Statistical Inference following Self–Designing Clinical Trials with Binary Response

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Outline

Self–Designing Clinical Trials

- introduction of "self–designing clinical trials" by Fisher (1998, Statist. Med.) for general setting of normal variables with known variances
- in Hartung (2001, Contr. Clin. Trials; 2006, Biom. J.) the distributional restriction is lifted by using a combining method of p–values
  - inverse normal method
- adaptive choice of both sample sizes and weights of the several study parts
- the rejection of the null hypothesis is tested just once at the end of the trial

Of Interest

- consider for a real valued parameter θ the test problem

$$H_0 : \theta = 0 \quad \text{versus} \quad H_1 : \theta > 0$$

  - test of level $\alpha/2$
  - confidence interval for θ of level $1 - \alpha$

- study is performed in K study parts where K is a finite random variable

Inverse Normal Method

in each step k, $k = 1, ..., K$:

- $\hat{\theta}_k$ unbiased estimator of θ
- test statistic T_k for testing H_0 vs. H_1
  assumption:
  - T_k is continuously distributed, otherwise approximative (binary case in detail later)
  - $T_k = T_k(\hat{\theta}_k)$ is (strictly) monotone increasing in $\hat{\theta}_k$

  $\hookrightarrow$ $T_k(\hat{\theta}_k - \theta)$ is (strictly) monotone decreasing in θ
- p-value $p_k = p_k(\theta) = 1 - F_{H_0}(T_k(\hat{\theta}_k - \theta))$
- transformation $z_k = \Phi^{-1}(1 - p_k) \sim N(0, 1)$ for true θ

Inverse Normal Method

- defining a sequence of nonnegative weights $w_1, ..., w_k, ...$ adaptively:
$$w_k = \hat{w}\{stage(0), ..., stage(k-1)\}$$

- with probability one under H_0 there exists a finite (random) K with
$$\sum_{k=1}^{K} w_k^2 = \sum_{k=1}^{\infty} w_k^2 = 1$$
then
$$Z_K = \sum_{k=1}^{K} w_k \, z_k = \sum_{k=1}^{\infty} w_k \, z_k \sim N(0,1) \quad \text{for true } \theta$$

- **decision rule:** H_0 is rejected at level $\frac{\alpha}{2}$ if $Z_{K|\theta=0} > \Phi^{-1}\left(1-\frac{\alpha}{2}\right)$

Practical Aspects

- specification of a lower bound for the weight of stage k
  $\Longrightarrow$ thus maximal number of stages is bounded

- also useful: specification of a minimal and maximal number of patients per stage

- during the course of the study design adaptions are possible and at every stage the next can be planned as the last one

- real planned studies for instance:
  - breast cancer study
  - Parkinson's disease study

Comment: fixing the weights a priori

$\Longrightarrow$ nearly an adaptive group sequential design of O'Brien and Fleming type (see Hartung, 2006, Biom. J.)

Overall p-Value

- overall p-value at trial termination:

$$p(\theta) = 1 - \Phi(Z_K(\theta))$$

  - $p(\theta)$ is a pivotal quantity increasing in θ
  - $p(\theta)$ follows an uniform distribution F on [0,1]

Confidence Interval and Point Estimator

construction of an $(1-\alpha)$–confidence interval for θ at the end of the trial

(see also: Liu and Chi, 2001; Wassmer, 2003; Hartung and Knapp, 2006)

- lower and upper bound:

$$\hat{\theta}_L = p^{-1}(\alpha/2) \quad \text{and} \quad \hat{\theta}_U = p^{-1}(1-\alpha/2)$$

- midpoint of the confidence interval:

$$\hat{\theta}_{1/2} = p^{-1}(1/2)$$

$\hookrightarrow$ median unbiased estimator for θ

Binary Outcomes

- parallel group design with

$$X_1 \sim B(n_1, p_1) \quad \text{and} \quad X_2 \sim B(n_2, p_2)$$

- parameters of interest:
  - risk difference: $D = p_1 - p_2$
  - logarithmic risk ratio: $\log RR = \log(p_1/p_2)$
  - logarithmic odds ratio: $\log OR = \log\left(\frac{p_1/(1-p_1)}{p_2/(1-p_2)}\right)$

Notation

fourfold table at stage k

treatment	success	failure	total
1	$n_{11,k}$	$n_{12,k}$	n_{1k}
2	$n_{21,k}$	$n_{22,k}$	n_{2k}
	$n_{11,k} + n_{21,k}$	$n_{12,k} + n_{22,k}$	n_k

Risk Difference

- estimation of $D = p_1 - p_2$ at stage k:

$$\hat{D}_k = \hat{p}_{1k} - \hat{p}_{2k} = \frac{n_{11,k}}{n_{1k}} - \frac{n_{21,k}}{n_{2k}}$$

- estimation of the variance of $\hat{D}_k$ at stage k:

$$\widehat{Var}(\hat{D}_k) = \widehat{Var}(\hat{p}_{1k}) + \widehat{Var}(\hat{p}_{2k}) = \frac{\hat{p}_{1k}(1-\hat{p}_{1k})}{n_{1k}-1} + \frac{\hat{p}_{2k}(1-\hat{p}_{2k})}{n_{2k}-1}$$

Logarithmic Risk Ratio

- estimation of $\log RR = \log(p_1/p_2)$ at stage k:

$$\log \widehat{RR}_k = \log\left(\hat{p}_{1k}/\hat{p}_{2k}\right) = \log\left(\frac{n_{11,k}/n_{1k}}{n_{21,k}/n_{2k}}\right)$$

- estimation of the variance of $\log \widehat{RR}_k$ at stage k:

$$\widehat{Var}(\log \widehat{RR}_k) = \frac{1}{n_{11,k}} - \frac{1}{n_{1k}} + \frac{1}{n_{21,k}} - \frac{1}{n_{2k}}$$

Logarithmic Odds Ratio

- estimation of $\log OR = \log((p_1/(1-p_1))/(p_2/(1-p_2)))$ at stage k:

$$\log \widehat{OR}_k = \log\left(\frac{\hat{p}_{1k}/(1-\hat{p}_{1k})}{\hat{p}_{2k}/(1-\hat{p}_{2k})}\right) = \log\left(\frac{n_{11,k}\ n_{22,k}}{n_{12,k}\ n_{21,k}}\right)$$

- estimation of the variance of $\log \widehat{OR}_k$ at stage k:

$$\widehat{Var}(\log \widehat{OR}_k) = \frac{1}{n_{11,k}} + \frac{1}{n_{12,k}} + \frac{1}{n_{21,k}} + \frac{1}{n_{22,k}}$$

Characteristics of the Test Statistic

- Test Statistic at stage k:

$$T_k = \frac{\hat{\theta}_k - \theta}{\sqrt{\widehat{Var}(\hat{\theta}_k)}} \overset{appr.}{\sim} N(0,1)$$

- $\frac{\partial\, T_k}{\partial\, \theta} = \frac{-1}{\sqrt{\cdots}} < 0 \Longrightarrow T_k$ is strictly monotone decreasing in θ

Example: Logarithmic Risk Ratio

$\alpha = 0.05$

stage k	sample size per group	weight w_k	log risk ratio	p–value p_k
1	20	0.447	0.368	0.108
2	63	0.559	0.288	0.024
3	56	0.698	0.381	0.009

test decision:

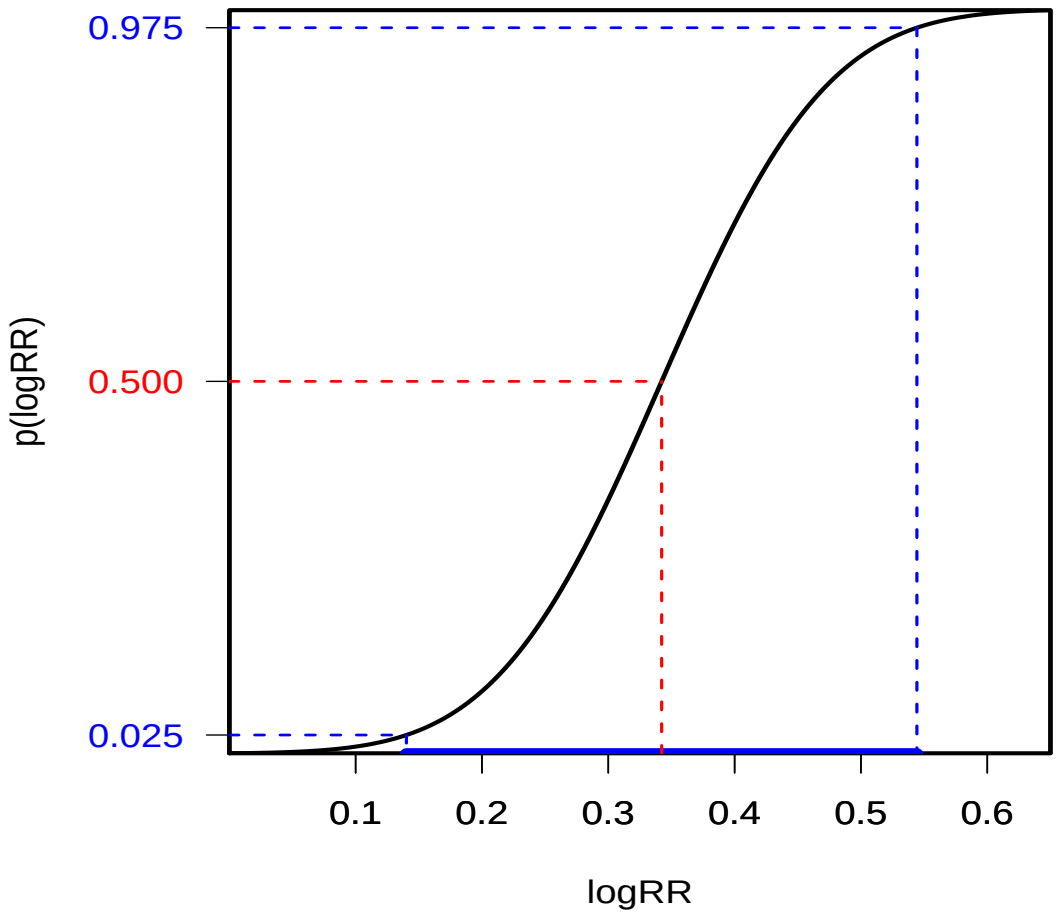
$$Z_{3|\log RR=0} = 3.320 > \Phi^{-1}(1 - 0.025) \Longrightarrow \text{rejection of } H_0$$

after trial termination:

- estimation of $\log RR = \log(p_1/p_2)$
- construction of an 95%-confidence interval for $\log RR$

Example: Logarithmic Risk Ratio

overall p–value: $p(\log RR) = 1 - \Phi(Z_K(\log RR))$



$$\log \widehat{RR}_{1/2} = 0.342$$

$$KI(\log RR) = [0.140, 0.544]$$

Some Simulation Results

- construction of a confidence interval with confidence level 95% and median unbiased estimation of D, $\log RR$ and $\log OR$

  $\hookrightarrow$ investigation of the

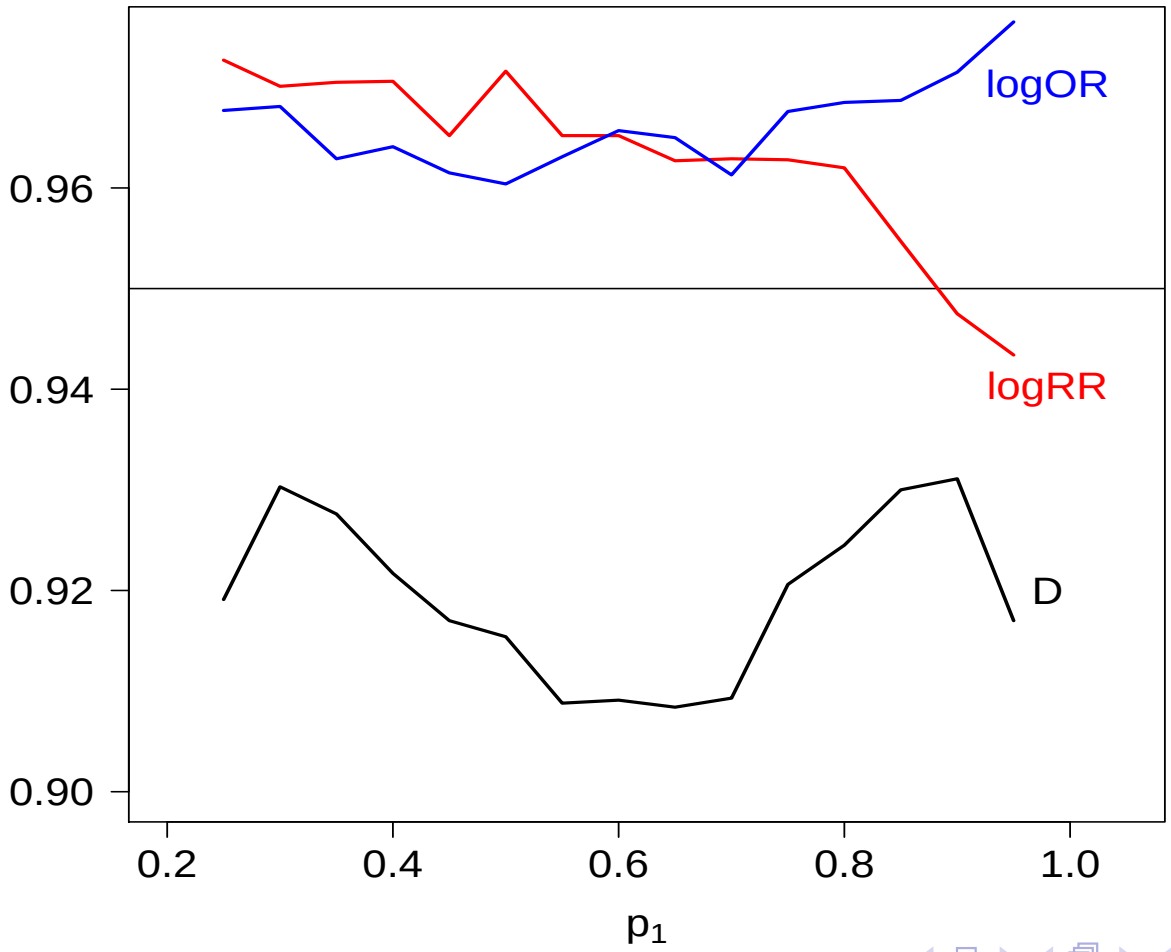
  - coverage probability of the confidence interval
  - average length of the confidence interval
  - point estimation

- adaptive choices of sample sizes and weights:
  learning rules of Hartung (2001, Contr. Clin. Trials)

- number of realized stages: *range*: $1 \leq K \leq 6$, *mean*: $\overline{K} \approx 3$

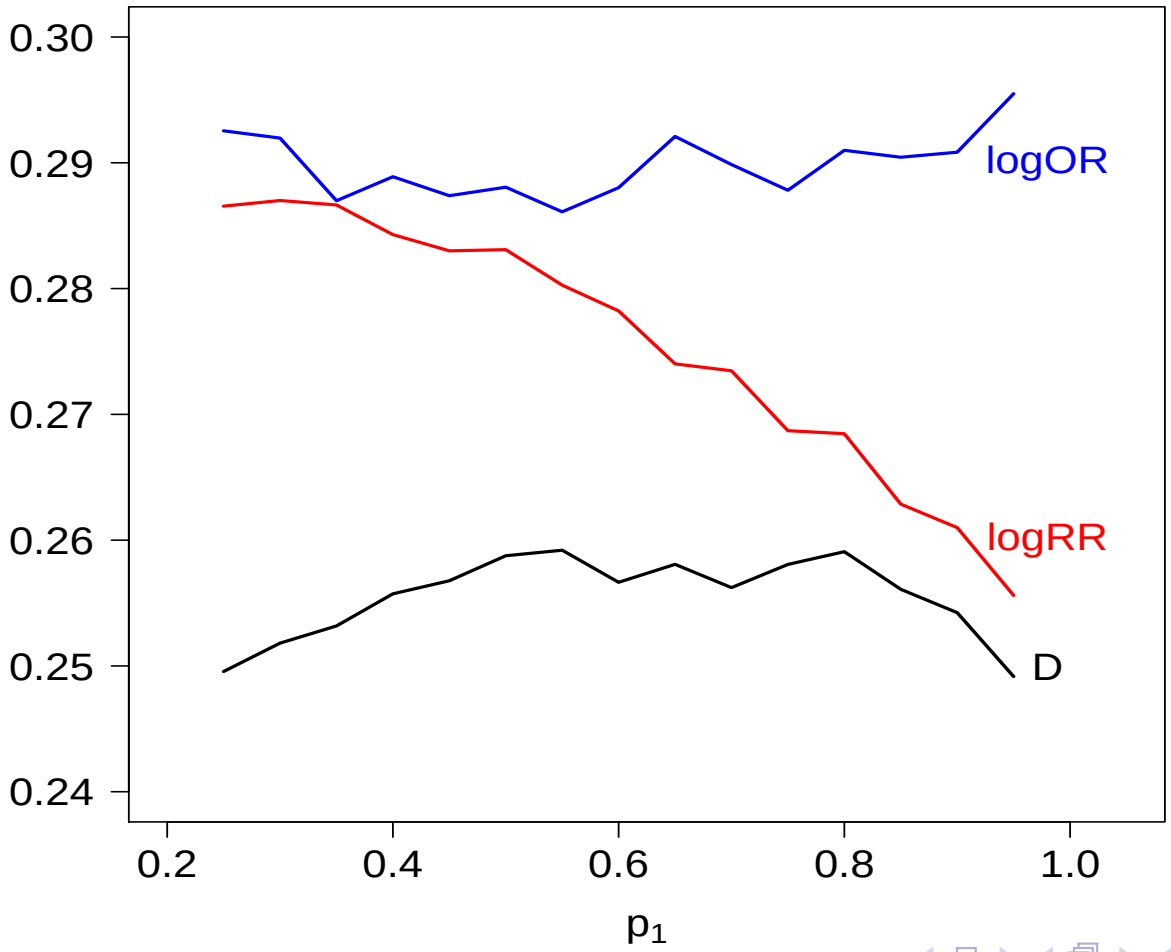
Coverage Probability of the Confidence Interval

- $D = \log RR = \log OR = 0.2$ fixed, $p_1 = 0.25, 0.3, ..., 0.95$



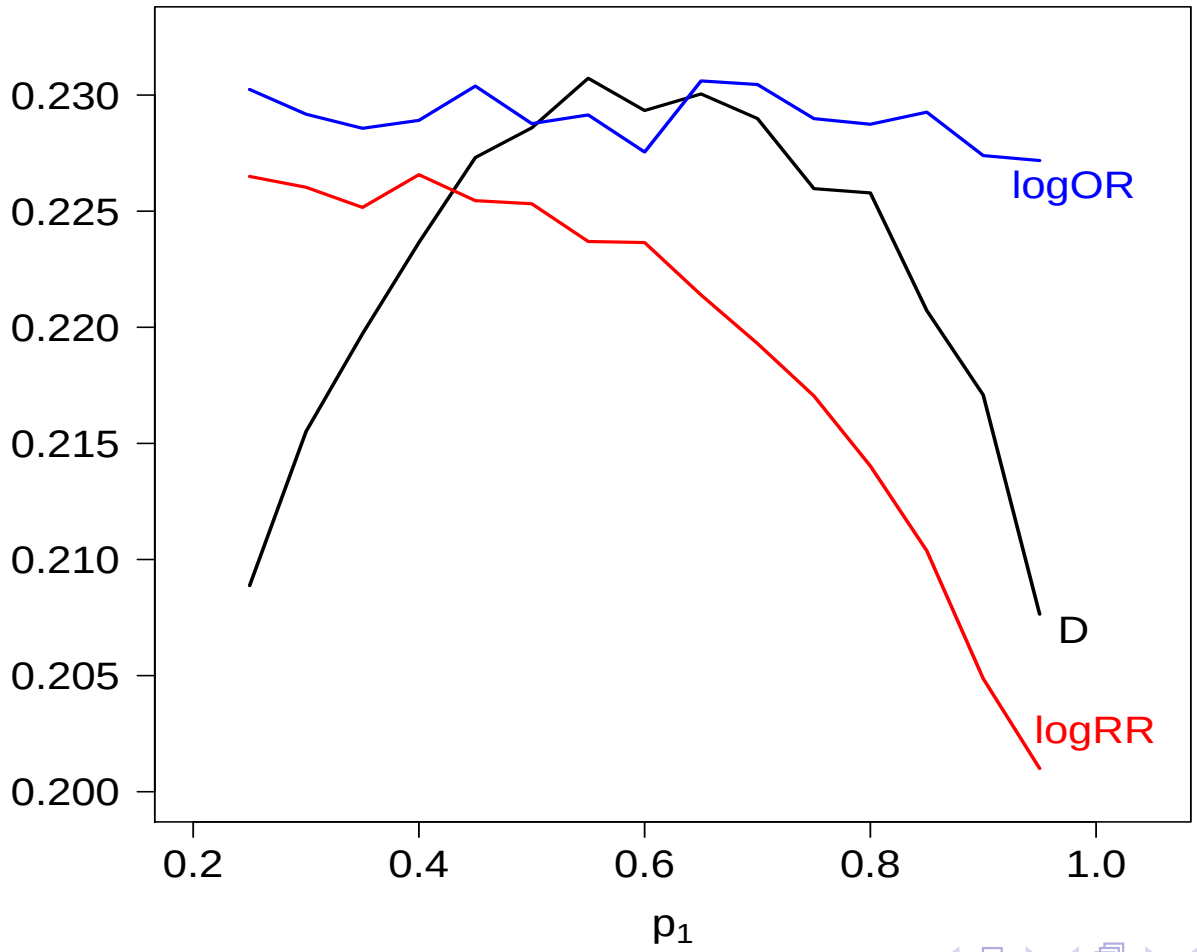
Average Length of the Confidence Interval

- $D = \log RR = \log OR = 0.2$ fixed, $p_1 = 0.25, 0.3, ..., 0.95$



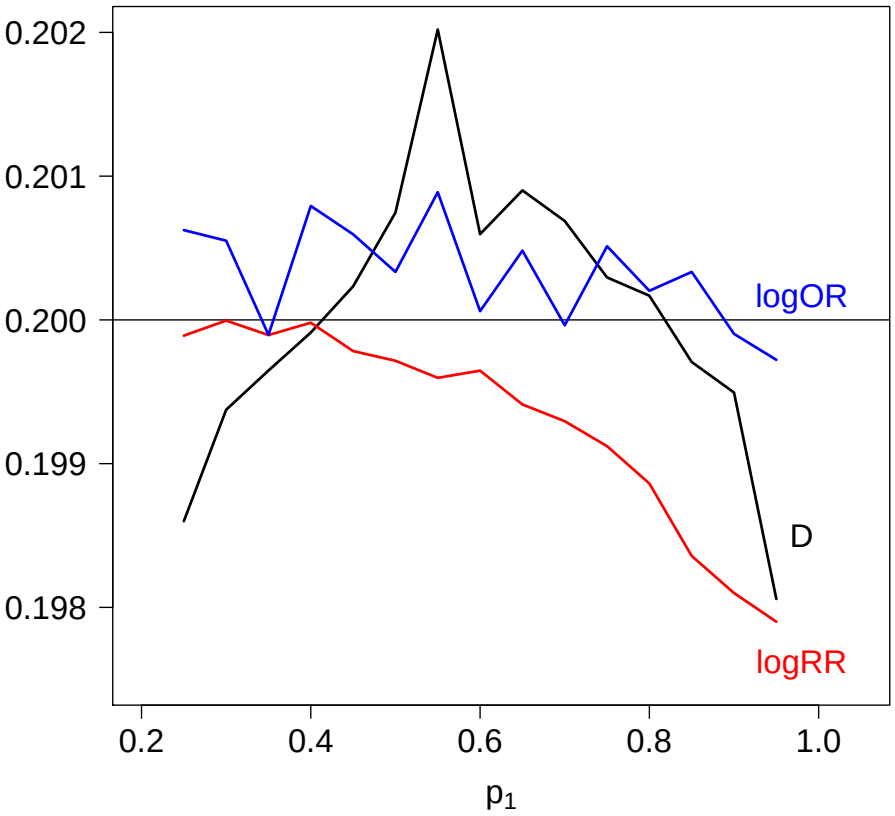
Median unbiased Estimation

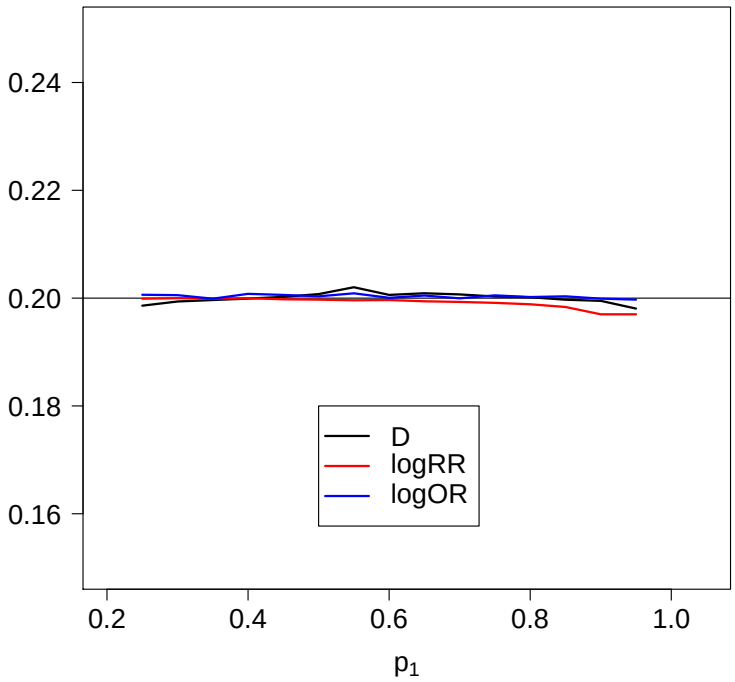
- $D = \log RR = \log OR = 0.2$ fixed, $p_1 = 0.25, 0.3, ..., 0.95$



Empirical Median of the Estimator

- $D = \log RR = \log OR = 0.2$ fixed, $p_1 = 0.25, 0.3, ..., 0.95$





Final Remarks

risk difference:

- using test statistics with an improved estimator of the variance of $\hat{D}$ or continuity corrected test statistics results in less liberal confidence intervals

  (Stansen and Hartung, talk at the conference "Evaluation im Gesundheitswesen", Bochum, 2006)

logarithmic risk ratio:

- improvements for the estimator of the variance of $\log \widehat{RR}$ have been worked out

  but: $\log RR$ is not symmetric around $1/2$

  $\Longrightarrow$ improvement is possible on one side only

Final Remarks

logarithmic odds ratio:

- the estimator of the variance of $\log \widehat{OR}$ can be improved by using the results of Hartung and Knapp (2004)

  $\Longrightarrow$ resulting confidence interval is less conservative

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