

High-dimensional covariate model building: evaluating clinical relevance using selection and full modeling approaches in population PK analyses



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CONTEXT

- Covariate analysis is key in population PK modeling to identify and quantify variability between individuals and guide dose adjustments, reducing under- or over-exposure risks
- Covariate model building methods fall into 2 families:
 - Covariate selection methods (e.g. SCM [1], SCM+ [2]): studying the effect of selected covariates
 - Full modeling methods (e.g. FFEM [3], FLEM [4,5]): studying all covariate effects of the predefined set
- Covariate impacts on drug exposure are visualized using forest plots, showing covariate effect ratios (CER) with their confidence intervals (CI) relative to a reference; covariate clinical relevance (CCR) can be inferred from the position of CER and CI relative to the reference area and the reference line
- In a previous study, we compared CCR adequacy using FFEM, SCM, and SCM+ with 7 covariates (5 continuous, 2 categorical), 14 predefined relationships, finding all methods satisfactory [6]
- There is a need to extend this comparison to a more complex framework and to include FLEM

OBJECTIVE

To assess the accuracy of CCR evaluation using SCM+, FFEM, and FLEM algorithms implemented in PsN within a high-dimensional covariate framework, including 19 covariates (12 continuous, 7 categorical) and 70 predefined relationships, with various covariate effect sizes and correlation levels

SIMULATION STUDY

Covariate database

- Data from the National Health and Nutrition Examination Survey (NHANES) of 2013/14
- 12 continuous, 7 categorical covariates (Table 1 & 2)
- Correlations (Fig. 1): -0.56 to 0.8
- 5,765 unique individuals

Table 1 - Summary of continuous covariate distributions

Covariates	Med [Min - Max]
Body weight (BW, kg)	76.1 [29.2 - 222.6]
Age (AGE, years)	40.9 [12.0 - 79.0]
Albumine (ALB, g/L)	43.0 [24.0 - 56.0]
Alkaline phosphatase (ALK, IU/L)	79.6 [9.0 - 907.0]
Aspartate aminotransferase (AST, U/L)	24.7 [10.0 - 338.0]
Alanine aminotransferase (ALT, U/L)	24.1 [6.0 - 536.0]
Creatine phosphokinase (CPK, IU/L)	157.2 [6.0 - 3,966.0]
Creatinine (CRE, μmol/L)	77.0 [30.1 - 1,539.0]
Bilirubin (BILL, μmol/L)	10.9 [1.7 - 121.4]
Globulin (GLO, g/L)	28.2 [14.0 - 52.0]
Triglycerides (TRI, mmol/L)	1.6 [0.2 - 33.7]
Uric acid (URA, μmol/L)	317.5 [41.6 - 791.1]

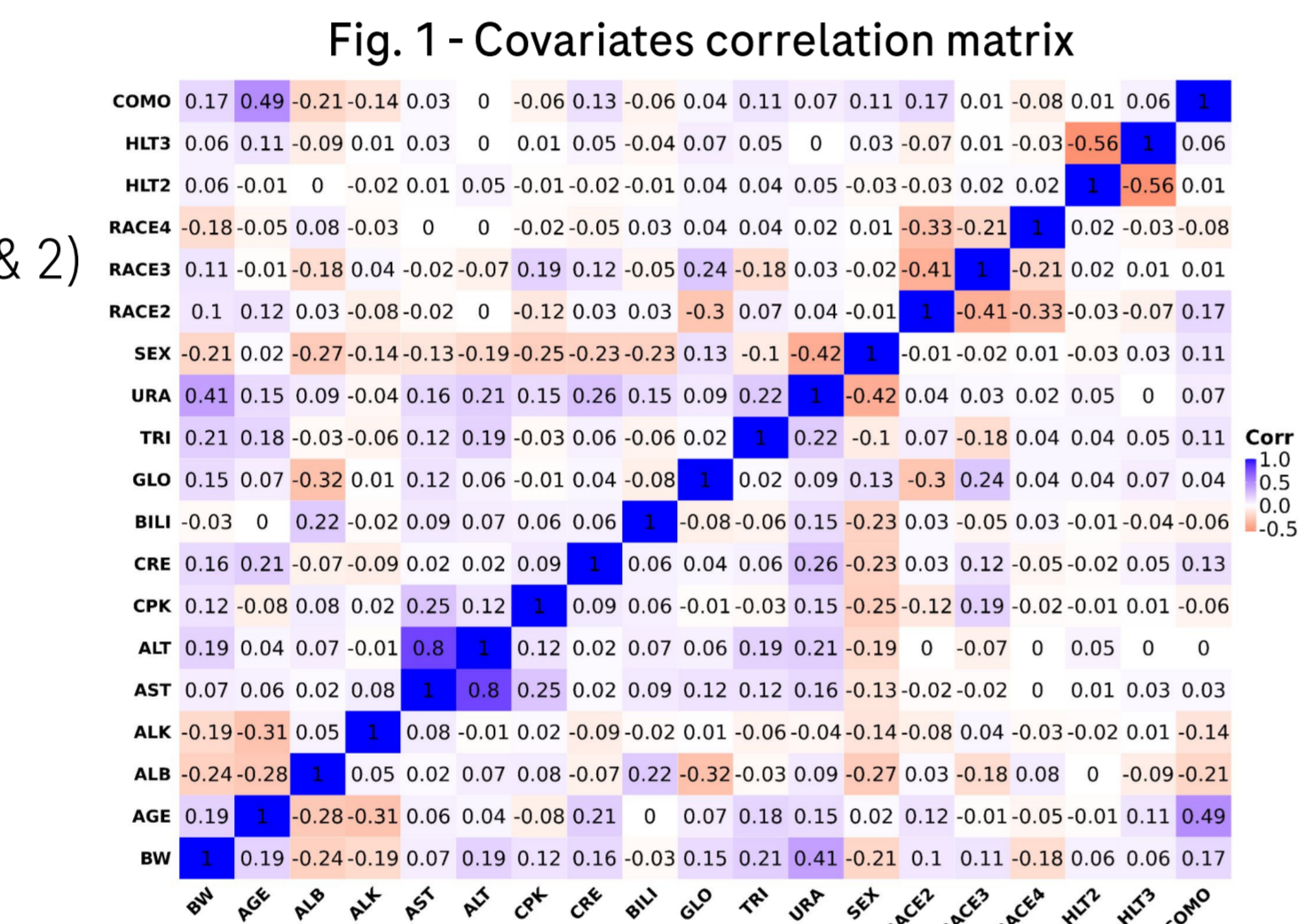
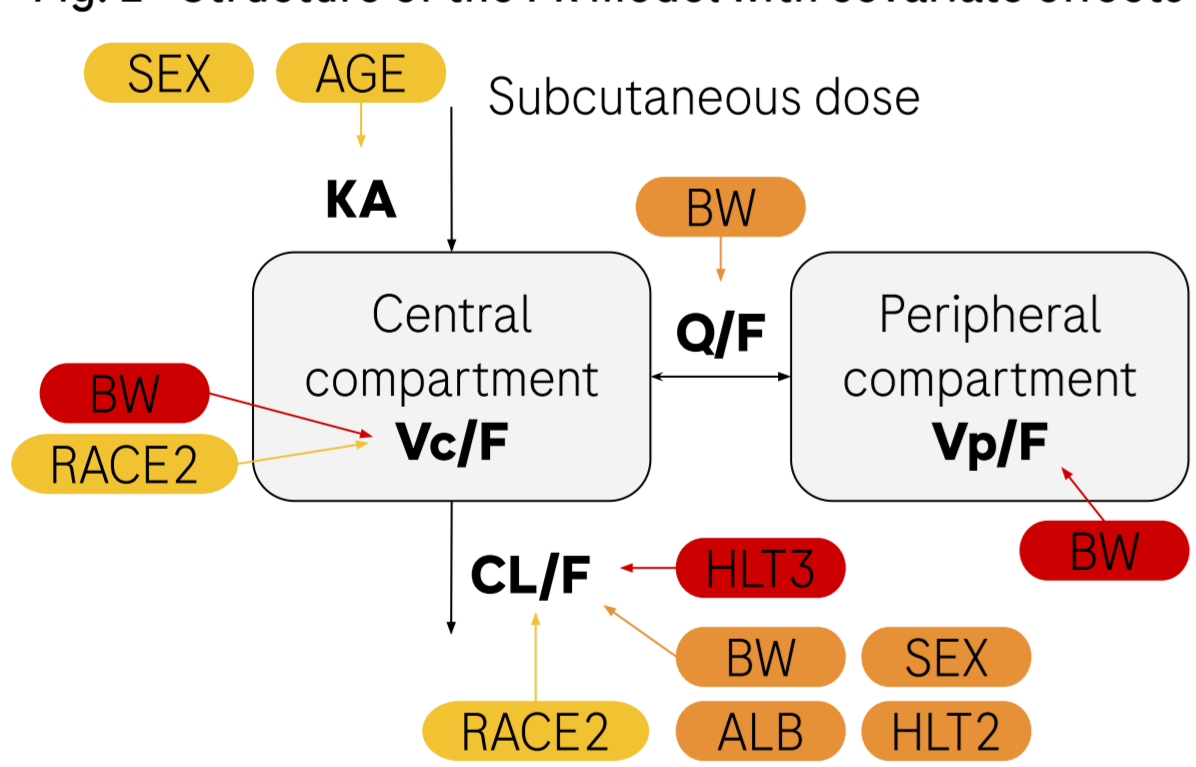


Table 2 - Summary of categorical covariate distributions

Covariates	Category, non REF / REF	%
Sex (SEX)	Female / Male	51.3 / 48.7
White race (RACE2)	White / Non-white	39.1 / 60.9
Black race (RACE3)	Black / Non-black	20.8 / 79.2
Other race (RACE4)	Others / None-other	14.4 / 85.6
Good health status (HLT2)	Good / Not-good	40.8 / 59.2
Poor health status (HLT3)	Poor / Not-poor	31.2 / 68.8
Comorbidities (COMO)	Yes / No	48.4 / 51.6

Population PK model

Fig. 2 - Structure of the PK model with covariate effects



- Simplified PK model inspired by a real-case example of patients with severe dermatitis treated with dupilumab [7]
- 12 covariate-parameter relationships with varying effect sizes based on the CER value:
 - 3 with **high simulated effects** (CER = 1.60 | 0.40)
 - 5 with **medium simulated effects** (CER = 1.40 | 0.60)
 - 4 with **small simulated effects** (CER = 1.25 | 0.75)

$$CL/F_i = \mu_{CL/F} \times \left(\frac{BW_i}{76.1}\right)^{\beta_{CL/F,BW}} \times \left(\frac{ALB_i}{43}\right)^{\beta_{CL/F,ALB}} \times \left(1 + \beta_{CL/F,SEX} \times SEX_i\right) \times \left(1 + \beta_{CL/F,RACE2} \times RACE2_i\right) \times \left(1 + \beta_{CL/F,HLT2} \times HLT2_i\right) \times \left(1 + \beta_{CL/F,HLT3} \times HLT3_i\right) \times e^{\eta_{CL/F,i}}$$

μ : fixed effect
 $\beta_{covariate}$: covariate effect on a parameter
 $\eta \sim N(0, \Omega)$: between subject random-effects of individual i
 Ω : variance-covariance matrix

Simulation settings

- 100 simulated datasets, N = 300 patients, n = 33 | 38 PK sampling times per patients
- Sampling design inspired by two real clinical trials
 - Phase IIb trial: 5 dosing regimens, multiple-dose administrations, primarily sparse peak and trough sampling
 - Phase I trial: rich sampling added after first and last doses
- Covariates sampled with replacement

Covariate analysis

- SCM+, FFEM, FLEM and the reference model (RM, i.e. the simulated model) applied to each dataset
- FLEM covariate effects computed in a multivariate (multi) a univariate (uni) manner [4,5]
- 70 predefined covariate-parameter relationships tested for SCM+ and FFEM; 95 for FLEM
- CER computed using P10/90 for continuous covariates and the non REF category for categorical ones

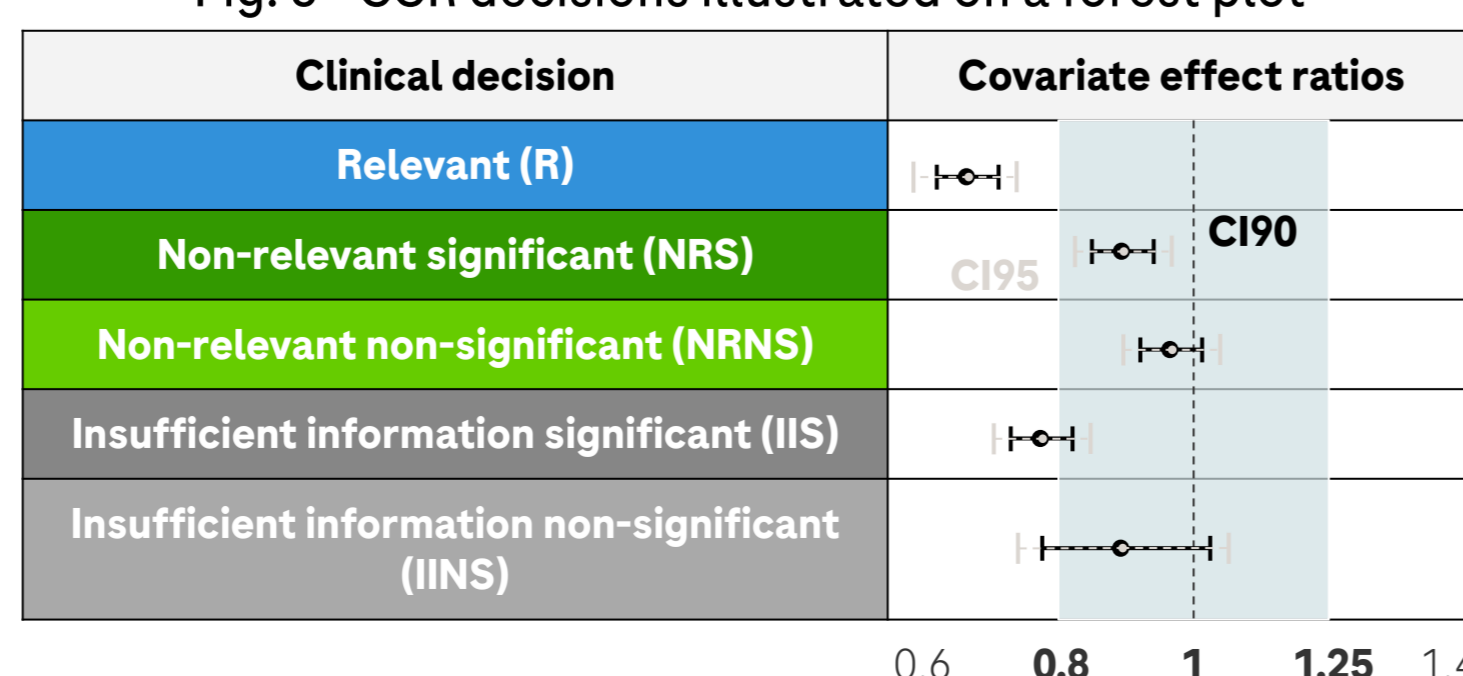
Parameter estimation

- NONMEM 7.5.1, PsN 5.4.0
- FOCEI algorithm for SCM+, FFEM and RM; IMPMAP for FLEM (AUTO = 1, NITER = 500)
- SE derived from S cross-product gradient matrix; 1000 draws for FLEM covariate effects
- Issues: minimization error → 5 retries, parameters near boundaries → fixed to 0

Results evaluation

- CCR evaluation (Fig. 3)**
 - Reference: typical individual
 - Reference area: [0.8 - 1.25] i.e. change of ± 20% in log-parameter value
 - Clinical relevance: assessed using CI90
 - Significance: assessed using CI95
 - Accuracy: comparison with the RM results
- OFV, BICc [8] and runtime**

Fig. 3 - CCR decisions illustrated on a forest plot



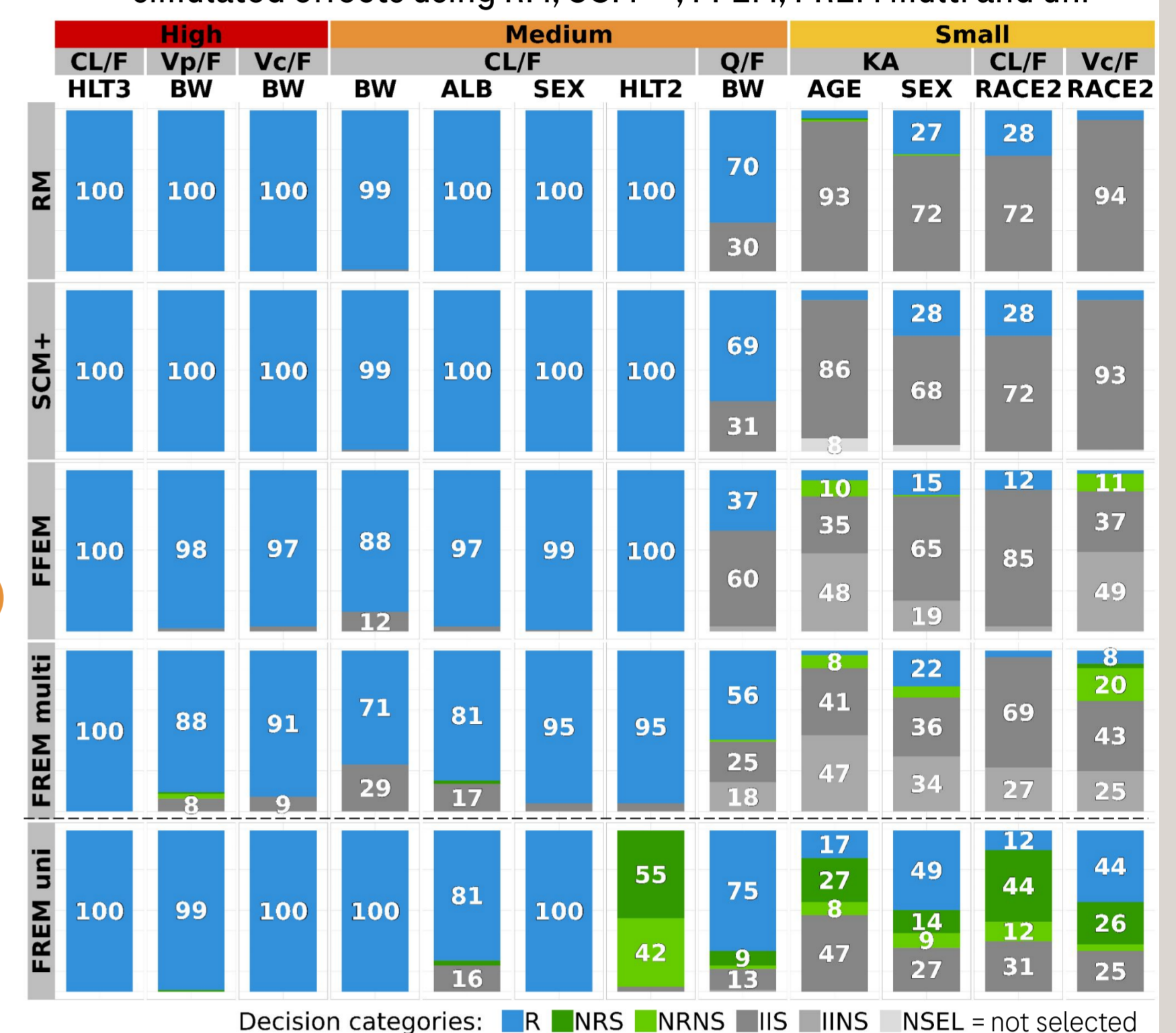
RESULTS

CCR evaluation

Covariates with a simulated effect

- High simulated effects (Fig. 5, left)**
 - RM**: always **R** (100%)
 - SCM+**: same results as RM
 - FFEM**: almost always **R** (97-100%), otherwise **IIS** (0-30%)
 - FLEM multi**: mainly **R** (88-100%), otherwise **IIS** (0-9%) or hardly ever **NRS / NRNS**
 - FLEM uni**: almost always **R** (99-100%), otherwise hardly ever **NRS**
- Medium simulated effects (Fig. 5, mid)**
 - RM**: mainly **R** (70-100%), otherwise **IIS** (0-30%)
 - SCM+**: same results as RM
 - FFEM**: mainly **R** (37-100%) / **IIS** (0-60%), otherwise hardly ever **IINS**
 - FLEM multi**: mainly **R** (56-95%), otherwise **IIS** (5-29%) / **IINS** or hardly ever **NRS / NRNS**
 - FLEM uni**: mainly **R** (0-100%) / **NRS / NRNS**, otherwise **IINS**

Fig. 5 - CCR decisions for covariates with high, medium and small simulated effects using RM, SCM+, FFEM, FLEM multi and uni



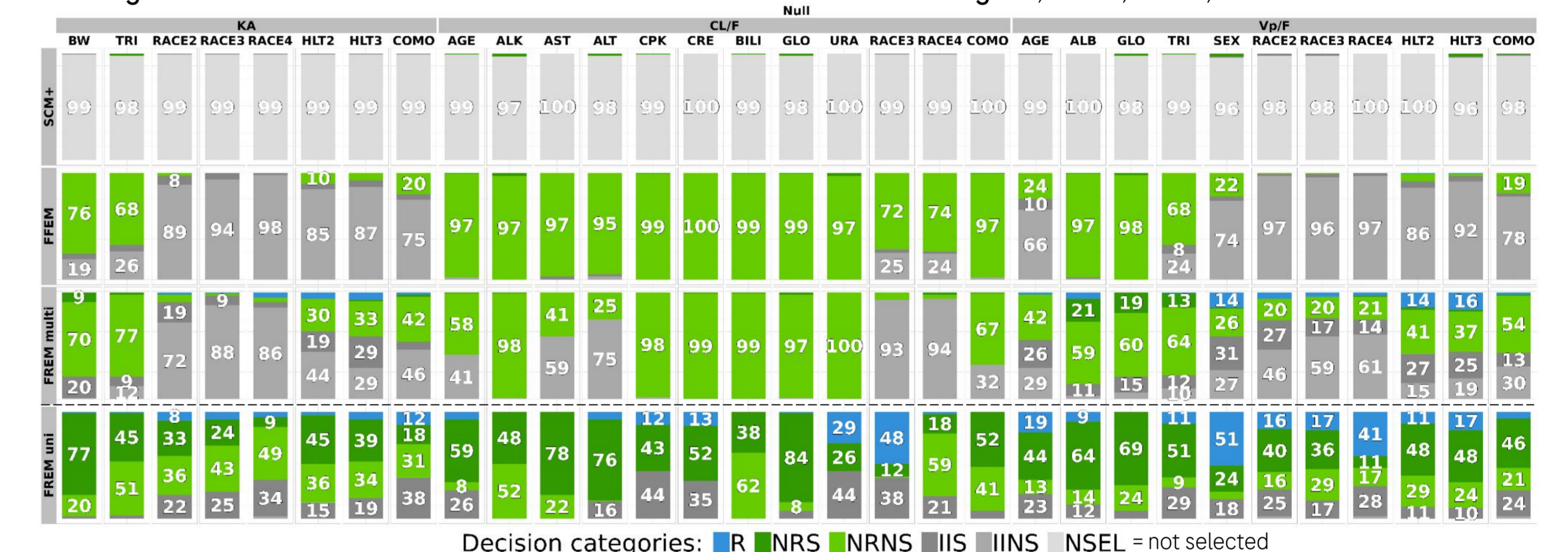
* SCM+ select exactly the simulated model in 58% of the cases; in the 42% remaining cases: 1, 2, or 3 extra null-effect relationships were selected in 20%, 6%, and 3% of the cases, resp. A single small-effect relationship was missed in 3% of the cases; 1 small-effect relationship was missed and 1, 3, or 4 extra null-effect relationships were selected in 4%, 5%, and 1% of cases

Small simulated effects (Fig. 5, right)

- RM**: mainly **IIS** (72-94%), otherwise **R** (5-28%) or hardly ever **NRS / NRNS**
- SCM+**: results overall as RM but never **NRS / NRNS**; 1 relationship missed in 13% of models, with a maximum of 8% for AGE effect on KA
- FFEM**: mainly **IIS** (35-85%) / **IINS**, otherwise **R** (3-15%) / **NRNS**, never **NRS**
- FLEM multi**: mainly **IIS** (36-69%) / **IINS**, otherwise **R** (4-22%) / **NRNS** or hardly ever **NRS**
- FLEM uni**: mainly **R** (12-49%) / **IIS** (25-47%) / **NRS**, otherwise **NRNS** (5-12%), never **IINS**

Covariate with a null simulated effect (Fig. 6, only results on KA, CLF and Vp/F shown)

Fig. 6 - CCR decisions for covariates with a null simulated effect using RM, SCM+, FFEM, FLEM multi and uni



- SCM+**: mainly not selected (96-100%), otherwise hardly ever **NRS / IIS**; in total 39% of the models included at least 1 and up to 4 additional null-effect relationships
- FFEM**: mainly **NRNS** (0-100%) / **IINS** (0-98%), otherwise **IIS** or hardly ever **NRS / R** (HLT2 & HLT3 on Vp/F); higher proportion of I for categorical covariates (2-98%) compared to continuous ones (0-66%)
- FLEM multi**: mainly **NRNS** (2-100%) / **IINS** (0-94%), otherwise **IIS / NRS / R** (0-16%); same trend observed for the 25 additional relationships tested; of note estimated correlation between CL/F and KA was of 0.02 [-0.43, 0.52] (med [min - max]) and of 0.30 [-0.16, 0.62] between CL/F and Vp/F
- FLEM uni**: mainly **NRS** (9-84%) / **NRNS** (0-62%) / **R** (1-51%) / **IIS**, otherwise hardly ever **IINS** (0-2%)

OFV, BICc and runtime

Table 3 - OFV, BICc and runtime obtained on the 100 simulated datasets with RM, SCM+, FFEM and FLEM

	OFV, Med [Min - Max]	P (μ, β, dim(Ω), a+b)	BICc, Med [Min - Max]	Runtime hours, Med [Min - Max]
RM	48,530 [47,215 - 49,913]	24 (5+12+5+2)	48,674 [47,359 - 50,057]	0.038 [0.037 - 0.041]
SCM+	48,530 [47,215 - 49,891]	23 - 27 (5+(11-15)+5+2)	48,674 [47,359 - 50,052]	15.5 [6.5 - 27.0]
FFEM	48,466 [47,160 - 49,834]	82 (5+70+5+2)	48,939 [47,635 - 50,309]	1.4 [0.4 - 5.7]
FLEM	41,299 [40,007 - 43,047]	326 (5+19+300+2)	43,166 [41,874 - 44,914]	7.0 [3.7 - 7.6]

OFV and BICc

- FFEM outperformed SCM+ for OFV but not for BICc due to more parsimonious models
- FLEM can not be compared due to differences regarding dataset, covariate encoding and Ω matrix

Runtime

- FFEM was 10 times faster than SCM+
- FLEM take 5 times longer than FFEM, but not the same estimation methods (IMPMAP vs FOCEI)

CONCLUSION

- SCM+, FFEM and FLEM multi (+ uni) provided satisfactory CCR assessment in high-dimensional settings, but covariates with small effects remain challenging; SCM+ missed relationships in up to 8% of cases while FFEM and FLEM multi showed a higher proportion of IINS and NRNS
- For covariates with no effect, SCM+ mainly did not select these relationships, though at the cost of losing information that FFEM or FLEM could capture; FLEM multi found them R in up to 16% of the cases which could be explained by the estimated correlation between PK parameters
- To ensure robust covariate analysis, both a covariate selection method and full modeling method should be used to fully assess CCR and achieve a parsimonious model suitable for prediction