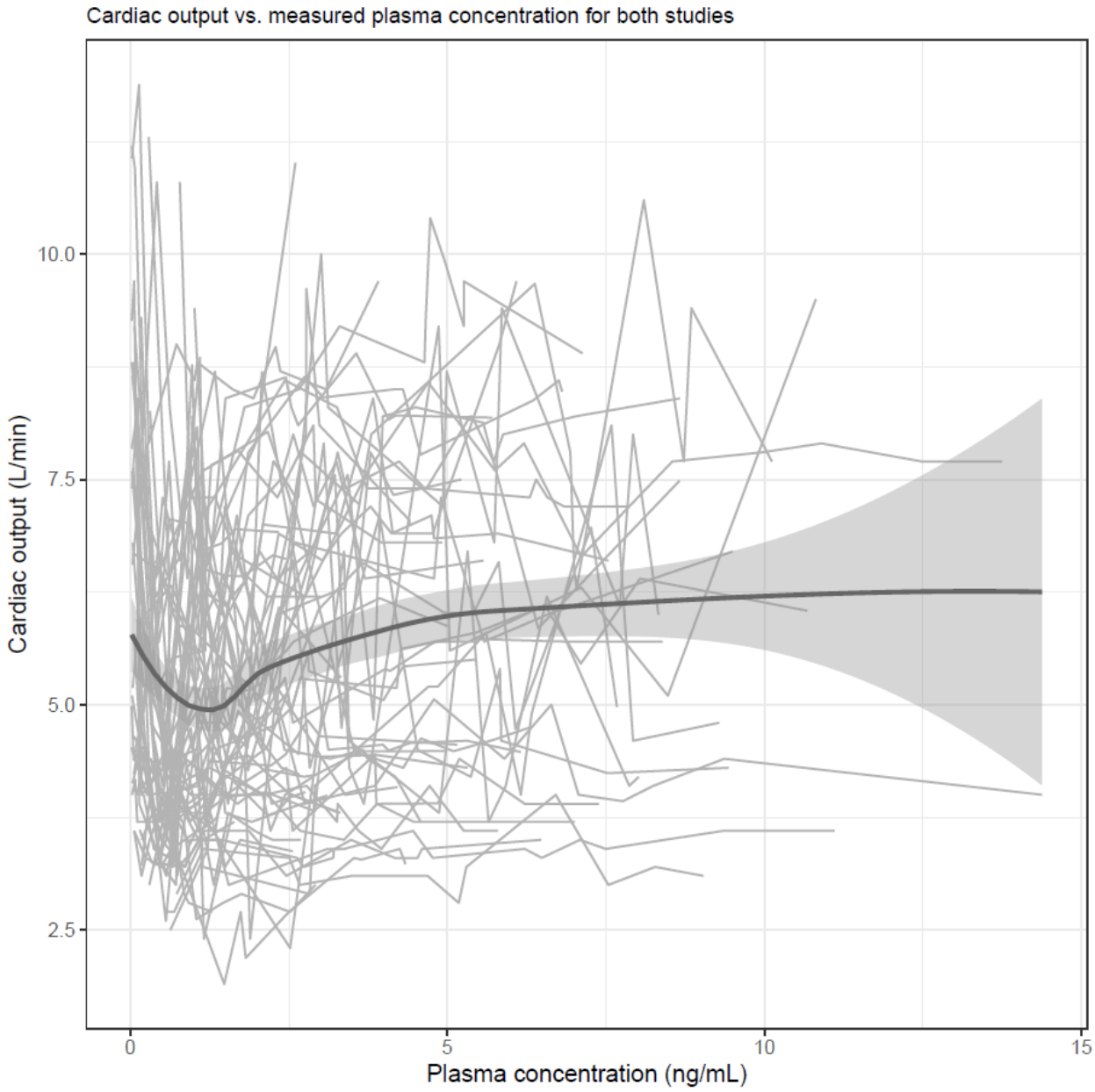
Figure S1. Measured cardiac output versus measured dexmedetomidine plasma concentrations for all subjects in the analysis.
Figure S1a shows the measured cardiac output versus the measured dexmedetomidine plasma concentrations for all subjects. Figure S1b shows the relative change from baseline cardiac output for each individual versus the measured dexmedetomidine plasma concentrations. The black solid line is a non-parametric smoother to the data and the grey shaded area denotes the 95% confidence interval for the non-parametric smoother.



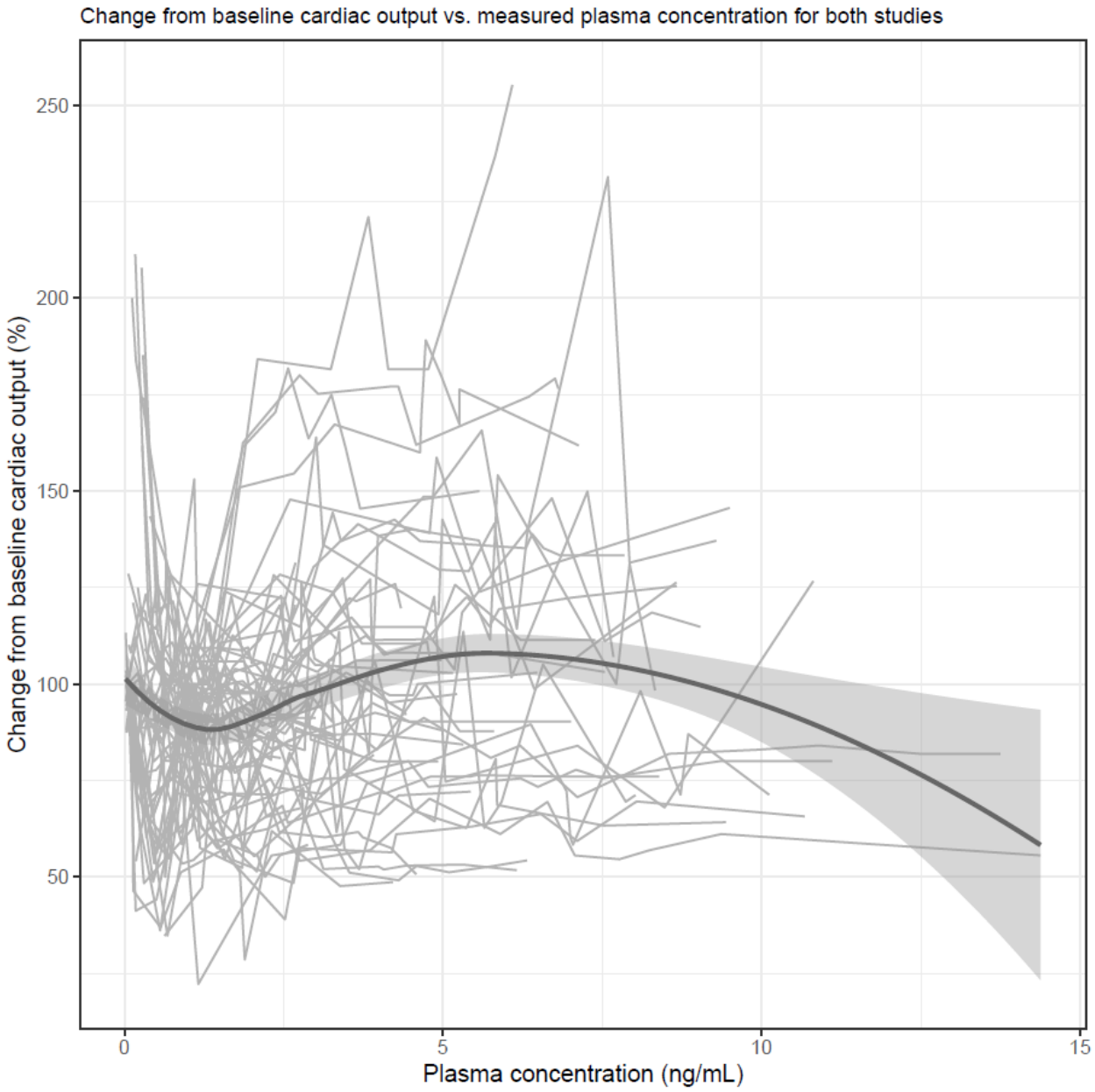

Change from baseline cardiac output vs. measured plasma concentration for both studies
Change from baseline cardiac output (%)
250
200
150
100
50
0
5
10
15
Plasma concentration (ng/mL)

Figure S2. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the linear 3-compartment model.

The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the linear 3-compartment model.

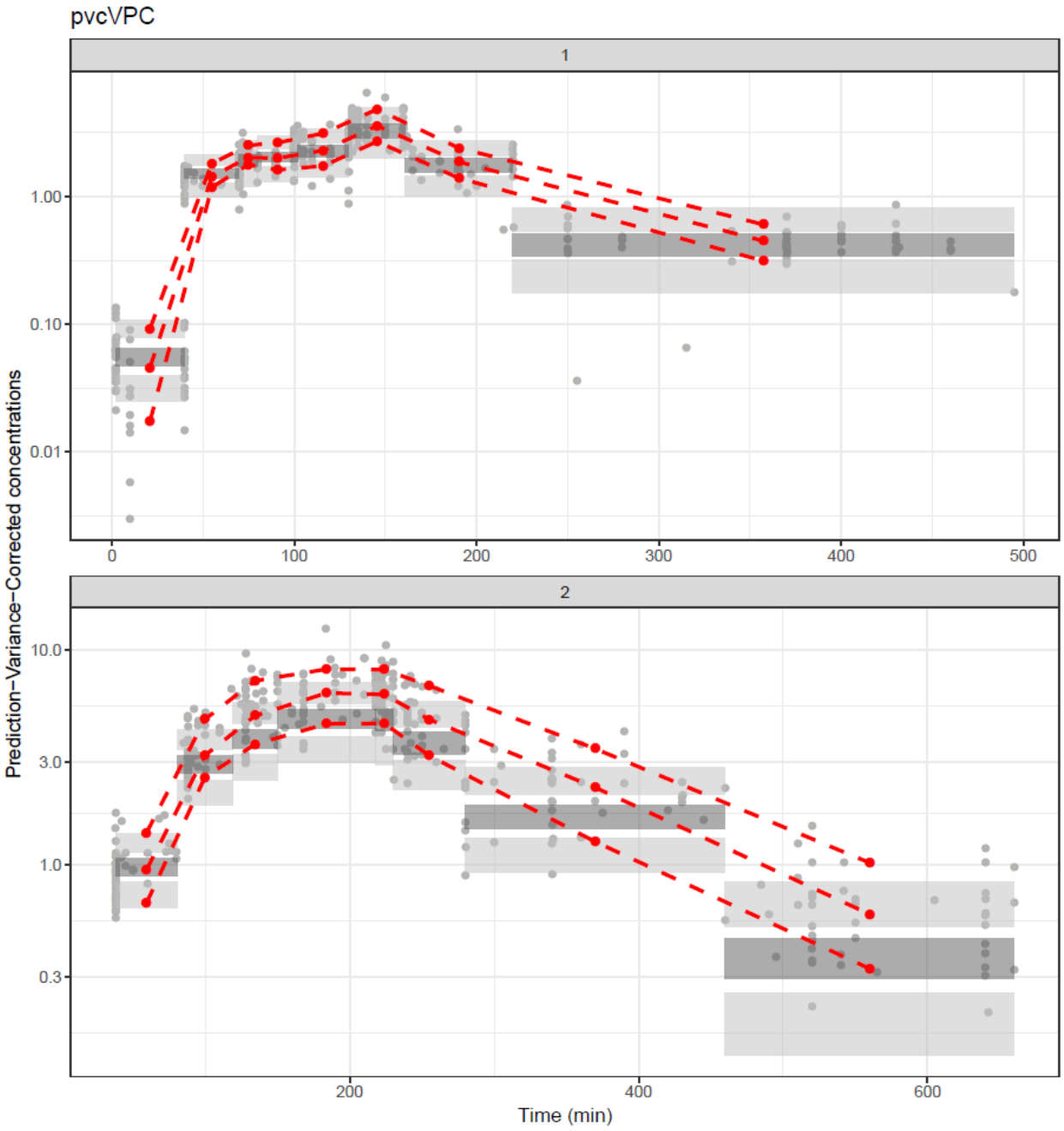


Figure S3. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the non-linear 3-compartment model.

The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the non-linear 3-compartment model.

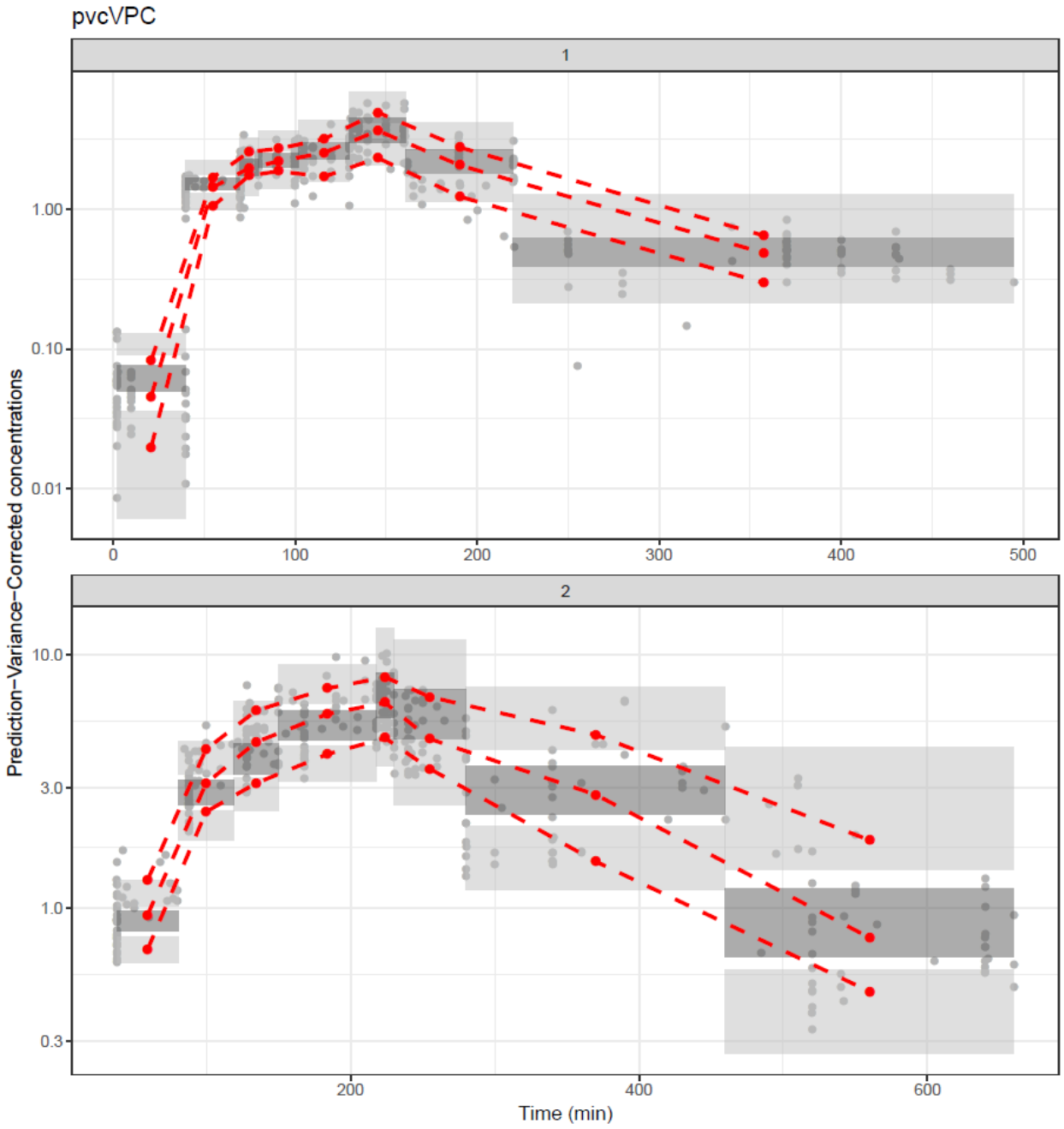


Figure S4. Log-likelihood profiles for the final model/
The vertical solid line shows the maximum likelihood estimate. The shaded area corresponds to the 95% confidence interval around the maximum likelihood estimate. The vertical dashed lines and the numbers in the legend denote the upper and lower 95% confidence bound and the relative standard error (RSE) of the maximum likelihood estimate.

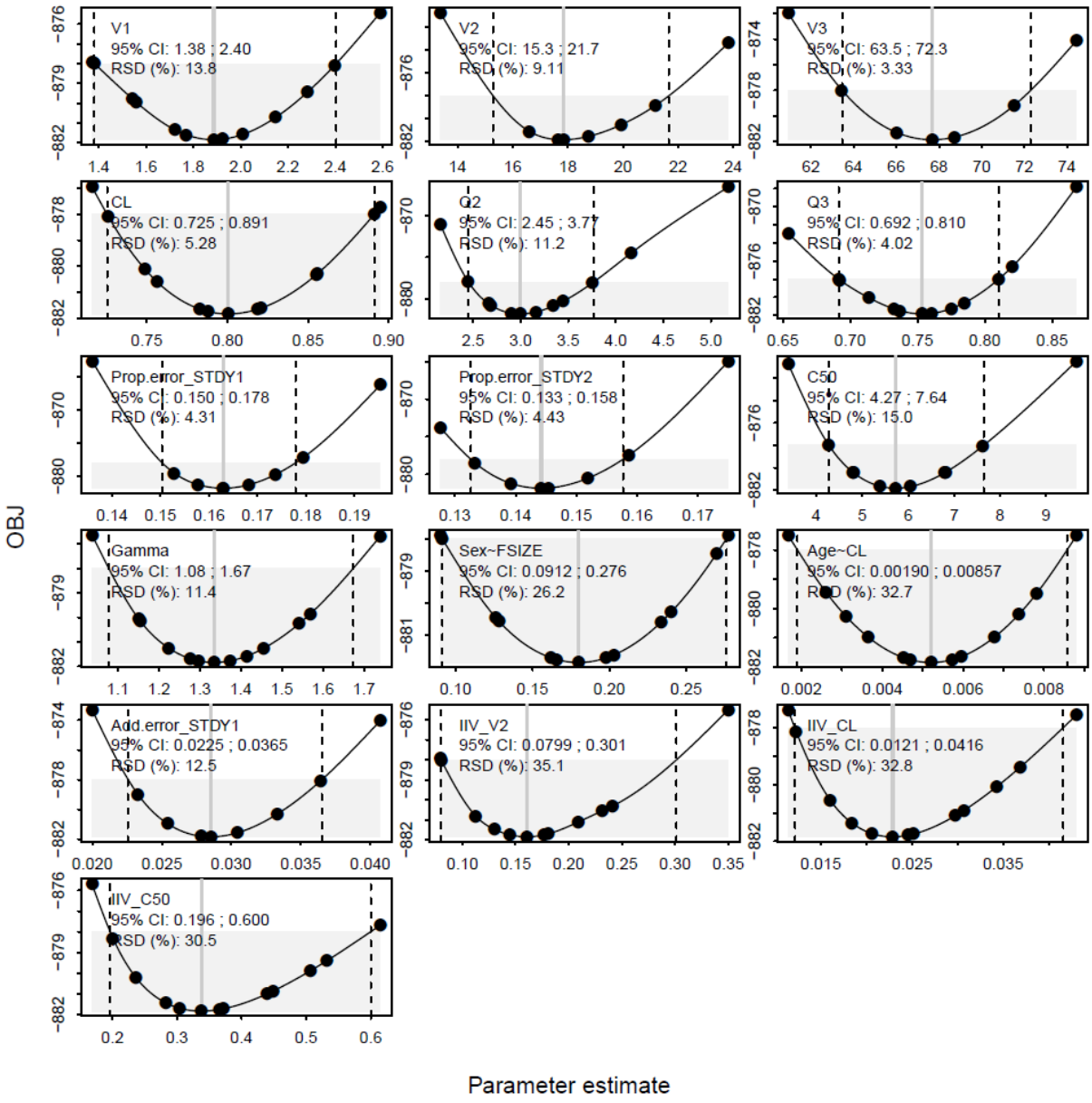


Figure S5. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the final model. The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the final model.

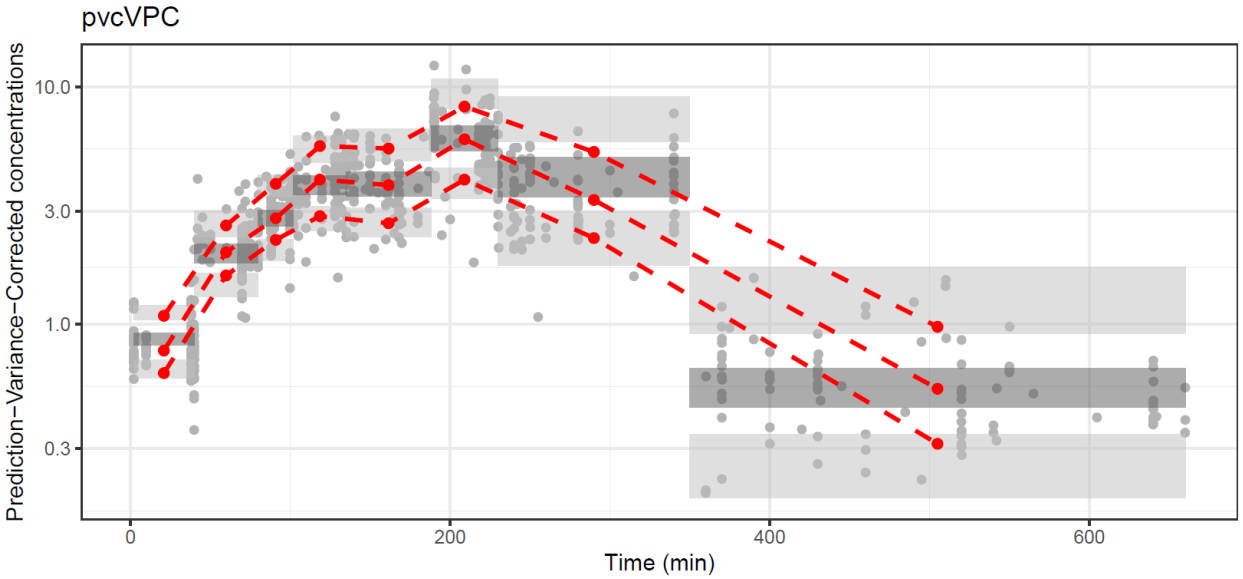


Figure S6. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the final model stratified for total body weight.

The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the final model.

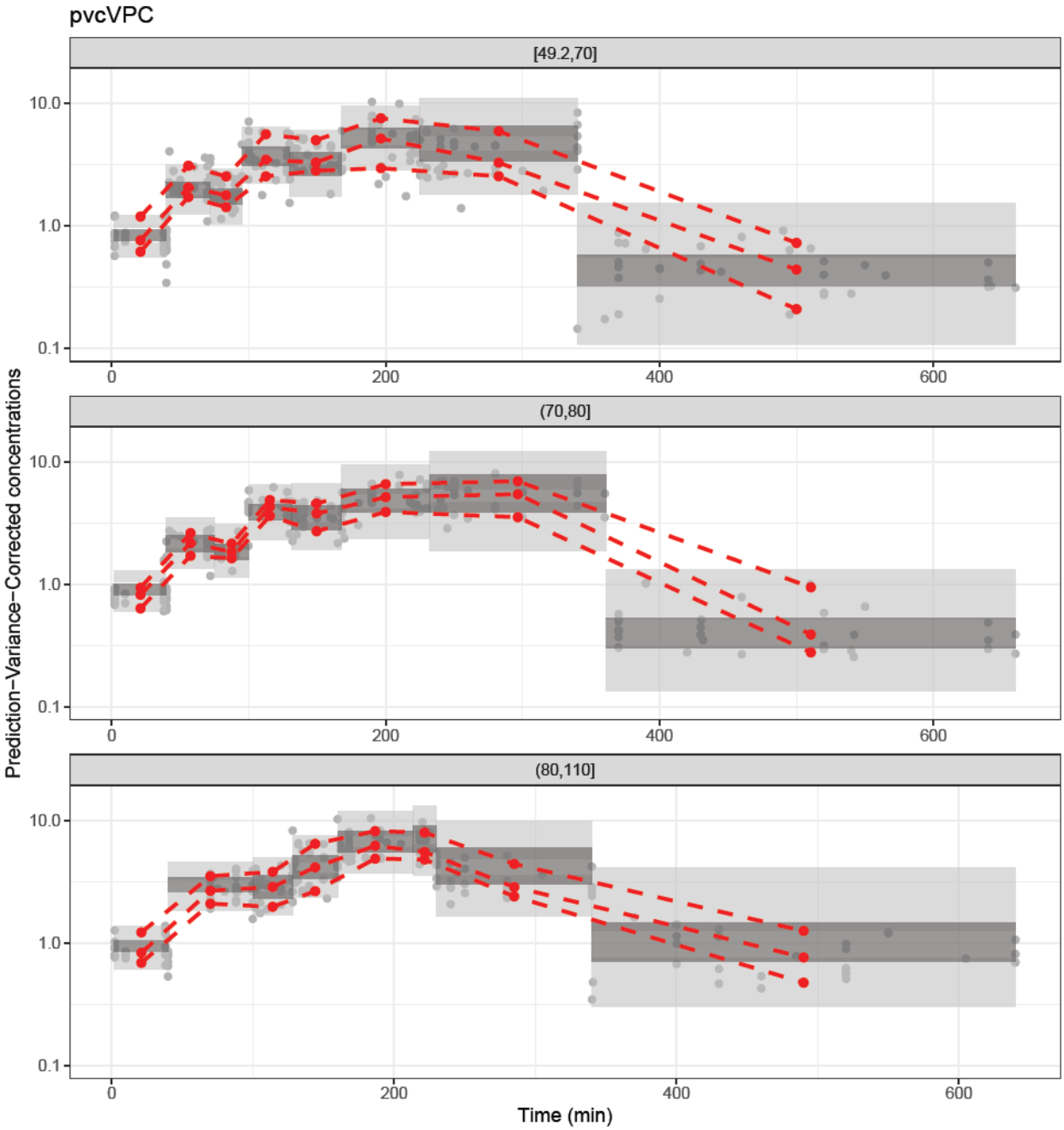


Figure S7. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the final model stratified for sex (1: males, 2: females).
The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the final model.

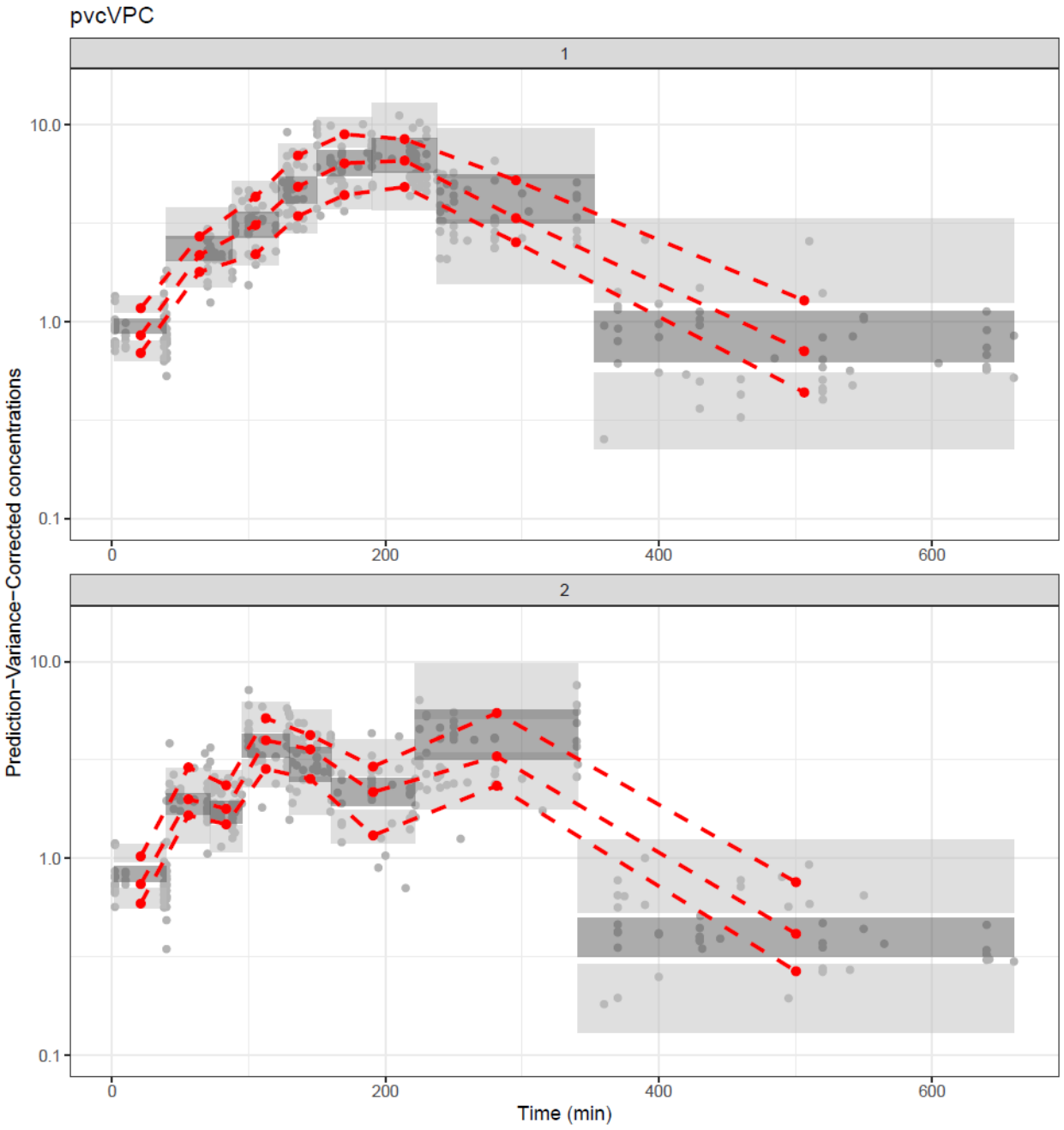


Figure S8. Prediction- variance-corrected Visual Predictive Check (pvcVPC) for the final model stratified for age.

The dashed red lines show the median and the 2.5% and 97.5% percentiles of the observed prediction-variance corrected concentrations. The shaded (dark) grey areas show the 95% prediction intervals for the final model.

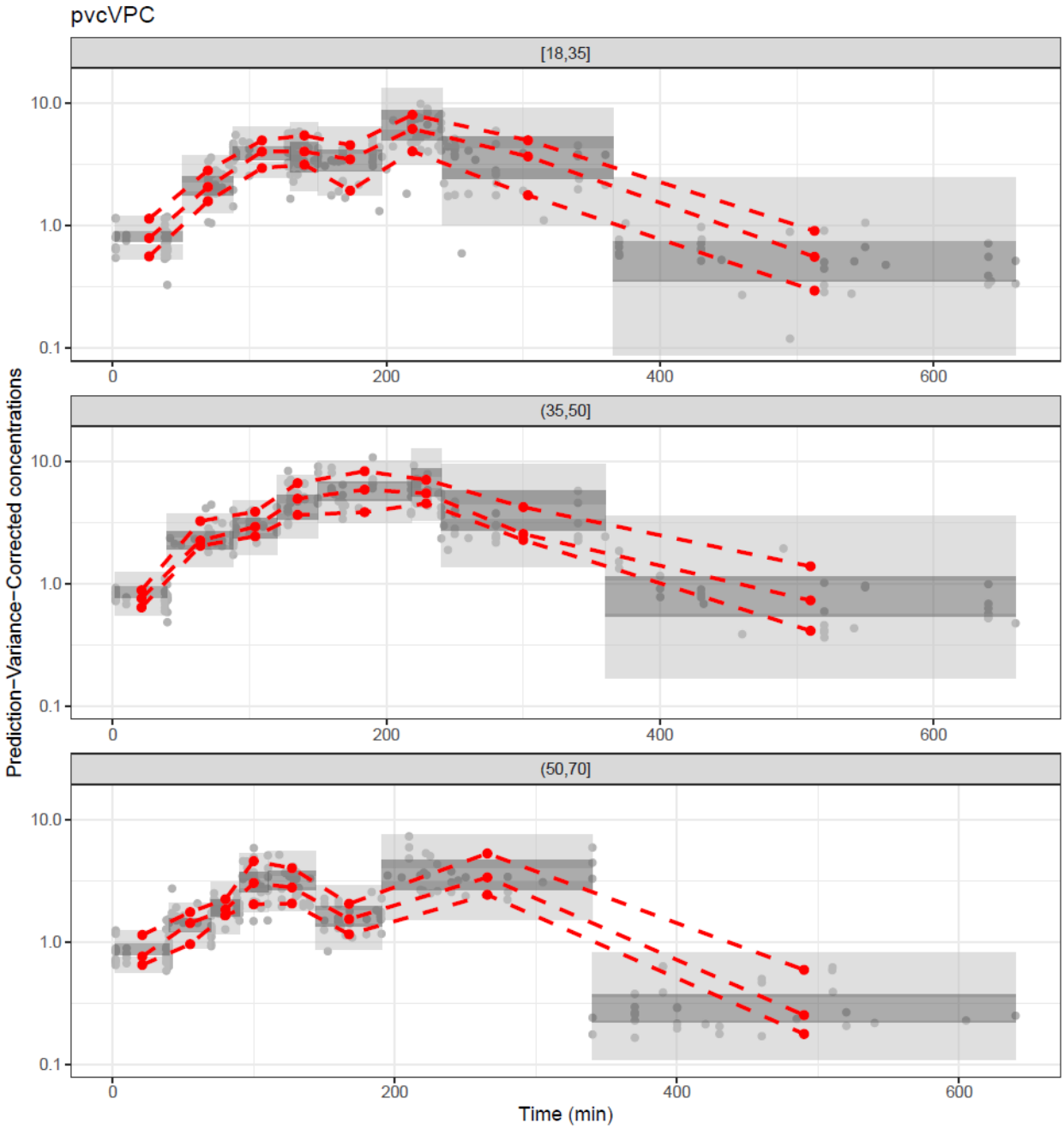


Figure S9. Influence of covariates in the final model.
Time vs. dexmedetomidine concentration at simulated increasing TCI targets comparing subjects with different characteristics. Simulations were performed using the linear model as driving model (blue), i. e.: the system searched the dose needed to reach the given target concentration (1 to 10 ng·mL^{-1}) as quickly as possible. Using this same dose, the system calculated what the theoretical real concentration would be using the non-linear parameters (gray). The shaded area surrounding the median prediction is the 95% prediction interval. 1000 randomly generated subjects were used for the simulations. The ratio between linear and nonlinear model is depicted in the lower panel per target concentration.