thetasen	1.23	0.37	3.36	0.00	0.51	1.94
tausqspe	1.16	0.50	2.32	0.02	0.18	2.14
tausqsen	1.16	0.50	2.32	0.02	0.18	2.14
covtausq	-0.54	0.46	-1.18	0.24	-1.44	0.36

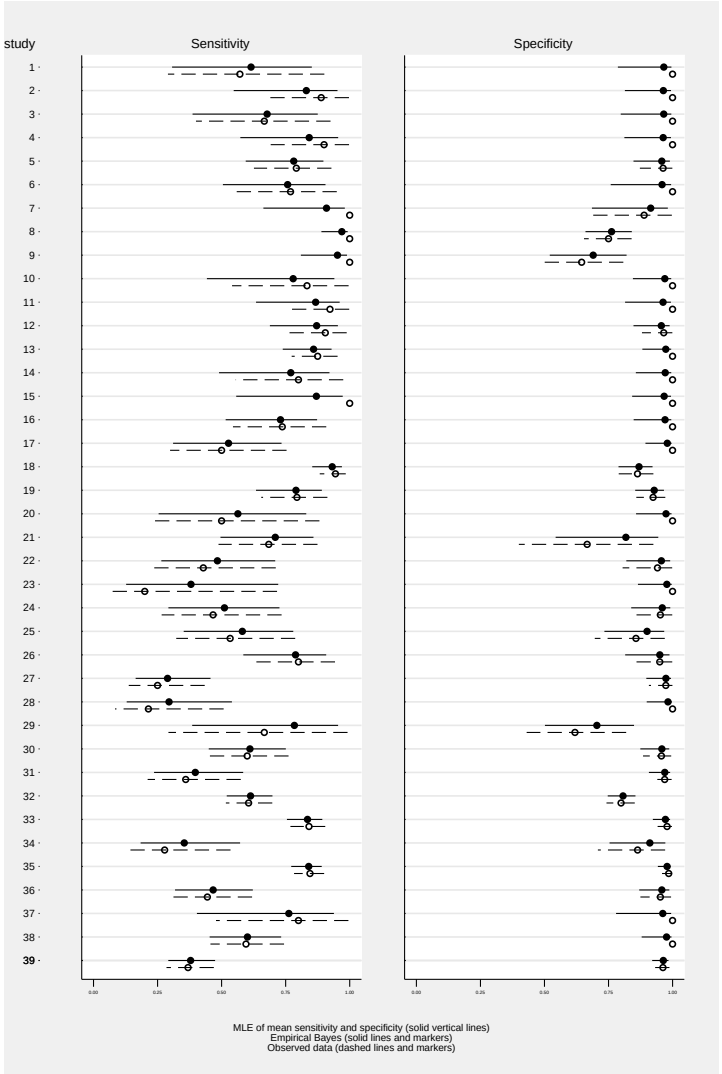
parameter	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Sens	0.77	0.06	12.07	0.00	0.65	0.90
Spec	0.89	0.04	22.13	0.00	0.81	0.97
DOR	3.29	0.43	7.59	0.00	2.44	4.14
LRP	6.85	2.29	2.99	0.00	2.36	11.34
LRN	0.26	0.07	3.71	0.00	0.12	0.39

parameter	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Isqspe	0.65	0.08	7.67	0.00	0.48	0.82
Isqsen	0.82	0.05	16.45	0.00	0.72	0.91
Isqbiv	0.72	0.06	12.41	0.00	0.61	0.83

University of Michigan
Medical School

Empirical Bayes predicted versus observed test outcomes

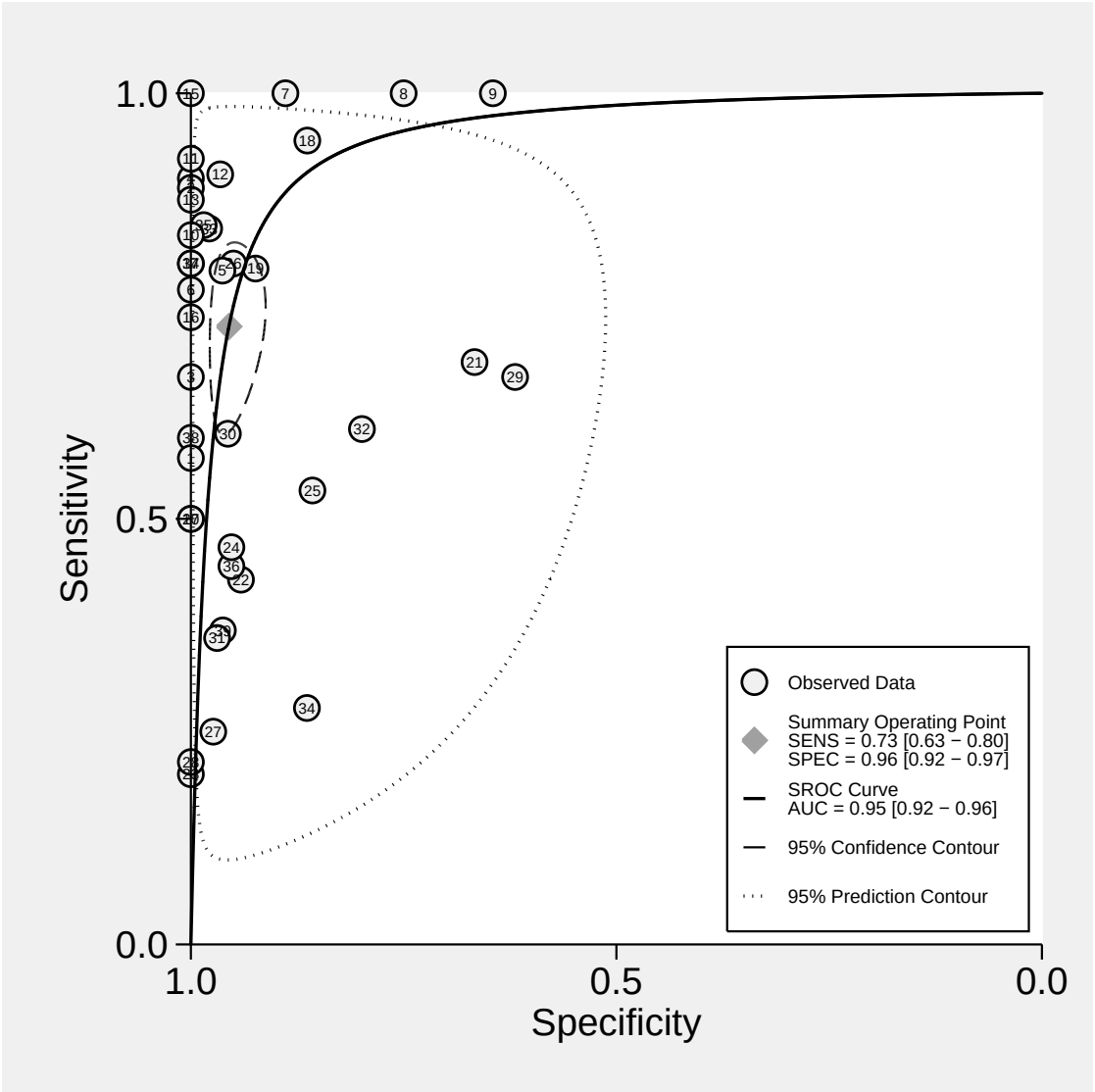
midas, ebpred(forest)



University of Michigan
Medical School

Summary ROC curve

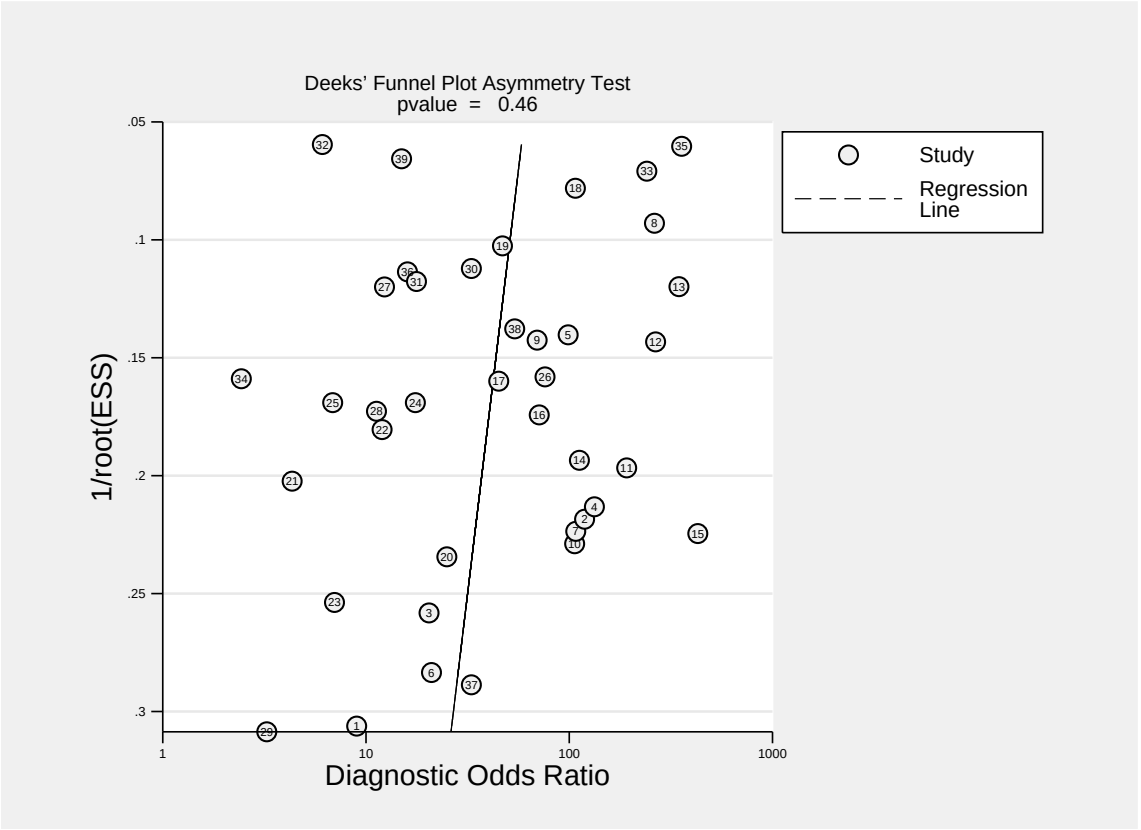
midas, sroc(pred conf mean curve)



University of Michigan
Medical School

Funnel plot with superimposed regression line

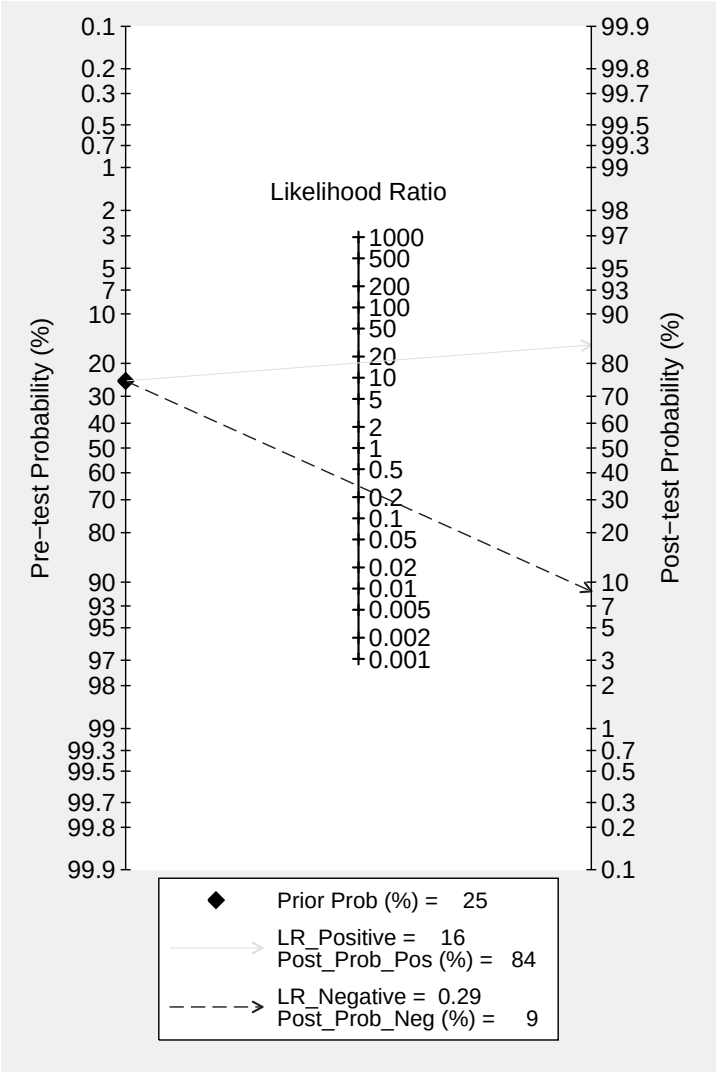
midas, pubbias



University of Michigan
Medical School

Fagan plot (Bayes Nomogram)

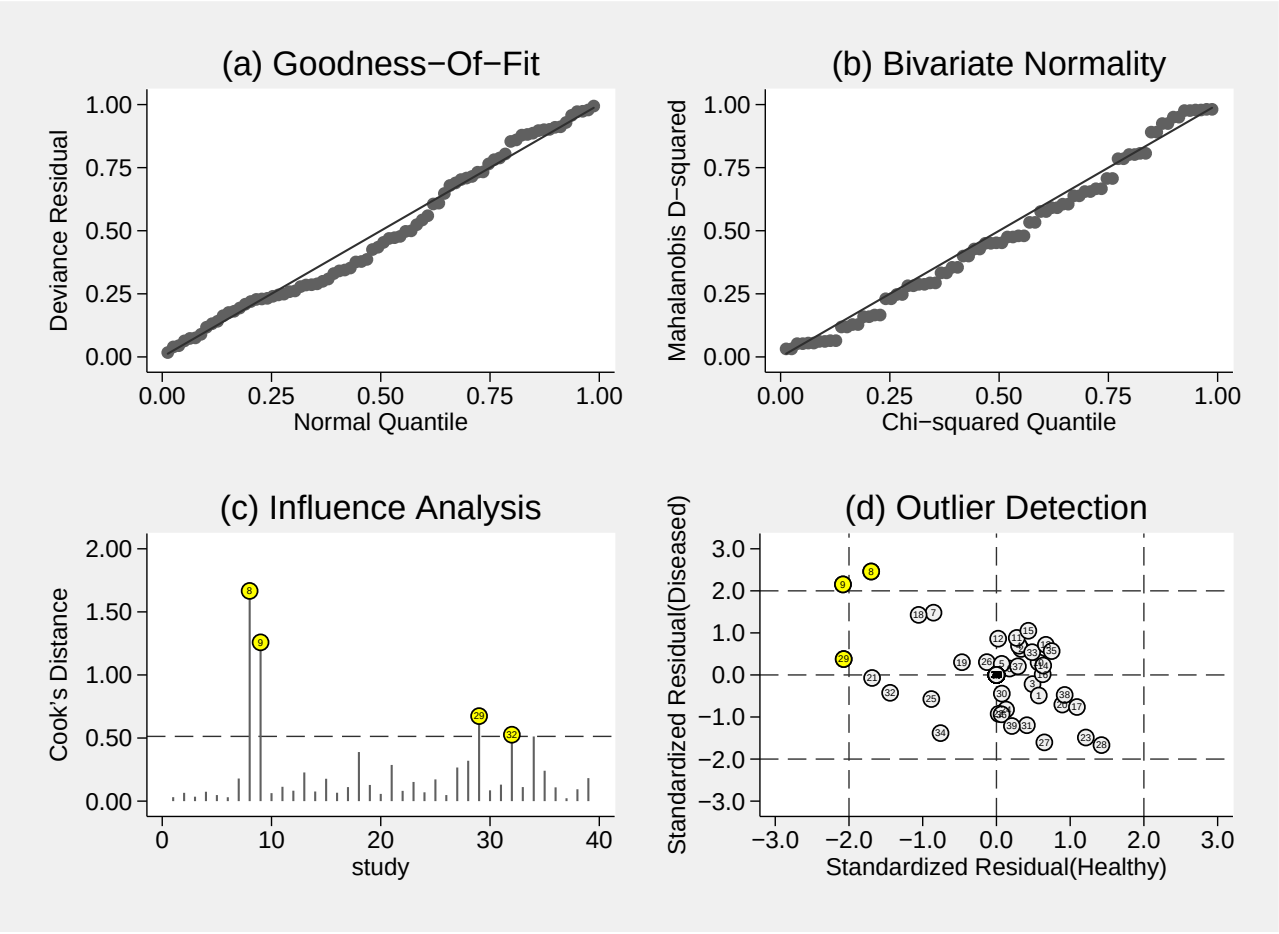
midas, fagan(0.25)



University of Michigan
Medical School

Residual-based goodness-of-fit, bivariate normality, influence and outlier detection analyses

midas, moddiag



University of Michigan Medical School

CONCLUDING REMARKS

1. Ado-file will be available shortly after conference on SSC.
2. To include bayesian estimation in future version
3. Thanks for your rapt attention

University of Michigan
Medical School