Evaluating the accuracy of diagnostic systems by means of meta-analysis

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Introduction and Background of Diagnostic Setting

The SROC and the Littenberg-Moses Approach

SROC-Modelling

Profile or Adjusted Profile Likelihood?

Simulation Study

Application to BNP Meta-Analysis

Incorporating Heterogeneity by Means of a Mixed Model

Often studies are done in medicine or psychology to determine:

discriminatory ability of a diagnostic test to separate people

- **with** a specific disease (or condition)
- from those **without**

in fact, diagnostic systems are all around us!

Measures of Diagnostic Accuracy

- **Specificity**: $P(T- \mid D-) = 1 - u$
  Probability of a negative test result for a healthy person
- **Sensitivity**: $P(T+ \mid D+) = p$
  Probability of a positive test result for a diseased person

Estimating Diagnostic Accuracy

- **Specificity**: $\widehat{P(T-|D-)} = 1 - \hat{u} = \frac{n-x}{n}$
  where x are the number of false-positives out of n healthy individuals, $n - x$ are the true-negatives

- **Sensitivity**: $\widehat{P(T+|D+)} = \hat{p} = \frac{y}{m}$
  where y are the number of true-positives out of m diseased individuals, $y - m$ are the false-negatives

Frequently available:

- a variety of diagnostic studies
- providing diagnostic measures

$$x_i, n_i \text{ (specificity)}$$

$$y_i, m_i \text{ (sensitivity)}$$

- for $i = 1, ..., k$
- leading to the field of **meta-analysis**

An Example: Meta-Analysis of Diagnostic Accuracy of Natriuretic Peptides for Heart Failure

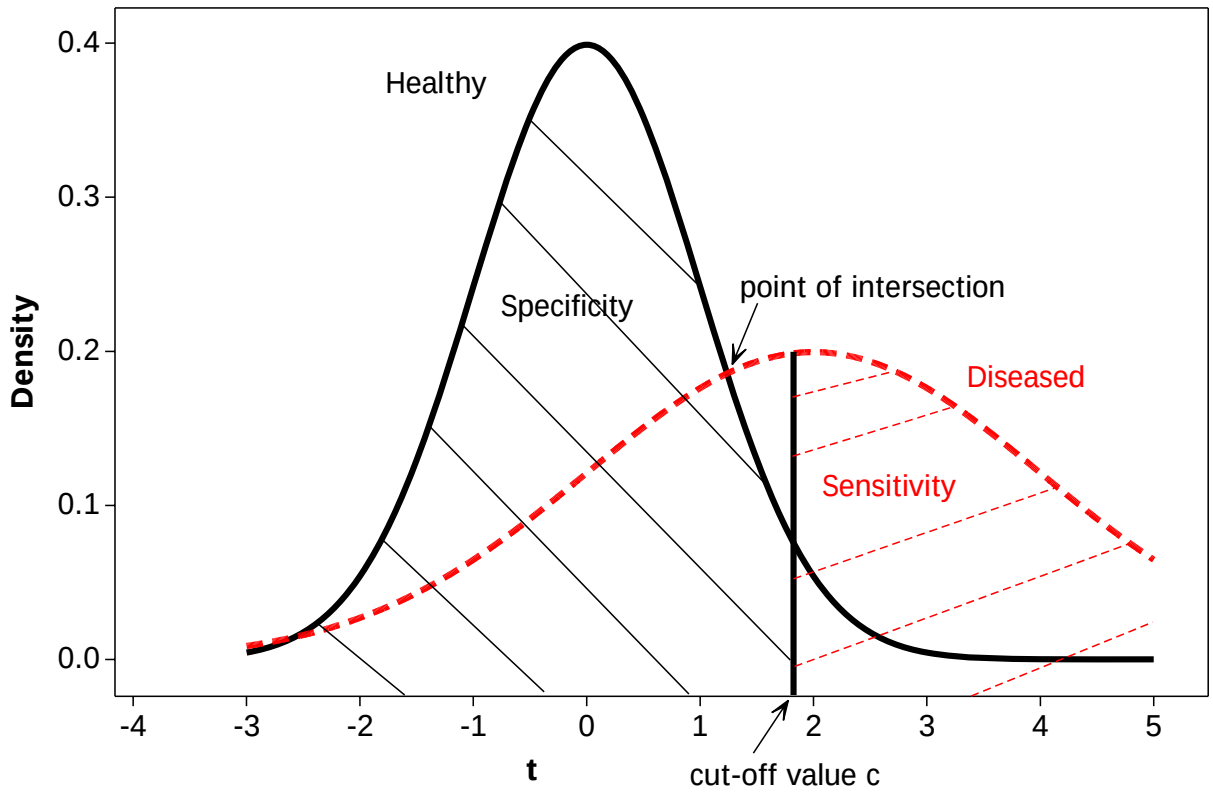
- diagnosis of heart failure is difficult
- overdiagnosis and underdiagnosis is occurring
- natriuretic peptides have been proposed as a diagnostic test
- meta-analysis provided by Doust *et al.* (2004) for brain natriuretic peptide (BNP)
- restriction on studies that use left ventricular ejection fraction of 40% or less as gold standard

Data of Meta-Analysis on Diagnostic Accuracy of BNP for Heart Failure

	diseased		healthy		
study	y(TP)	$m-y$(FN)	$n-x$(TN)	x(FP)	$n+m$
Bettenc. 2000	29	7	46	19	101
Choy 1994	34	6	22	13	75
Valli 2001	49	9	78	17	153
Vasan 2002a	4	6	1612	85	1707
Vasan 2002b	20	40	1339	71	1470
Hutcheon 2002	29	2	102	166	299
Landray 2000	26	14	75	11	126
Smith 2000	11	1	93	50	155

The Cut-off Value Problem

- Why not proceed with the **available armada of meta-analysis methods**?
- continuous or ordered categorical test uses **cut-off value**


Healthy
Specificity
point of intersection
Diseased
Sensitivity
Density
0.4
0.3
0.2
0.1
0.0
-4
-3
-2
-1
0
1
2
3
4
5
t
cut-off value c

The Cut-off Value Problem

- sensitivities and specificities from different studies **not comparable**
- different values for sensitivity and specificity might be due to different **diagnostic accuracy** or **different cut-off value**
- cut-off problem introduces **bias of unknown direction and size**

The SROC-diagram for meta-analytic situations

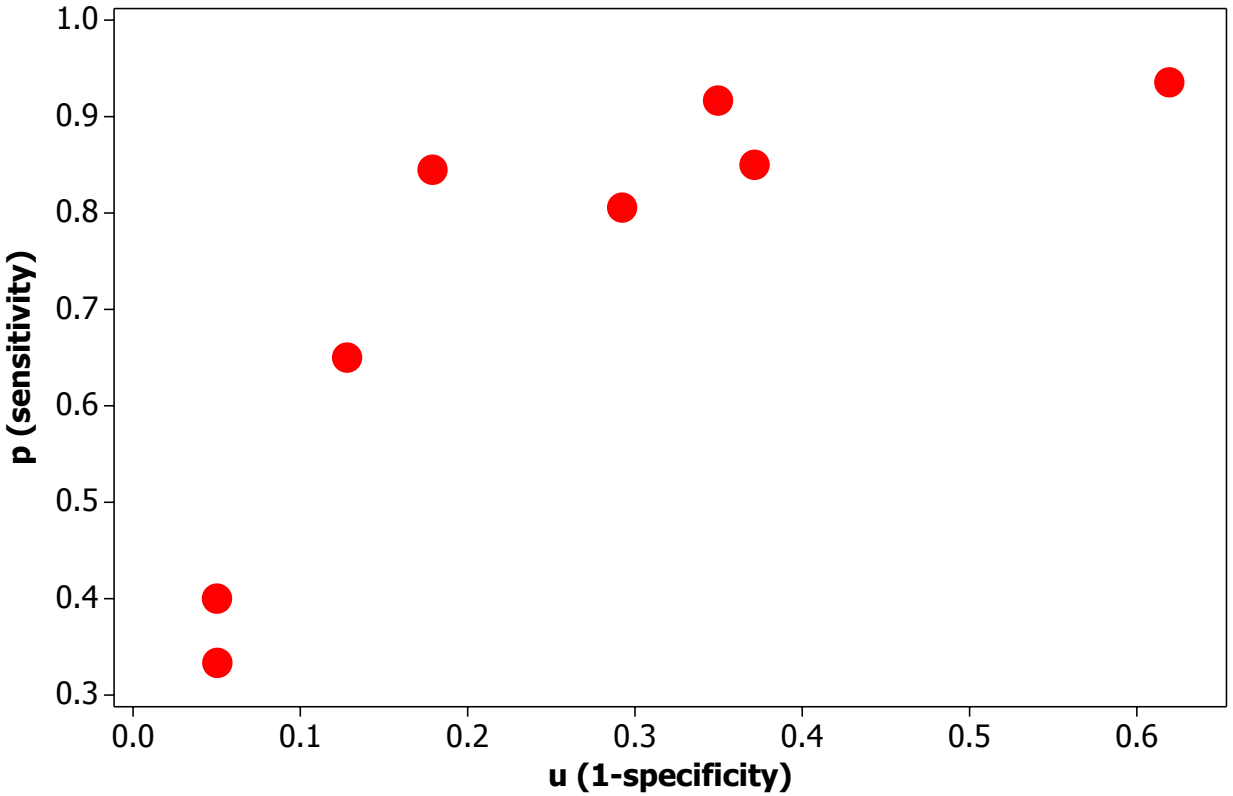
- Consider the pairs (sensitivity, 1-specificity) estimated by

$$(\hat{p}_i, \hat{u}_i) = (y_i/m_i, x_i/n_i)$$

for $i = 1, ..., k$

- include them in a ROC diagram
- it is called **summary** ROC because the points relate to **different studies** instead of **different cut-off values**

SROC-diagram for MA of BNP and Heart Failure



Few Comments on Littenberg-Moses

The DS-Equation

Littenberg and Moses (1993) suggest to fit

$$D = \alpha + \beta S$$

and reconstruct the SROC-curve from fitted values of α and β where

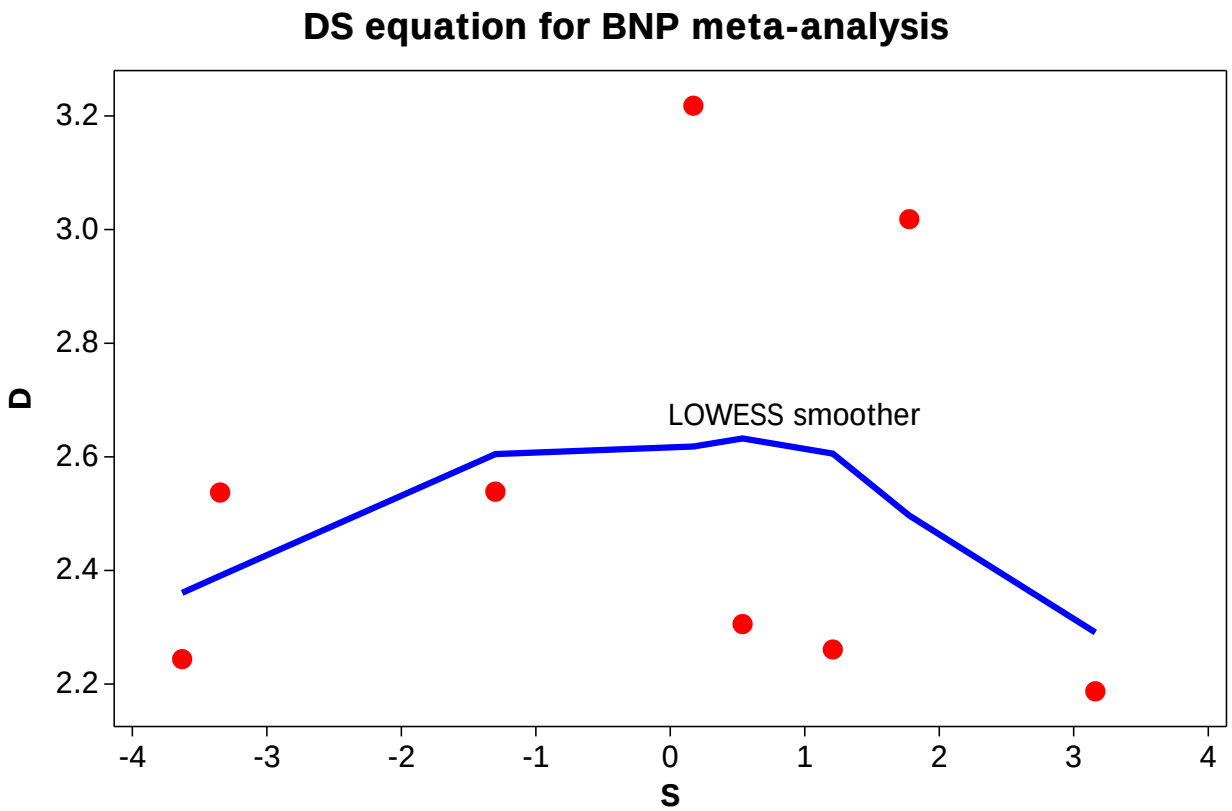
- $D = \log DOR = \log \frac{p}{1-p} - \log \frac{u}{1-u}$
- $S = \log \frac{p}{1-p} + \log \frac{u}{1-u}$

Interpretation:

- α is **summary log-DOR**
- adjusted by means of S for potential **cut-off value effect**

Problem with Littenberg-Moses:

- DS-Equation almost never met in practice


DS equation for BNP meta-analysis
LOWESS smoother
D
S
3.2
3.0
2.8
2.6
2.4
2.2
-4
-3
-2
-1
0
1
2
3
4

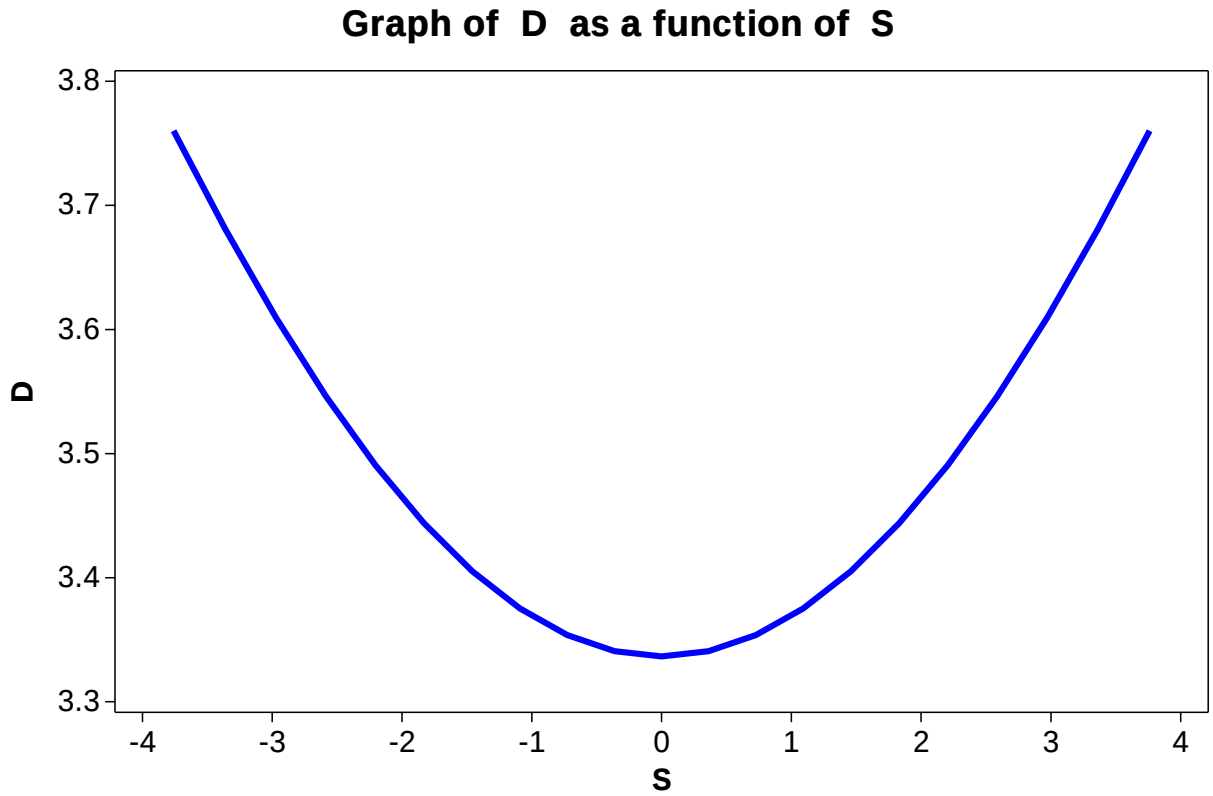
Explanation?

theoretical situation:

- healthy: $T \sim N(0,1)$, so $P(T < c | \textit{healthy}) = \Phi(c)$
- diseased $T \sim N(2,1)$, so $P(T \geq c | \textit{diseased}) = 1 - \Phi(c-2)$

dependency of D on S?

- cut-off varies: $c = 0, 0.1, ..., 2$
-
- How is the relation between D and S?


Graph of D as a function of S
3.8
3.7
3.6
3.5
3.4
3.3
D
-4
-3
-2
-1
0
1
2
3
4
S

Modelling of the SROC-diagram

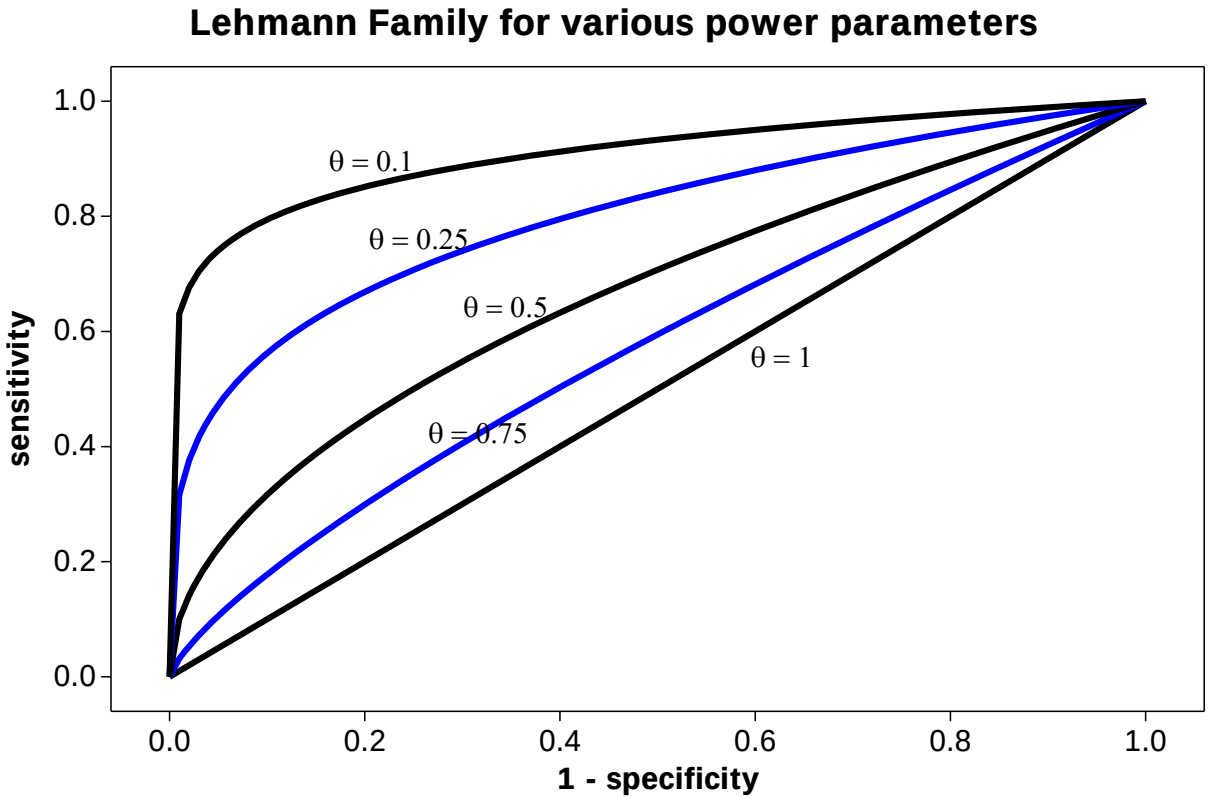
- Consider the **Lehmann family** for $\theta > 0$ and $i = 1, ..., k$ (Le 2006):

$$p_i = u_i^{\theta}$$

- or as a simple slope-only model

$$\log p_i = \theta \log u_i$$

- note model has **one parameter of interest** θ and k **nuisance parameters** $u_1, ..., u_k$
- note that θ represents the **diagnostic power** whereas the nuisance parameter captures heterogeneity in the specificities


Lehmann Family for various power parameters
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
θ = 0.1
θ = 0.25
θ = 0.5
θ = 0.75
θ = 1

Inference

- consider the product-binomial likelihood as the joint distribution of Y_i and X_i for the $i-$th study (index is suppressed for notational convenience)

$$\binom{m}{y} p^y (1-p)^{m-y} \times \binom{n}{x} u^x (1-u)^{n-x}$$

- which we replace by the normal approximation for $\log Y_i$ and $\log X_i$

$$\frac{1}{\sqrt{2\pi s^2}} \exp\{-\frac{1}{2}\frac{(\log y - \log(mp))^2}{s^2}$$

$$\times \frac{1}{\sqrt{2\pi t^2}} \exp\{-\frac{1}{2}\frac{(\log x - \log(nu))^2}{t^2}$$

Inference

- the normal approximation for $\log Y_i$ and $\log X_i$

$$\frac{1}{2\pi st}\exp\{-\frac{1}{2}\frac{(\log y - \log(mp))^2}{s^2}\}\times\exp\{-\frac{1}{2}\frac{(\log x - \log(nu))^2}{t^2}\}$$

- with the Taylor-series variance estimates
  $s^2 = \frac{1}{y} - \frac{1}{m}$ and $t^2 = \frac{1}{x} - \frac{1}{n}$
- consider now the log-likelihood for study i

$$-\frac{1}{2}\frac{(\log y - \log(mp))^2}{s^2} - \frac{1}{2}\frac{(\log x - \log(nu))^2}{t^2}$$

Inference

- and further with setting brackets differently

$$-\frac{1}{2s^2}(\log y - \log m - \log p)^2 - \frac{1}{2t^2}(\log x - \log n - \log u)^2$$

$$= -\frac{1}{2s^2}(\underbrace{\log y - \log m}_{z} - \log p)^2 - \frac{1}{2t^2}(\underbrace{\log x - \log n}_{w} - \log u)^2$$

$$= -\frac{1}{2s^2}(z - \overbrace{\theta \log u}^{\log p})^2 - \frac{1}{2t^2}(w - \log u)^2$$

Inference

- leading to the log-likelihood

$$\ell(\theta, u') = -\frac{1}{2s^2}(z - \theta u')^2 - \frac{1}{2t^2}(w - u')^2$$

- maximizing $\ell(\theta, u')$ in u' for **fixed** θ leads to

$$\hat{u}'_\theta = \frac{\theta t^2 z + s^2 w}{t^2\theta^2 + s^2}$$

- plugging $\hat{u}'_\theta$ in provides the **profile log-likelihood**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2s^2}(z - \theta\hat{u}'_\theta)^2 - \frac{1}{2t^2}(w - \hat{u}'_\theta)^2$$

Inference

- plugging $\hat{u}'_\theta$ in provides the **profile log-likelihood**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2s^2}(z - \theta\hat{u}'_\theta)^2 - \frac{1}{2t^2}(w - \hat{u}'_\theta)^2$$

  with $\hat{u}'_\theta = \frac{\theta t^2 z + s^2 w}{t^2\theta^2 + s^2}$

- ... **after some work** ... simplifies to

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2}\frac{(z - w\theta)^2}{t^2\theta^2 + s^2}$$

  a profile log-likelihood of **remarkable simplicity**

Why profile likelihood?

- eliminates nuisance parameter
- **two forms** of the model:

$$\log p = \theta \log u \ \textbf{or} \ \log u = \frac{1}{\theta} \log p$$

- it is invariant if u or p chosen to be the nuisance parameter

$$\ell(\theta, \hat{u}'_\theta) = \ell(\theta, \hat{p}'_\theta)$$

- suitable for **symmetric** regression problems

Profile or Adjusted Profile Likelihood?

- $\ell(\theta)$ is **almost Gaussian**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2} \underbrace{\frac{(z - w\theta)^2}{t^2\theta^2 + s^2}}_{\sigma^2(\theta)}$$

- it differs **only** from

$$L(\theta) = -\frac{1}{2} \log \sigma^2(\theta) - \frac{1}{2} \frac{(z - w\theta)^2}{\sigma^2(\theta)}$$

by $\frac{1}{2} \log \sigma^2(\theta)$

Profile or Adjusted Profile Likelihood?

- $\frac{1}{2}\log\sigma^2(\theta)$ corresponds to the **adjustment factor** $\hat{I}(\hat{u}_\theta)^{-1/2}$
- suggested by Cox and Reed (1987); Lee, Nelder Pawitan (2006); Murphy and van der Vaart (2000):

$$\hat{I}(\hat{u}_\theta) = -\frac{\partial^2}{\partial u'^2}\ell(\theta, u') = \frac{\partial^2}{\partial u'^2}\left(\frac{1}{2s^2}(z-\theta\hat{u}')^2 + \frac{1}{2t^2}(w-\hat{u}')^2\right)$$

$$= \frac{t^2\theta^2 + s^2}{s^2t^2}$$

- where, for fixed θ, $\hat{I}(\hat{u}_\theta)$ is the **observed Fisher information** $\hat{I}(u)$ evaluated at $\hat{u}_\theta$

Profile or Adjusted Profile Likelihood?

- as can be seen directly from above that

$$-\frac{1}{2}\log[\hat{I}(\theta)] + \ell(\theta) = L(\theta)$$

- providing an **excellent** justification of the adjusted profile likelihood

Full Sample Profile Likelihoods

for a sample of k studies

- we have the **full-sample profile** log-likelihood

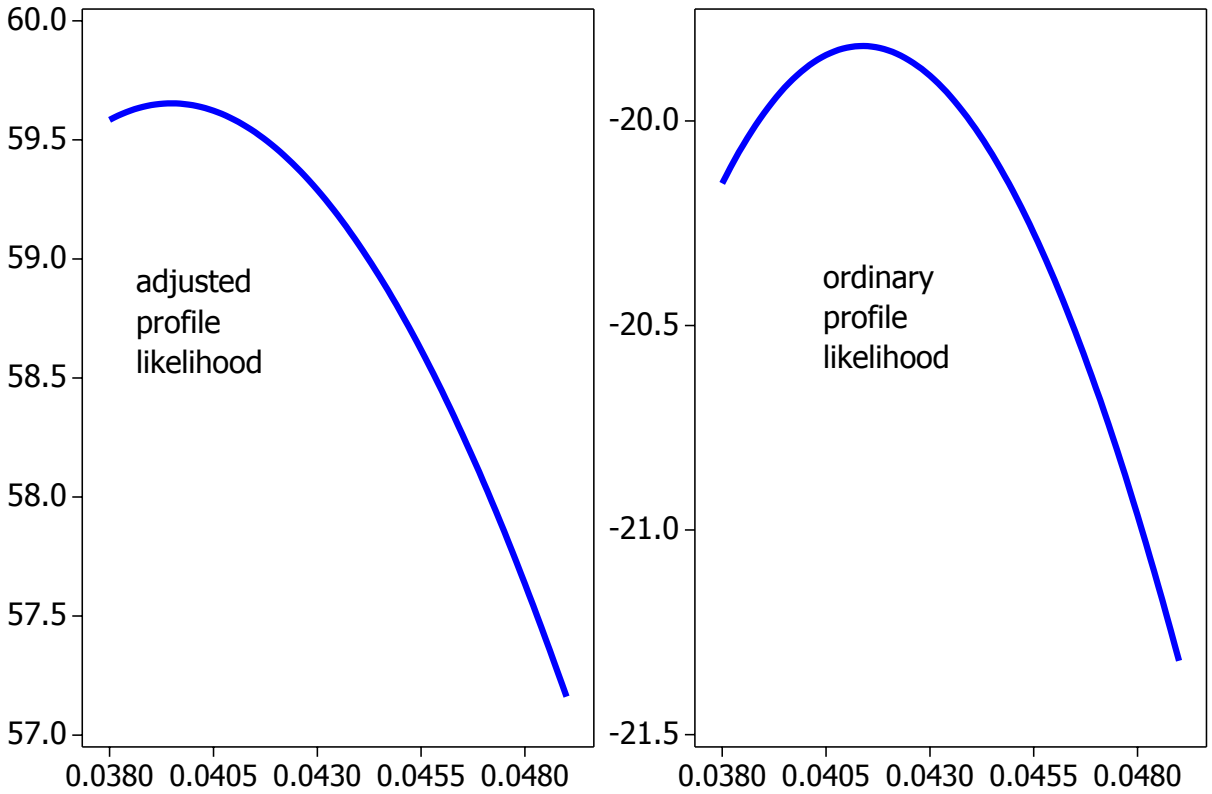
$$\ell(\theta) = -\sum_i \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

- and the **full-sample adjusted profile** log-likelihood

$$L(\theta) = -\sum_i \frac{1}{2} \log \sigma_i^2(\theta) - \sum_i \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

where $\sigma_i^2(\theta) = t_i^2\theta^2 + s_i^2$.

Ordinary and Adjusted Profile Likelihoods



Estimation: Maximum Profile Likelihood

- score for the **ordinary profile likelihood**

$$\frac{d}{d\theta}\ell(\theta) = -\frac{d}{d\theta}\sum_i \frac{1}{2}\frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

$$= \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} + \frac{1}{2}\frac{(z_i - w_i\theta)^2\sigma_i^2(\theta)'}{\sigma_i^4(\theta)}$$

- and the score for the **adjusted profile likelihood**

$$\frac{d}{d\theta}L(\theta) = \frac{d}{d\theta}\ell(\theta) - \frac{d}{d\theta}\sum_i \frac{1}{2}\log\sigma_i^2(\theta)$$

$$= \frac{d}{d\theta}\ell(\theta) - \frac{1}{2}\sum_i \frac{\sigma_i^2(\theta)'}{\sigma_i^2(\theta)}$$

Estimating Equation Approach

- suggestion: fix θ in $\sigma_i^2(\theta)$ and maximize the Gaussian loss in θ:

$$-\sum_i \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

- or solve the estimating equation

$$\sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} = 0$$

- leading to the **iterative reweighted least-squares** approach:

$$\theta = \frac{\sum_i z_i w_i/\sigma_i^2(\theta)}{\sum_i w_i^2/\sigma_i^2(\theta)}$$

Estimating Equation Approach

- neither ordinary nor adjusted profile likelihood is equivalent to IWLS
- look at the score for the **adjusted profile likelihood**

$$= \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} + \frac{1}{2}\frac{\overbrace{(z_i - w_i\theta)^2}^{\sigma_i^2(\theta)}\sigma_i^2(\theta)'}{\sigma_i^4(\theta)} - \frac{1}{2}\frac{\sigma_i^2(\theta)'}{\sigma_i^2(\theta)}$$

$$\approx \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)}$$

- close to **estimating equation** approach

Simulation Study

- previous analysis suggests: profile and adjusted profile likelihood inference differs
- but how much? Look at **Bias and variance**!
- how **valid** are the second derivate approximations of the true variances for both likelihoods ?

Simulation Study: Design

for $i = 1, ..., k = 10$:

1. $u_i \sim U[0.05, .5]$
2. use model: $p_i = u_i^\theta$ for $\theta = 0.1, 0, 2, 0.3$
3. $n_i, m_i \sim Po(100)$ or $n_i, m_i \sim Po(10)$ (sparsity case)
4. $Y_i \sim Bin(p_i, m_i)$ and $X_i \sim Bin(u_i, n_i)$
5. determine various estimators of θ
6. replicate this process 1,000 times

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.1$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 100$			
IWLS	0.0961	0.0104	-
PMLE	0.0977	0.0104	0.0119
APMLE	0.0960	0.0101	0.0117
$E(n_i) = E(m_i) = 10$			
IWLS	0.0899	0.0291	-
PMLE	0.0981	0.0313	0.0561
APMLE	0.0812	0.0260	0.0468

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.2$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 100$			
IWLS	0.1959	0.0153	-
PMLE	0.1988	0.0153	0.0194
APMLE	0.1955	0.0151	0.0191
$E(n_i) = E(m_i) = 10$			
IWLS	0.1722	0.0499	-
PMLE	0.1917	0.0536	0.0838
APMLE	0.1597	0.0442	0.0654

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.3$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 100$			
IWLS	0.2953	0.0210	-
PMLE	0.3004	0.0211	0.0262
APMLE	0.2953	0.0208	0.0255
$E(n_i) = E(m_i) = 10$			
IWLS	0.2693	0.0694	-
PMLE	0.3011	0.0742	0.1137
APMLE	0.2517	0.0622	0.0869

Simulation Study: Results for small n but large k

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator* $k=100$

estimator for $\theta = 0.3$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 20$			
IWLS	0.2753	0.0153	-
PMLE	0.2970	0.0156	0.0189
APMLE	0.2718	0.0143	0.0164

Simulation Study: Conclusions

large n_i, m_i

- all three estimators behave similar
- minimal gain in efficiency with APMLE
- Fisher information estimate a bit conservative for variance estimation

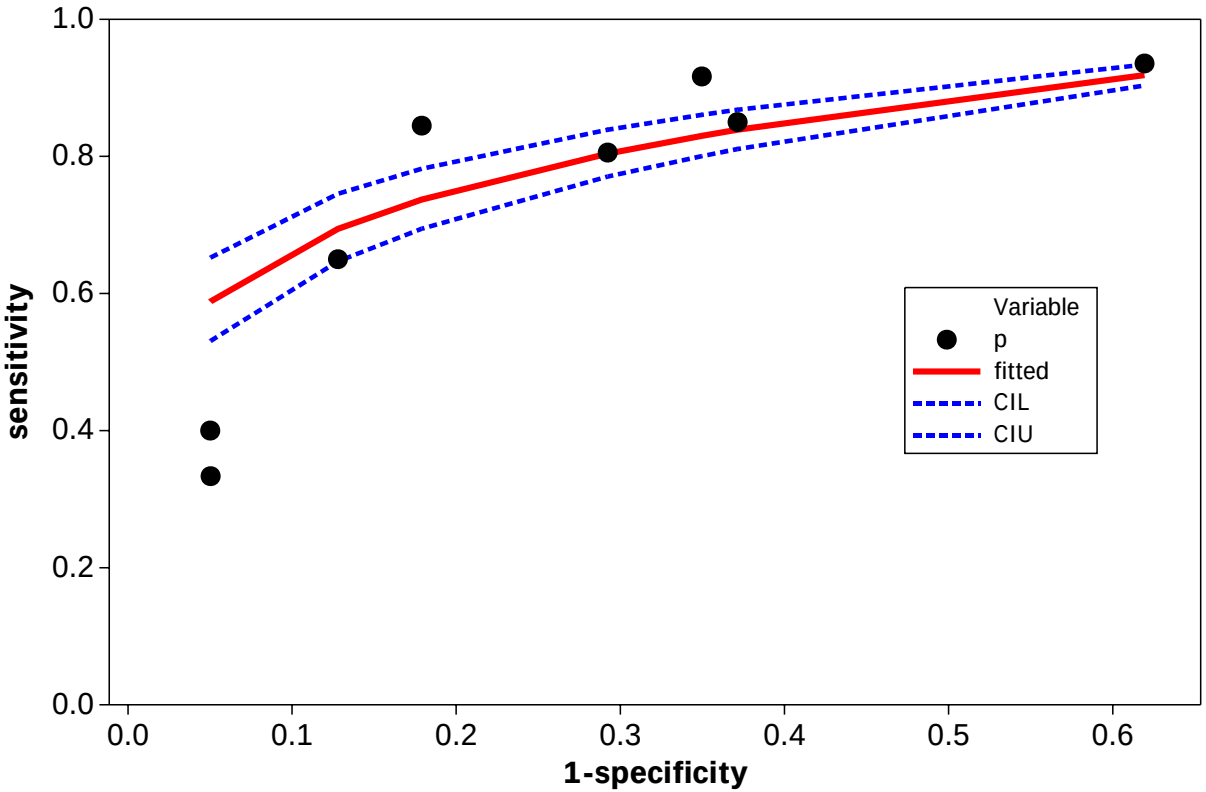
small n_i, m_i

- ordinary PMLE less biased
- APMLE more efficient
- Fisher information estimate overestimates variance of PMLE and APMLE

Application to BNP Meta-Analysis

- APMLE for $L(\theta)$ provides $\hat{\theta} = 0.1774$
- PMLE for $\ell(\theta)$ provides $\hat{\theta} = 0.1802$
- and IWLS gives $\hat{\theta} = 0.1755$

Observed and Fitted Lehmann Model



Goodness-of-Fit

- since $E(Z_i) = \theta \log u_i$ and $E(W_i) = \log u_i$
- it follows
$$E(Z_i - \theta W_i) = 0$$
- also $Var(Z_i) = s_i^2$ and $Var(\theta W_i) = \theta^2 t_i^2$
- hence
$$Var(Z_i - \theta W_i) = s_i^2 + \theta^2 t_i^2$$
- so that
$$\frac{Z_i - \theta W_i}{\sqrt{s_i^2 + \theta^2 t_i^2}} \sim N(0, 1)$$

Goodness-of-Fit

χ^2- statistic

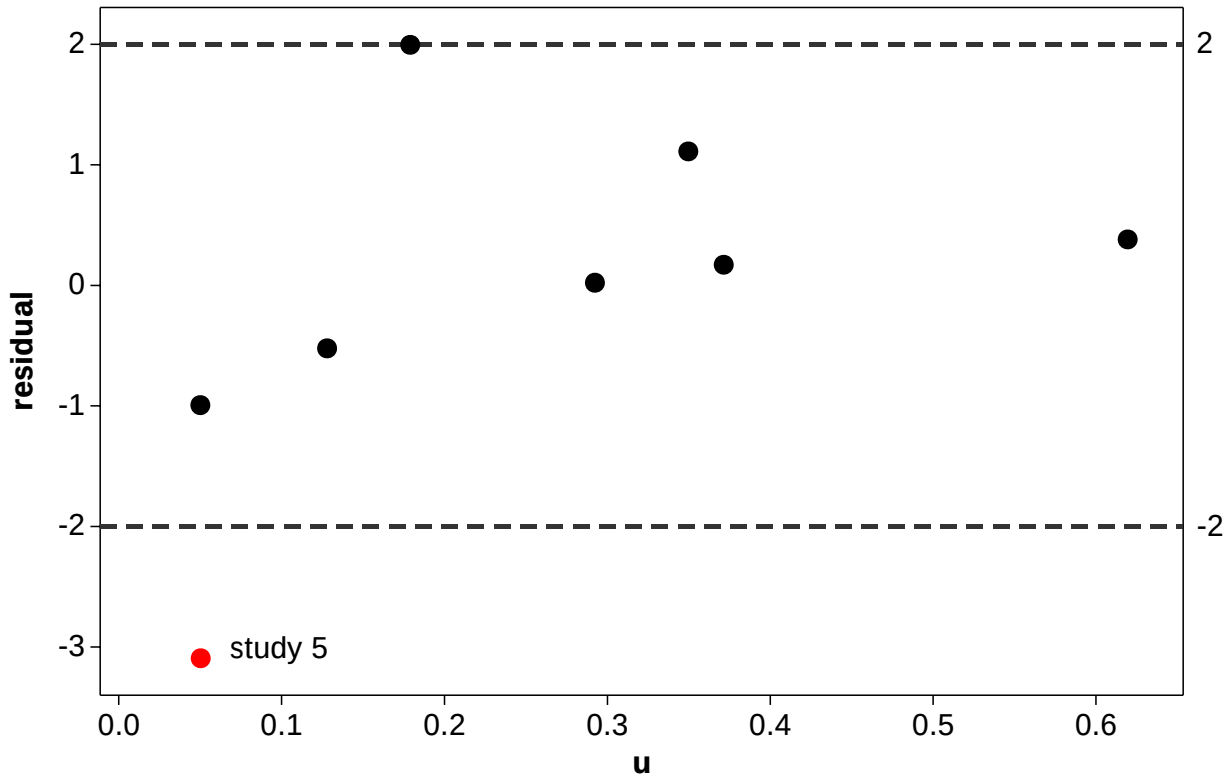
$$\chi^2_{k-1} = \sum_{i=1}^{k} \frac{(Z_i - \hat{\theta} W_i)^2}{s_i^2 + \hat{\theta}^2 t_i^2}$$

BNP meta-analysis

based upon **all** 8 studies: $\chi^2_7 = 16.23$ and $P = 0.0231$
based upon 7 Studies (without **study 5**): $\chi^2_6 = 6.66$ and $P = 0.4655$ since plot of residuals:

$$\frac{Z_i - \hat{\theta} W_i}{\sqrt{s_i^2 + \hat{\theta}^2 t_i^2}}$$

provides evidence that study 5 is source of heterogeneity


2
1
0
-1
-2
-3
residual
2
-2
study 5
0.0
0.1
0.2
0.3
0.4
0.5
0.6
u

Incorporating Heterogeneity

- known: heterogeneity is **frequent** in meta-analytic settings
- often required to incorporate heterogeneity into the model building process
- in addition: comparative issues are confounded by forms of heterogeneity
- this will be illustrated with an example from **alcohol use disorder** identification

Meta-Analysis on Diagnostic Accuracy of the Alcohol Use Disorder Identification Test (AUDIT)

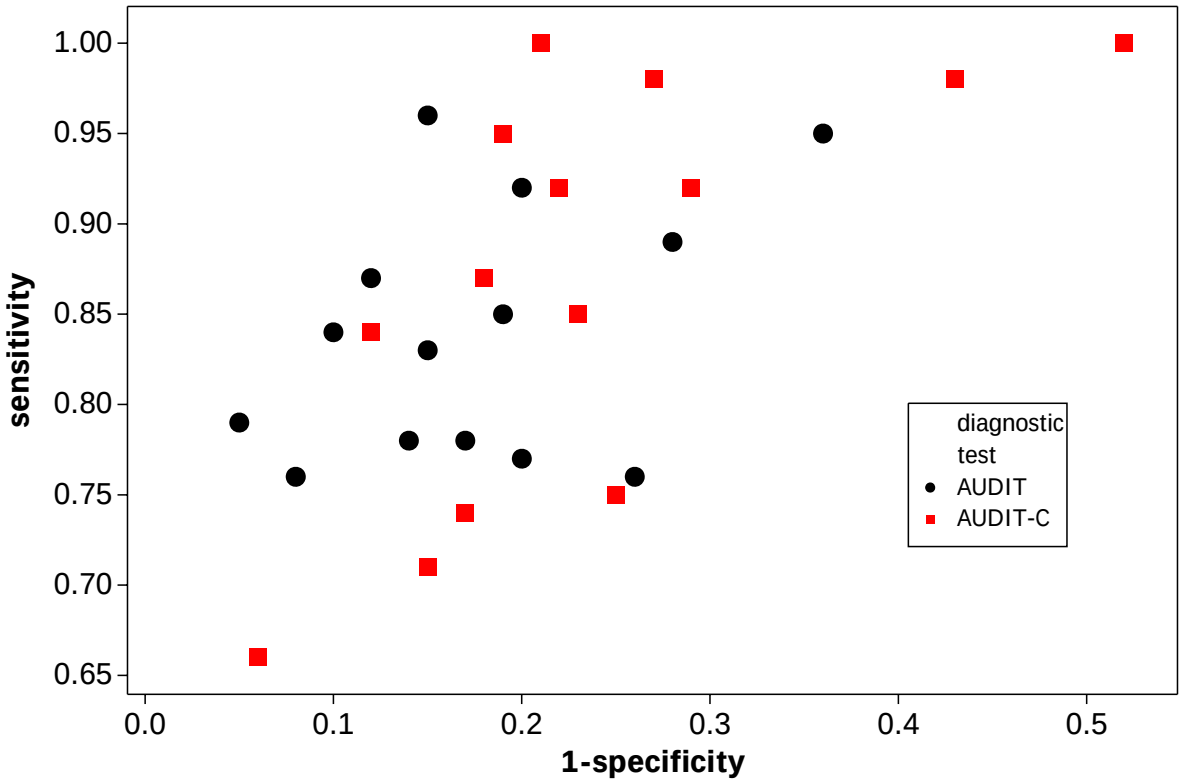
- Kristen *et al.* (2008): *Are 3 Questions enough to detect unhealthy alcohol use?*
- 10-item AUDIT and abbreviated 3-item version AUDIT-C to detect unhealthy alcohol use
- Purpose: is AUDIT-C is as accurate as the full AUDIT
- MA of 14 studies for the AUDIT as follows

	alcohol disorder		no disorder		
study	y(TP)	$m - y$(FN)	$n - x$(TN)	x(FP)	$n + m$
1	48	7	738	101	894
2	138	39	1506	309	1992
3	24	5	173	31	233
4	37	2	227	127	393
5	137	12	936	234	1319
6	73	13	127	30	243
7	53	14	508	27	602
8	571	180	5707	496	6954
9	54	10	172	19	255
10	148	44	2687	672	3551
11	143	18	334	130	625
12	47	13	464	76	600
13	34	1	65	12	112
14	154	49	261	92	555

Meta-Analysis on Diagnostic Accuracy of the Alcohol Use Disorder Identification Test (AUDIT)

- the MA also includes studies on the AUDIT-C
- MA of 14 studies for the AUDIT-C as follows

	alcohol disorder		no disorder		
study	y(TP)	$m - y$(FN)	$n - x$(TN)	x(FP)	$n + m$
1	47	9	738	101	894
2	126	51	1543	272	1992
3	19	10	192	12	233
4	36	3	276	78	393
5	130	19	959	211	1319
6	84	2	89	68	243
7	67	0	423	112	602
8	751	0	2977	3226	6954
9	59	5	136	55	255
10	142	50	2788	571	3551
11	137	24	358	107	625
12	57	3	437	103	600
13	34	1	56	21	112
14	152	51	264	88	555


1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
sensitivity
0.0
0.1
0.2
0.3
0.4
0.5
1-specificity
diagnostic test
AUDIT
AUDIT-C

ROC curves of AUDIT and AUDIT-C:

- no clear **evidence** for either/or
- highly **unsmooth**
- evidence of **heterogeneity**

How well is the Lehmann model supported in the data?

scatterplot of $\log p$ **vs.** $\log u$**:**

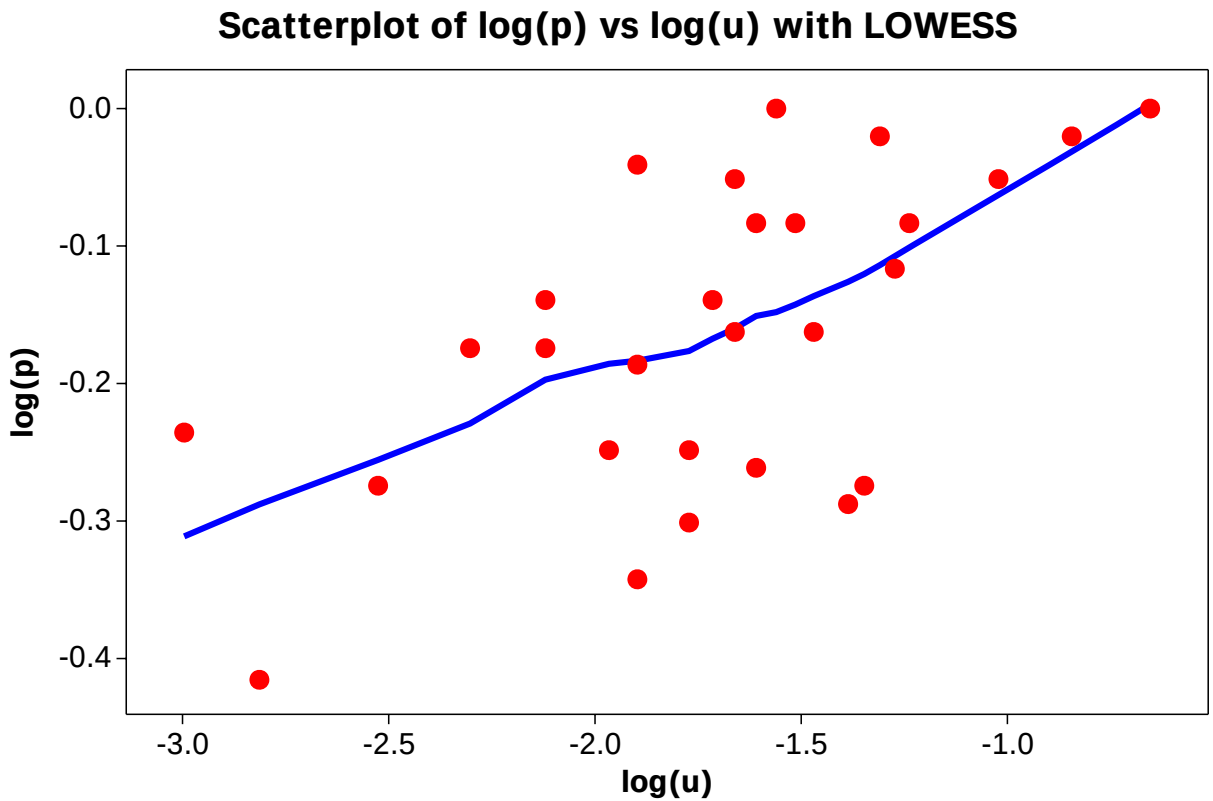
since

$$p = u^{\theta}$$

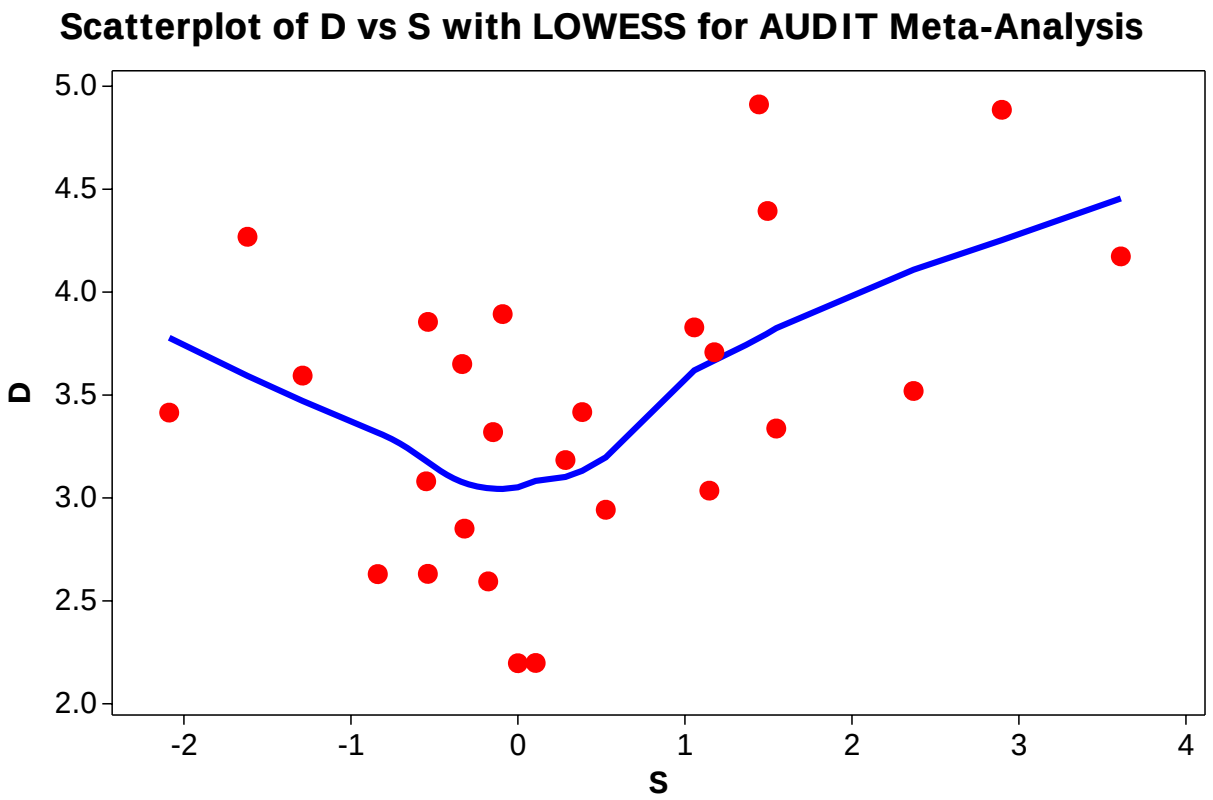
is equivalent to

$$\log p = \theta \log u$$

we look at the linearity of scatterplot $\log p$ vs. $\log u$


Scatterplot of log(p) vs log(u) with LOWESS
0.0
-0.1
-0.2
-0.3
-0.4
log(p)
-3.0
-2.5
-2.0
-1.5
-1.0
log(u)

Littenberg-Moses would be problematic here



Extension to a Random Effect Model

for a sample of k studies

- the **full-sample adjusted profile** log-likelihood is

$$L(\theta) = -\sum_{i=1}^{k} \frac{1}{2} \log \sigma_i^2(\theta) - \sum_{i=1}^{k} \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

  where $\sigma_i^2(\theta) = t_i^2\theta^2 + s_i^2$

- this suggests to consider Z_i conditional upon W_i

$$Z_i = w_i\theta + \epsilon_i$$

- so that

$$Z_i | w_i \sim N(w_i\theta, \sigma_i^2(\theta))$$

Extension to a Random Effect Model

- this can be extended by a further **random effect** δ_i, independent of ϵ_i, with $E(\delta_i) = 0$ and $Var(\delta_i) = \tau^2$

$$Z_i = w_i\theta + \delta_i + \epsilon_i$$

- so that

$$Z_i|w_i \sim N(w_i\theta, \sigma_i^2(\theta) + \tau^2)$$

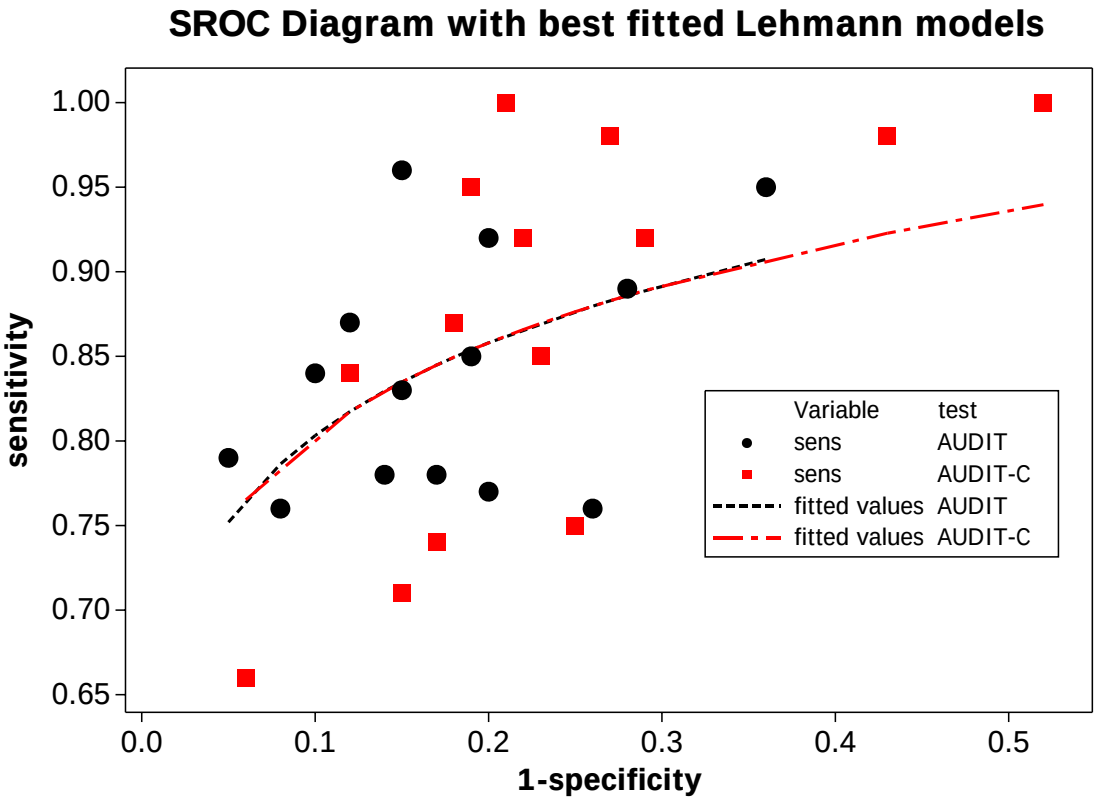
- the **full-sample adjusted profile** log-likelihood with **random effect** is

$$L(\theta, \tau^2) = -\sum_{i=1}^{k} \frac{1}{2} \log[\sigma_i^2(\theta) + \tau^2] - \sum_{i=1}^{k} \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta) + \tau^2}$$

where $\sigma_i^2(\theta) = t_i^2\theta^2 + s_i^2$

Analysis of Diagnostic Accuracy for AUDIT Meta-Analysis Data

Test	$\hat{\theta}$	$\hat{\tau}^2$	χ^2	P-value
— homogeneity —				
AUDIT	0.09836	-	54.45	< 0.001
AUDIT-C	0.09145	-	3,200	< 0.001
— heterogeneity (mixed model) —				
AUDIT	0.09402	0.00457	13.07	0.36
AUDIT-C	0.09516	0.00825	13.85	0.31


SROC Diagram with best fitted Lehmann models
sensitivity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.0
0.1
0.2
0.3
0.4
0.5
1-specificity
Variable test
sens AUDIT
sens AUDIT-C
fitted values AUDIT
fitted values AUDIT-C

Analysis of Diagnostic Accuracy for AUDIT Meta-Analysis Data: Interpretation

MA shows that

- AUDIT and AUDIT-C have similar diagnostic accuracy
- heterogeneity for AUDIT-C is considerably larger

Further Work in Progress

- general linear model approach to include **observed heterogeneity** in form of **covariates**
- nonparametric mixture approach to model **unobserved heterogeneity**
- **classification** of studies into different components of **homogeneous diagnostic accuracy**