Institute of Medical Biometry and Epidemiology

Reestimation of the prevalence in a confirmatory diagnostic accuracy study

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Sample size calculation in a confirmatory diagnostic accuracy study

sensitivity and specificity are co-primary endpoints

$\downarrow$

Intersection-Union Test:

$H_{0_{global}}$: $H_{0_{se}}$: $\theta_{se_0} = \theta_{se_1}$ $\cup$ $H_{0_{sp}}$: $\theta_{sp_0} = \theta_{sp_1}$

Sample size calculation

- Individual sample size calculation for sensitivity (n_{se}) and specificity (n_{sp})
- Total sample size N in dependence of the prevalence π:
  $N_{se} = n_{se}/\pi$ and $N_{sp} = n_{sp}/(1-\pi)$

  $\Rightarrow$ N = max(N_{se}, N_{sp})

The conventional sample size calculation

Example: $\theta_{se_0} = 0.75, \theta_{se_1} = 0.81, \theta_{sp_0} = 0.6, \theta_{sp_1} = 0.66,$
$\pi = 0.2, \alpha = 0.05, \beta_{se} = \beta_{sp} = 0.1$

- Individual sample size for sensitivity (n_{se}) and specificity (n_{sp}):

$$n_{se} = \frac{\left[z_{\alpha/2}\sqrt{V_0(\hat{\theta}_{se_1})} + z_{\beta_{se}}\sqrt{V_A(\hat{\theta}_{se_1})}\right]^2}{(\theta_{se_0} - \theta_{se_1})^2} = 508$$

$$n_{sp} = \frac{\left[z_{\alpha/2}\sqrt{V_0(\hat{\theta}_{sp_1})} + z_{\beta_{sp}}\sqrt{V_A(\hat{\theta}_{sp_1})}\right]^2}{(\theta_{sp_0} - \theta_{sp_1})^2} = 683$$

- Total sample size N in dependence of the prevalence π:

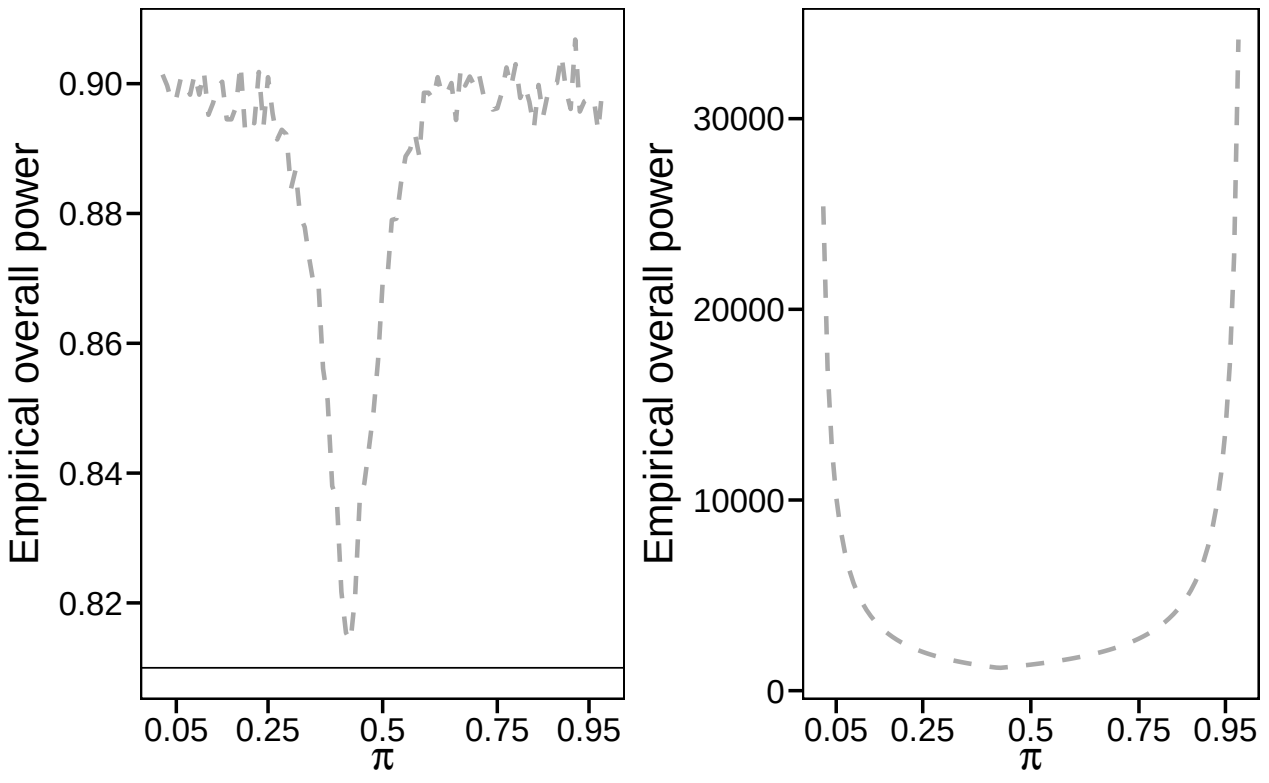
$N_{se} = n_{se}/\pi = 508/0.2 = 2540$

$N_{sp} = n_{sp}/(1-\pi) = 683/(1-0.2) = 853.75$

$\Rightarrow N = \max(N_{se}, N_{sp}) = 2540$

$$\text{Power}_{se} = \text{Power}_{sp} = 0.9$$

$$\Rightarrow \text{Power}_{se} \cdot \text{Power}_{sp} \geq \text{Power}_{overall} = 0.81$$



Optimal sample size calculation

Goal: optimal division of the overall power to both endpoints

$$N_{se} \stackrel{!}{=} N_{sp}$$

$$n_{se}/\pi \stackrel{!}{=} n_{sp}/(1-\pi)$$

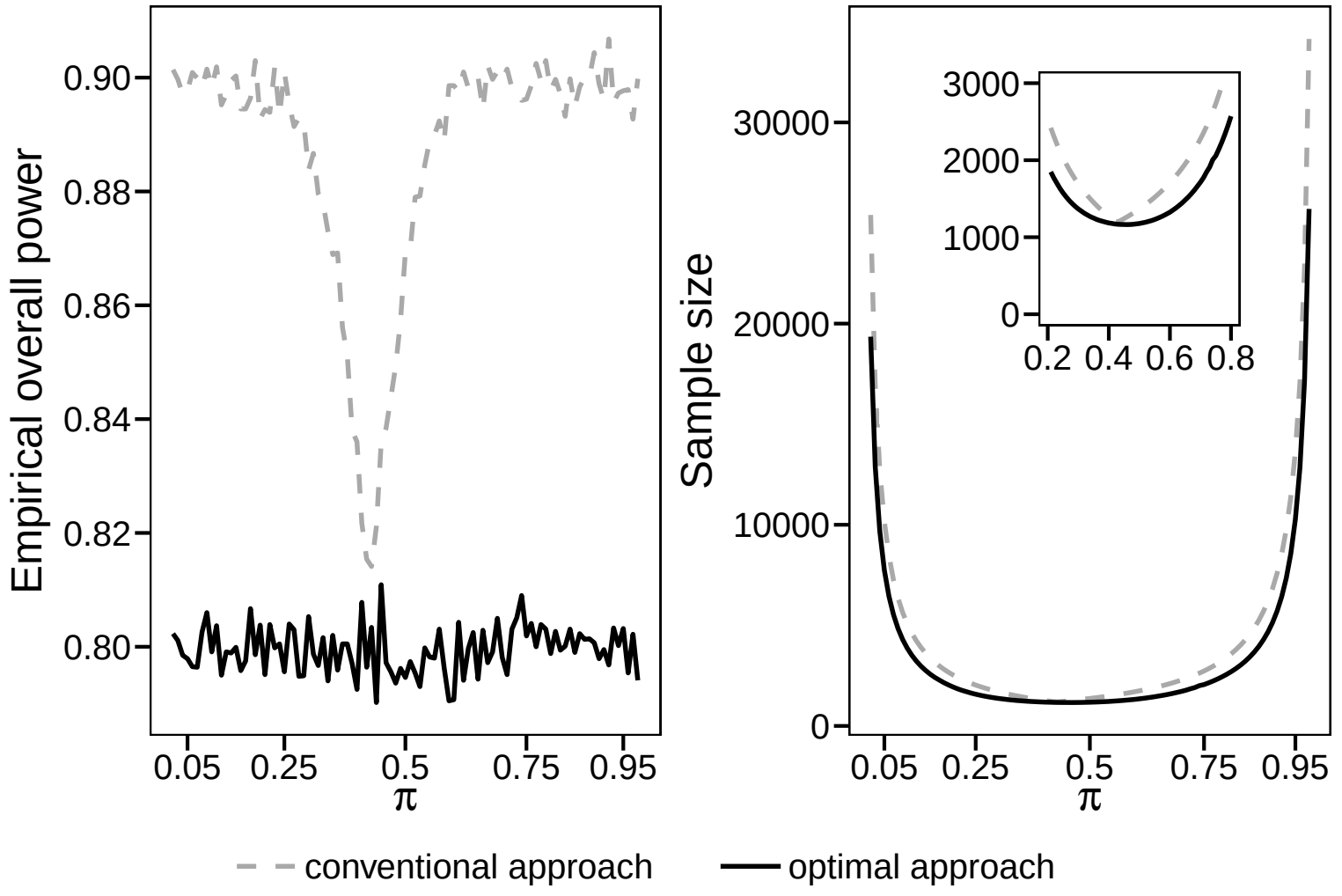
$$\frac{\left[z_{\alpha/2}\sqrt{V_0(\hat{\theta}_{se_1})} + z_{\beta_{se}}\sqrt{V_A(\hat{\theta}_{se_1})}\right]^2}{(\theta_{se_0} - \theta_{se_1})^2 \cdot \pi} \stackrel{!}{=} \frac{\left[z_{\alpha/2}\sqrt{V_0(\hat{\theta}_{sp_1})} + z_{\beta_{sp}}\sqrt{V_A(\hat{\theta}_{sp_1})}\right]^2}{(\theta_{sp_0} - \theta_{sp_1})^2 \cdot (1-\pi)}$$

Under the condition:

$$\text{Power}_{se} \cdot \text{Power}_{sp} \stackrel{!}{=} \text{Power}_{overall}$$

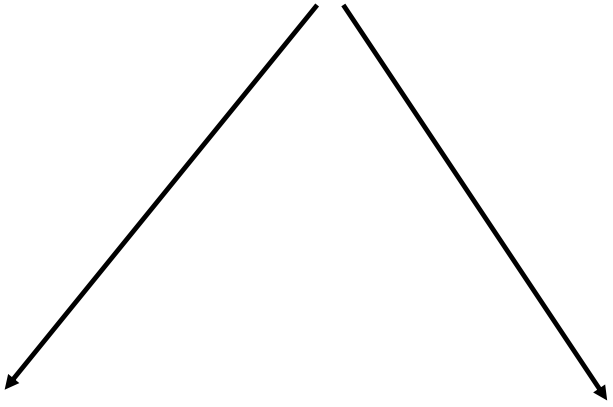
$$(1-\beta_{se}) \cdot (1-\beta_{sp}) \stackrel{!}{=} \text{Power}_{overall}$$

$$\beta_{sp} = \frac{1 - \beta_{se} - \text{Power}_{overall}}{1-\beta_{se}}$$


Empirical overall power
0.90
0.88
0.86
0.84
0.82
0.80
0.05
0.25
0.5
0.75
0.95
π
Sample size
30000
20000
10000
0
3000
2000
1000
0
0.2
0.4
0.6
0.8
conventional approach
optimal approach

Blinded reestimation of the prevalence

Initial sample size calculation with assumed prevalence



Fixed design

Recruitment of the calculated sample size

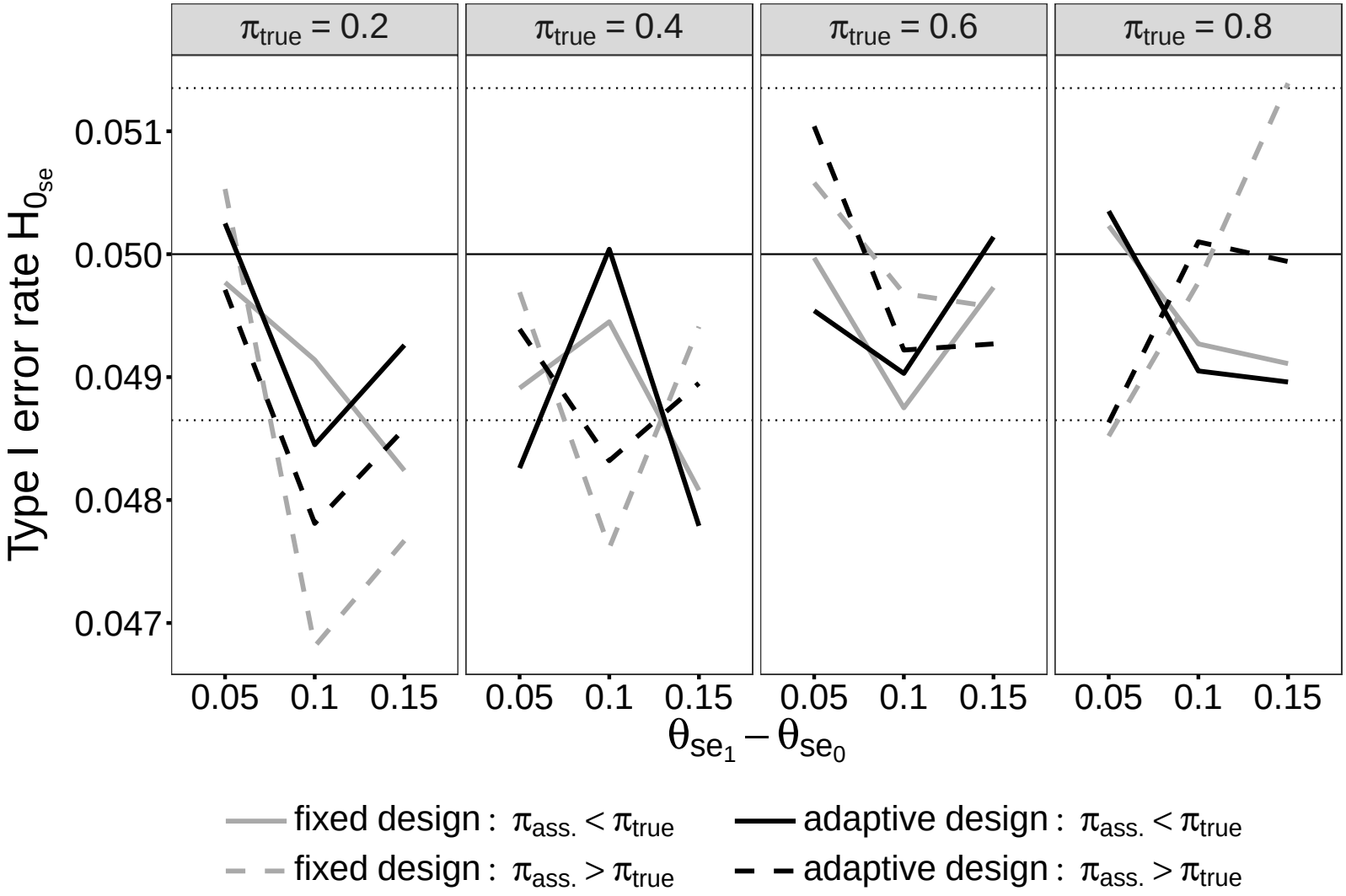
Adaptive design with blinded reestimation of prevalence

1) Recruitment of patients until the predetermined size of internal pilot study
2) Reestimation of the prevalence and of the sample size
3) Recruitment of further patients until final sample size is reached

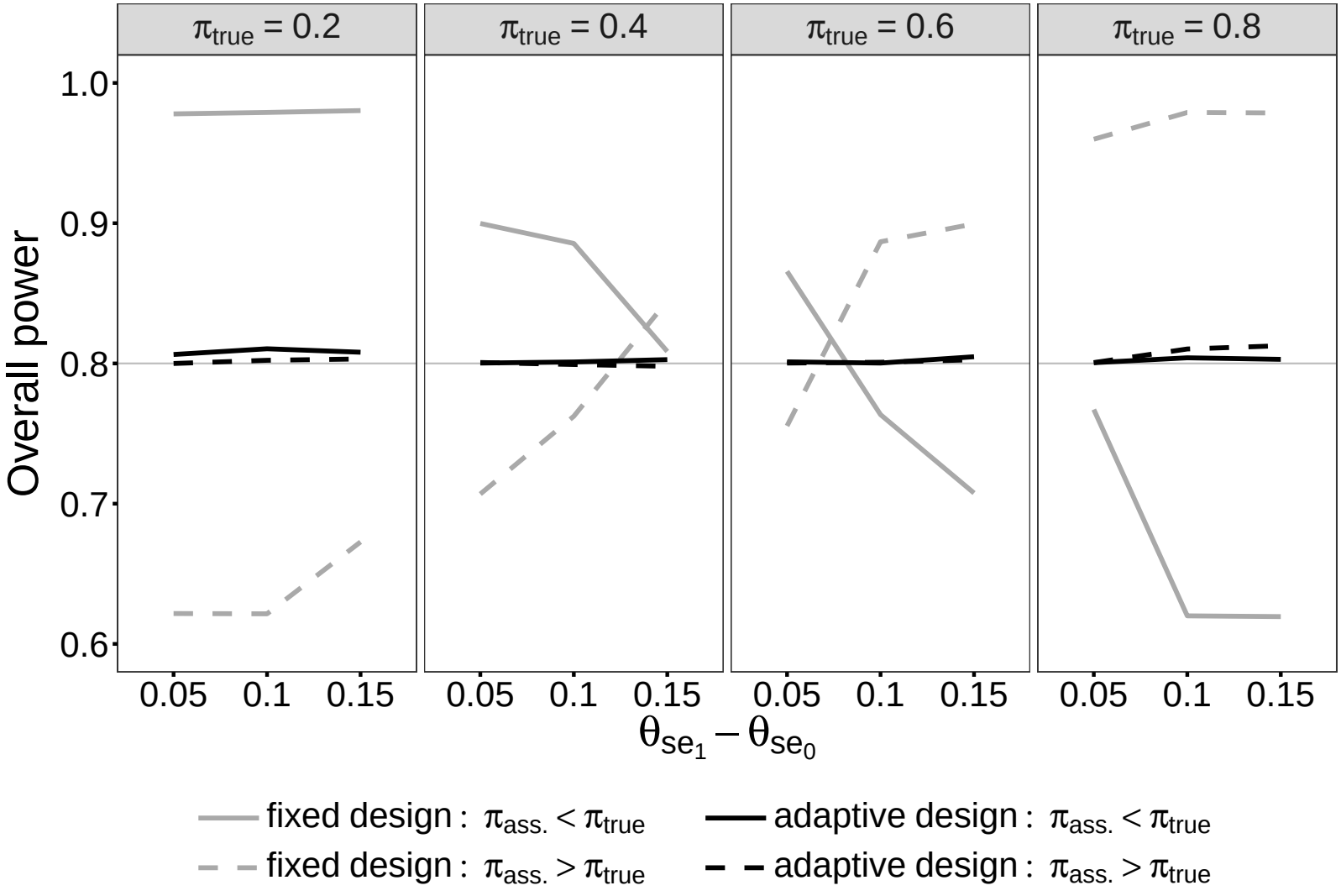
Simulation study

	2592 scenarios 100,000 replications
Fraction for reestimation ψ	0.02, 0.1, 0.3, 0.5, 0.9
True prevalence π_{true}	0.2, 0.4, 0.6, 0.8
Assumed prevalence $\pi_{\text{ass.}}$	π_{true} - 0.1, π_{true} + 0.1
Minimum sensitivity θ_{se_0}	0.6, 0.7, 0.8
Minimum specificity θ_{sp_0}	0.6, 0.7, 0.8
Under H$_0$: $\theta_0 = \theta_1$	
Significance level α	0.05 (two-sided, per endpoint)
Sensitivity exp. test θ_{se_1}	0.6, 0.7, 0.8
Specificity exp. test θ_{sp_1}	0.6, 0.7, 0.8
Under H$_1$: $\theta_0 \neq \theta_1$	
Overall power $1 - \beta$	0.8
θ_{se_1}	θ_{se_0} + 0.05, θ_{se_0} + 0.1, θ_{se_0} + 0.15
θ_{sp_1}	θ_{sp_0} + 0.05, θ_{sp_0} + 0.1, θ_{sp_0} + 0.15

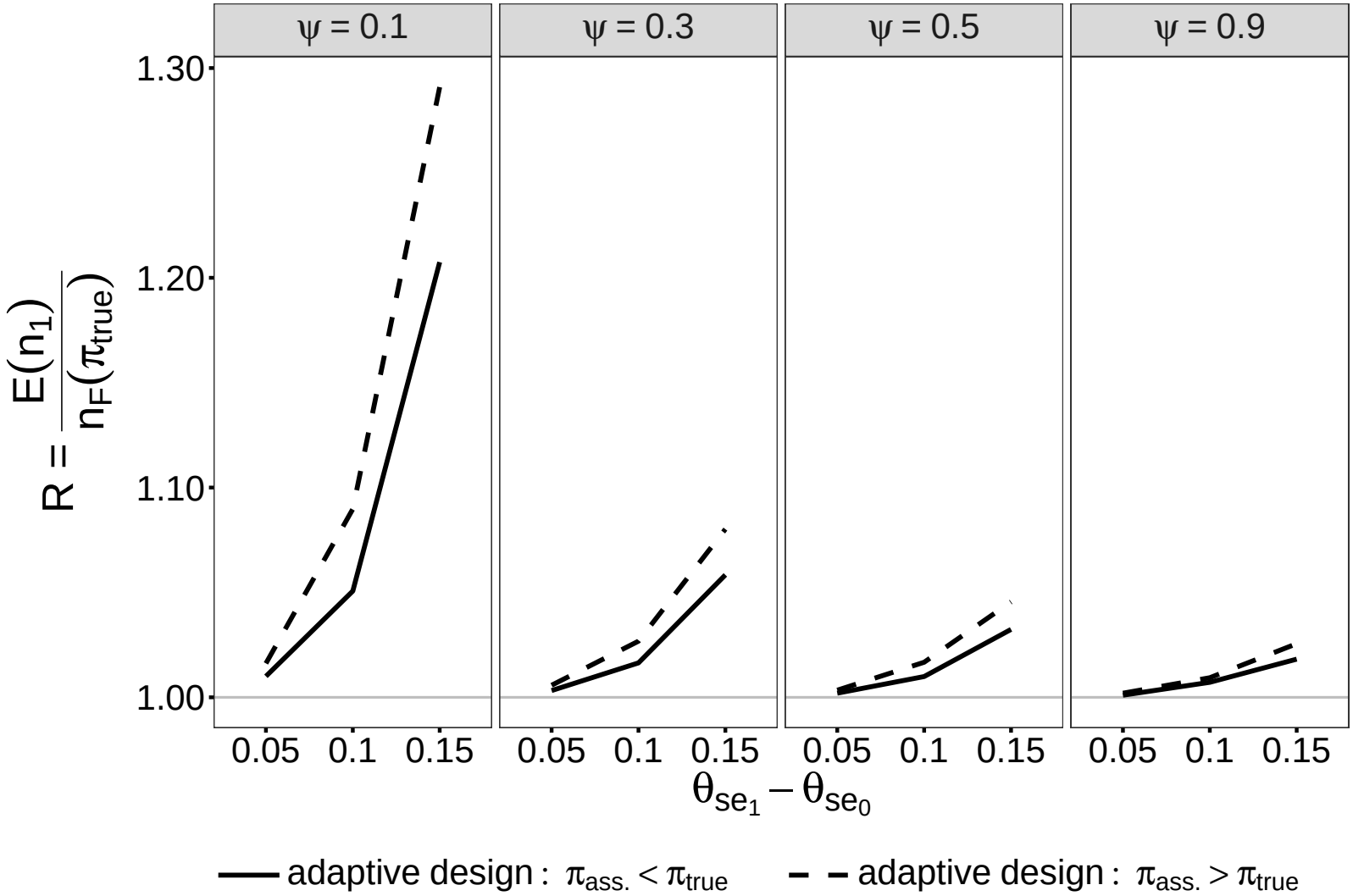
Scenarios: $\theta_{se_0} = 0.6, \theta_{sp_0} = 0.6, \theta_{sp_1} = 0.7, \psi = 0.5$



Scenarios: $\theta_{se_0} = 0.6, \theta_{sp_0} = 0.6, \theta_{sp_1} = 0.7, \psi = 0.5$



Scenarios: $\pi_{\text{true}} = 0.4, \theta_{\text{se}_0} = 0.8, \theta_{\text{sp}_0} = 0.8, \theta_{\text{sp}_1} = 0.95$



Conclusion

- Optimal sample size calculation to avoid an overpowered study
- Type I error rate is not inflated in the adaptive design
- Optimal power in the adaptive design, fixed design is over- or underpowered
- Optimal size of the internal pilot study with one-time reestimation: $\psi = 50\%$

Further steps

- Application of the optimal sample size calculation to the unpaired and paired design
- Application of the internal pilot study to the unpaired and paired design

References

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3. Obuchowski, N. A. (1998). Sample size calculations in studies of test accuracy. Statistical Methods in Medical Research, 7(4), 371-392.
4. Zhou, X. H., McClish, D. K., Obuchowski, N. A. (2009). Statistical methods in diagnostic medicine (Vol. 569). John Wiley Sons.