MIDASINLA: MIDAS GOES BAYESIAN VIA R-INLA

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Outline

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Diagnostic Meta-analysis

Methodological Concepts

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)

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Meta-Analysis Of Sensitivity And Specificity

The majority of analytic methods assume that data from every study consist of the four numbers relating to how the test categorizes individuals at a particular threshold

	Reference Test (Diseased)	Reference Test (Healthy)
Test Positive	True Positive (a)	False Positive (b)
Test Negative	False Negative (c)	True Negative (d)

Sensitivity (true positive rate) The proportion of subjects with disease who are correctly identified as such by test (a/a+c)

Specificity (true negative rate) The proportion of subjects without disease who are correctly identified as such by test (d/b+d)

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Meta-Analysis Of Sensitivity And Specificity

Numerous meta-analysis methods exist for combining binary diagnostic test results from multiple studies including:

1. Meta-analysis of sensitivity and specificity separately by
   - Direct Pooling
   - Fixed-Effects Modeling
   - Random-Effects Modeling
2. Summary ROC (Logit-Threshold) Meta-analysis
3. Joint Statistical Modeling Of Sensitivity And Specificity With Mixed Effects Models:
   - Bivariate Random-effects Model
   - Hierarchical Summary ROC Regression Model

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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)

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)

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With-in Study Variability

$$TN_i|\mu_i \sim Bin(TN_i + FP_i, Sp_i)$$

$$TP_i|\nu_i \sim Bin(TP_i + FN_i, Se_i)$$

$$logit(Sp_i) = X_i\alpha + \mu_i$$

$$logit(Se_i) = Z_i\beta + \nu_i$$

1. The index i represents study i in the meta-analysis.
2. TN_i, FP_i, TP_i and FN_i represent the number of true negatives, false positives, true positives, and false negatives.
3. X_i, Z_i represent possibly overlapping vectors of covariates.

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Between-Study Variability

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

1. 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
2. The correlation parameter is constrained to $[-1, 1]$.

3. The correlation parameter, ρ, may be reparameterized using Fisher's z-transformation as

$$\rho^\star = \textbf{logit}\left(\frac{\rho+1}{2}\right)$$

which assumes values over the whole real line.

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Frequentist 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.

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midas: Stata Module for Frequentist Estimation

1. **midas** (acronym for meta-analytical integration of diagnostic test accuracy studies), a user-written command for implementation of some of the contemporary statistical methods for meta-analysis of 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 **xtmelogit** (Stata release 10) with post-estimation procedures for model diagnostics and empirical Bayes predictions.

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midas: Stata Module for Frequentist Estimation

1. Summary 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.

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Limitations of Classical Estimation

1. Frequentist estimation techniques are fraught with nonconvergence
2. May produce invalid Wald-based confidence intervals and correlation parameters, especially with sparse data.
3. Bayesian approaches may surmount these and other problems

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Objective

Provide **Stata** users with a user-friendly alternative module for diagnostic accuracy meta-analysis:

1. Accurate and reliable in the presence of sparse data and/or after failure of likelihood-based estimation

2. Powered by deterministic Bayesian inference using integrated nested Laplace approximations (INLA) instead of stochastic simulation by Markov Chain Monte Carlo Methods

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Motivation

" ....The possibility of using the bivariate and hierarchical summary receiver operating characteristics methods for pooling the indices was explored using the modules **metandi** and **midas** in Stata; however, these models converged only for the overall MR measure. For the other measures, the numbers in the cells of the 2X2 tables were small; therefore, the models either failed or produced an estimate of the between-study correlation of -1 or +1, which is likely to be associated with nonconvergence and unstable pooled estimates....."-Thayyil et al.

Cerebral Magnetic Resonance Biomarkers in Neonatal Encephalopathy: A Meta-analysis. Pediatrics 2010; 125(2):e382-e395

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Motivation

Riley and colleagues re-analyzed 10 studies included in the review by Glas et al. of the telomerase marker for the diagnosis of bladder cancer. For this data set, estimation problems were reported by Riley et al. who

- Used PROC NLMIXED for the analysis of a generalized bivariate random effects meta-analysis model.
- Tried different starting values all resulting in an estimated between-study correlation of -1, differing parameter estimates and very large standard errors.
- Cited the small number of studies as a cause of their estimation problem, especially the inability to estimate the correlation parameter.

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Architecture Of Presentation

1. Provide an overview of integrated nested Laplace approximation (INLA) as an alternative bayesian method.

2. Discuss application of an **R** interface to the C-based INLA program to bivariate diagnostic meta-analysis.

3. Exemplify application of INLA by means of a user-written ado-file integrating **R-INLA** estimation with pre- and post-estimation data processing within **Stata**.

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Bayesian Inference

1. Model parameters are random quantities and subject to prior knowledge.
2. Bayesian analysis starts with the specification of a posterior model.
3. The posterior model describes the probability distribution of all model parameters conditional on the observed data and some prior knowledge.

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Bayesian Inference

1. The posterior distribution has two components: a likelihood, which includes information about model parameters based on the observed data, and a prior, which includes prior information (before observing the data) about model parameters.

2. The likelihood and prior models are combined using the Bayes rule to produce the posterior distribution.

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Bayesian Inference

1. The posterior distribution is used to derive
   - point estimates such as posterior means, medians, percentiles.
   - interval estimates such as credible intervals.
2. Statistical tests can be expressed as probability statements based on the estimated posterior distribution.

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Bayesian Markov Chain Monte Carlo Simulation

Bayesian approaches commonly use MCMC methods:

1. Metropolis algorithm proposed in Metropolis and Ulam (1949) and Metropolis et al. (1953) which generates a sequence of states, each obtained from the previous one, according to a Gaussian proposal distribution centered at that state.

2. Gibbs sampling(Gelfand et al. 1990), where the updates are the full conditional distributions of each parameter given the rest of the parameters.

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Bayesian Markov Chain Monte Carlo Simulation

1. Bayesian inference based on an MCMC sample is valid only if the Markov chain has converged and the sample is drawn from the desired posterior distribution.

2. It is important that we verify the convergence for all model parameters and not only for a subset of parameters of interest.

3. The problem with assessing convergence of MCMC is that there is no single conclusive convergence criterion.

4. The diagnostic usually involves checking for several necessary (but not necessarily sufficient) conditions for convergence.

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Bayesian Markov Chain Monte Carlo Simulation

MCMC methods are not without limitations, in particular,

1. Successive values in a chain may be strongly dependent, so the values in the chain cannot be treated as a random sample from the posterior.
2. The chain requires starting values and choice will influence the early part of the chain
3. difficult to decide how long the chain needs to be run to adequately represents the posterior probabilities of the candidate models.

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Integrated Nested Laplace approximation (INLA)

1. INLA is a new approach to Bayesian implementation of latent Gaussian models

2. A latent Gaussian model is a hierarchical model with **non-Gaussian response variables** and a **Gaussian latent field** controlled by a few **hyperparameters**.

3. These include (generalized) linear mixed, dynamic, spatial and spatiotemporal models

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Integrated Nested Laplace approximation (INLA)

1. INLA provides approximations to the posterior marginals of the latent variables which are both very accurate and extremely fast to compute
2. INLA uses deterministic approximations instead of simulation/sampling
3. INLA treats latent Gaussian models in a general way, thus allowing for a great deal of automation in the inferential procedure

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INLA Algorithm

Combination of Laplace approximations and numerical integration to directly approximate in 3 steps:

$$\pi(x_i|y) = \int_\theta \pi(x_i|\theta, y)\pi(\theta|y)d\theta \tag{1}$$

1. Laplace approximation to $\pi(\theta|y)$.
2. Laplace approximation (or its simplified version) to $\pi(x_i|\theta, y)$.
3. Approximation of x_i by numerical computation of the integral as a finite sum

$$\tilde{\pi}(x_i|y) = \sum_k \tilde{\pi}(x_i|\theta_k, y) \times \tilde{\pi}(\theta_k|y) \times \Delta_k,$$

Posterior marginals for θ_j are similarly obtained from $\tilde{\pi}(\theta|y)$.

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INLA OUTPUT

1. The output of INLA consists of posterior marginal distributions, which can be summarized via means, variances, and quantiles.

2. Importantly for model comparison, the normalizing constant $p(y)$ is calculated. The evaluation of this quantity is not straightforward using MCMC

3. The deviance information criterion is popular as a model selection tool. In random-effects models, the implicit approximation in its use is valid only when the effective number of parameters is much smaller than the number of independent observations

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Software For Implementing INLA

1. The **inla** program is written in C and built on the open source **GMRFLib** library.

2. The model and options for INLA are specified through an **ini** file which is processed by **inla**.

3. An R-package called **INLA**, which works as an interface, is available with usage similar to the **glm** routine in **R**.

4. Both the **inla** program and the **R** package are available for Unix, Windows and Mac and freely downloadable from **http://www.R-INLA.org**.

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Bivariate Model As A Latent Gaussian Model

1. The **non-Gaussian response** is given in bivariate form: $y = (y_1, \ldots, y_I)^T$ where $y_i = (TP_i, TN_i)$ for $i = 1, \ldots, I$.

2. The **Hyperparameters** are $\theta = (\sigma^2_\mu, \sigma^2_\nu, \rho)^T$ assuming a zero-mean normal distribution with high variance such as 0.001^{-1} for the regression parameters (μ, ν, α and β)

3. The **Latent Gaussian Field** is $x = (\mu, \nu, \alpha^T, \beta^T, \mu^T, \nu^T)^T$ with $\mu = (\mu_1, \ldots, \mu_I)^T$, $\nu = (\nu_1, \ldots, \nu_I)^T$ and $\dim(x) = \dim(\alpha) + \dim(\beta) + 2(1 + I)$.

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Bivariate Model As A Latent Gaussian Model

Assuming that $\{y_i : i = 1, \ldots, I\}$ are conditionally independent the posterior distribution is given by

$$\pi(x, \theta|y) \propto \pi(\theta)\pi(x|\theta) \prod_i \pi(y_i|x_i, \theta),$$

where $\pi(\cdot|\cdot)$ denotes the conditional density of its arguments.

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Bivariate Model As A Latent Gaussian Model

We are mainly interested in the posterior marginals

$$\pi(x_i|y) = \int_\theta \underbrace{\int_{x_{-i}} \pi(x,\theta|y)dx_{-i}}_{\pi(x_i,\theta|y)=\pi(x_i|\theta,y)\pi(\theta|y)} \; d\theta,$$

$$\pi(\theta_j|y) = \int_{\theta_{-j}} \underbrace{\int_x \pi(x,\theta|y)dx}_{\pi(\theta|y)} \; d\theta_{-j}.$$

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Priors For Hyperparameters

The following prior distributions may be assigned to the hyperparameters:

$$\rho^\star \sim \mathcal{N}(0, 1/0.4)$$

The prior precision of 0.4 corresponds, roughly, to a uniform prior on $[-1, 1]$ for ρ. For the other hyperparameters we assign the following prior distributions

$$\log \tau_\mu \sim \text{LogGamma}(0.25, 0.025)$$
$$\log \tau_\nu \sim \text{LogGamma}(0.25, 0.025)$$

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Alternative Precision Matrix

Instead of specifying separate prior distributions for the hyperparameters we could also assume that the precision matrix

$$\mathbf{W} \sim \text{Wishart}_p(r, R^{-1}), \quad p = 2,$$

where the Wishart distribution has density

$$\pi(\mathbf{W}) = c^{-1}|\mathbf{W}|^{(r-(p+1))/2} \exp\left\{-\frac{1}{2}\text{Trace}(\mathbf{WR})\right\}, \quad r > p+1$$

and

$$c = 2^{(rp)/2}|\mathbf{R}|^{-r/2}\pi^{(p(p-1))/4}\prod_{j=1}^{p}\Gamma((r+1-j)/2).$$

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Alternative Precision Matrix

Then,

$$\mathrm{E}(\mathbf{W}) = r\mathbf{R}^{-1}, \quad \text{and} \quad \mathrm{E}(\mathbf{W}^{-1}) = \mathbf{R}/(r-(p+1)).$$

The parameters are r, R_{11}, R_{22} and R_{12}, where

$$R = \begin{pmatrix} R_{11} & R_{12} \\ R_{21} & R_{22} \end{pmatrix}$$

and $R_{12} = R_{21}$ due to symmetry. The `inla` function reports the posterior distribution for the hyperparameters $\log \tau_\mu, \log \tau_\nu$ and $\rho^\star$

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Example using R-INLA

Paul and colleagues re-analyzed 10 studies included in the review by Glas et al. of the telomerase marker for the diagnosis of bladder cancer. They compared the results of estimation by MCMC, INLA and NLMIXED. The estimates for μ , ν , and σ_μ are very similar over all approaches. The summary estimates of σ_μ, σ_μ and ρ are shown in table below:

	σ_μ	σ_μ	ρ
MCMC	0.40(0.18,0.82)	1.81(1.10,3.43)	-0.88(-0.99,-0.18)
INLA	0.41(0.21,0.79)	1.80(1.08,3.07)	-0.89(-0.99,-0.26)
NLMIXED	0.43(0.21,0.85)	1.82(1.04,3.18)	-1.00(-1.00,+1.00)

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Example using R-INLA

1. NLMIXED fails to report reliable estimates for the between-study correlation and estimates ρ to be -1 with confidence interval ranging from -1 to 1
2. A confidence interval covering the whole parameter space is uninformative
3. Neither of the Bayesian approaches show an estimation problem and both yield comparable results.

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Data Format

Data for the first 5 of 10 studies represented by two consecutive rows of data set.

	Y	N	tp	tn	diid
1	25	33	1	0	1
2	25	26	0	1	2
3	17	21	1	0	3
4	11	14	0	1	4
5	88	104	1	0	5
6	31	47	0	1	6
7	16	26	1	0	7
8	80	83	0	1	8
9	40	57	1	0	9
10	137	138	0	1	10

1. 1st row contains the number of diseased, TPs and an index.
2. 2nd row contains the number of non-diseased, TNs and an index.

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Specification

```
> formula <- Y~f(diid,model= "2diid",
+ param=c(0.25,0.025,.25,0.025,0,.2)) +
+ tp + tn - 1
```

1. The function **f(id, model="2diid", ...)** is used to define the bivariate mixed effects by setting **model="2diid"**.

2. The argument **param** contains parameters for prior distributions for each of the hyperparameters.

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Estimation

```
model = inla(formula,family="binomial", data=telomerase, Ntrials=N,
+ quantiles = quantiles, control.inla = list(strategy = "Laplace",
+ npoints=20, int.strategy = "grid", derived.only = FALSE),
+ control.compute = list(dic=T, cpo=T, mlik=T),
+ lincomb = list("tptn" = "tp 1 1 tn 1 1"))
```

1. The likelihood family and additional parameters are specified by calling the main function **inla()**.
2. More reliable estimates of the hyperparameters are obtained by specifying **hyper = inla.hyperpar(model)** to re-fit the model obtained by **inla()**.

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Case Study Description

1. PET or Positron Emission Tomography uses radiolabeled glucose analog to evaluate tumor metabolism
2. This radiological test may be used to stage and/or examine the extent of breast cancer
3. Uncertainty about the axillary staging performance of FDG-PET has fueled conflicting practice and policy decisions
4. A rigorous examination of the growing body of published data on axillary FDG-PET is needed

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Case Study Data Sources

1. Comprehensive computer search of English Language medical literature using primarily the PUBMED (MEDLINE) database
2. Cross-citation with other databases (such as EMBASE, ISI WEB OF KNOWLEDGE, Wiley Interscience, ScienceDirect)
3. Identification of original peer-reviewed full-length articles evaluating axillary FDG-PET in human subjects published between January 1, 1990 and January 31, 2008

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Case Study Data Sources

1. Search was conducted using database-specific Boolean search strategies based on: ("breast neoplasm" OR "breast cancer" OR "breast malignancy") AND ("Positron emission tomography" OR "FDG-PET") AND ("axillary staging" OR "axillary metastases" OR "axillary node metastases" OR "axillary node staging")

2. Search strategies were augmented with a manual search of reference lists from identified articles and recent subject-area journals for additional articles

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Case Study Data Set

Table: Dataset

Idnum	Author	Year	TP	FP	FN	TN	SIZE
1	Tse	1992	4	0	3	3	10
2	Adler1	1993	8	0	1	10	18
3	Hoh	1993	6	0	3	5	14
4	Crowe	1994	9	0	1	10	20
5	Avril	1996	19	1	5	26	51
6	Bassa	1996	10	0	3	3	16
7	Scheidhauer	1996	9	1	0	8	18
8	Utech	1996	44	20	0	60	124
9	Adler2	1997	19	11	0	20	50
10	Palmedo	1997	5	0	1	14	20
11	Noh	1998	12	0	1	11	24
12	Smith	1998	19	1	2	28	50
13	Rostom	1999	42	0	6	26	74
14	Yutani1	1999	8	0	2	16	26
15	Hubner	2000	6	0	0	16	22
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
32	Wahl	2004	66	40	43	159	308
33	Zornoza	2004	90	2	17	91	200
34	Weir	2005	5	3	13	19	40
35	Gil-Rendo	2006	120	2	22	131	275
36	Kumar	2006	16	2	20	40	80
37	Stadnik	2006	4	0	1	5	10
38	Chung	2006	25	0	17	18	51
39	Veronesi	2006	38	5	65	128	236
40	Cermik	2008	40	15	39	125	219
41	Ueda	2008	34	6	25	118	183
42	Fuster	2008	14	0	6	32	52
43	Heuser	2008	8	0	2	20	30

Programming Framework

midasinla

1. Generates **R** script using the "file open", "file write" and "file close" commands in **Stata**
2. Transforms test data into **INLA** format and export to **R** as comma-separated data
3. Runs **R** script in batch mode using user-written **rsource** adofile
   To install type in Stata command prompt : **"ssc install rsource"**
4. Processes and displays exported **INLA** results in **Stata**

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Estimation Syntax for midasinla

```
syntax varlist(min=4  max=4) [if] [in] [, ID(varname)
Link(string)  WISHart APProximation(string)
INTegration(string)   NIP(integer 20)   MANual
SORTby(varlist min=1) Rout  HPD Level(cilevel)
noESTimates FITstats noHEADer REVman   *];
```

- The required **varlist** is the data from the contingency tables of index and reference test results.
- Each data row contains the 2x2 data for one observation (i.e. study).
- The **varlist** MUST contain variables for *a*, *b*, *c* and *d* in that order:

	Reference Test (Diseased)	Reference Test (Healthy)
Test Positive	True Positive (a)	False Positive (b)
Test Negative	False Negative (c)	True Negative (d)

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Estimation Syntax for midasinla: options

1. **Link**(string) Choice of logit (default), probit or cloglog
2. **WISHart** Use the inverse wishart prior for variance-covariance hyperparameters
3. **APProximation**(string) The strategy to use for the approximations; one of "gaussian", "simple" or "laplace" (default)
4. **INTegratio**n(string) The integration strategy to use; one of "grid"(default) or "ccd"
5. **NIP**(integer 20) Number of integration points. Works only with laplace as approximation strategy.
6. **MANual** to calculate CPO and PIT values manually.

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Estimation Syntax for midasinla: options

1. **ID(varname)** required for subsequent use with forest plot option on replay
2. **SORTby(varlist)** variables which you want data to be sorted by for forest plotting
3. **Rout** display R code in results window
4. **noESTimates** Do not display estimation results
5. **FITstats** display model diagnostic statistics such as DIC, deviance, marginal likelihood
6. **noHEADer** do not display header
7. **REVman** display data that can be exported to diagnostic module of Cochrane collaboration software (Revman)

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Post-Estimation Syntax for midasinla

```
syntax [if] [in] [,
FITstats noHEADer  noESTimates  REVman )
FORest  SROC(string)  FAGAN(numlist min=1 max=3)
CONDIProb(string)  UPVstats(numlist min=2 max=2
LRMatrix LINPred FITted DENsityplot
CPO PIT 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)
*]
```

Use of post-estimation options illustrated with worked example

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DESCRIPTIVE REPORTING

code:

```
midasinla tp fp fn tn
```

result:

```
-------------------------------------------------------------
Meta-analysis of Diagnostic Accuracy Studies
Via Bivariate Generalized Linear Mixed Modeling
Estimation Method: Integrated Nested Laplace Approximations
Approximation Strategy: Full Laplace
Integration Strategy: GRID
Family: Binomial
Link: logit
Covariance Matrix Prior: Inverse Wishart
Number of studies                                =        43
Reference-positive Units                         =      1322
Reference-negative Units                         =      1758
Pretest Prob of Disease                          =      0.45
-------------------------------------------------------------
```

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Model Diagnostic Statistics

code:

```
midasinla tp fp fn tn, id(author)
```

result:

```
Log marginal-likelihood (Integration)          =   -223.63
Log marginal-likelihood (Gaussian)             =   -224.35
Mean of the Deviance                           =   284.09
Deviance of the Mean                           =   228.63
Effective number of parameters                 =     55
Deviance Information Criterion                 =   339.56
Cross-validated Logarithmic Score              =   13.09
```

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FIXED AND RANDOM EFFECTS ESTIMATES

code:

```
midasinla tp fp fn tn, id(author) fit wishart
```

result:

```
------------------------------------------------------------------------------
Parameter |  mean      sd       se     median  [95% Cred.Interval]
----------+-------------------------------------------------------------------
mu1       |  0.9167  0.1973  0.0213  0.9075  0.5346  1.3059
mu2       |  3.0317  0.2349  0.0253  3.0334  2.5968  3.5195
sigma11   |  1.3371  0.4592  0.0495  1.2511  0.6705  2.5463
sigma22   |  1.2266  0.3897  0.0420  1.2058  0.5764  2.2987
sigma12   | -0.3647  0.0808  0.0087 -0.3499 -0.5267 -0.2179
------------------------------------------------------------------------------
```

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SUMMARY TEST PERFORMANCE ESTIMATES

code:

```
midasinla tp fp fn tn, id(author) fit wishart
```

result:

Parameter	mean	sd	se	median	[95% Cred.	Interval]
SEN	0.7127	0.0402	0.0043	0.7125	0.6306	0.7868
SPE	0.9529	0.0103	0.0011	0.9541	0.9307	0.9712
LRP	15.9086	3.8368	0.4137	15.4067	10.0250	24.8820
LRN	0.3015	0.0424	0.0046	0.3003	0.2220	0.3905
LDOR	3.9484	0.3093	0.0334	3.9754	3.3790	4.5818

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HETEROGENEITY/INCONSISTENCY STATISTICS

code:

```
midasinla tp fp fn tn, id(author) fit wishart
```

result:

```
------------------------------------------------------------------------
Parameter|  mean     sd       se       median    [95% Cred.Interval]
---------+--------------------------------------------------------------
I^2      | 0.4325   0.0556   0.0060   0.4286     0.3152    0.5416
I^2sen   | 0.2825   0.0668   0.0072   0.2755     0.1693    0.4363
I^2spe   | 0.2665   0.0598   0.0064   0.2682     0.1491    0.4113
------------------------------------------------------------------------
```

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PARAMETERS FOR EXPORT INTO REVMAN

code:

```
midasinla, nohead noestimates rev
```

result:

```
Bivariate Model Estimates:
E(logitse)                                    =    0.9167
E(logitsp)                                    =    3.0317
Var(logitse)                                  =    1.3371
Var(logitsp)                                  =    1.2266
Cov(logits)                                   =   -0.3647
Confidence and Prediction Regions:
SE(E(logitse))                                =    0.0213
SE(E(logitsp))                                =    0.0253
Cov(Es)                                       =    0.0008
Number of Studies                             =        43
```

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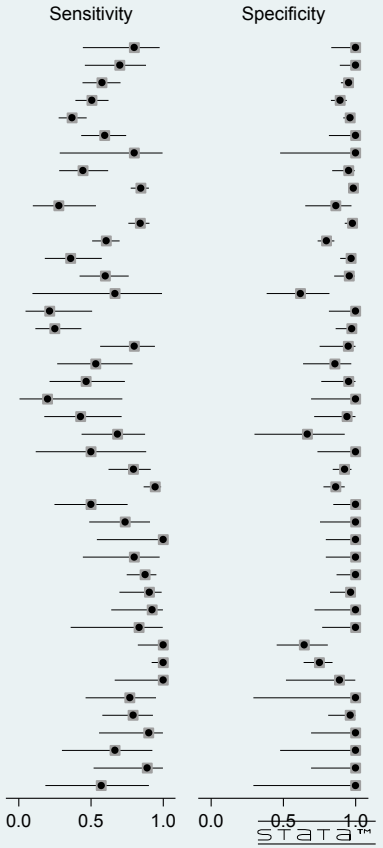
FOREST PLOT

code:

```
midasinla, forest nohead noestimates
```

result:

Studyid	TP	FP	FN	TN	Sensitivity (95% CrI)	Specificity (95% CrI)
Heuser	8	0	2	20	0.80 [0.44 - 0.97]	1.00 [0.83 - 1.00]
Fuster	14	0	6	32	0.70 [0.46 - 0.88]	1.00 [0.89 - 1.00]
Ueda	34	6	25	118	0.58 [0.44 - 0.70]	0.95 [0.90 - 0.98]
Cermik	40	15	39	125	0.51 [0.39 - 0.62]	0.89 [0.83 - 0.94]
Veronesi	38	5	65	128	0.37 [0.28 - 0.47]	0.96 [0.91 - 0.99]
Chung	25	0	17	18	0.60 [0.43 - 0.74]	1.00 [0.81 - 1.00]
Stadnik	4	0	1	5	0.80 [0.28 - 0.99]	1.00 [0.48 - 1.00]
Kumar	16	2	20	40	0.44 [0.28 - 0.62]	0.95 [0.84 - 0.99]
Gil-Rendo	120	2	22	131	0.85 [0.77 - 0.90]	0.98 [0.95 - 1.00]
Weir	5	3	13	19	0.28 [0.10 - 0.53]	0.86 [0.65 - 0.97]
Zornoza	90	2	17	91	0.84 [0.76 - 0.90]	0.98 [0.92 - 1.00]
Wahl	66	40	43	159	0.61 [0.51 - 0.70]	0.80 [0.74 - 0.85]
Lovrics	9	2	16	63	0.36 [0.18 - 0.57]	0.97 [0.89 - 1.00]
Inoue	21	2	14	44	0.60 [0.42 - 0.76]	0.96 [0.85 - 0.99]
Fehr	2	8	1	13	0.67 [0.09 - 0.99]	0.62 [0.38 - 0.82]
Barranger	3	0	11	18	0.21 [0.05 - 0.51]	1.00 [0.81 - 1.00]
Van_Hoeven	8	1	24	37	0.25 [0.11 - 0.43]	0.97 [0.86 - 1.00]
Rieber	16	1	4	19	0.80 [0.56 - 0.94]	0.95 [0.75 - 1.00]
Nakamoto2	8	3	7	18	0.53 [0.27 - 0.79]	0.86 [0.64 - 0.97]
Nakamoto1	7	1	8	20	0.47 [0.21 - 0.73]	0.95 [0.76 - 1.00]
Kelemen	1	0	4	10	0.20 [0.01 - 0.72]	1.00 [0.69 - 1.00]
Guller	6	1	8	16	0.43 [0.18 - 0.71]	0.94 [0.71 - 1.00]
Danforth	13	3	6	6	0.68 [0.43 - 0.87]	0.67 [0.30 - 0.93]
Yang	3	0	3	12	0.50 [0.12 - 0.88]	1.00 [0.74 - 1.00]
Schirrmeister	27	6	7	73	0.79 [0.62 - 0.91]	0.92 [0.84 - 0.97]
Greco	68	13	4	82	0.94 [0.86 - 0.98]	0.86 [0.78 - 0.93]
Yutani2	8	0	8	22	0.50 [0.25 - 0.75]	1.00 [0.85 - 1.00]
Ohta	14	0	5	13	0.74 [0.49 - 0.91]	1.00 [0.75 - 1.00]
Hubner	6	0	0	16	1.00 [0.54 - 1.00]	1.00 [0.79 - 1.00]
Yutani1	8	0	2	16	0.80 [0.44 - 0.97]	1.00 [0.79 - 1.00]
Rostom	42	0	6	26	0.88 [0.75 - 0.95]	1.00 [0.87 - 1.00]
Smith	19	1	2	28	0.90 [0.70 - 0.99]	0.97 [0.82 - 1.00]
Noh	12	0	1	11	0.92 [0.64 - 1.00]	1.00 [0.72 - 1.00]
Palmedo	5	0	1	14	0.83 [0.36 - 1.00]	1.00 [0.77 - 1.00]
Adler2	19	11	0	20	1.00 [0.82 - 1.00]	0.65 [0.45 - 0.81]
Utech	44	20	0	60	1.00 [0.92 - 1.00]	0.75 [0.64 - 0.84]
Scheidhauer	9	1	0	8	1.00 [0.66 - 1.00]	0.89 [0.52 - 1.00]
Bassa	10	0	3	3	0.77 [0.46 - 0.95]	1.00 [0.29 - 1.00]
Avril	19	1	5	26	0.79 [0.58 - 0.93]	0.96 [0.81 - 1.00]
Crowe	9	0	1	10	0.90 [0.55 - 1.00]	1.00 [0.69 - 1.00]
Hoh	6	0	3	5	0.67 [0.30 - 0.93]	1.00 [0.48 - 1.00]
Adler1	8	0	1	10	0.89 [0.52 - 1.00]	1.00 [0.69 - 1.00]
Tse	4	0	3	3	0.57 [0.18 - 0.90]	1.00 [0.29 - 1.00]



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SUMMARY ROC

1. Logit estimates of sensitivity, specificity and respective variances are used to construct a hierarchical summary ROC curve.

2. The summary ROC curve may be displayed with or without
   - Observed study data,
   - Summary operating point,
   - 95% Confidence region and/or
   - 95% Prediction region.

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SUMMARY ROC

1. The 95% confidence region around the summary estimate of sensitivity and specificity may be viewed as a two-dimensional confidence interval.

2. The main axis of the 95% confidence region reflects the correlation between sensitivity and specificity (threshold effect).

3. The 95% prediction region depicts a two-dimensional standard deviation of the individual studies.

4. The area of the 95% prediction region beyond the 95% confidence region reflects extent of between-study variation.

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SUMMARY ROC

1. The area under the curve (AUROC), serves as a global measure of test performance.
2. The AUROC is the average TPR over the entire range of FPR values.
3. The following guidelines have been suggested for interpretation of intermediate AUROC values:
   - **low** accuracy (0.5>= AUC <= 0.7),
   - **moderate** accuracy (0.7 >= AUC <= 0.9), or
   - **high** accuracy (0.9 >= AUC <= 1)

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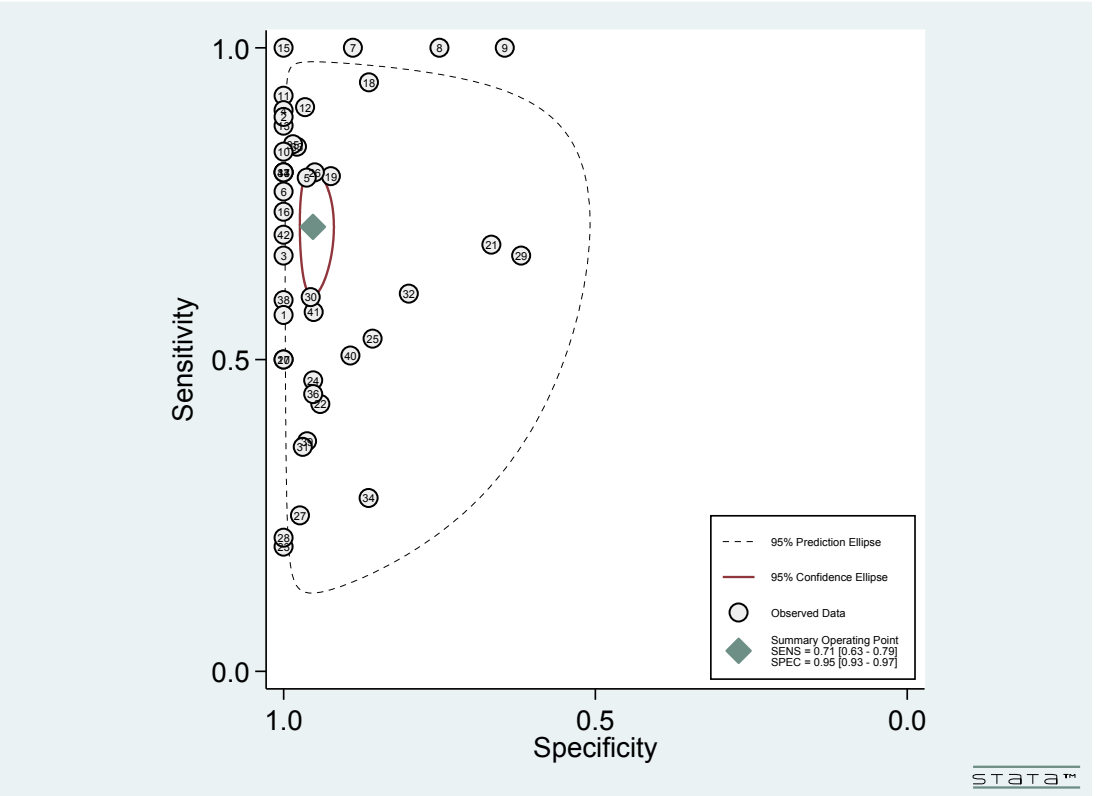
SUMMARY ROC

code:

```
midasinla, sroc(mean prede confe data lgnd) ///
nohead noestimates
```

result:



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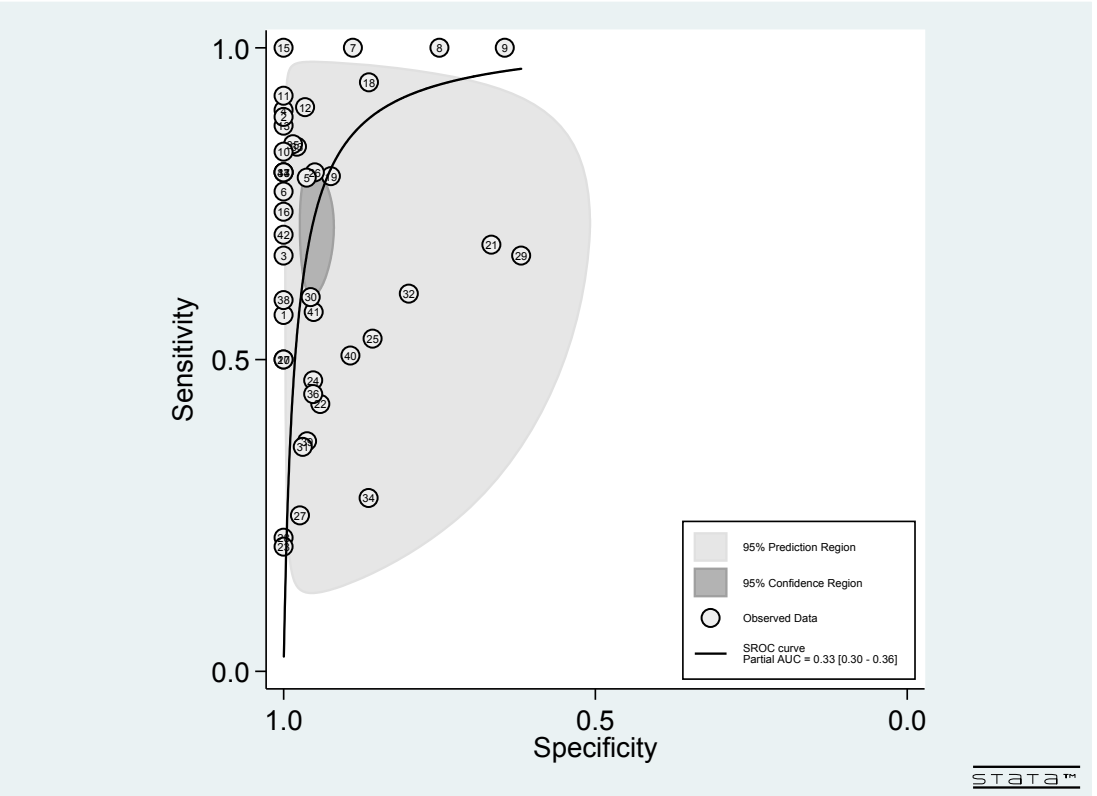
SUMMARY ROC

code:

```
midasinla, sroc(tcurve predr confr data lgnd)  ///
nohead noestimates
```

result:



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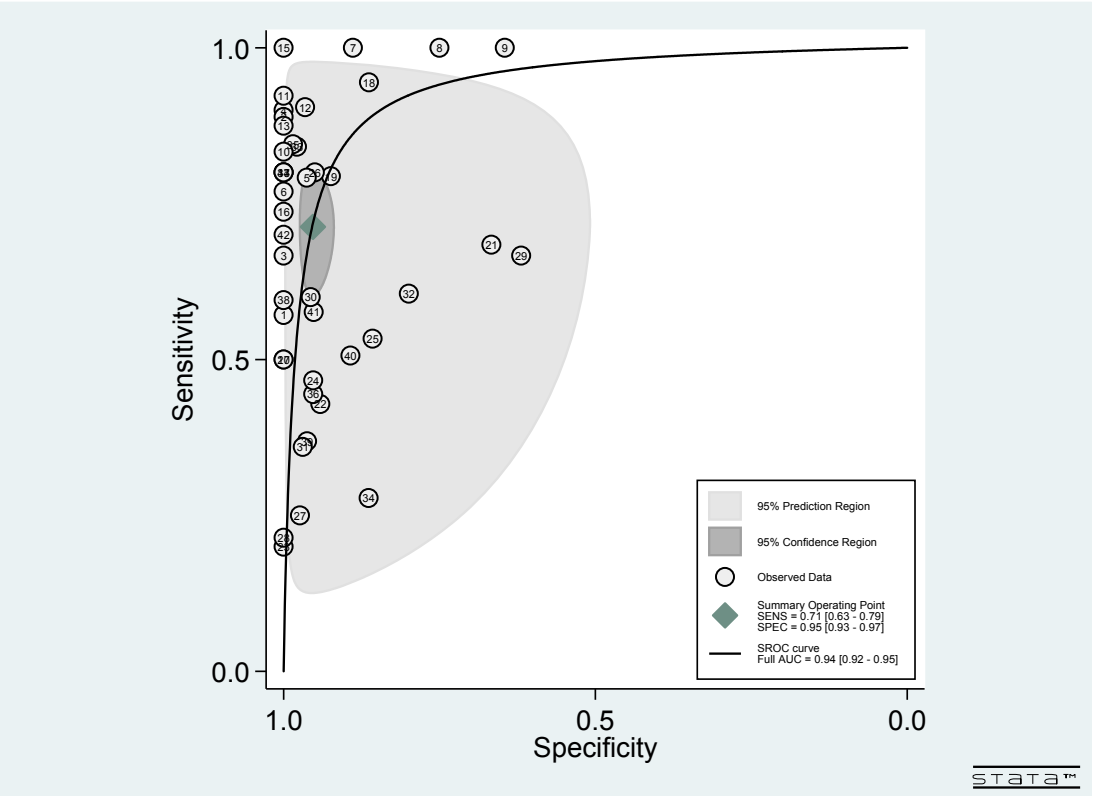
SUMMARY ROC

code:

```
midasinla, sroc(fcurve predr confr data lgnd)  ///
nohead noestimates
```

result:



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FAGAN NOMOGRAM

1. The patient-relevant utility of a diagnostic test is evaluated using the likelihood ratios to calculate post-test probability(PTP) as follows: Pretest Probability=Prevalence of target condition PTP= LR $\times$ pretest probability/[(1-pretest probability)$\times$ (1-LR)]

2. This concept is depicted visually with Fagan's nomograms.

3. When Bayes theorem is expressed in terms of log-odds, the posterior log-odds are linear functions of the prior log-odds and the log likelihood ratios.

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FAGAN NOMOGRAM

1. A Fagan plot consists of a vertical axis on the left with the prior log-odds, an axis in the middle representing the log-likelihood ratio and an vertical axis on the right representing the posterior log-odds.

2. Lines are then drawn from the prior probability on the left through the likelihood ratios in the center and extended to the posterior probabilities on the right.

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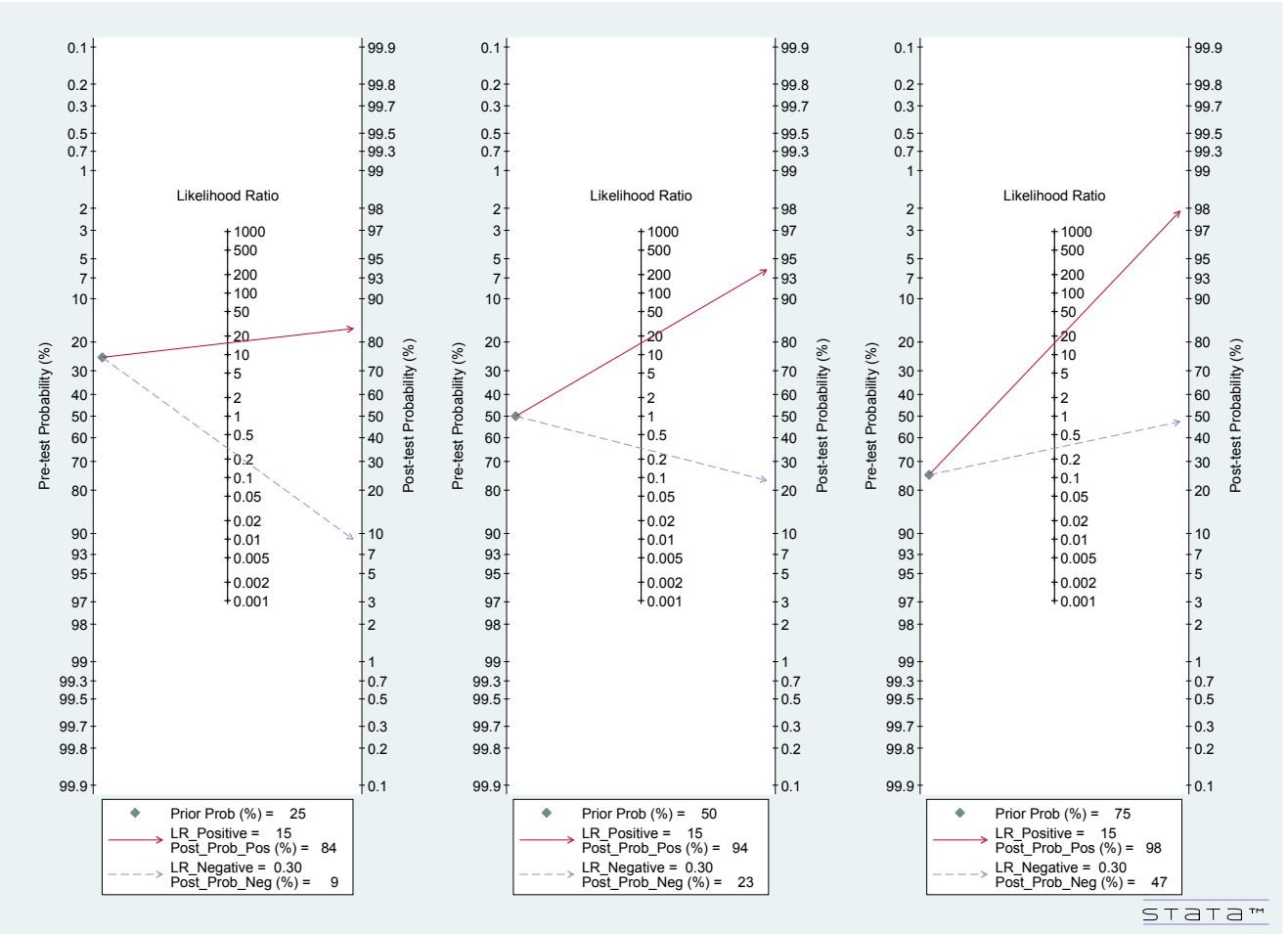
FAGAN NOMOGRAM

code:

```
midasinla, fagan(0.25 0.50 0.75) nohead noestimates
```

result:



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CONDITIONAL PROBABILITY PLOTS

1. The conditional probability of disease given a positive OR negative test, the so-called positive (negative) predictive values are critically important to clinical application of a diagnostic procedure.

2. They depend not only on sensitivity and specificity, but also on disease prevalence (p).

3. The probability modifying plot is a graphical sensitivity analysis of predictive value across a prevalence continuum defining low to high-risk populations.

4. It depicts separate curves for positive and negative tests.

5. The user draws a vertical line from the selected pre-test probability to the appropriate likelihood ratio line and then reads the post-test probability off the vertical scale.

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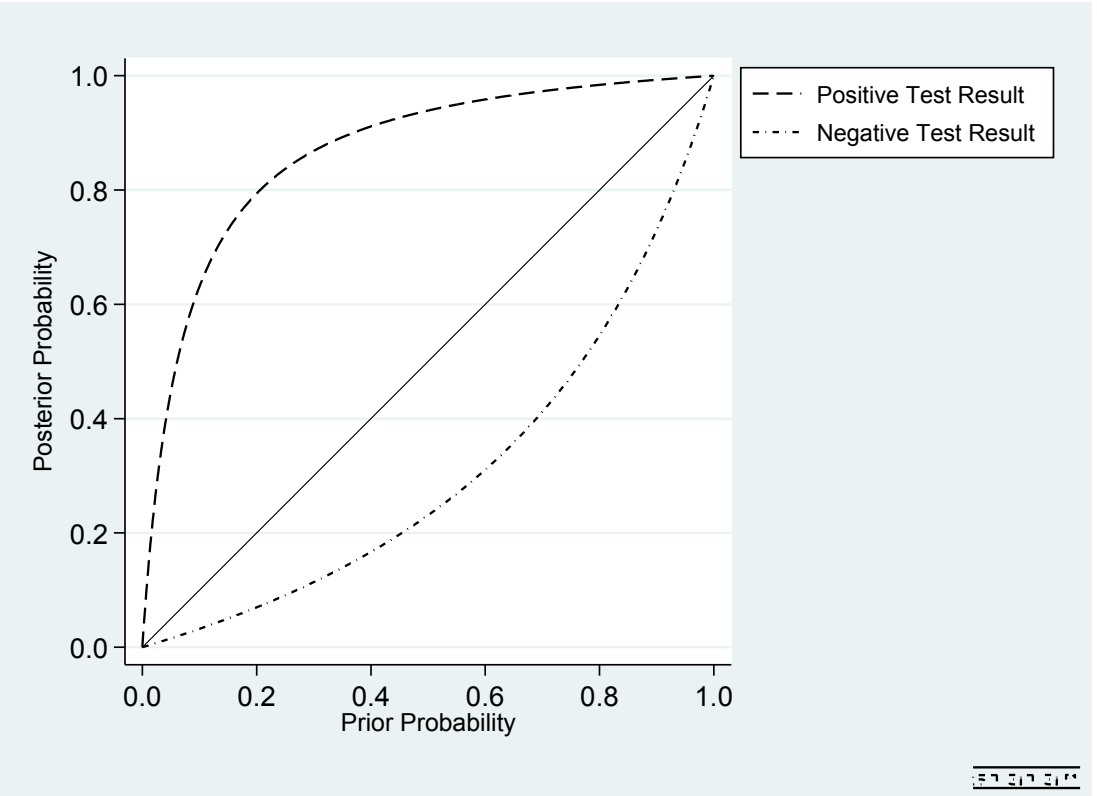
CONDITIONAL PROBABILITY PLOTS

code:

```
midasinla, condiprob(full) nohead noestimates
```

result:



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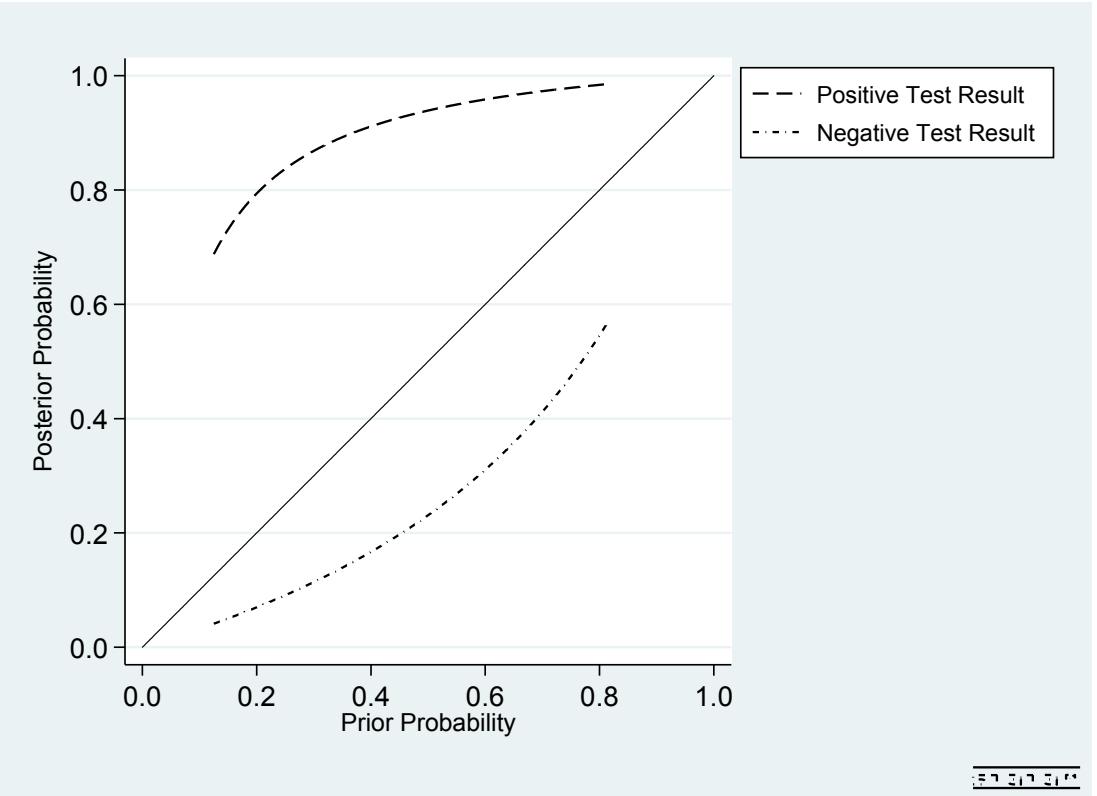
CONDITIONAL PROBABILITY PLOTS

code:

```
midasinla, condiprob(trunc) nohead noestimates
```

result:



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UNCONDITIONAL PREDICTIVE VALUES

1. General summary statistics have also been introduced for when it may be of interest to evaluate the effect of prevalence(p) on predictive values: unconditional positive and negative predictive values, which permit prevalence heterogeneity.

2. These measures are obtained by integrating their corresponding conditional (on p) versions with respect to a prior distribution for p.

3. The prior posits assumptions about the risk level in a hypothetical population of interest, e.g. low, high, moderate risk, as well as the heterogeneity in the population.

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UNCONDITIONAL PREDICTIVE VALUES

code:

```
midasinla, upv(0.25 0.75) nohead noestimates
```

result:

```
Prevalence Heterogeneity/Unconditional Predictive Values
--------------------------------------------------------------------
Prior Distribution (Uniform)                 =   0.25 - 0.75

Unconditional Positive Predictive Value      =   0.93 [0.93 - 0.93]

Unconditional Negative Predictive Value      =   0.75 [0.75 - 0.75]
--------------------------------------------------------------------
```

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GRAPHICAL MODEL DIAGNOSTIC

1. Leverage plots show each study's leverage plotted against their deviance residual

2. Such plots can be used to check how each study is affecting the overall model fit and DIC

3. Curves of the form $x^2 + y = c$, c=1,2,3,..., where x represents

   deviance residual and y represents the leverage, are marked on the plots

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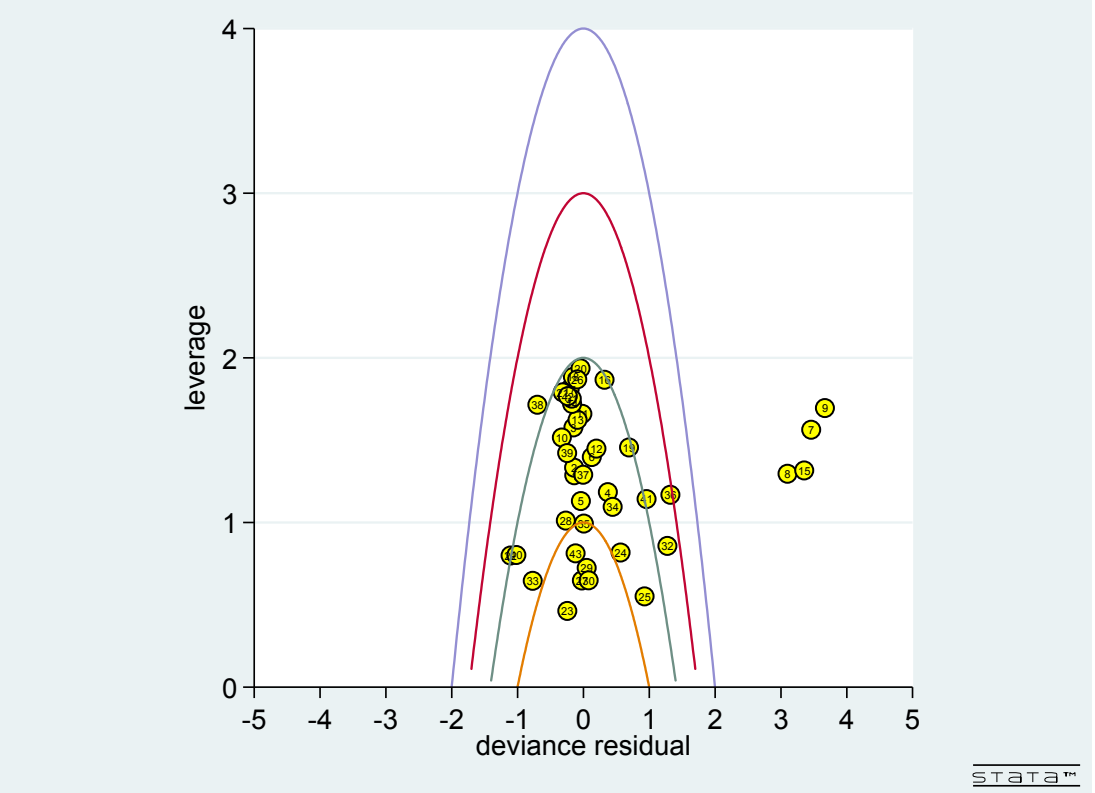
GRAPHICAL MODEL DIAGNOSTIC

code:

```
midasinla, moddiag nohead noestimates
```

result:



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GRAPHICAL MODEL DIAGNOSTIC

1. Study points lying on such parabolas each contribute an amount c to the DIC.

2. Studies which lie outside the parabolas can generally be identified as contributing to the models poor fit.

3. Studies with a high leverage are influential, which means that they have a strong influence on the model parameters that generate their fitted values.

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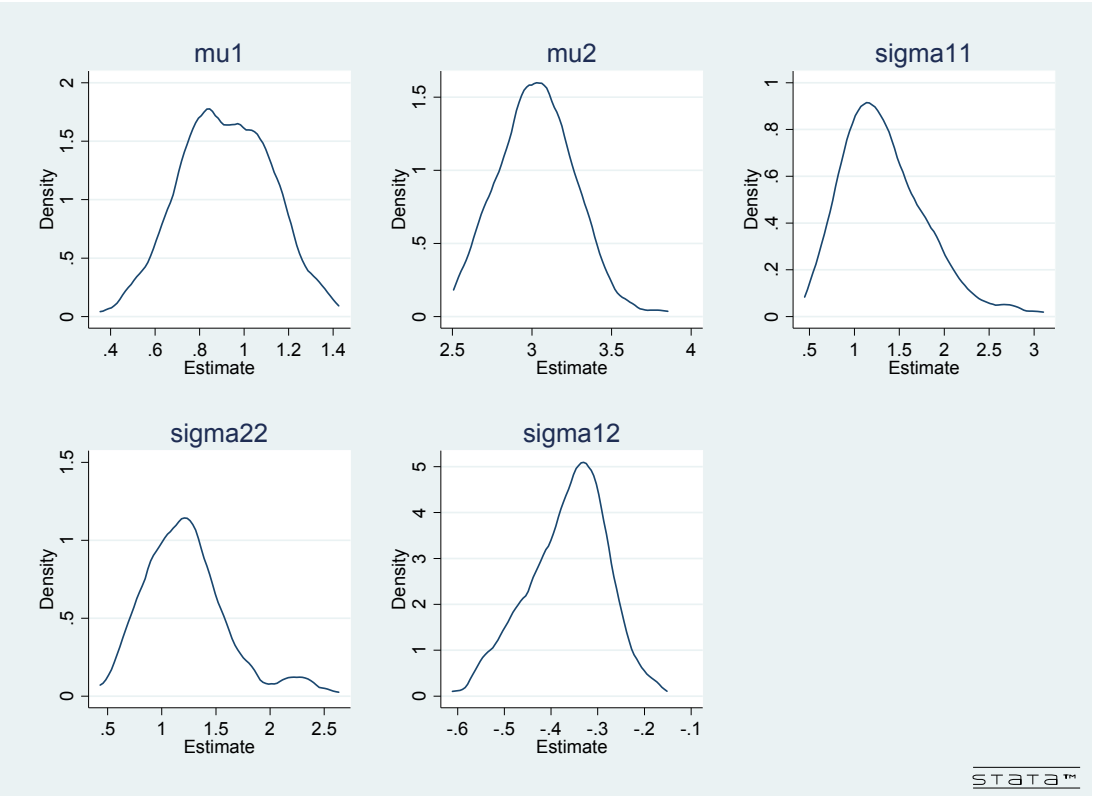
MODEL FIT

code:

```
midasinla, densityplot nohead noestimates
```

result:



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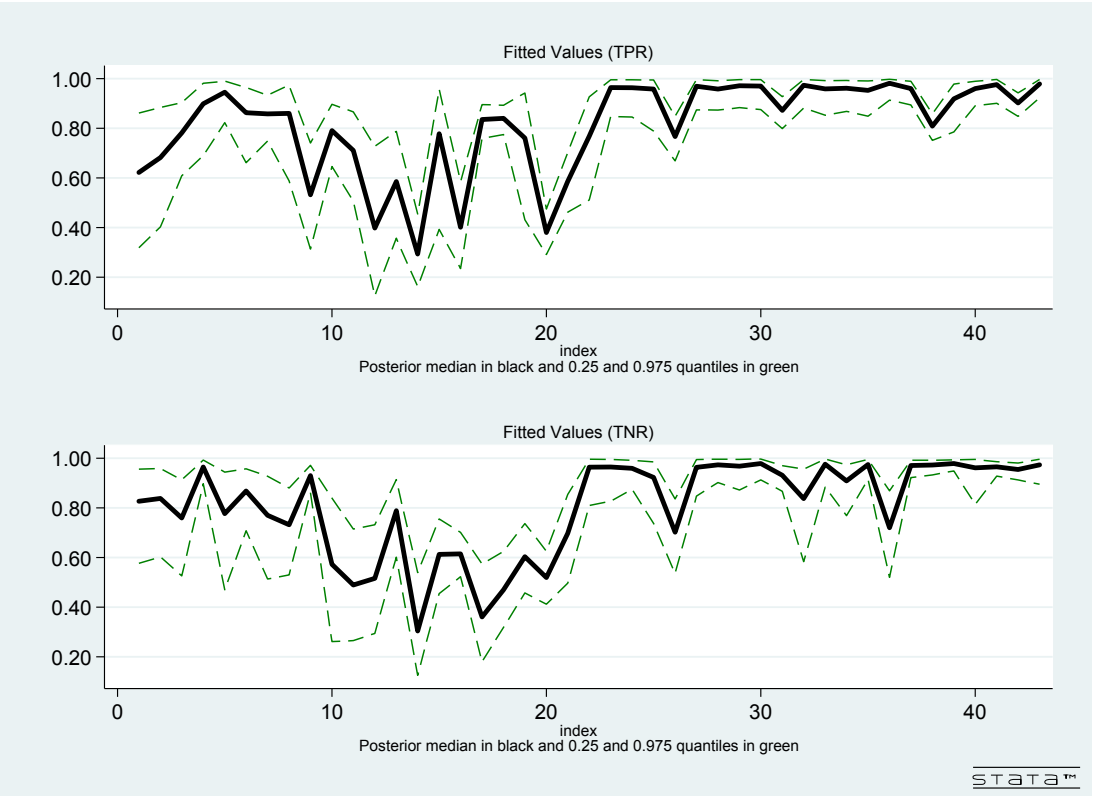
FITTED VALUES

code:

```
midasinla, fitted nohead noestimates
```

result:



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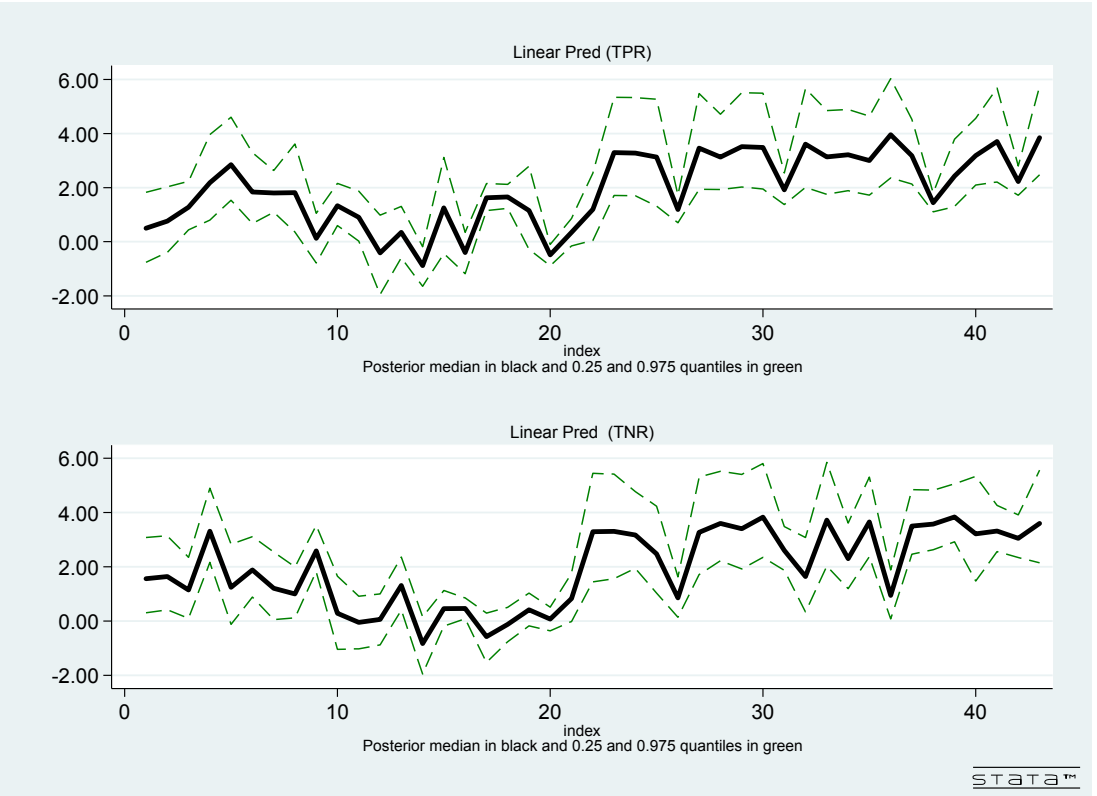
LINEAR PREDICTION

code:

```
midasinla, linpred nohead noestimates
```

result:



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How to install **R**

1. Current binary versions of R run on Windows XP or later, including on 64-bit versions
2. To install use R-3.2.0-win.exe. Just double-click on the icon and follow the instructions.
3. If you have an account with Administrator privileges you will be able to install R in the Program Files area and to set all the optional registry entries; otherwise you will only be able to install R in your own file area.

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How to install **R**

1. You may need to confirm that you want to proceed with installing a program from an unknown or unidentified publisher.

2. After installation you should choose a working directory for R. You will have a shortcut to Rgui.exe on your desktop and/or somewhere on the Start menu file tree, and in the Quick Launch part of the taskbar (Vista and earlier).

3. Right-click each shortcut, select Properties... and change the Start in field to your working directory. (If your account was not the one used for installation, you may need to copy the shortcut before editing it.)

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How to install R packages

1. Open **R**.
2. Type in the command on single line:

   install.packages(c("Foreign","mvtnorm","numDeriv","'R.utils") ,dependencies=TRUE,

   repos="http://cran.r-project.org")
3. To install the INLA package you type either of:
   - **install.packages("INLA",repos="http://www.math.ntnu.no/inla/R/stable")**
   - **install.packages("INLA",repos="http://www.math.ntnu.no/inla/R/testing")**

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CONCLUSIONS

- Likelihood-based estimation of bivariate generalized linear mixed meta-analysis models may fail to convege because of sparse data or small number of studies, providing unreliable estimates for the between-study correlation with uninformative confidence intervals ranging from -1 to 1 (covering the whole parameter space).

- Bayesian MCMC simulation may obviate the problems of maximum likelihood but has its on problems of requiring diagnostic checks for convergence, computational expense and uncertainty about required number and length of chains

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CONCLUSIONS

- Integrated nested Laplace approximations provides inferentially accurate, computationally fast and deterministic alternative to MCMC-based bayesian analysis

- **midasinla**, a subcommand of the user-written **midas** ado-file integrating **R-INLA** estimation with pre- and post-estimation data processing within **Stata**, provide **Stata** users with a user-friendly, accurate and reliable alternative module for diagnostic accuracy meta-analysis in the presence of sparse data and/or after failure of likelihood-based estimation.

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1. M. Paul, A. Riebler, L. M. Bachmann, H. Rue, L. Held. (Bayesian bivariate meta-analysis of diagnostic test studies using integrated nested Laplace approximations. Statistics in Medicine 2010; 29(12): 325-1339)

2. H Rue, S. Martino, N. Chopin. (Approximate Bayesian inference for latent Gaussian models using integrated nested Laplace approximations. Journal of the Royal Statistical Society, Series B 2009; 71(2): 319-392)

3. Martino S, Rue H. (Implementing Approximate Bayesian Inference using Integrated Nested Laplace Approximation: a Manual for the inla Program, Department of Mathematical Sciences, NTNU, Norway 2009).

4. Roger Newson. (rsource: Stata module to run R from inside Stata using an R source file. http://ideas.repec.org/c/boc/bo**code/s456847.html)**

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