PMX in France

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Joakim Nyberg (presenter)

Niclas Jonsson

Omission bias - The definition

Definition of omission bias:

- The bias in the regressor coefficients (covariate effects) that a misspecified model infers when the model is not including the true effect on all parameters
  - True clearance $CL = \theta_{CL} \cdot \left(\frac{WT}{70}\right)^{\beta_{CL,WT}} \cdot e^{\eta_{CL,i}}$
  - True volume of distribution $V = \theta_V \cdot \left(\frac{WT}{70}\right)^{\beta_{V,WT}} \cdot e^{\eta_{V,i}}$
  - Misspecified clearance where weight is omitted: $CL = \theta_{CL} \cdot e^{\eta_i}$ but still included on volume of distribution

typical values θ, covariate coefficients β and random effects η_i

Statistics: Omitted variable bias (OVB), mostly work in linear models without random effects

Omission bias

The solution?

Include all covariates on all parameters

Is it really feasible?

Issues?

- Even full models are often based on pre-specification* and might be difficult to estimate
- Interpretation
  - Are all covariates physiological, if not, confusing to include?
  - Mechanistic models?
- Run-times might be unreasonable?
- Inclusion of false and non predictive covariates
  - Inclusion bias?

* CPT Pharmacometrics Syst Pharmacol. 2024 May;13(5):710-728.

Inclusion bias

Definition of inclusion bias

The bias from including false covariate(s) relationships on “some” parameters

Issues?

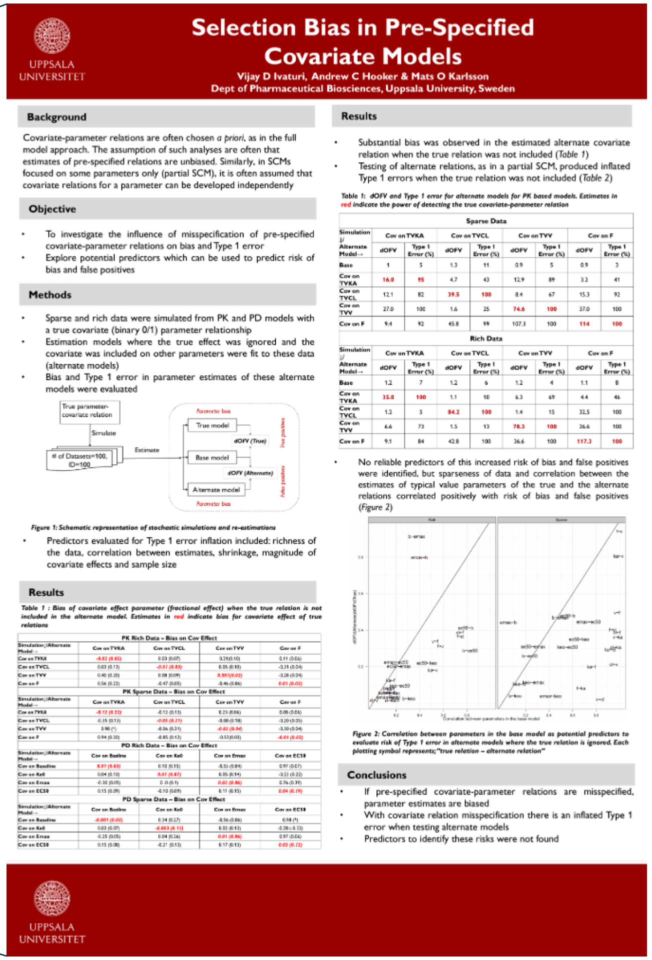
- Do we have unbiased estimators given the approximation methods and non-linear nature of non-linear mixed effect models?
- If estimated, given some bias, could lead to wrong mechanistic understanding?

Omission bias in Pharmacometrics

Pharmacometrics: (V. Ivaturi, AC. Hooker, MO. Karlsson Page 2011)

- Looked at one true covariate-parameter at time
- No correlation structure in IIV
- Spare and rich data
- Investigating impact on bias and type I error

Conclusions: Misspecified cov-param relationships gives bias and inflated type I error



This work aims to provide insight into omission bias and inclusion bias

Full model approaches
(aka Pre-specification methods)

FFEM (Full *fixed* effects model)

- Aims to include all pre-specified parameter-covariate relationships in the model.
- Involves a user guided removal of correlated covariates from the pre-specified scope to:
  - manage estimation stability
  - obtain independent estimates of the covariate coefficients

PAGE 2011

FREM (Full *random* effects model)

- Is an innovative covariate modeling method.
- Is unique in that it treats covariates as *observations* instead of independent variables.
- Always includes all covariates on all parameters associated with covariates.

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ARTICLE

An introduction to the full random effects model

Gunnar Yngman[1] | Henrik Bjugård Nyberg[1] | Joakim Nyberg[2] | E. Niclas Jonsson[2] | Mats O. Karlsson[1,2]

CPT: Pharmacometrics & Systems Pharmacology. 2022;11(2).

Why are correlations and missing covariate data not an issue for FREM?

The base model:

$$CL = \theta_{CL} \cdot e^{\eta_{CL}}$$
$$V = \theta_V \cdot e^{\eta_V}$$

$$\Omega_{PK} = \begin{bmatrix} \omega_{CL} & cov(CL, V) \\ cov(CL, V) & \omega_V \end{bmatrix}$$

Adding the covariates as observations:

ID	TIME	AMT	DV	WT	SEX	RACE	FREMTYPE
1	0	100	0	75	1	2	0
1	0	.	75	75	1	2	1
1	0	.	1	75	1	2	2
1	1	.	0.86	75	1	2	0
1	2	.	0.69	75	1	2	0

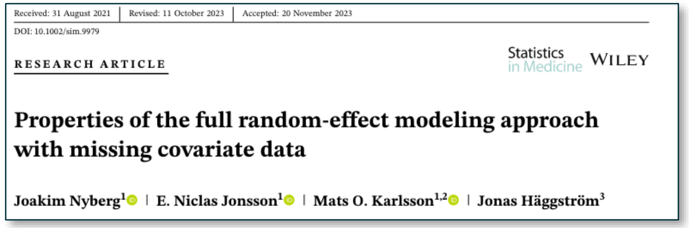
FREMTYPE:
0: PK
1: WT
2: SEX

$$Y = \begin{cases} F(1+\varepsilon_1) & FREMTYPE = 0 \\ \theta_{WT} + \eta_3 + \varepsilon_{\varepsilon \to 0} & FREMTYPE = 1 \\ \theta_{SEX} + \eta_4 + \varepsilon_{\varepsilon \to 0} & FREMTYPE = 2 \end{cases}$$

$$\Omega_{FREM} = \begin{bmatrix} \Omega_{PK} & cov(\eta_{PK}, \eta_{cov}) \\ cov(\eta_{PK}, \eta_{cov}) & \Omega_{cov} \end{bmatrix}$$

Correlations between covariates are a part of the model instead of being ignored (=assumed to be 0).

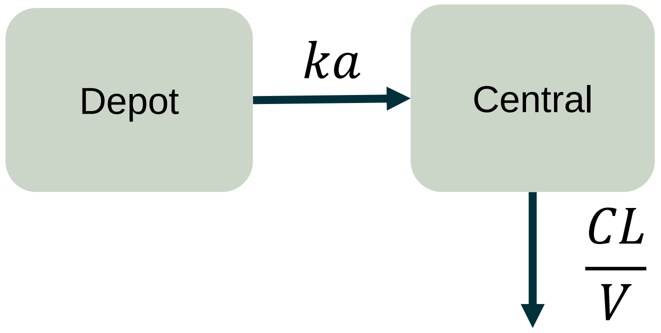
Missing covariates are not an issue since they are treated as observations.

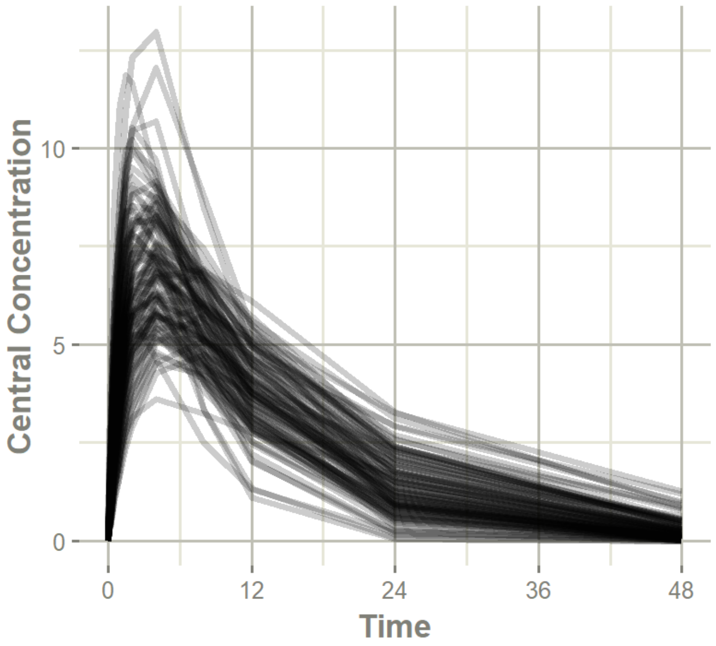

Received: 31 August 2021 | Revised: 11 October 2023 | Accepted: 20 November 2023
DOI: 10.1002/sim.9979
RESEARCH ARTICLE
Statistics in Medicine WILEY
Properties of the full random-effect modeling approach with missing covariate data
Joakim Nyberg[1] | E. Niclas Jonsson[1] | Mats O. Karlsson[1,2] | Jonas Häggström[3]

- FREM gives precise and unbiased estimates even with 90% missing data
- Mean imputation shows bias already at 10% missing rates.
- Complete case analysis was less precise than FREM and could only handle <70% missing covariates

Simulation setup – model and design

- Allometric scaling [WT~logN(log(70),0.2], on either CL,V or both, fixed or estimated
- Rich sampling (n=13) & Rich data (N=100)
- Correlated parameters: Diagonal Omega, Full Omega Block (FREM) or Block CL/V, corr~0.4, IIV 30% CL/V, 50% Ka
- Data generating model using combinations (of the above) parameters
- Assumes no missing data (observation and covariates)





Monte Carlo scenarios

Simulation models

- No covariates / IIV correlation
- No covariates / No IIV correlation
- Allometric on V / IIV correlation
- Allometric on V / No IIV correlation
- Allometric on CL / IIV correlation
- Allometric on CL / No IIV correlation
- Allometric on both / IIV correlation
- Allometric on both / No IIV correlation

Estimation models

- No covariates / IIV correlation
- FREM
- Allometric on V / IIV correlation
- No covariates / No IIV correlation
- Allometric on CL / IIV correlation
- Allometric on V / No IIV correlation
- Allometric on both / IIV correlation
- Allometric on CL / No correlation
- FREM (no KA) / IIV correlation
- Allometric on both / No IIV correlation

No IIV correlation

Full covariance (IIV) matrix

IIV correlation (CL,V)

Estimated allometric scaling

Simulation models

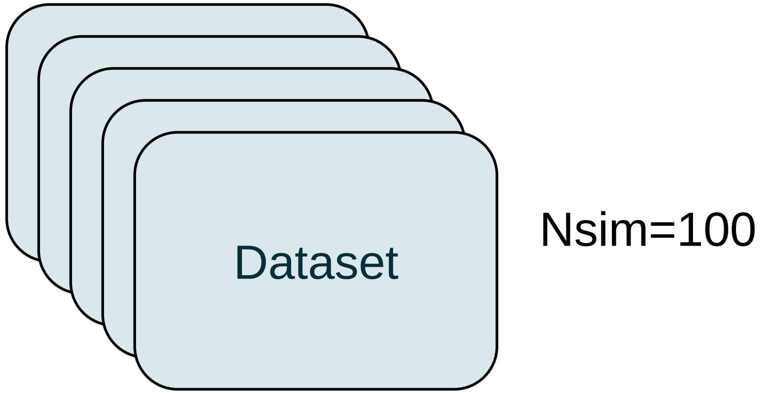
Fixed allometric scaling
Not shown in this presentation

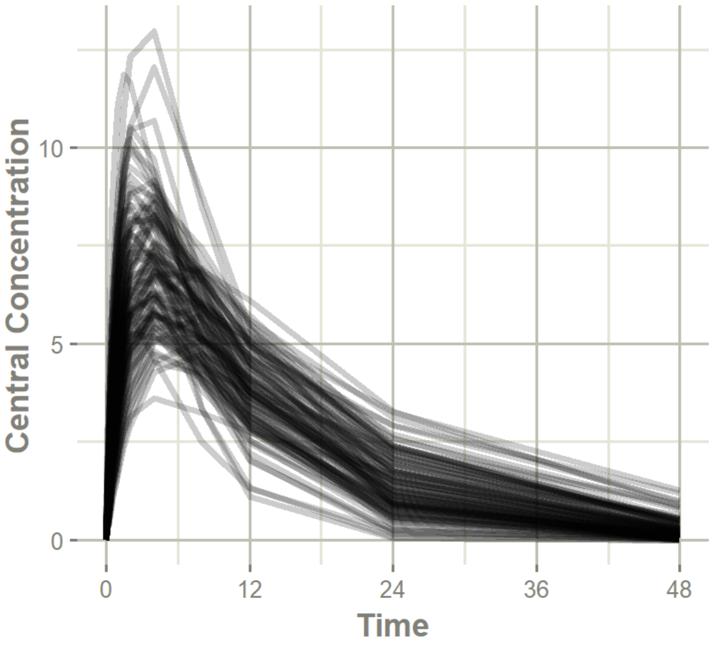
Model structures:
- No covariates
- Allometric scaling on CL
- Allometric scaling on V
- Allometric scaling on CL & V
- FREM (CL, V, Ka)
- FREM (CL,V)

Both first order conditional with interaction estimation method and Important sampling investigated

Simulation setup

- Monte Carlo simulations, Nsim=100 per model
- 8 different data generation models
- Re-estimated with 16 different FFEM and 2 FREM
- No resampling of WT covariate (N=100), same for each Monte Carlo simulation
- In total 144*2 different scenarios

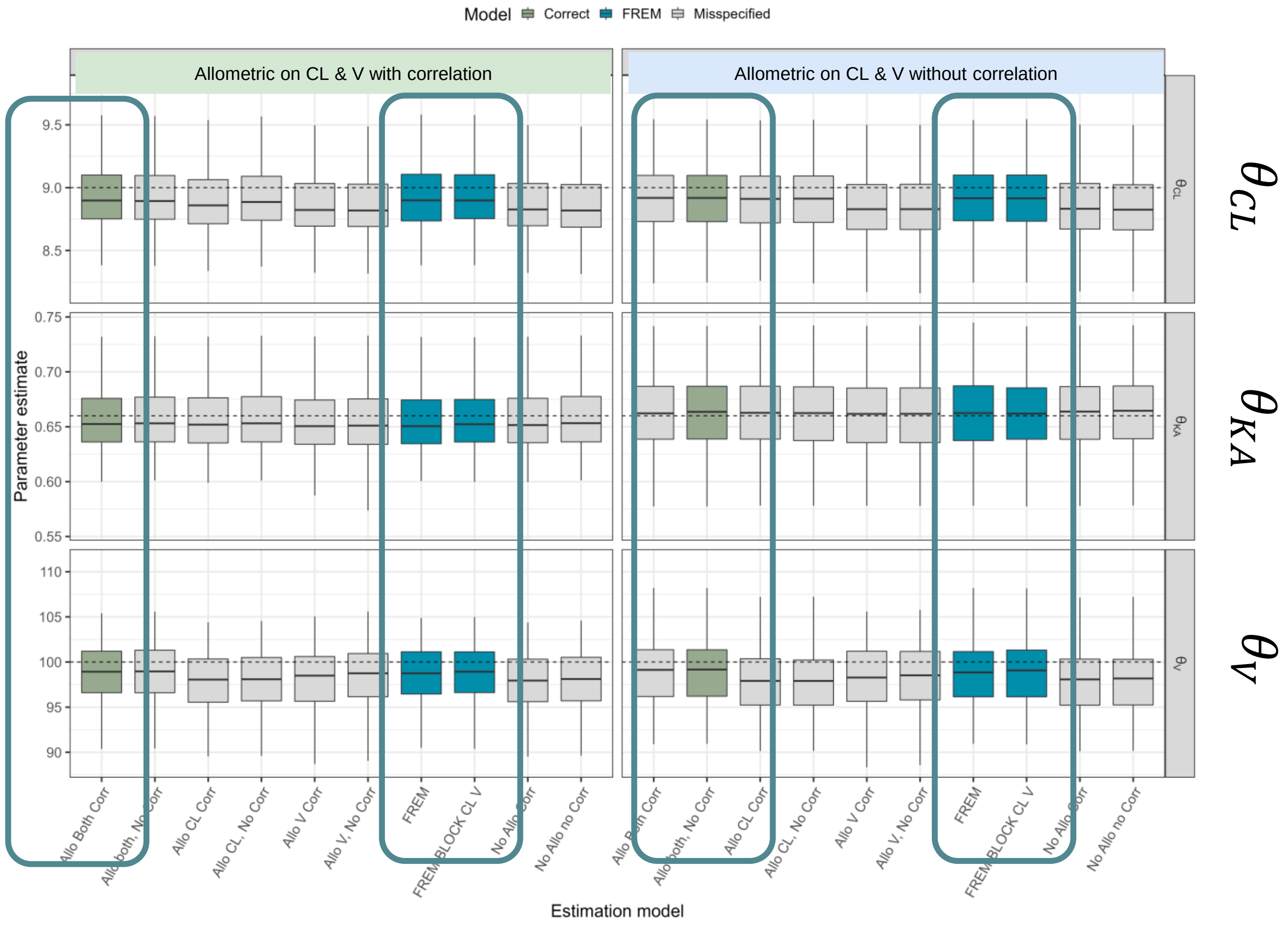




Results – Typical parameters

Minor omission bias effect on typical parameters

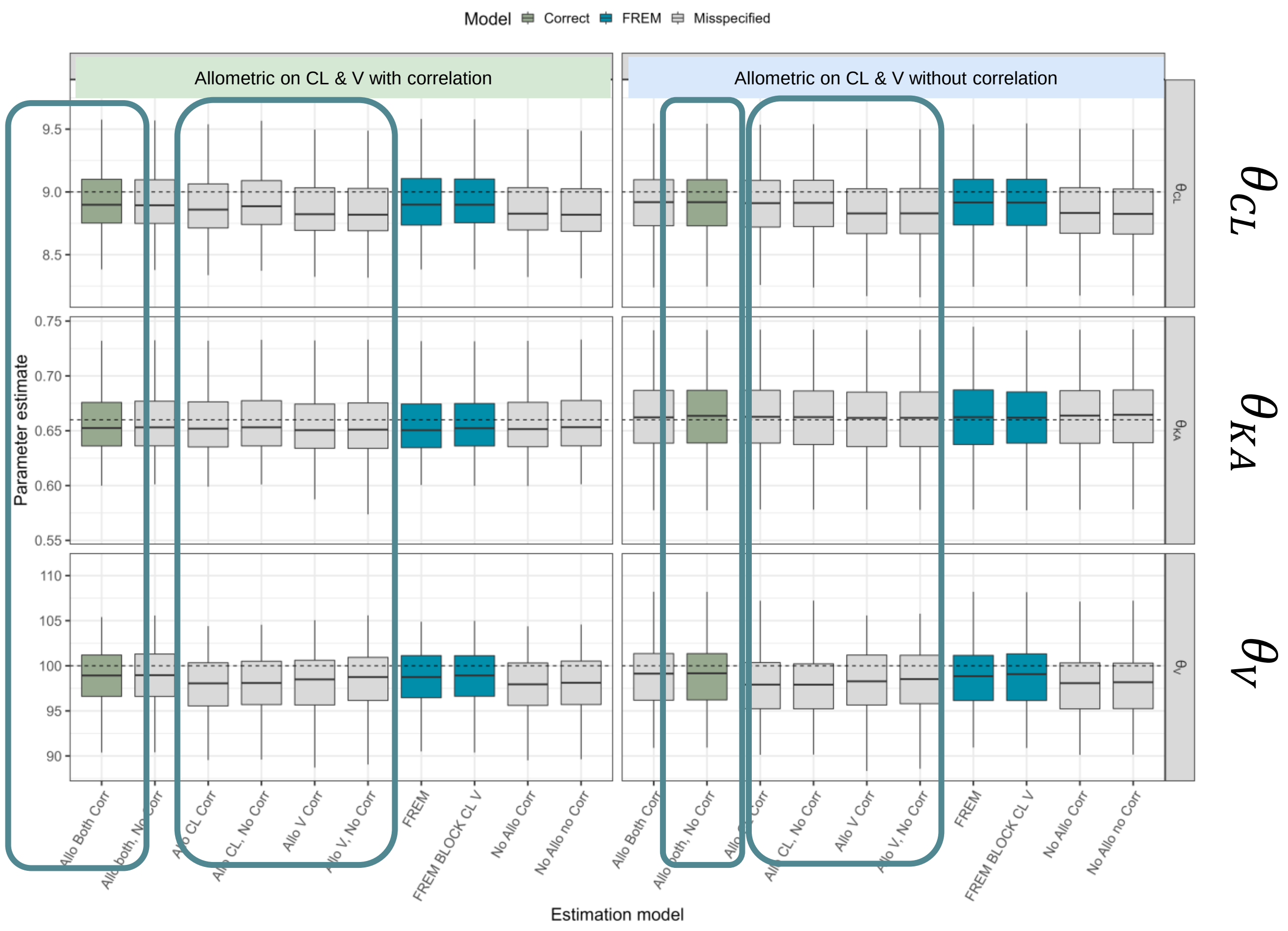
- Correct model and FREM performs similarly



Results – Typical parameters

Minor omission bias effect on typical parameters

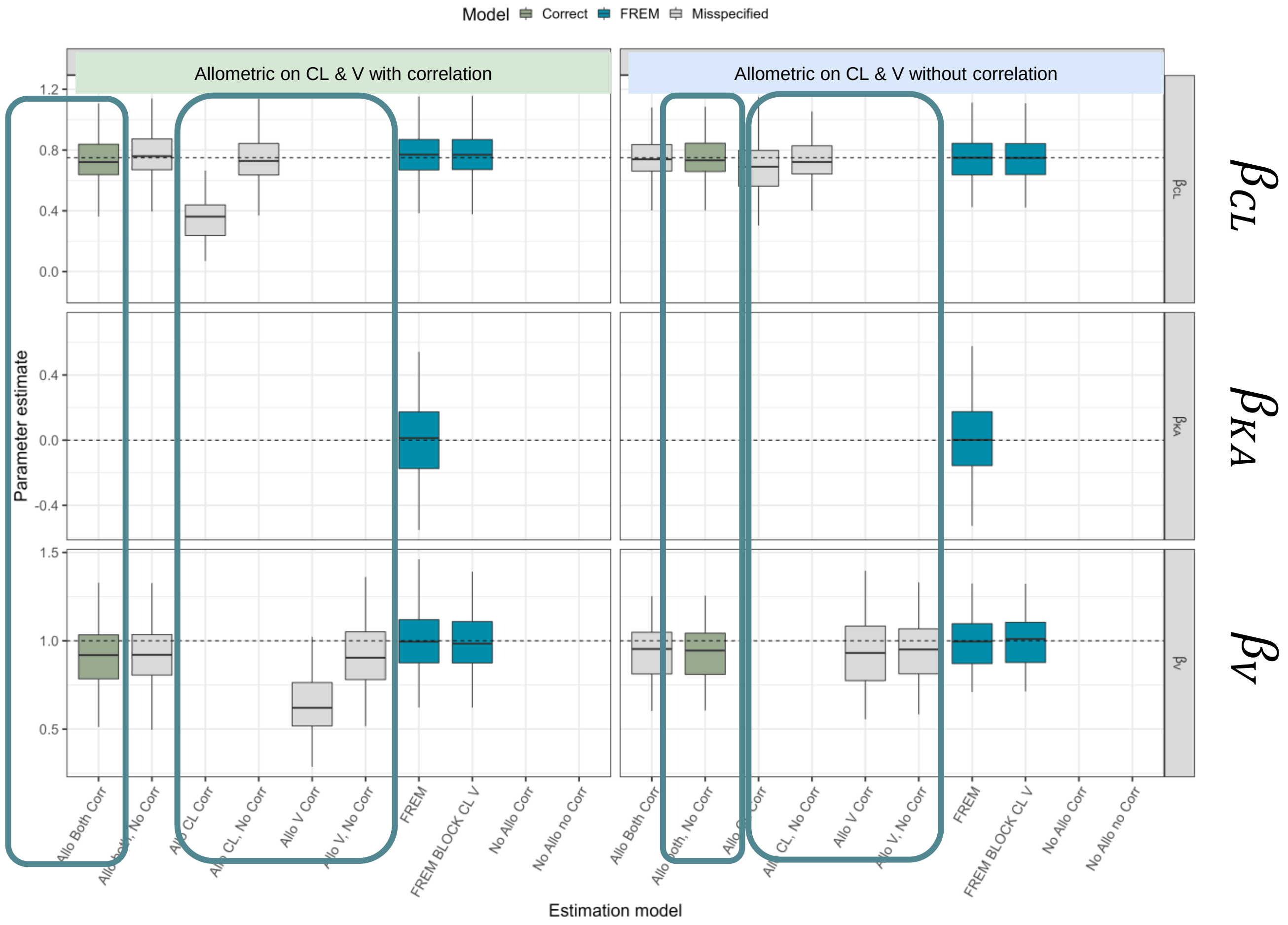
- Correct model and FREM performs similarly
- Tendency to underpredict parameters (CL,V) when excluding the covariate on one or both parameters



Results – Covariate coefficients

Omission bias effect on covariate coefficients:

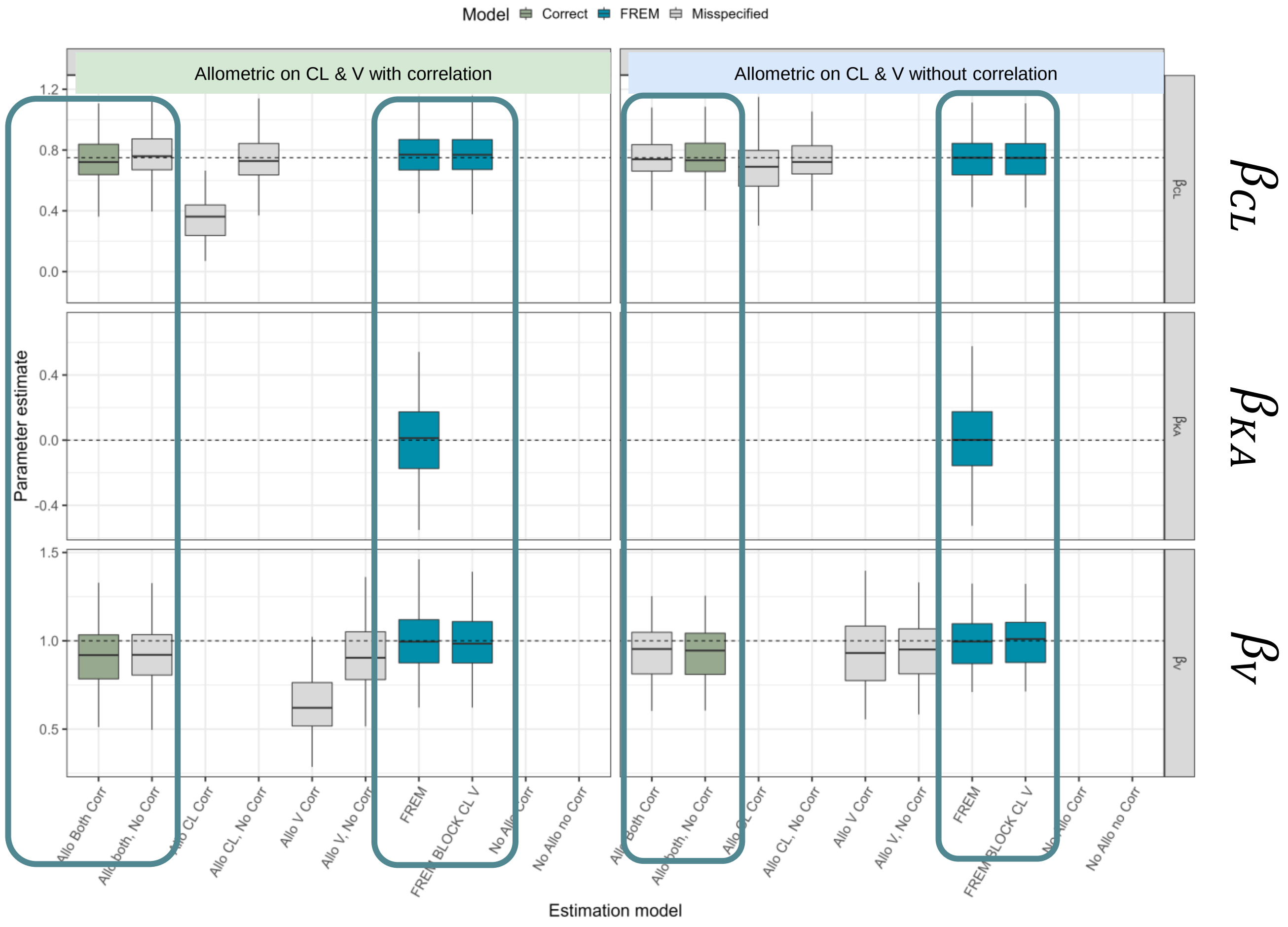
- Misspecified models biased (>with correlation in data)



Results – Covariate coefficients

Omission bias effect on covariate coefficients:

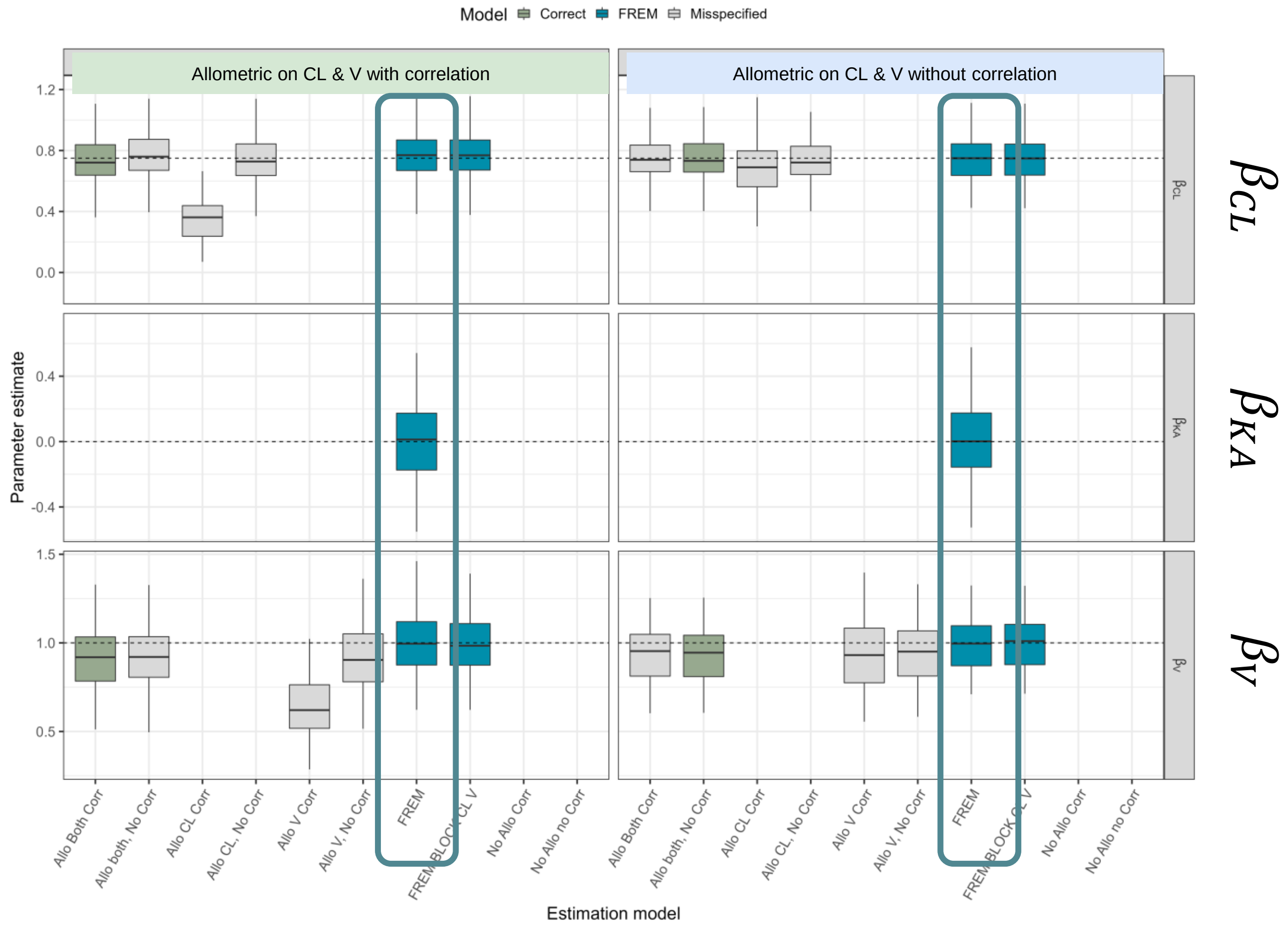
- Misspecified models biased (>with correlation in data)
- FREM less bias compared to FFEM



Results – Covariate coefficients

Omission bias effect on covariate coefficient:

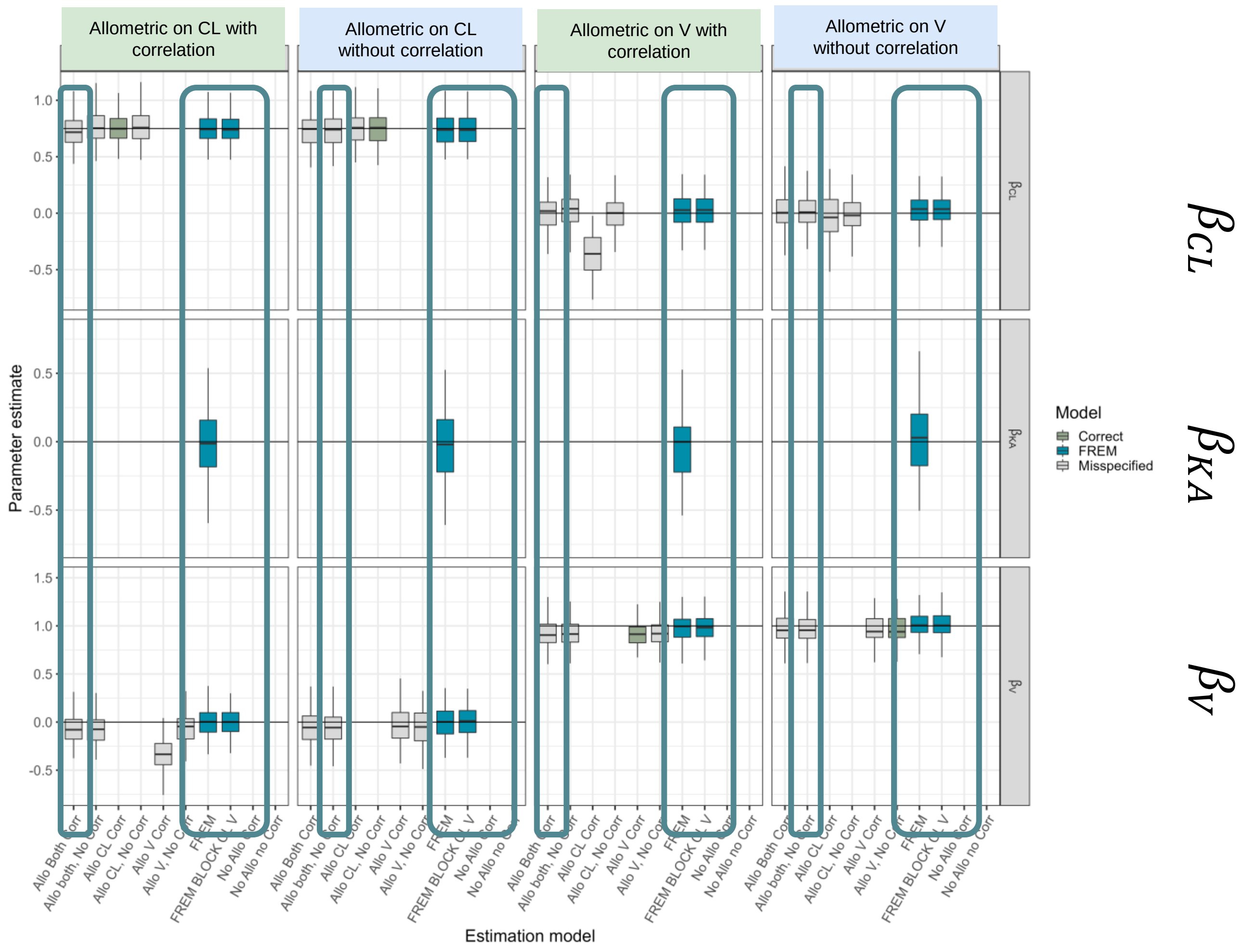
- Misspecified models biased (>with correlation in data)
- FREM less bias compared to FFEM
- **Inclusion bias:** FREM unaffected (no bias) by allometric coefficient on Ka



Results – Covariate coefficients in full models

Inclusion bias:

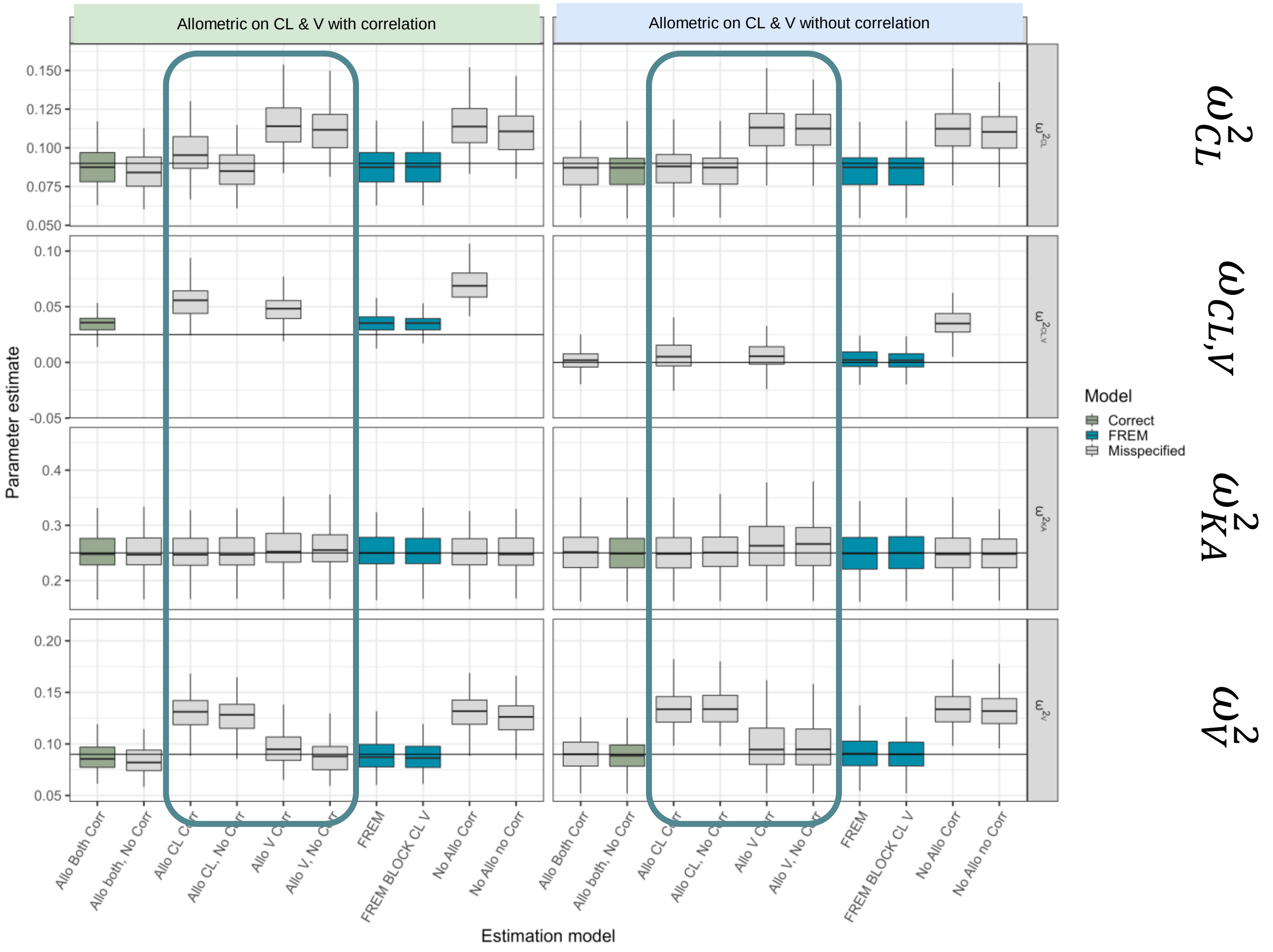
- Full models works quite well (slight advantage with FREM vs FFEM)



Results – Interindividual variability

Omission bias:

- Variance estimates increases when covariate-parameters relationships are excluded (less explained variability)

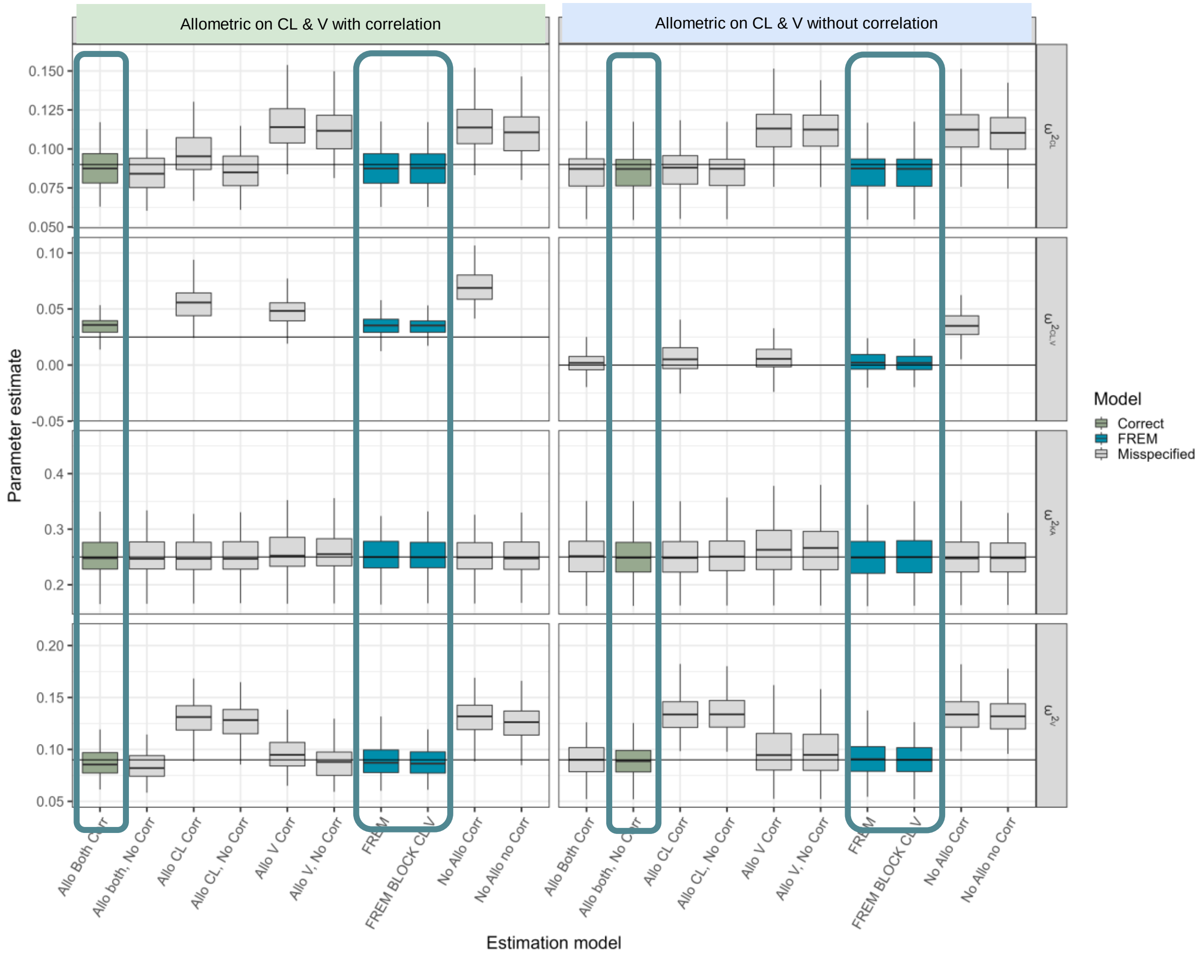


Results – Interindividual variability

Omission bias:

- Variance estimates increases when covariate-parameters relationships are excluded (less explained variability)

- FREM and FFEM (correct model) both performs well



ω_{CL}^2

$\omega_{CL,V}$

ω_{KA}^2

ω_{V}^2

Conclusions

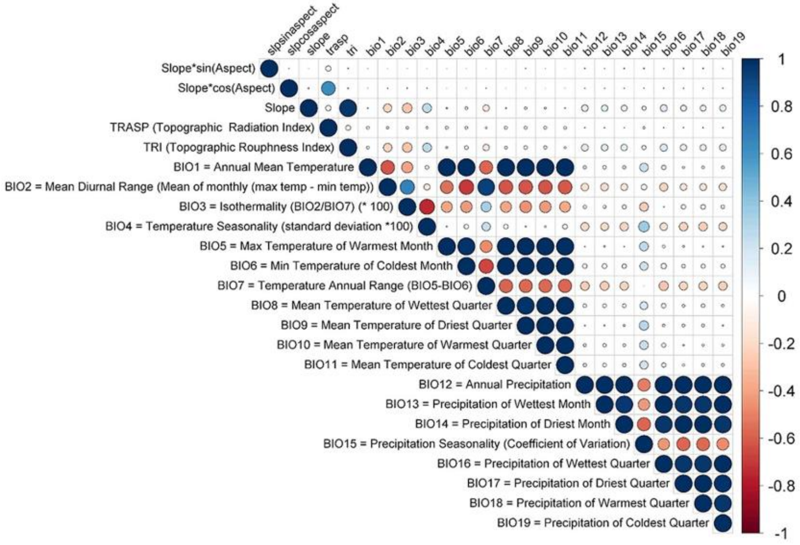
- Assumptions we make have an impact on the bias/precision of the covariate effects
  - Use full IIV block or not
  - Use Full model or not
    - FREM or FFEM

- Parameter-covariate scope (reduction or not) FREM seems to perform well in all scenarios, sometime even better than the corresponding FFEM

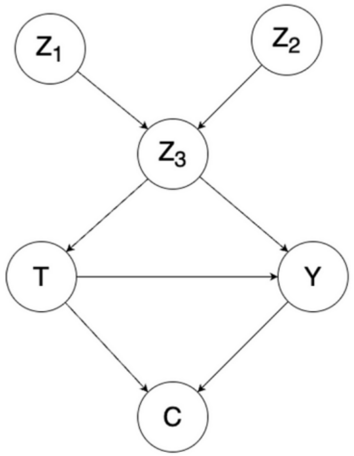
- We get omission bias in covariate coefficients and variance estimates (IIV) when not including true covariates (FFEM)

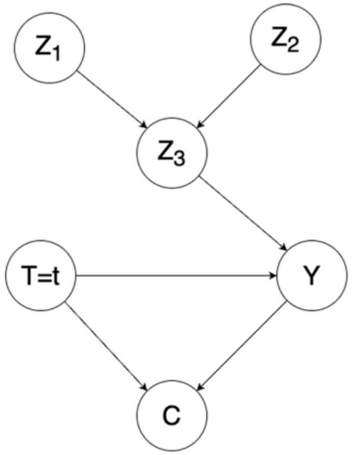
Future perspectives

- Investigate additional scenarios with multiple correlated covariates on multiple parameters
  - Report type 1 error - selection bias
  - Consequences for stepwise model building approaches?



- Link this work to causality and consequences of inclusion/omission bias w.r.t casual effects





Pharmetheus®

Conversion to FFEM with only one covariate from the FREM model

$$\Omega_{FREM} = \begin{pmatrix} \Omega_{PK} & cov(\eta_{PK}, \eta_{cov}) \\ cov(\eta_{PK}, \eta_{cov}) & \Omega_{cov} \end{pmatrix} = \begin{pmatrix} \omega^2_{CL} & \omega_{CL,V} & \omega_{CL,WT} & \omega_{CL,SEX} \\ \omega_{CL,V} & \omega^2_{V} & \omega_{V,WT} & \omega_{V,SEX} \\ \omega_{CL,WT} & \omega_{V,WT} & \omega^2_{WT} & \omega_{WT,SEX} \\ \omega_{CL,SEX} & \omega_{V,SEX} & \omega_{WT,SEX} & \omega_{SEX} \end{pmatrix}$$

The corresponding FFEM models for CL and V are:

$$CL = \theta_{CL} \cdot e^{(\beta_{CL,WT}(WT-\overline{WT})+\eta'_{CL})}$$
$$V = \theta_{V} \cdot e^{(\beta_{V,WT}(WT-\overline{WT})+\eta'_{V})}$$

where

$$\beta_{CL} = \frac{\omega_{CL,WT}}{\omega^2_{WT}} \quad \beta_{V} = \frac{\omega_{V,WT}}{\omega^2_{WT}}$$

And the η's come from the corresponding ω's:

$$\omega^{2\prime}_{CL} = \omega^2_{CL} - \omega_{CL,WT}\beta_{CL} \qquad \omega^{2\prime}_{V} = \omega^2_{V} - \omega_{V,WT}\beta_{V}$$

- The covariates will always be additive to the corresponding η.
- The IIV must be adjusted to reflect the impact of the covariate.
- It is only the covariates we decide to include in the FFEM model that affects the FFEM coefficients.
- With multiple covariates it is also necessary to adjust the covariance term between the parameters.