Meta-analysis of diagnostic test accuracy studies with Stata: Simulation study

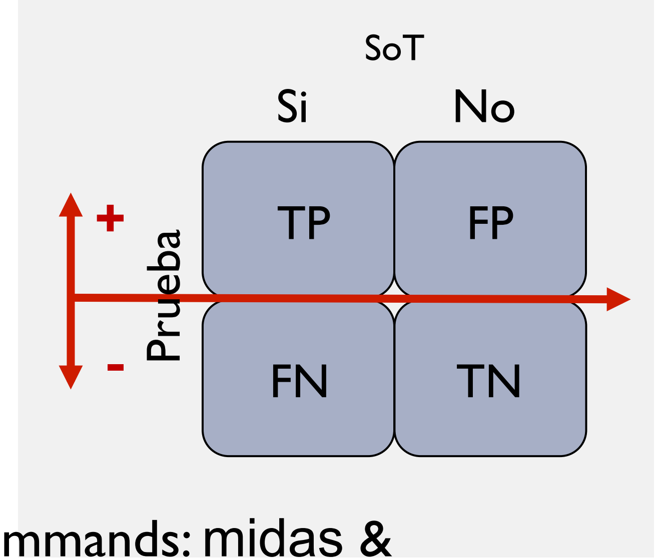
- Nieves Plana, Víctor Abraira, Javier Zamora
- *Unidad de Bioestadística Clínica. Hospital Ramón y Cajal, IRYCIS. Madrid*
- *CIBER Epidemiología y Salud Pública (CIBERESP)*

ciberesp
Centro de Investigación Biomédica en Red
Epidemiología y Salud Pública
instituto ramón y cajal de investigación sanitaria
irycis

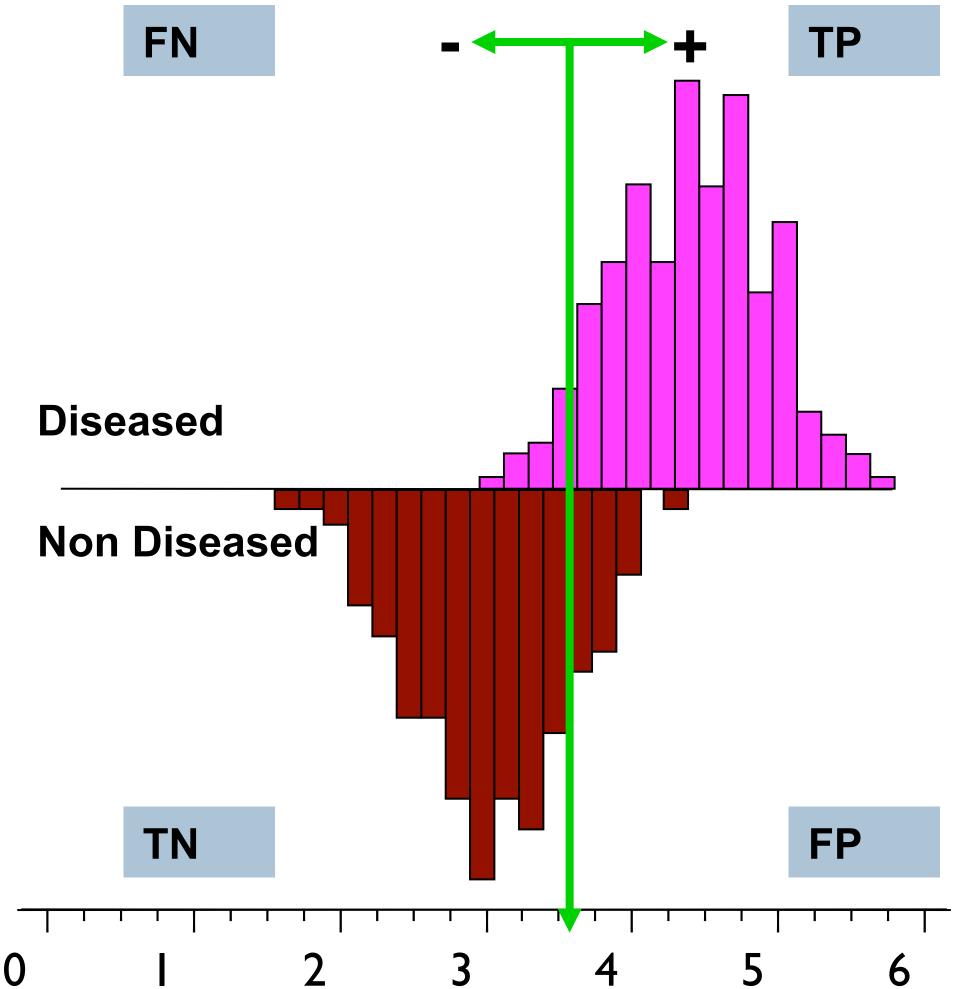
Contents

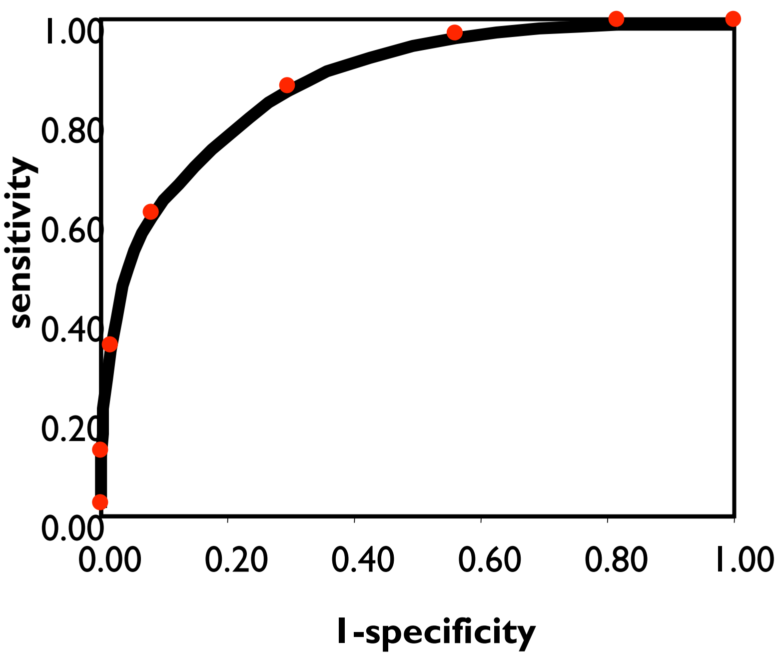
Background

- Meta-analysis of interventions
  - Heterogeneity
    - Several tools available (`metan`). Fixed and random effects model
- Diagnostic Accuracy Meta-analysis
  - Heterogeneity
  - Pooling a pair of indices (not just one)
  - Threshold effect
    - Non linear Mixed Models (user-written commands: midas & metandi)

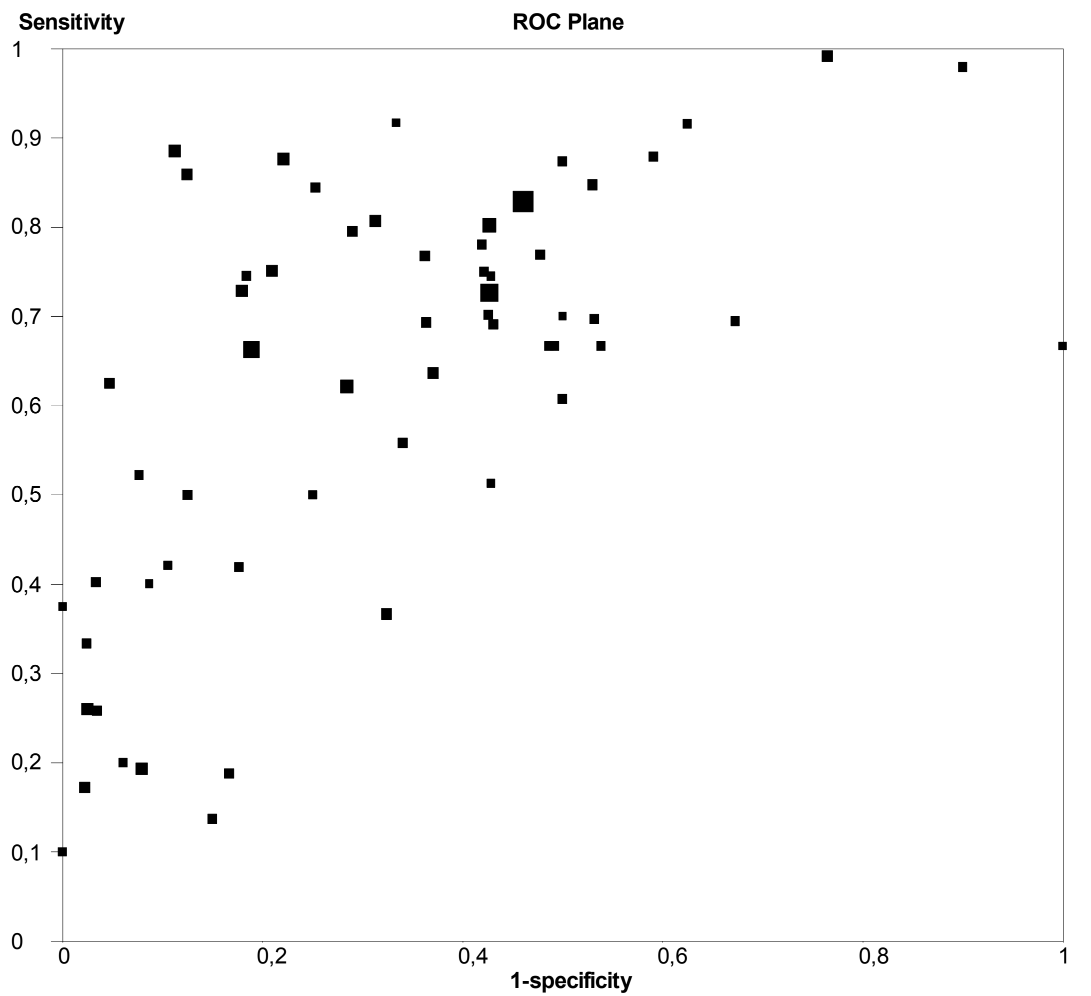


Threshold/spectrum effect





How to better summarize this?



Aims

- To check the performance of different analytical approaches and its dependence on characteristics of the scenario (variability and correlation).
- Two main approaches :
  - Univariate – separate pooling (metan)
    - Fixed effects
    - Random effects
  - Bivariate Mixed Effects Non Linear Model (`xtmelogit`) (Multilevel mixed-effects logistic regression) (metandi)

i. Methods

- Simulation study
  - Independent datasets generated for each scenario
  - Paired design (same data for the three models)
  - Sample size:

    1000 simulations will provide 82% power to detect differences as low as 3% in estimated proportions (assuming worst case of $p=q=.5$)

ii. Methods. Data generation

- Logits of sen y esp drawn from bivariate normal distribution

```
drawnorm u v, n(20) corr(rho) means(M) sds(SD)
```

$$\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} \approx N\left[\begin{pmatrix} u \\ v \end{pmatrix}, \Sigma\right], \quad \Sigma = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}$$

Logit(sen) and Logit(spe) were back transformed into the cells of the 2x2 crosstabulation TP, FP, FN and TN

Careful managment of pseudorandom number generator

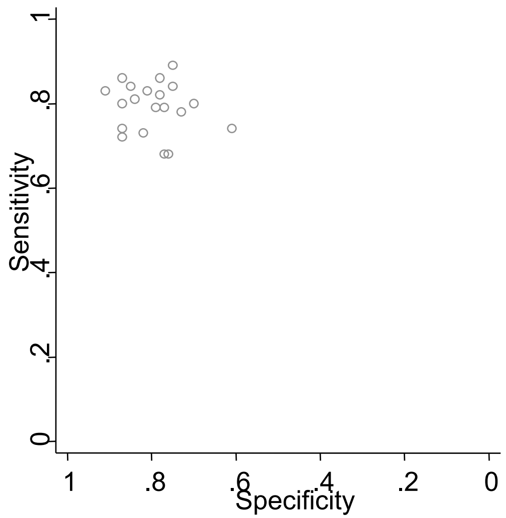
- `local semilla = c(seed)`
- `` set seed `semilla' ``

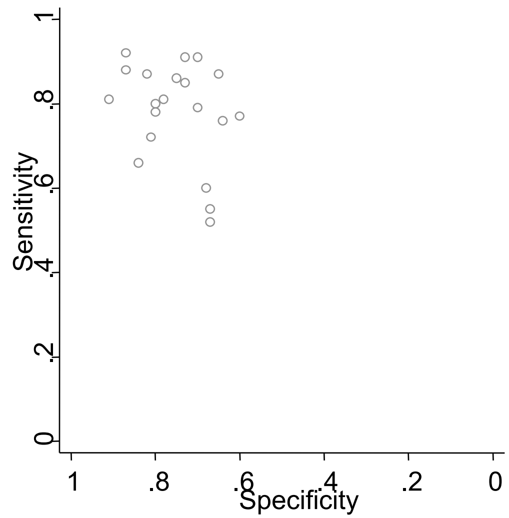
iii. Methods. Scenario definition

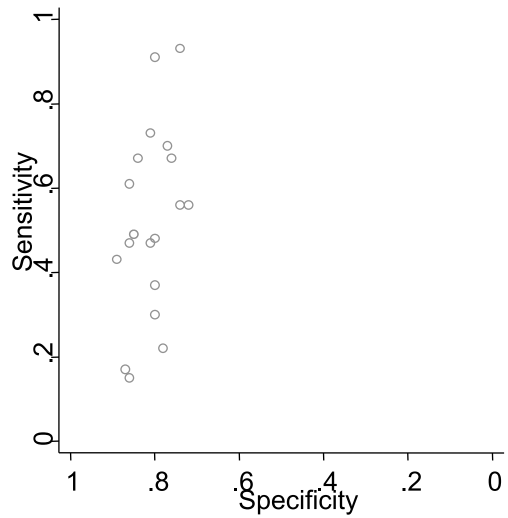
- N meta-analyses = 1000; N studies in each meta-analysis= 20
- Prevalence of disease = 50%
- N patients in each study = 200 (100 diseased & 100 non diseased)

	Scenario	beta1	beta2	rho	tau1	tau2
1a	No correlation, low heterogeneity	0.8	0.8	0	0.1	0.1
1b	No correlation; moderate heterogeneity	0.8	0.8	0	0.3	0.3
1c	No correlation; highly heterogeneous (sen)	0.5	0.8	0	0.9	0.1
2a	Moderate correlation; moderate heterogeneity	0.7	0.7	-0.5	0.7	0.7
2b	High correlation; high heterogenety	0.7	0.7	-0.9	0.9	0.9

ROC plots of scenarios 1a ,1b and 1c





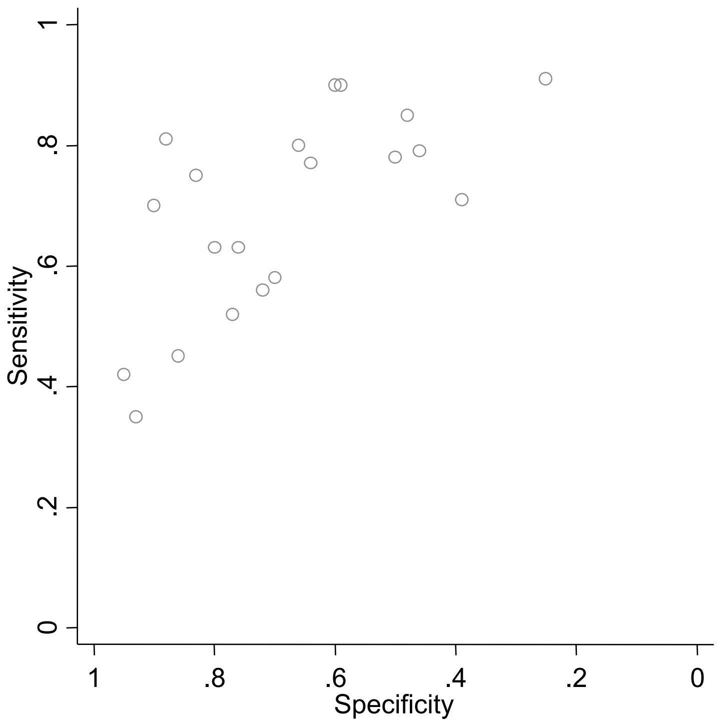


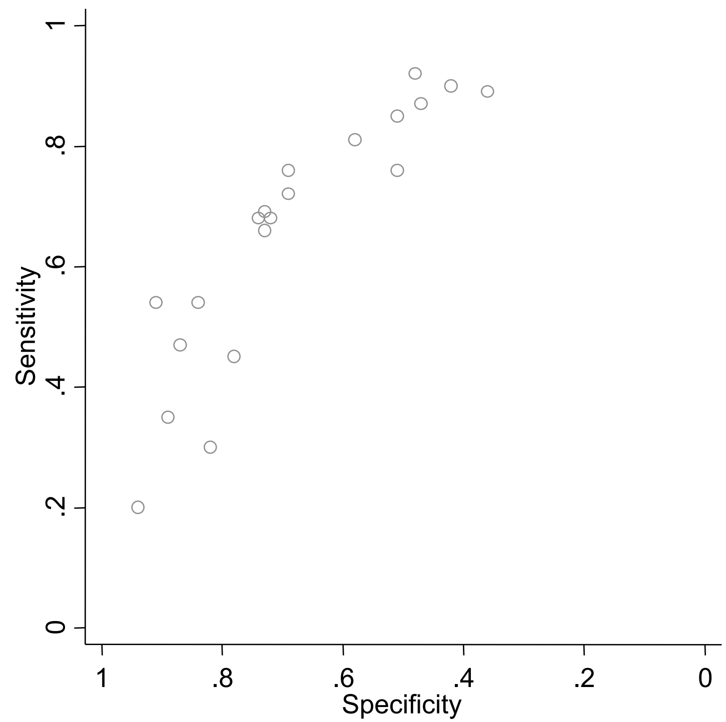
beta1=beta2= 0.8
tau1=tau2= 0.1
rho= 0

beta1=beta2=0.8
tau1=tau2= 0.3
rho= 0

beta1= 0.5 , tau1= 0.9
beta2= 0.8 , tau2= 0.1
rho= 0

ROC plots of scenarios 2a and 2b





beta1= 0.7, tau1= 0.7
beta2= 0.7, tau2= 0.7
rho= -0.5

beta1= 0.7, tau1= 0.9
beta2= 0.7, tau2= 0.9
rho= -0.9

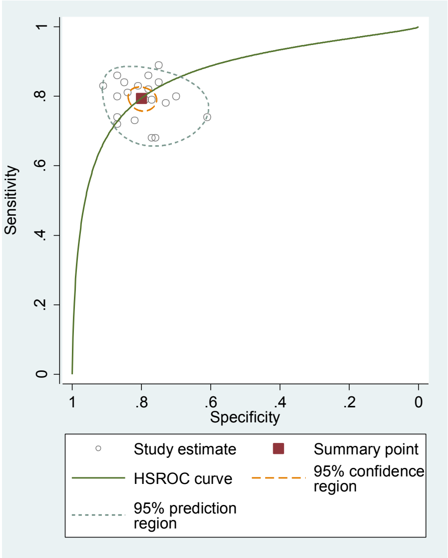
iv. Methods

- Statistics for comparison (user written command simsum):
  - BIAS
  - PRECISION: empirical standard error and RMS model-based standard error
  - COVERAGE of 95% CI

- Software : Stata version12

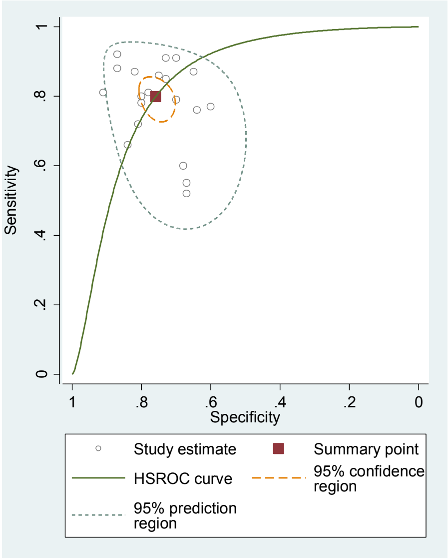
Results (Scenario 1ª)

Statistic	FIXED	RANDOM	BIVARIAT
Non-missing point estimates	1000	1000	962
Non-missing standard errors	1000	1000	962
Bias in point estimate	-.0096104	-.0063431	-.003501
Empirical standard error	.0115227	.0109236	.0109752
% gain in precision relative to method FIXED	.	11.27064	10.22604
RMS model-based standard error	.009156	.0116648	.3823881
Relative % error in standard error	-20.53949	6.785101	3384.103
Coverage of nominal 95% confidence interval	75.6	90.7	94.28275
Power of 5% level test	100	100	98.1289



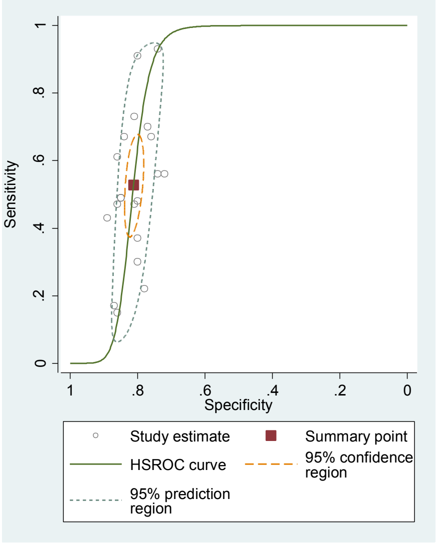
Results (Scenario 1b)

Statistic	FIXED	RANDOM	BIVARIATE
Non-missing point estimates	1000	1000	996
Non-missing standard errors	1000	1000	996
Bias in point estimate	-.0253788	-.0074427	-.0038669
Empirical standard error	.0219678	.0202583	.0203207
% gain in precision relative to method FIXED	.	17.58899	16.86721
RMS model-based standard error	.0092927	.0193442	.0190658
Relative % error in standard error	-57.69852	-4.512252	-6.175655
Coverage of nominal 95% confidence interval	35.7	87.3	91.96787
Power of 5% level test	100	100	100



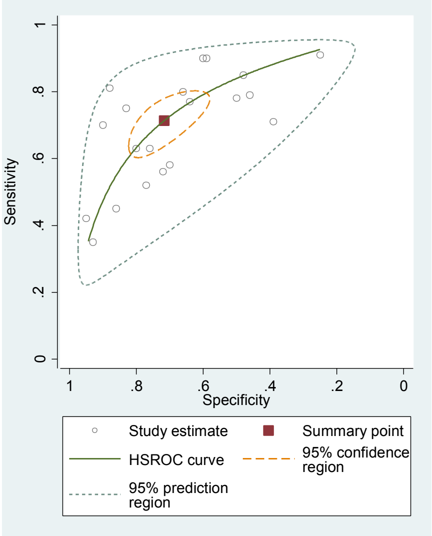
Results (Scenario 1c)

Statistic	FIXED	RANDOM	BIVARIATE
Non-missing point estimates	1000	1000	950
Non-missing standard errors	1000	1000	950
Bias in point estimate	-.0021265	-.0020453	-.0030439
Empirical standard error	.0391764	.0491348	.0543954
% gain in precision relative to method FIXED	.	-36.42722	-48.12902
RMS model-based standard error	.0105042	.0389663	.1023976
Relative % error in standard error	-73.18735	-20.69515	88.24679
Coverage of nominal 95% confidence interval	39.2	84	88.63158
Power of 5% level test	100	100	99.26316



Results (Scenario 2a)

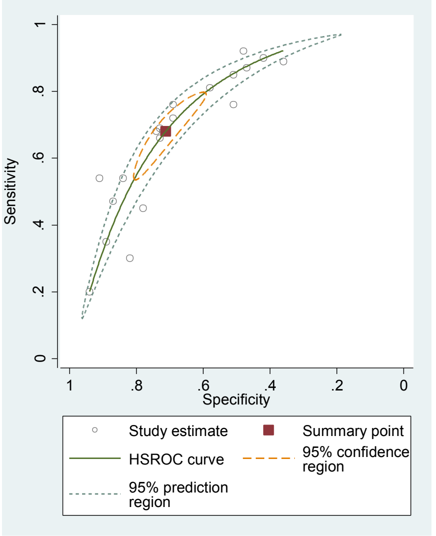
Statistic	FIXED	RANDOM	BIVARIATE
Non-missing point estimates	1000	1000	995
Non-missing standard errors	1000	1000	995
Bias in point estimate	-.0413069	-.0068732	-.0032639
Empirical standard error	.035567	.0381943	.0388863
% gain in precision relative to method FIXED	.	-13.28434	-16.34308
RMS model-based standard error	.0102007	.0330655	.037817
Relative % error in standard error	-71.31965	-13.42805	-2.749737
Coverage of nominal 95% confidence interval	22.4	84.4	92.76382
Power of 5% level test	100	100	100



Results (Scenario 2b)

```
. simsum sen, true(0.7) methodvar(method) id(ID) se(ee_sen) dropbig
```

Statistic	FIXED	RANDOM	BIVARIATE
Non-missing point estimates	1000	1000	987
Non-missing standard errors	1000	1000	987
Bias in point estimate	-.0484369	-.0062842	-.0016509
Empirical standard error	.0384232	.0425449	.0432747
% gain in precision relative to method FIXED	.	-18.43718	-21.16479
RMS model-based standard error	.0101703	.0358574	.5691451
Relative % error in standard error	-73.53075	-15.71873	1215.192
Coverage of nominal 95% confidence interval	17.7	83.1	92.9078
Power of 5% level test	100	100	95.03546



Summary of results: BIAS (SE)

BIAS (Empirical standard error)								
						Model		
Scenario	**β_1**	**β_2**	**τ1**	**τ2**	**ρ**	**FIXED**	**RANDOM**	**BIVARIATE**
1a	0.8	0.8	0.1	0.1	0	-0.0096 (0.0115)	-0.0063 (0.0109)	-0.0035 (0.0110)
1b	0.8	0.8	0.3	0.3	0	-0.0254 (0.0220)	-0.0074 (0.0203)	-0.0039 (0.0203)
1c	0.5	0.8	0.9	0.1	0	-0.0021 (0.0392)	-0.0020 (0.0491)	-0.0030 (0.0544)
2a	0.7	0.7	0.7	0.7	-0.5	-0.0413 (0.0356)	-0.0069 (0.0382)	-0.0033 (0.0389)
2b	0.7	0.7	0.9	0.9	-0.9	-0.0484 (0.0384)	-0.0063 (0.0425)	-0.0017 (0.0433)

Summary of results: RMS SE

RMS model-based standard error (Relative % error in standard error)								
						Model		
Scenario	β_1	β_2	τ1	τ2	ρ	FIXED	RANDOM	BIVARIATE
1a	0.8	0.8	0.1	0.1	0	0.0092 (-20.5395)	0.0117 (6.7851)	**0.3824 (3384.103)**
1b	0.8	0.8	0.3	0.3	0	0.0093 (-57.6985)	0.0193 (-4.5123)	0.0191 (-6.1757)
1c	0.5	0.8	0.9	0.1	0	0.0105 (-73.1874)	0.0390 (-20.6952)	0.1024 (88.2468)
2a	0.7	0.7	0.7	0.7	-0.5	0.0102 (-71.3197)	0.0331 (-13.4281)	0.0378 (-2.7497)
2b	0.7	0.7	0.9	0.9	-0.9	0.0102 (-73.5308)	0.0359 (-15.7187)	**0.5691 (1215.192)**

Summary of results: 95% CI coverage

Coverage of nominal 95% confidence interval								
						Método		
Escenario	β_1	β_2	τ1	τ2	ρ	FIXED	RANDOM	BIVARIATE (converged)
1a	0.8	0.8	0.1	0.1	0	75.6	90.7	94.3 (962)
1b	0.8	0.8	0.3	0.3	0	35.7	87.3	92.0 (996)
1c	0.5	0.8	0.9	0.1	0	39.2	84	88.6 (950)
2a	0.7	0.7	0.7	0.7	-0.5	22.4	84.4	92.8 (995)
2b	0.7	0.7	0.9	0.9	-0.9	17.7	83.1	92.9 (987)

Conclussions

- Univariate Fixed Effects Model is not well suited to pool accuracy indexes in almost all situations.
  - Unbiased estimators but with low standard errors and poor coverage.
- Univariate Random Effects Model could have a place when bivariate model fails to produce stable estimations.
- Bivariate model outperfoms the other methods but:
  - Showed convergence problems
  - Produces unstable estimators in scenarios with
    - high correlation between sensitivity and specificity
    - high homogeneity (low variance)

- Stata provides a nice framework for both fitting meta-analytical models and performing simulation studies.

Further works

- More comprehensive definition of simulation scenarios
  - Varying heterogeneity
  - Varying correlation
  - Varying sample sizes and number of studies

- Assessment of the performance using other summary measures:
  - LR, DOR,
  - Area of Confidence and prediction ellipses
  - MOR

User written commands

- **metan**

  Michael J Bradburn, Jonathan J Deeks, Douglas G Altman. Centre for Statistics in Medicine, University of Oxford, UK

- **metandi**

  Roger Harbord, Department of Social Medicine University of Bristol, UK

- **midas**

  Ben A. Dwamena, Division of Nuclear Medicin, Department of Radiology, University of Michigan, USA

- **simsum**

  Ian White, MRC Biostatistics Unit, Cambridge, UK

- Thank you very much

  - Nieves Plana (nieves.plana@hrc.es)
  - Víctor Abraira (victor.abraira@hrc.es)
  - Javier Zamora (javier.zamora@hrc.es)

SaludMadrid Hospital Universitario Ramón y Cajal Comunidad de Madrid instituto ramón y cajal de investigación sanitaria irycis ciberesp Centro de Investigación Biomédica en Red Epidemiología y Salud Pública