Generating uncertainty estimates in empirical forest plots

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Objective

- To investigate the use of empirical forest plots to approximate covariate effects of interest, even if the covariate is not in the model.
- To use individual parameter values and their uncertainties from samples of the conditional distribution of individual parameters [1] to approximate the effect size and uncertainty of covariates not included in the model.

Conclusions - Empirical forest plots:

- Estimate effect sizes for covariates not in the model.
- Can use either the final model with covariates or an initial model without.
- Should sample from conditional distributions in high shrinkage cases.
- May differ in uncertainties from parametric forest plots if covariates have low correlation with those in the model.

Background

Forest plots graphically represent covariate effect sizes in pharmacometrics models, aiding communication with researchers, clinicians, policymakers, and patients [2].

Typically, forest plots are based on final model parameter estimates and uncertainties, without using the data to create the plot (parametric forest plots).

If a covariate is not in the final model, its effect on the endpoint cannot be directly predicted.

Empirical forest plots approximate covariate effects not in the model, using model-predicted individual parameter values summarized by the covariate of interest (e.g., median clearance values for males and females).

Jonsson and Nyberg [2] compute individual parameter values based on typical model values and included covariate effects, avoiding shrinkage but possibly underestimating uncertainty.

If informative covariates are missed and no highly correlated covariate is present, the missed covariate will not appear impactful in empirical forest plots.

Methods

Generating Empirical Forest Plots

1. **Model Establishment**
   Develop a final model with covariate effects.
2. **Parameter Prediction**
   Predict individual parameter values using typical values, covariate effects, and the conditional mean of the individual conditional distribution of the parameter.
3. **Data Summarization**
   Summarize primary or secondary parameters based on covariates of interest for the forest plot.
4. **Uncertainty Computation**
   Calculate the uncertainty of the summary statistics using samples from the individual conditional distribution of the parameters and the population variance-covariance matrix from the model fit to data.
5. **Forest Plot Generation**
   Create the forest plot.

Simulation Study

A simulation study using NONMEM [3] and R [4] was performed, where data was simulated from various covariate models and then evaluated with the simulation model or with misspecified covariate models (including a base model without covariates).

Simulations included scenarios with models having covariates on parameters with low and high shrinkage.

The generated forest plots were compared to parametric forest plots.

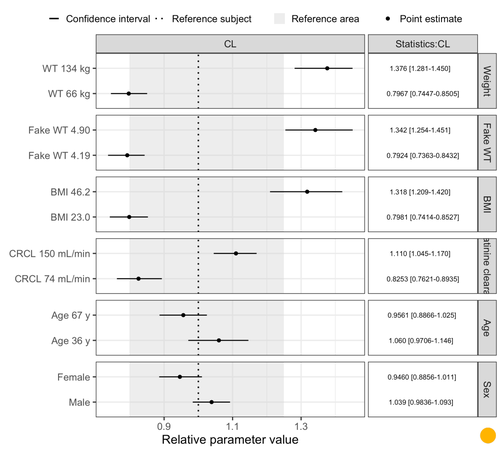
Results

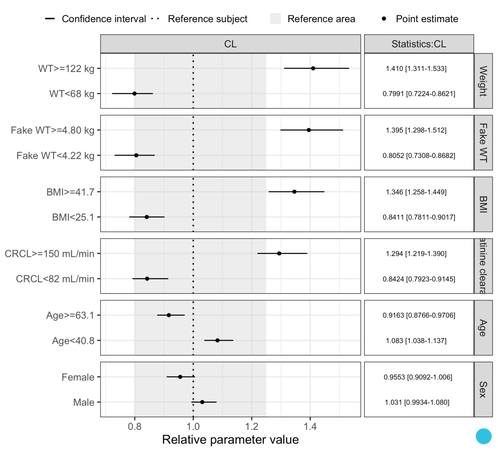
Univariate parametric forest plot (*gold standard*).

Empirical forest plot based on...
- typical parameter values (*current standard*).
- conditional distribution of individual parameters.
- individual parameters.

Situation 1 — Low shrinkage (~2%) on individual estimates

The estimation model matches the simulation model (WT on CL).

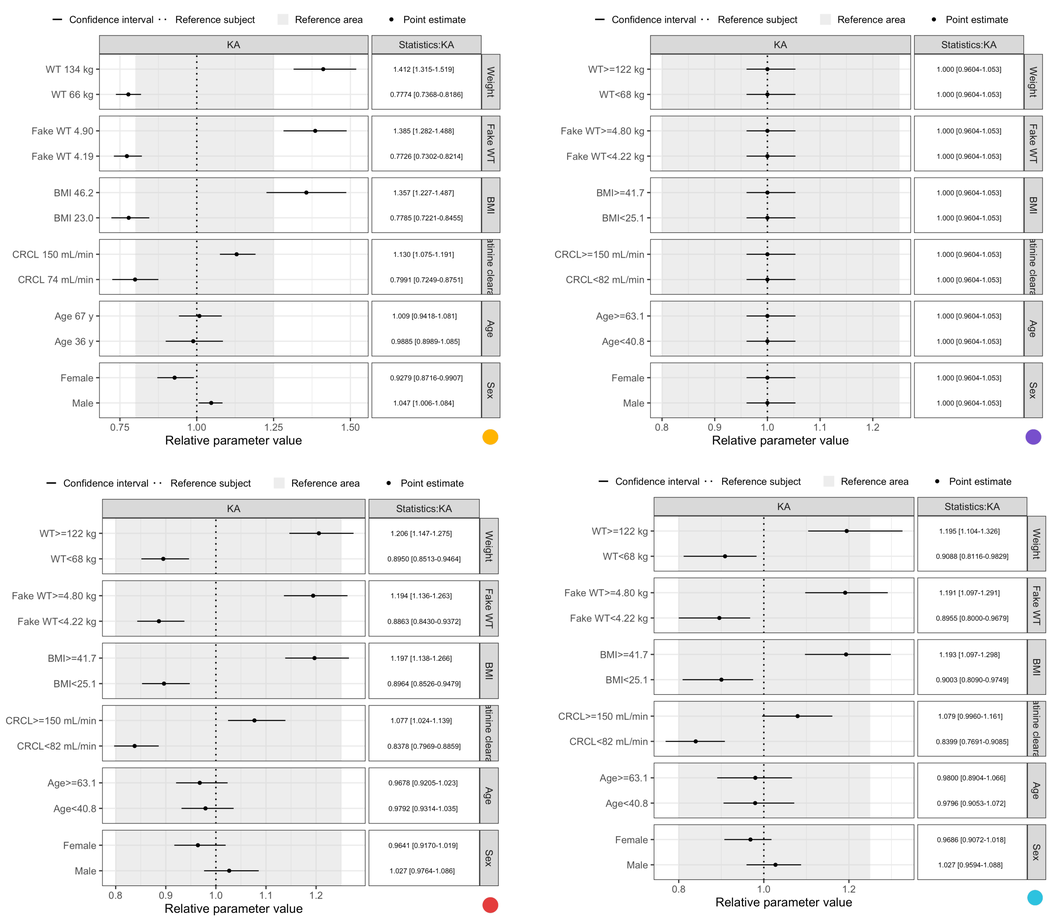




- Effects not in the model can be estimated using samples from individual conditional parameter distributions.
- Empirical forest plots provide accurate point estimates of effects.
- Uncertainty estimates are improved with sampling but do not match gold standard values.

Situation 2. — Higher shrinkage (~30%) on individual estimates

The estimation model has a different covariate model (no covariates) compared to simulation model (WT on Ka).



- Typical values alone in empirical forest plots do not reveal potential covariate effects.
- Empirical forest plots with individual parameter estimates resemble parametric forest plots.
- Sampling from conditional distributions improves uncertainty estimates but does not reach gold standard values.

Table 1: Summary of 3 different ways of computing an empirical forest plot compared to parametric gold standard.

	Point estimates		CI widths	
Empirical method	MAPE	MaxAPE	MAPE	MaxAPE
Original	3.07	12.54	23.36	56.26
With EBEs	3.56	16.64	22.30	46.22
Conditional distribution	3.55	16.60	23.42	43.59

	Point estimates		CI widths	
	MAPE	MaxAPE	MAPE	MaxAPE
	18.36	29.28	43.46	65.90
	8.73	15.05	36.51	53.28
	9.05	16.83	21.42	64.65

MAPE: mean absolute percentage error, MaxAPE: max absolute percentage error

References

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