Multiplicity Issues with Covariate Analysis: Strategies and Perspectives on Pre-specification of Pharmacometric Analyses

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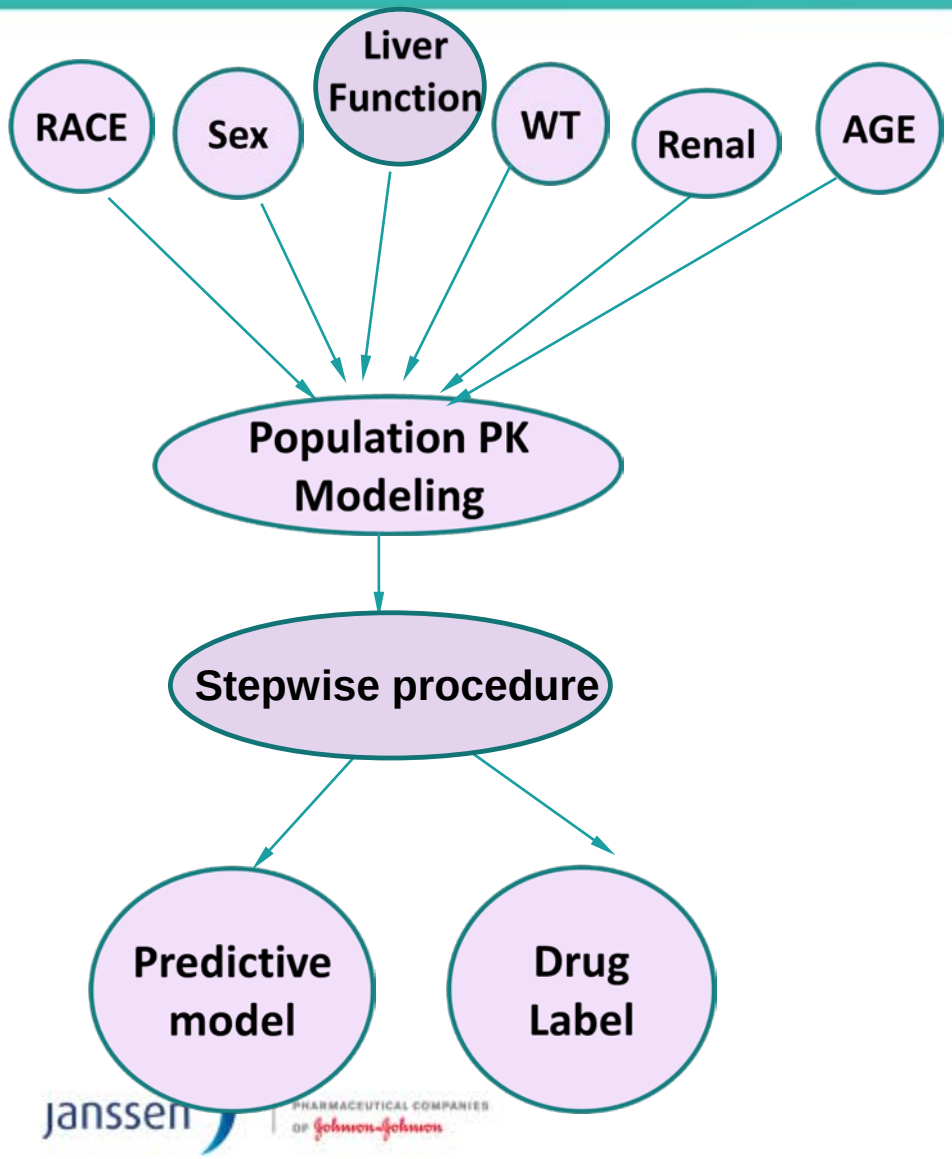
Population Pharmacokinetic (PPK) Model

- PPK models: particular case of NLME models in which response is drug concentration measured over time
- Models often expressed as systems of differential equations, representing transfer processes, with parameters having pharmacological interpretation
- PPK models often based on sparse sampling: few observations per subject, many subjects
- Baseline covariates often considered to explain inter-subject PK variability – potentially included in label

Covariate Analysis in PPK



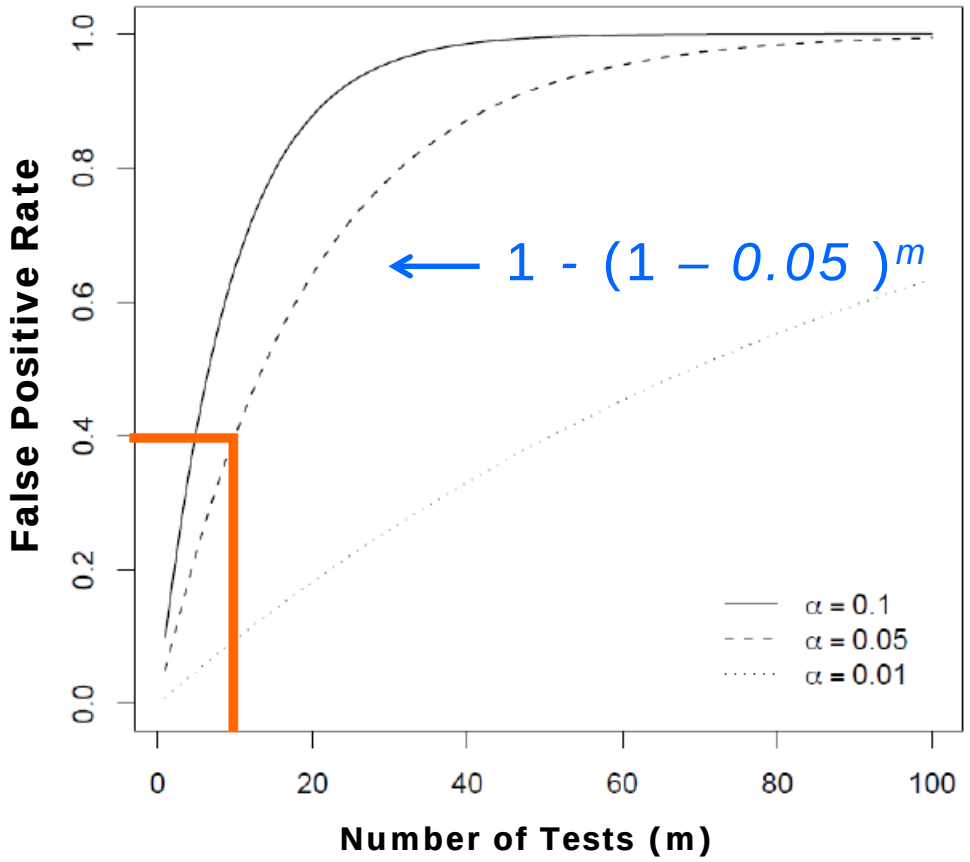
- Support drug labeling, e.g., during NDA/BLA submissions.
  - identify sub-populations with different PK
    - sub-therapeutic efficacy or toxicity.
  - Provide scientific rationale for dosing recommendation and adjustment
- Focus: stepwise selection
  - Full covariate approach is another popular method

PPK covariate language in a drug label

Covariate Effects:
Creatinine clearance was the most significant covariate on [redacted] clearance. The clinical importance of this finding is unknown, since less than 2% of [redacted] dose is excreted in the urine. This may be an artifact of the data as the current analysis data set did not include patients with moderate or severe renal impairment. Weight, age and sex were not significant covariates and, therefore, require no dose adjustment.

- Statistical significance of a covariate drives decision to include dose adjustment
  - Not significant → no dose adjustment
  - Significant → evaluate size of the effect
- Multiple covariates often evaluated – multiplicity leading to increase in false positive rate

Inflation of False Positive Rate in multiple statistical tests



- Theoretical calculation of false positive (FP) for independent tests:
  - 2 factors: sig level (α) and # of tests (m)
  - $1 - (1 - \alpha)^m$
- FP rate increases with larger values of m and α
- At $\alpha = 0.05$
  - m = 1 , FP = predefined 0.05
  - m = 2 , FP = 0.0975
  - m = 10, FP = 0.4
  - m = 40, FP = 0.9

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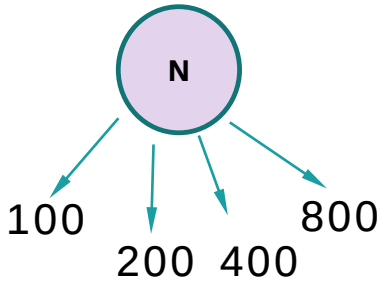
Multiplicity in PPK Covariate Analysis

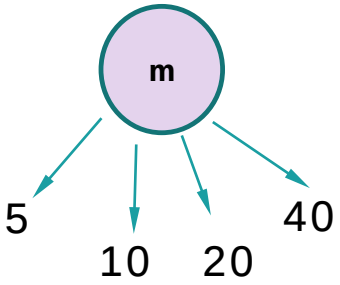
- Control of FP rate is of greater interest to sponsors, while lack of power to identify true covariate effect is key regulatory concern
- FP rate increases with number of candidate covariates (and PK parameters under consideration): pre-selection of relevant candidate covariates can improve multiplicity problem
- Multiple comparison procedures (MCP) can be used: need to balance control of FP and power
- Likelihood ratio test tends to inflate FP and can compound multiplicity issues: use of t-tests with EBEs can alleviate problem (combined with MCP)

Simulation study to evaluate multiplicity in covariate analysis for PPK

1. Number of subjects (sample size)

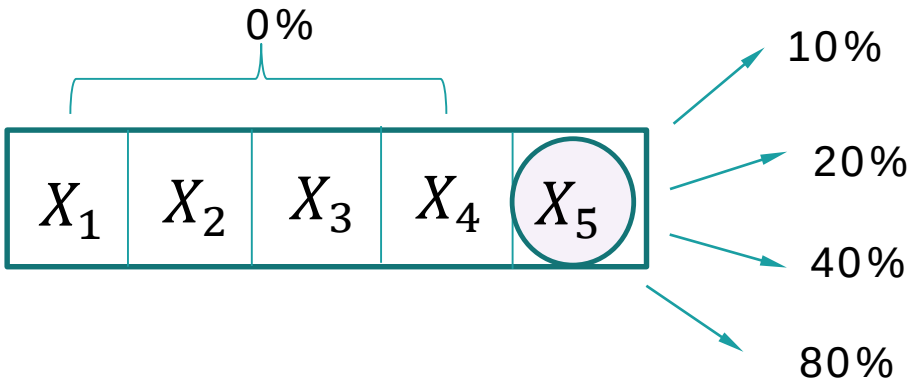


2. Number of covariates



3. Covariate Effect

Only 1 out m covariates has an effect on CL



4x4x4 = 64 simulation scenarios

- 10,000 PK datasets simulated for each scenario

- between subject variability = 30%
- Within subject variability = 20%
- # of samples per subject = 12
- Include all covariates in the model at once

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Simulation PK Model

Simple 1-compartment PK model

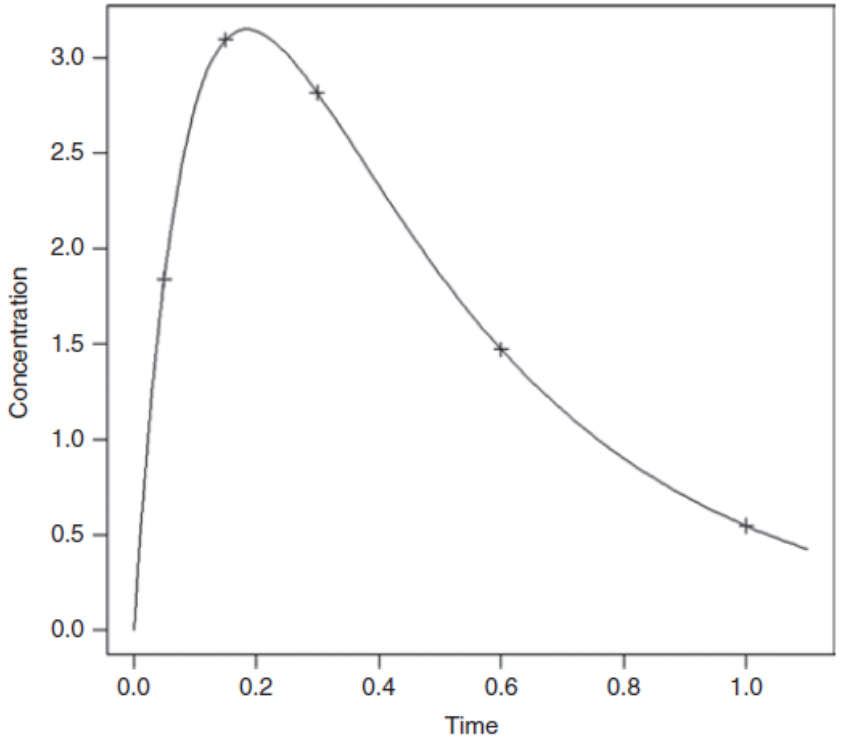
$$C_t = \frac{Dk_a}{V\left(k_a - \frac{CL}{V}\right)}\left[\exp\left(-\frac{CL}{V}t\right) - \exp(-k_a t)\right]$$

Between-Subject Variability

$$(\eta_{CLi}, \eta_{Vi})' \sim N\left(0, \begin{pmatrix} \omega_{CL}^2 & 0 \\ 0 & \omega_V^2 \end{pmatrix}\right)$$

Covariate Model (evaluated on CL)

$$\log(CL_i) = \mu_{CL} + \beta_1 x_1 + \ldots + \beta_m x_m + \eta_{CLi}$$



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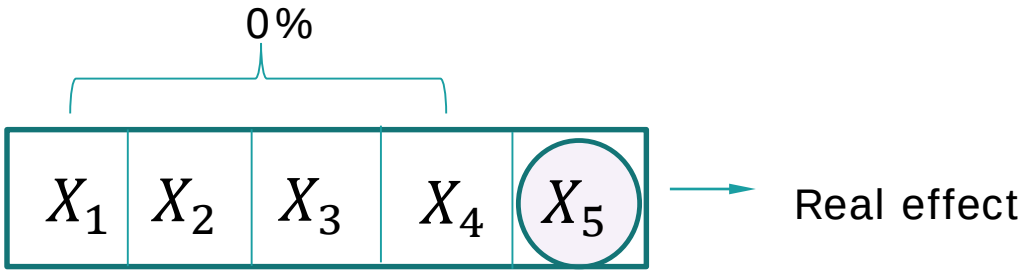
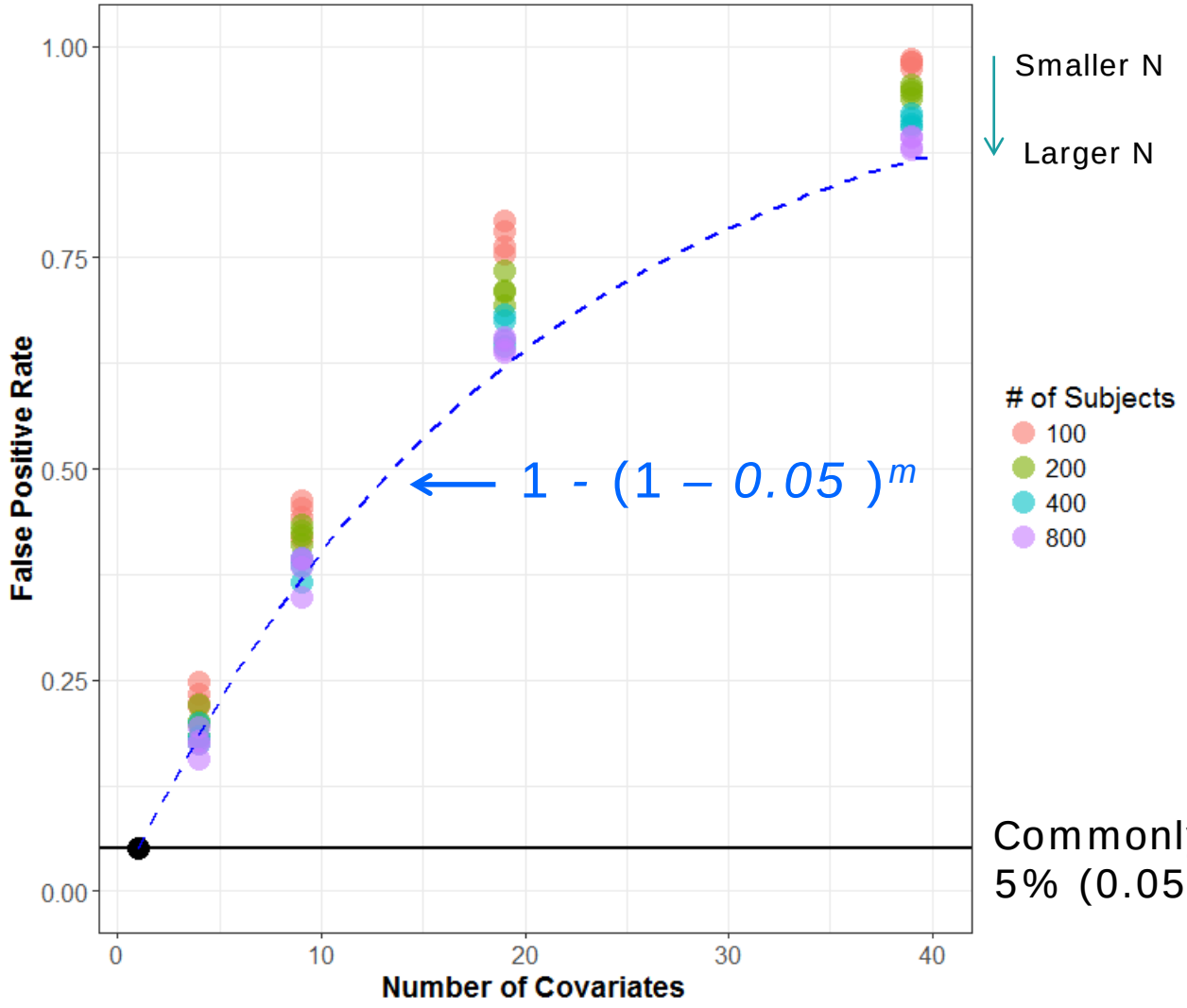
False Positive and Power in simulations



- **False Positive(FP): incorrectly detecting non-existing effect**
  - 5-covariate scenario: 4 with no effect and 1 with effect
  - FP = chance of detecting at least 1 significant effect among 4 covariates with no effect
- **Power:**
  - Detecting the one variable with real effect, but without false positive for other variables – correct identification

Results: FP Rate - no control of multiplicity



Commonly accepted 5% (0.05) error rate

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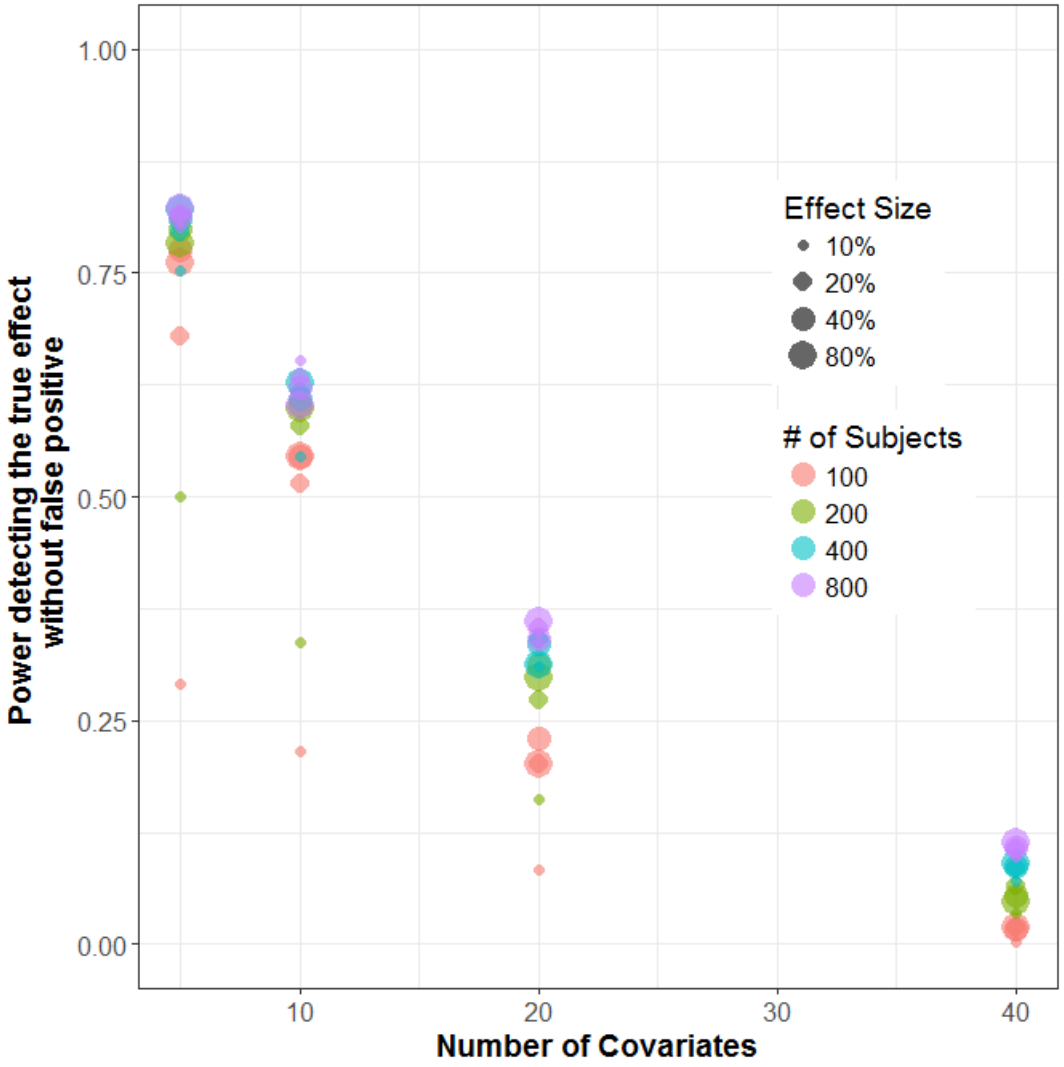
Influence on Power (no control of multiplicity)



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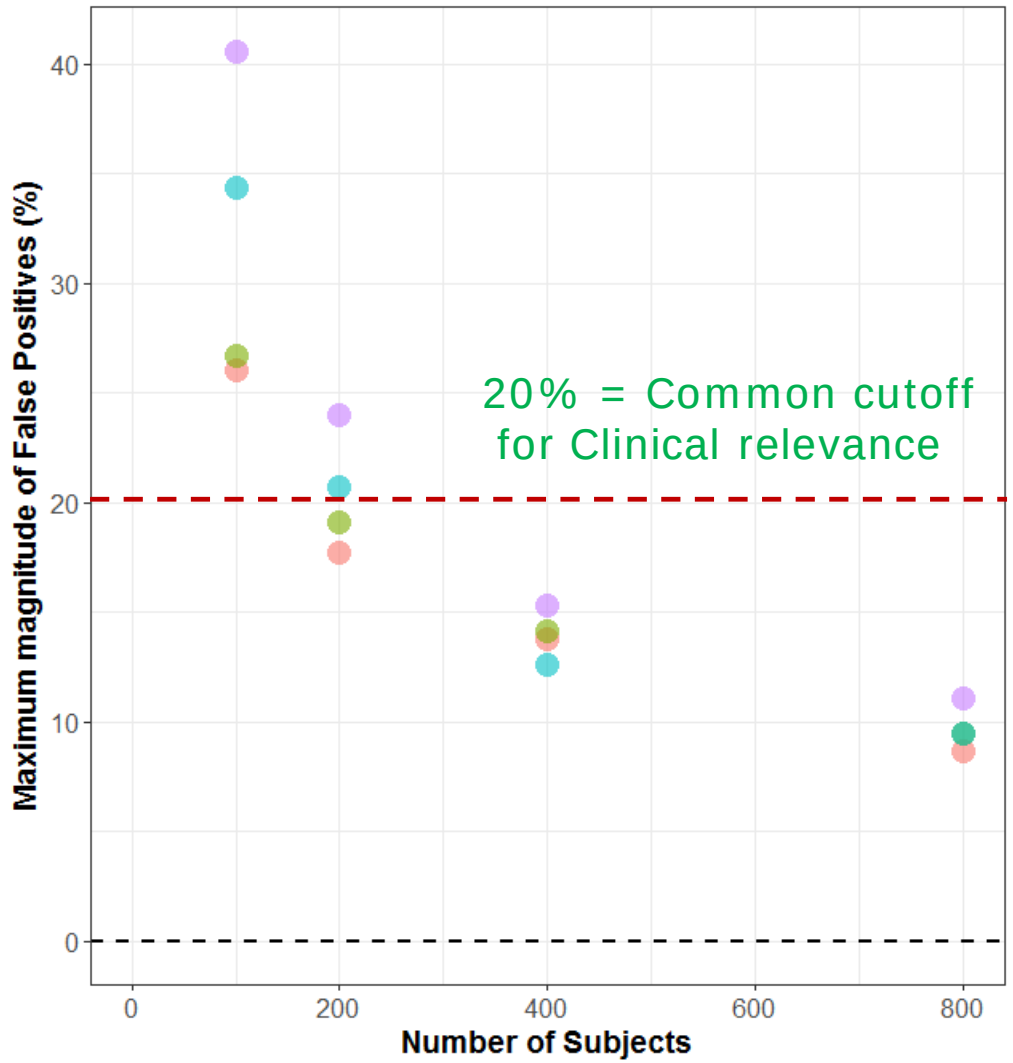
Potential size of FP effects



Best Case Scenario

12 samples/ subject

True value: no effect

Controlling multiplicity in PPK covariate analysis

346 Biometrical Journal **50** (2008) 3, 346–363 DOI: 10.1002/bimj.200810425

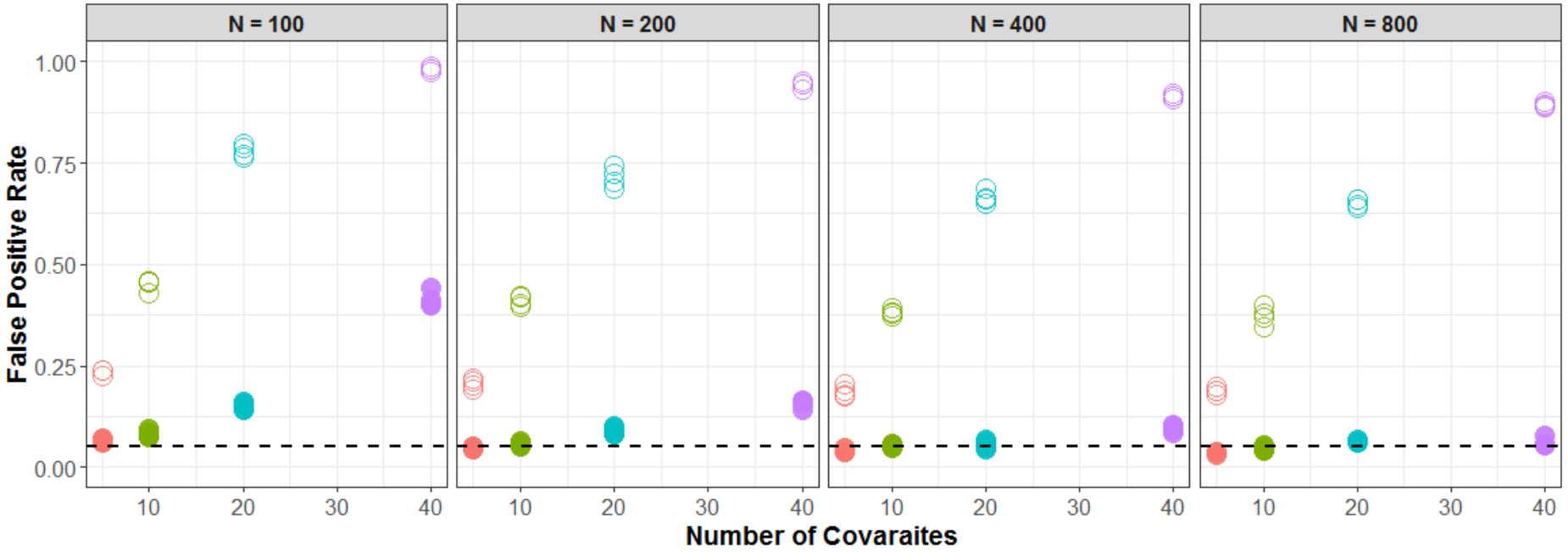
Simultaneous Inference in General Parametric Models

Torsten Hothorn[*,1], Frank Bretz[2], and Peter Westfall[3]

- Simultaneous confidence interval (Multivariate) approach
  - Critical value based on multivariate normal or t distribution (vs. univariate t → current practice = no control of multiplicity)
  - Use correlation structure involved in joint distribution of test stats
  - Only requires parameter estimates follow an asymptotic multivariate normal distribution and a consistent estimate of its covariance matrix

Control of FP rate with multivariate t approach

Multivariate t (control multiplicity) Univariate t test (no control)



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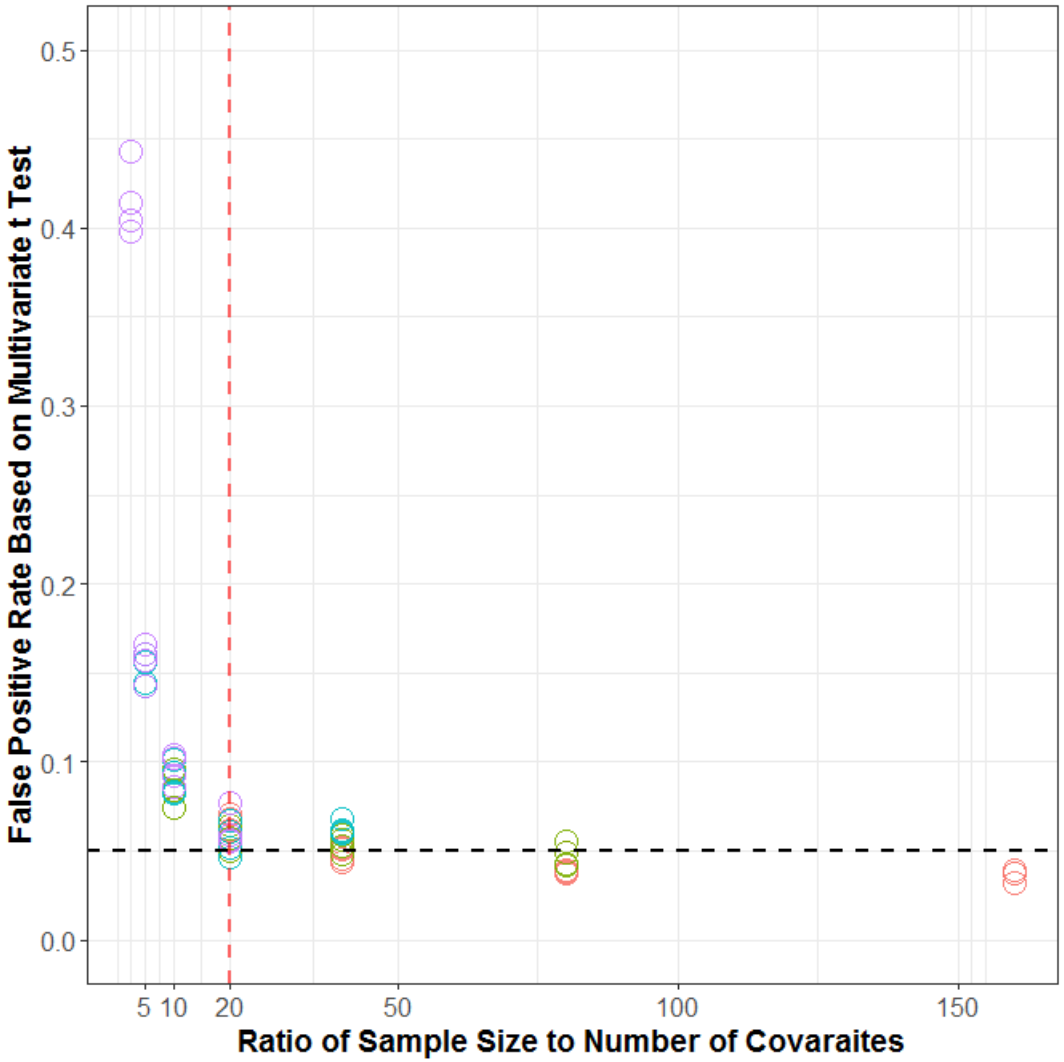
Performance of multivariate t approach



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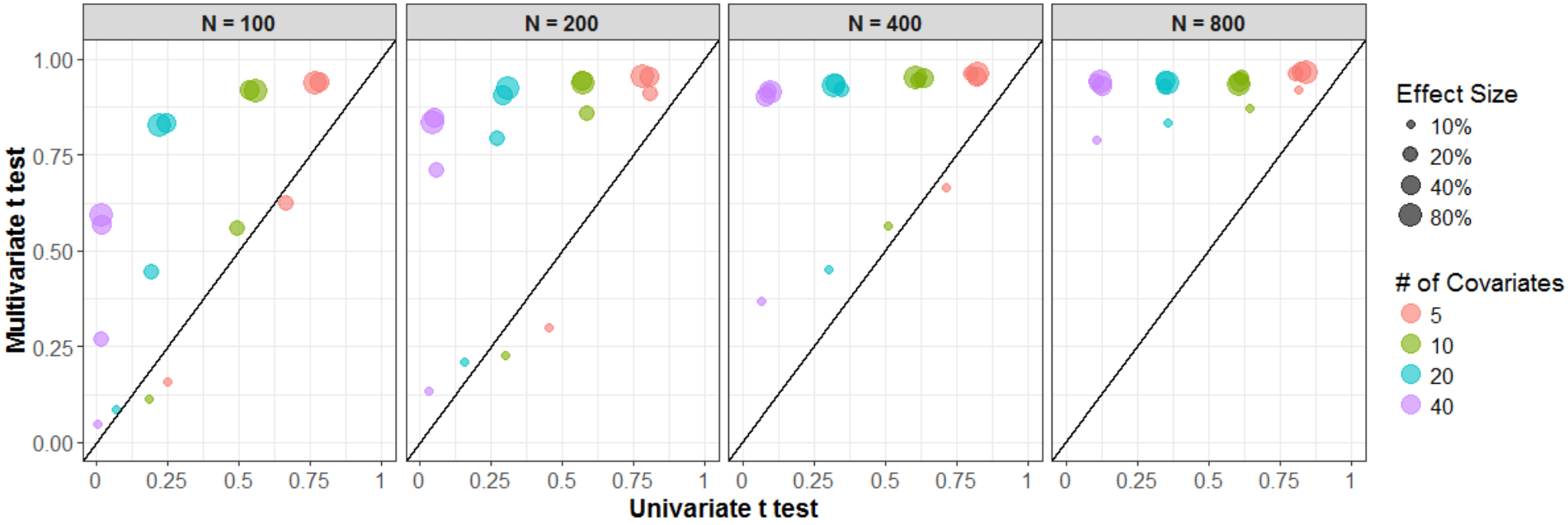
Comparing powers to detect true effect



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Conclusions

- Multiplicity could be an issue for PPK-based covariate analysis
- The FP rate increases with increasing # of covariates, and smaller sample size
- The FP will reduce the power for PPK analysis, and could be substantial in terms of effect size, particularly when sample size is small
- Sim CI based on multivariate t approach can a simple tool to control the FP, and should be considered for future practice for PPK analysis.
- Be selective for candidate variables and use prior information to guide variable selection before analysis.
- Collecting PK in more subjects could help to reduce chance and size of FP

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