Figure S1

Distribution of patient covariates in the final dataset.

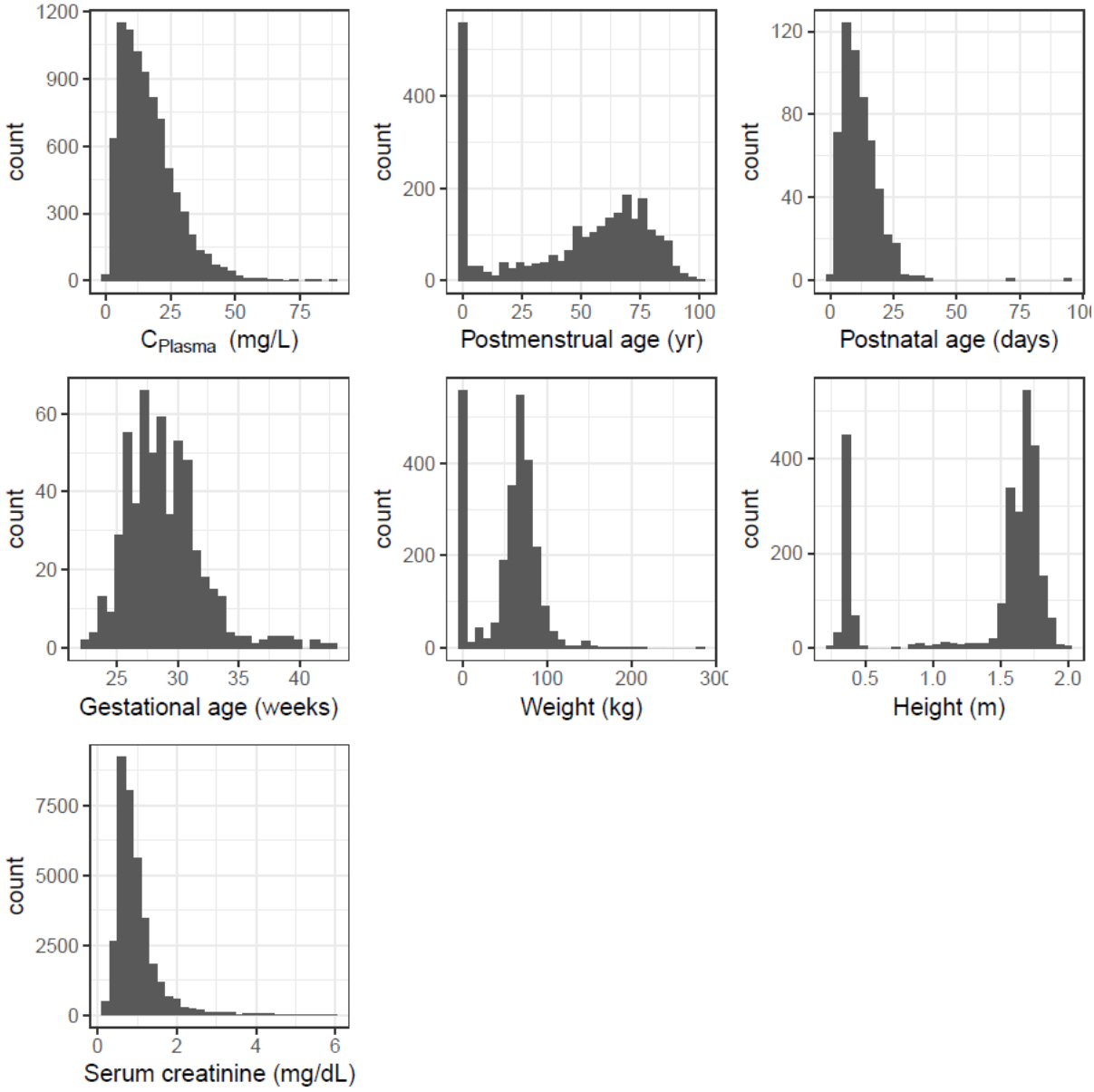


Figure S2

Scatterplot of SCR versus PMA for all patients in our dataset. The solid black line shows a non-parametric smooth of the data. The typical-for-PMA SCR_{std} according to equation 5 is shown with a dashed black line. A dotted black line shows the typical-for-PNA SCR_{std} according to Johansson et al.[36] for a male with a gestational age of 29 weeks (the median observed gestational age in our dataset).

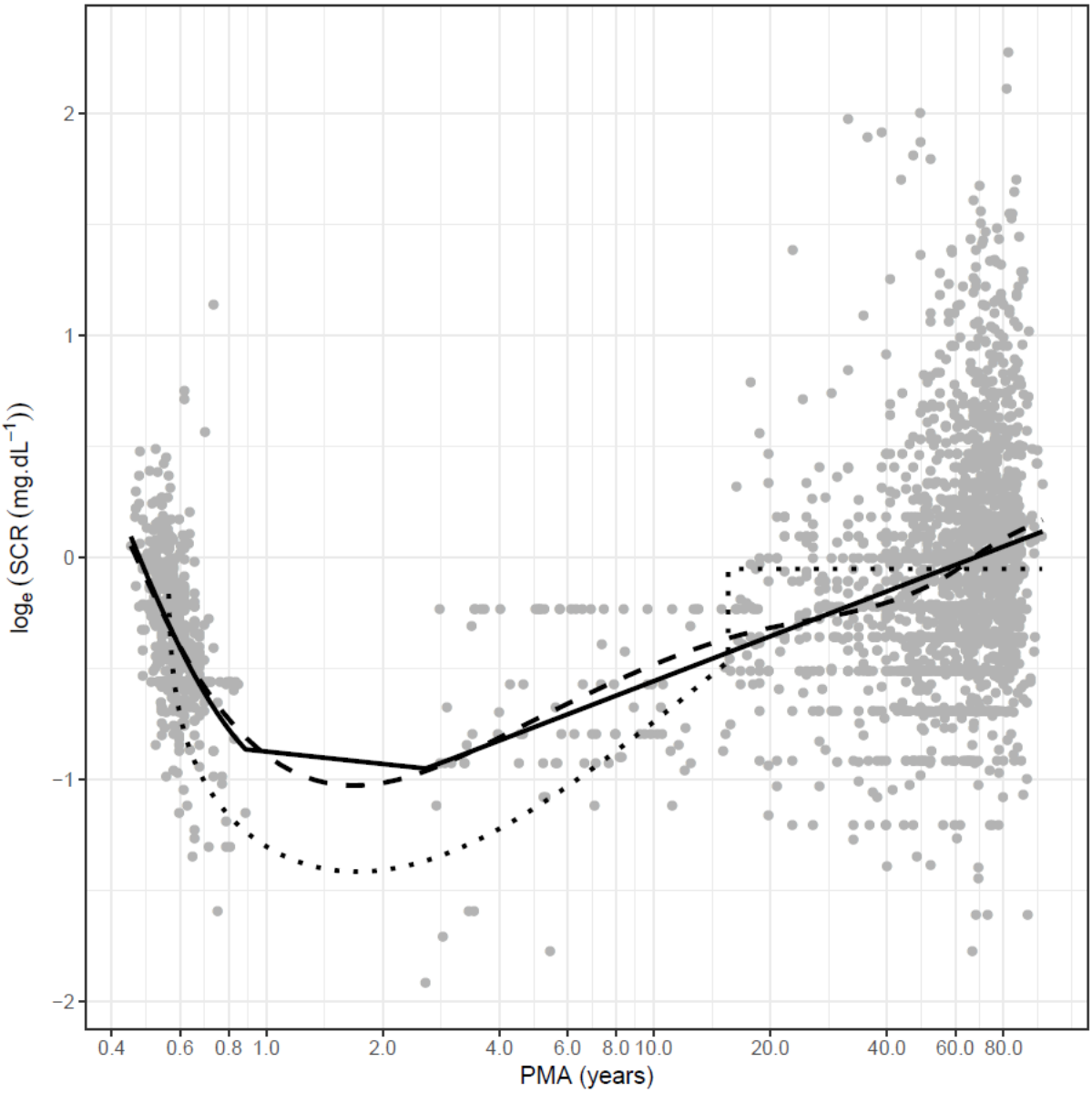
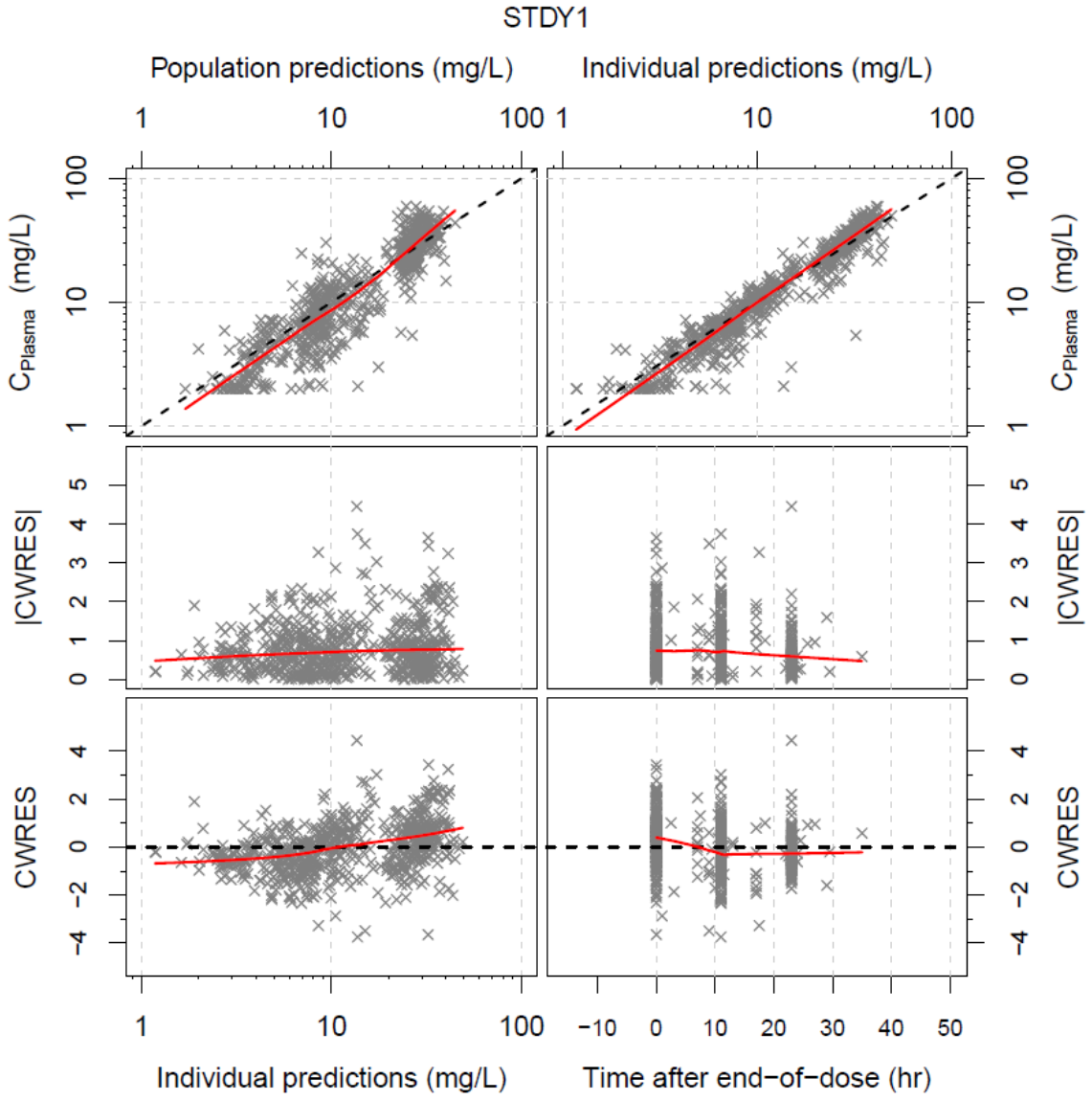
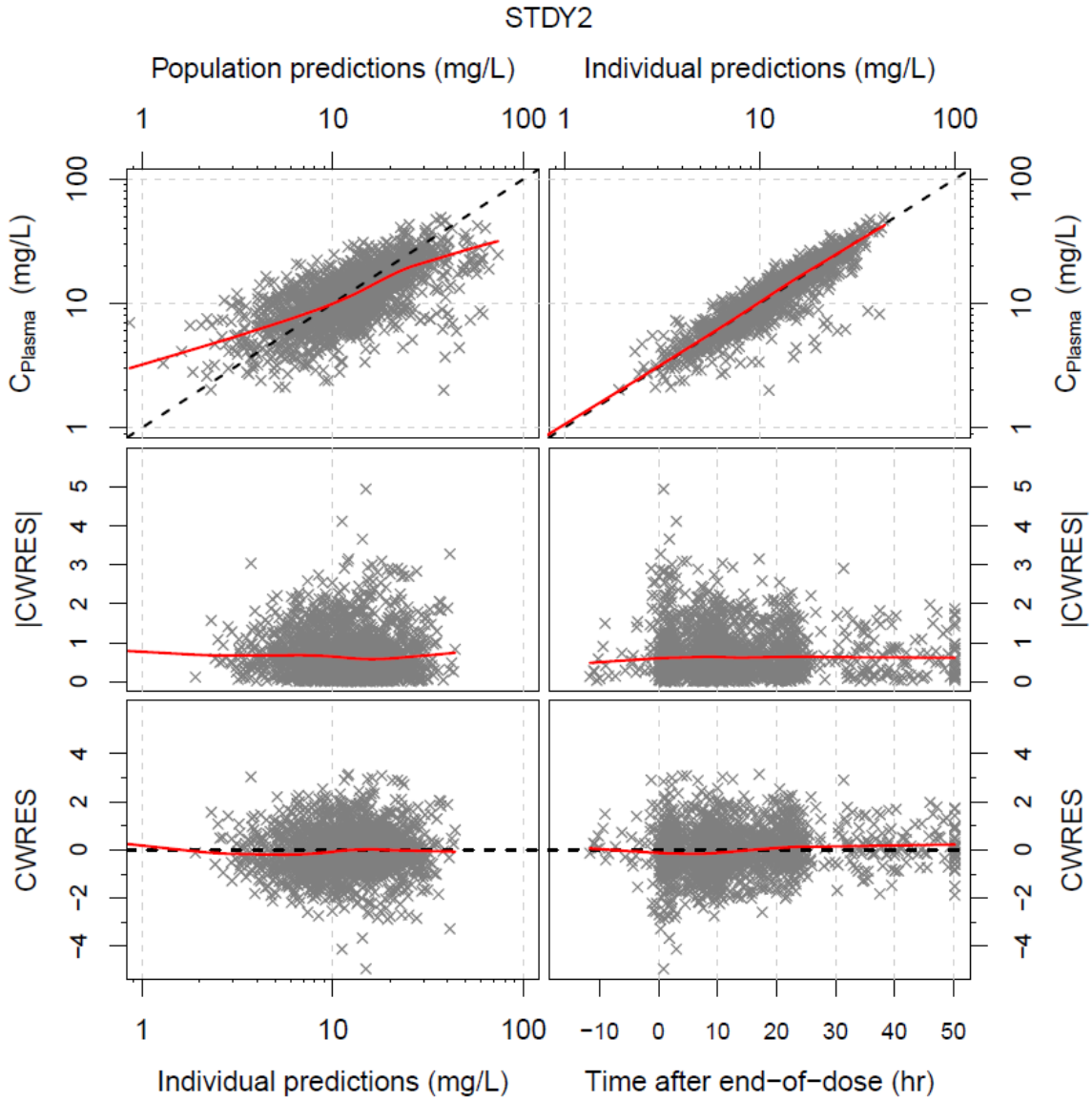
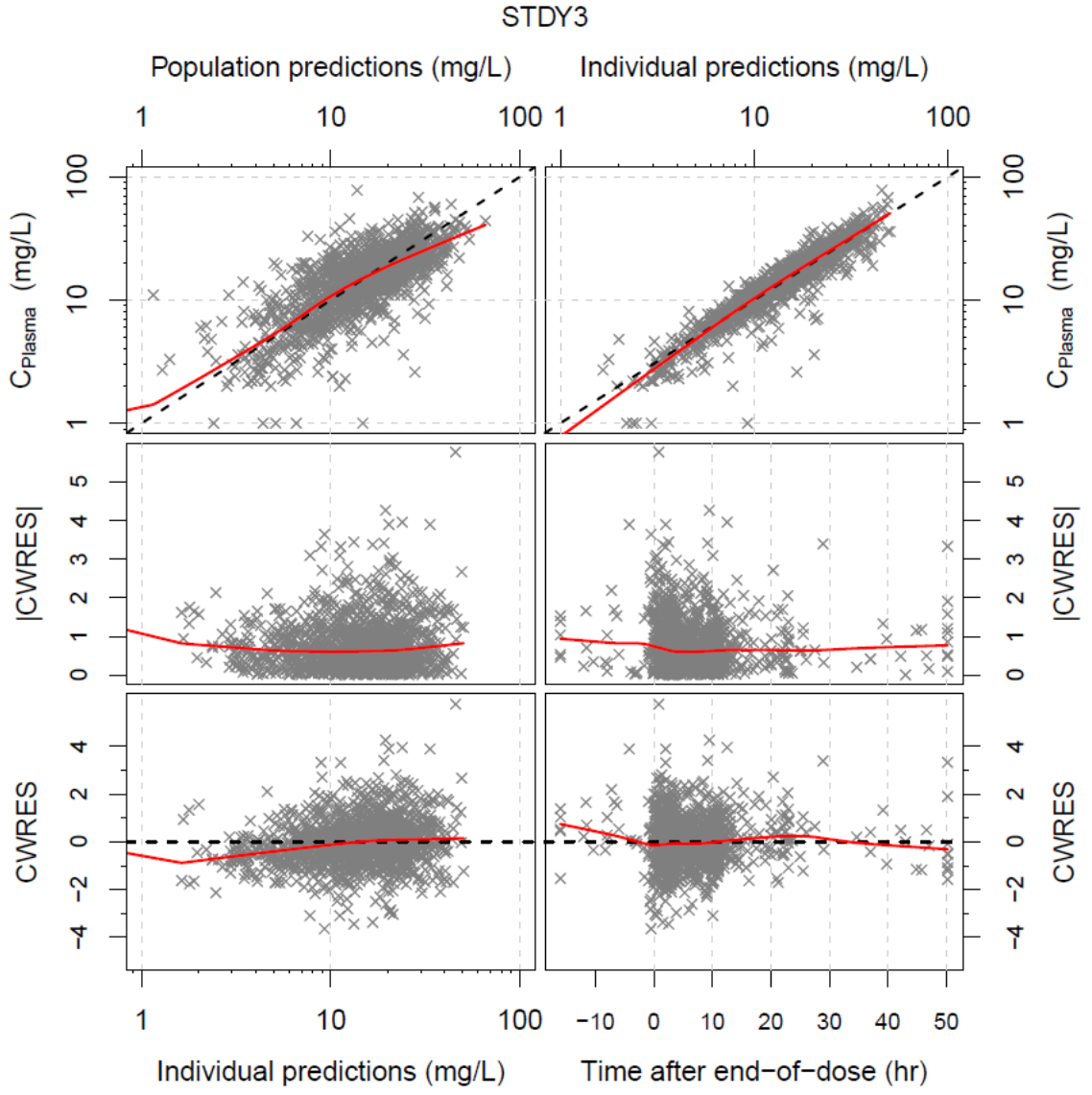


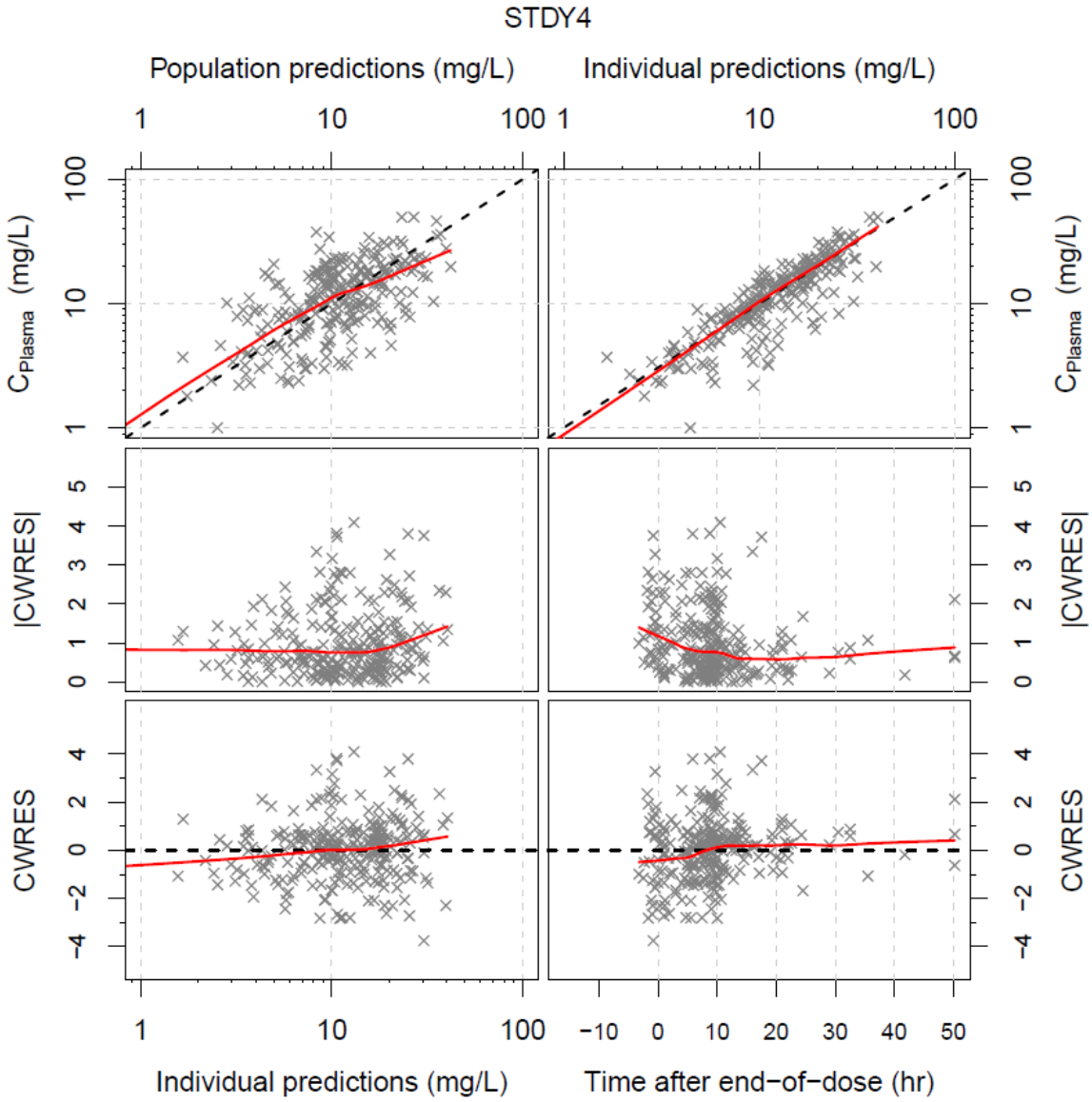
Figure S3

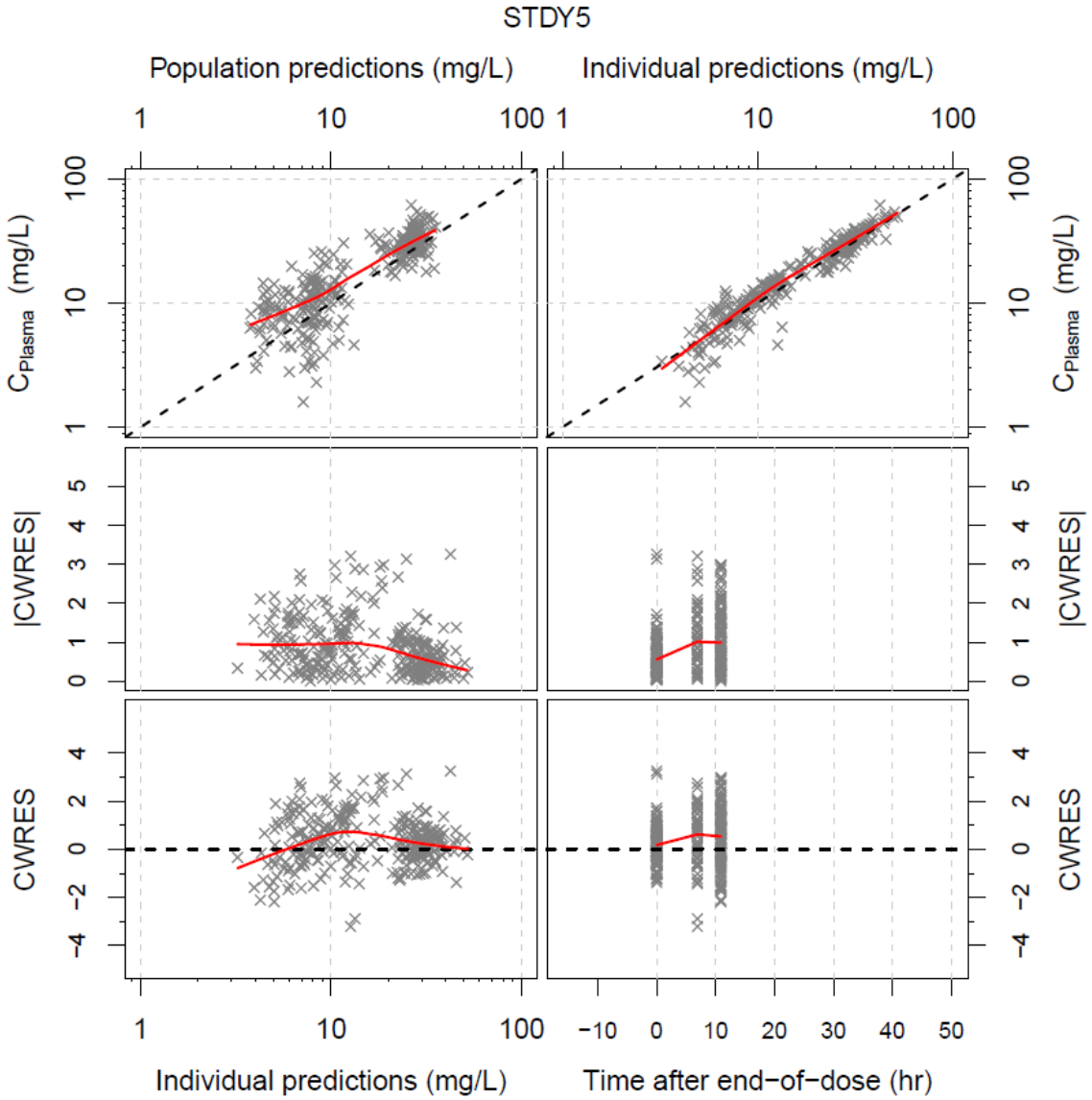
Goodness-of-fit plots stratified by study. Scatterplots show the distribution of (i) the observed vancomycin concentrations (Observed C_{plasma}) versus population and individual predictions and the (absolute) conditionally weighted residuals (|CWRES| and CWRES) versus individual predictions and time after the end-of-dose. Negative times denote observations taken when drug was infused, whereas positive times are observations after stopping the infusion. A dashed line denotes the line-of-unity or the zero line, whilst a red solid line shows a non-parametric smooth.

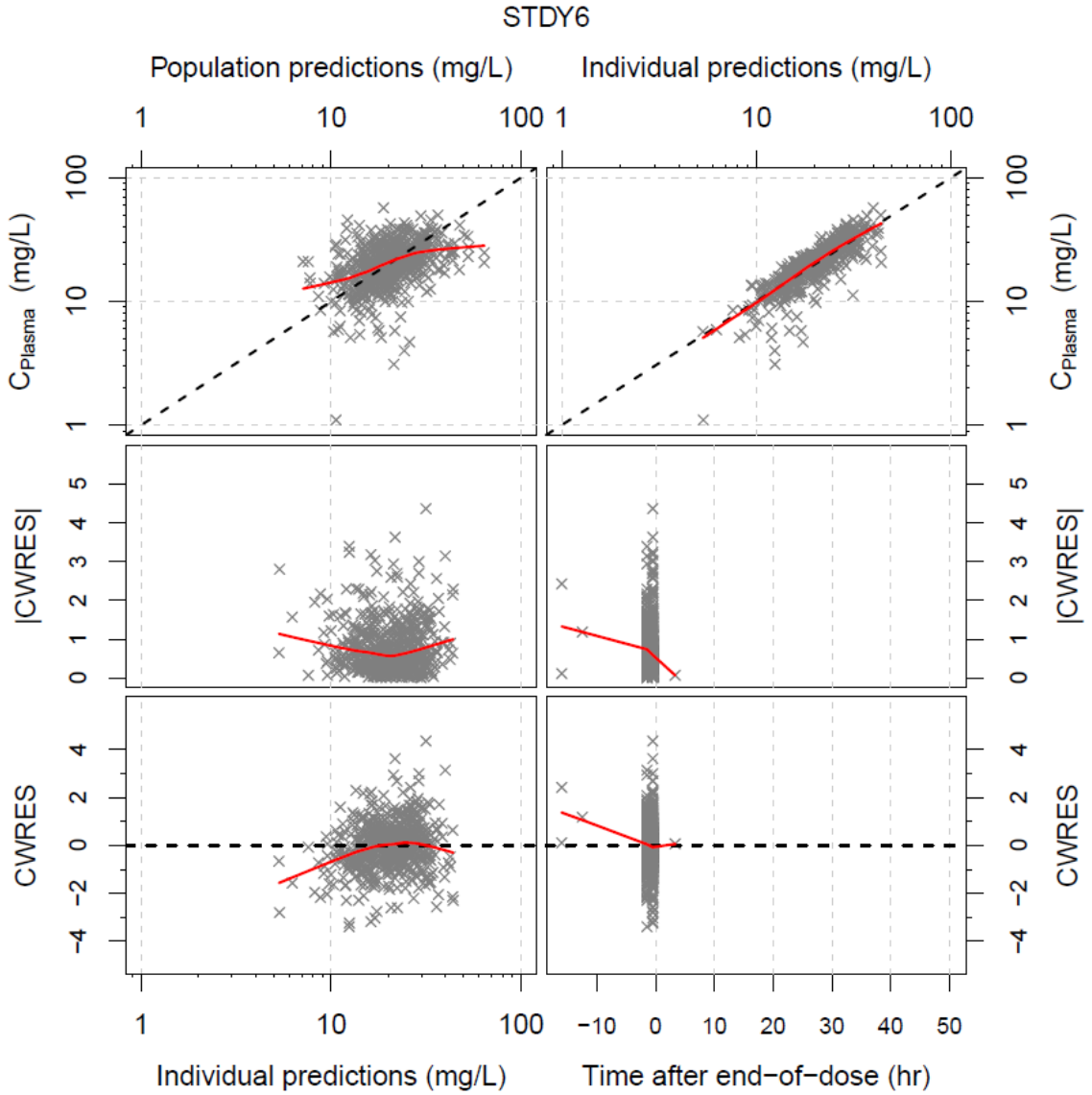


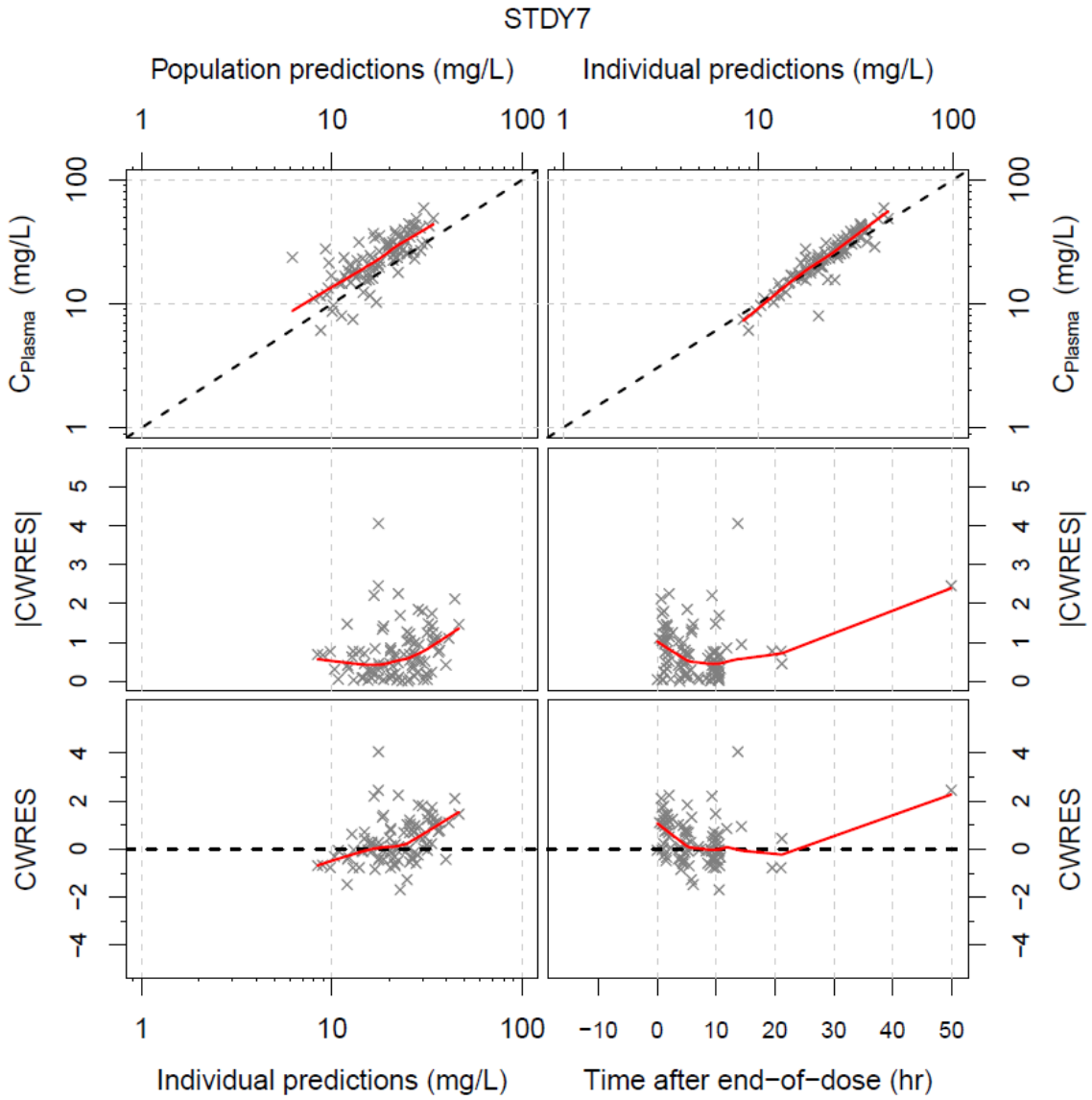

STDY2
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
−10
0
10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

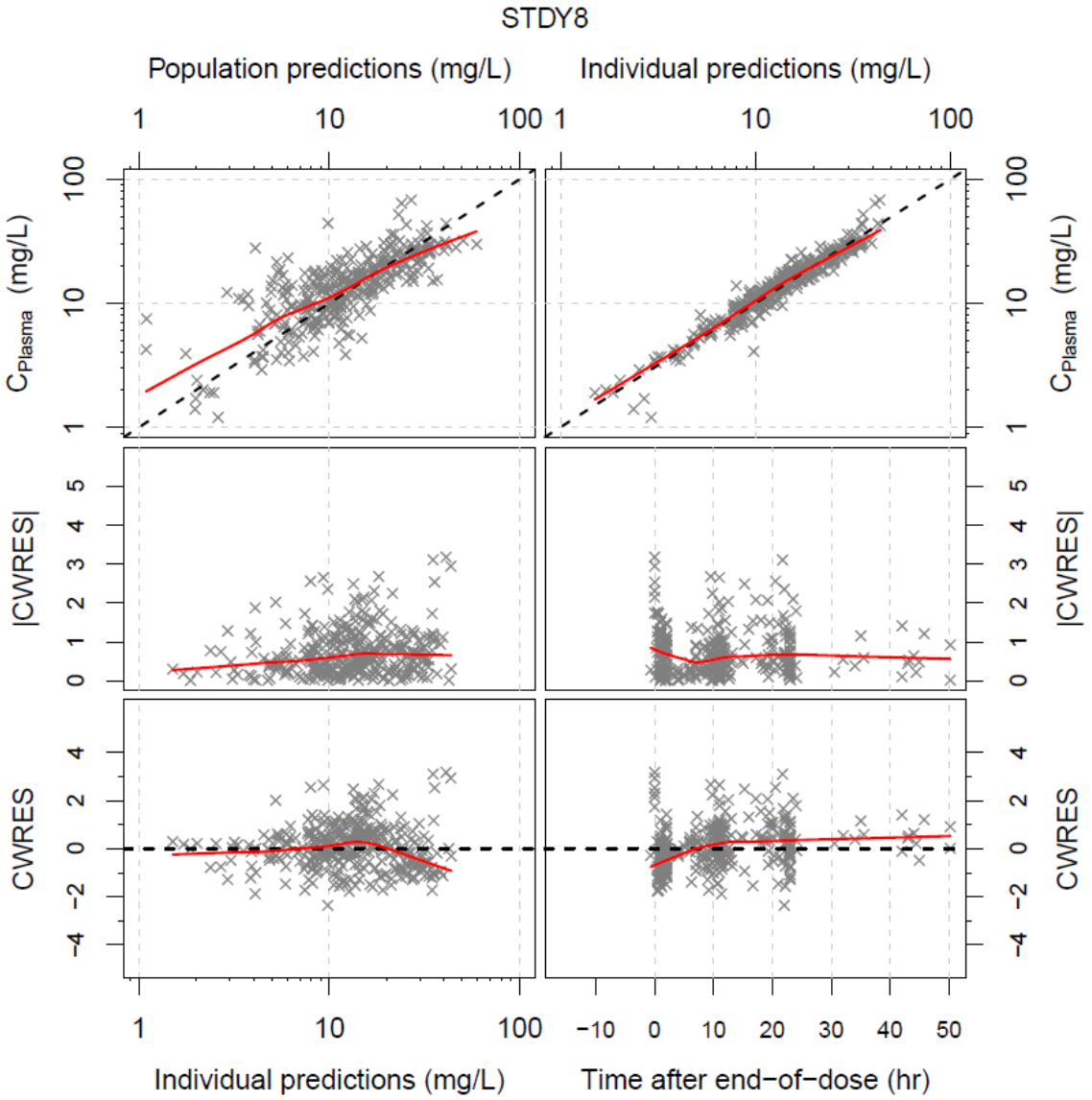

STDY3
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

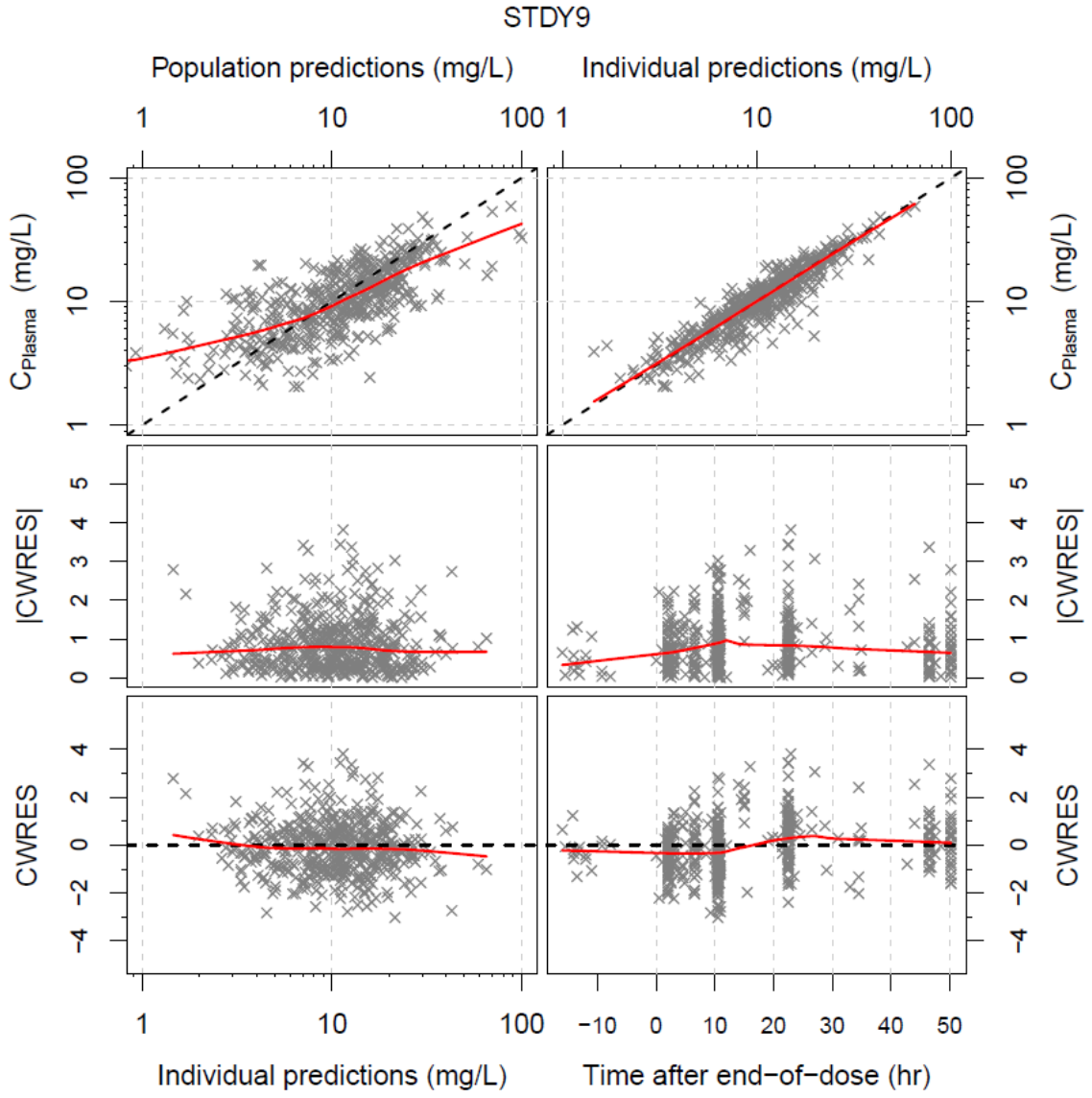

STDY4
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
−10
0
10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

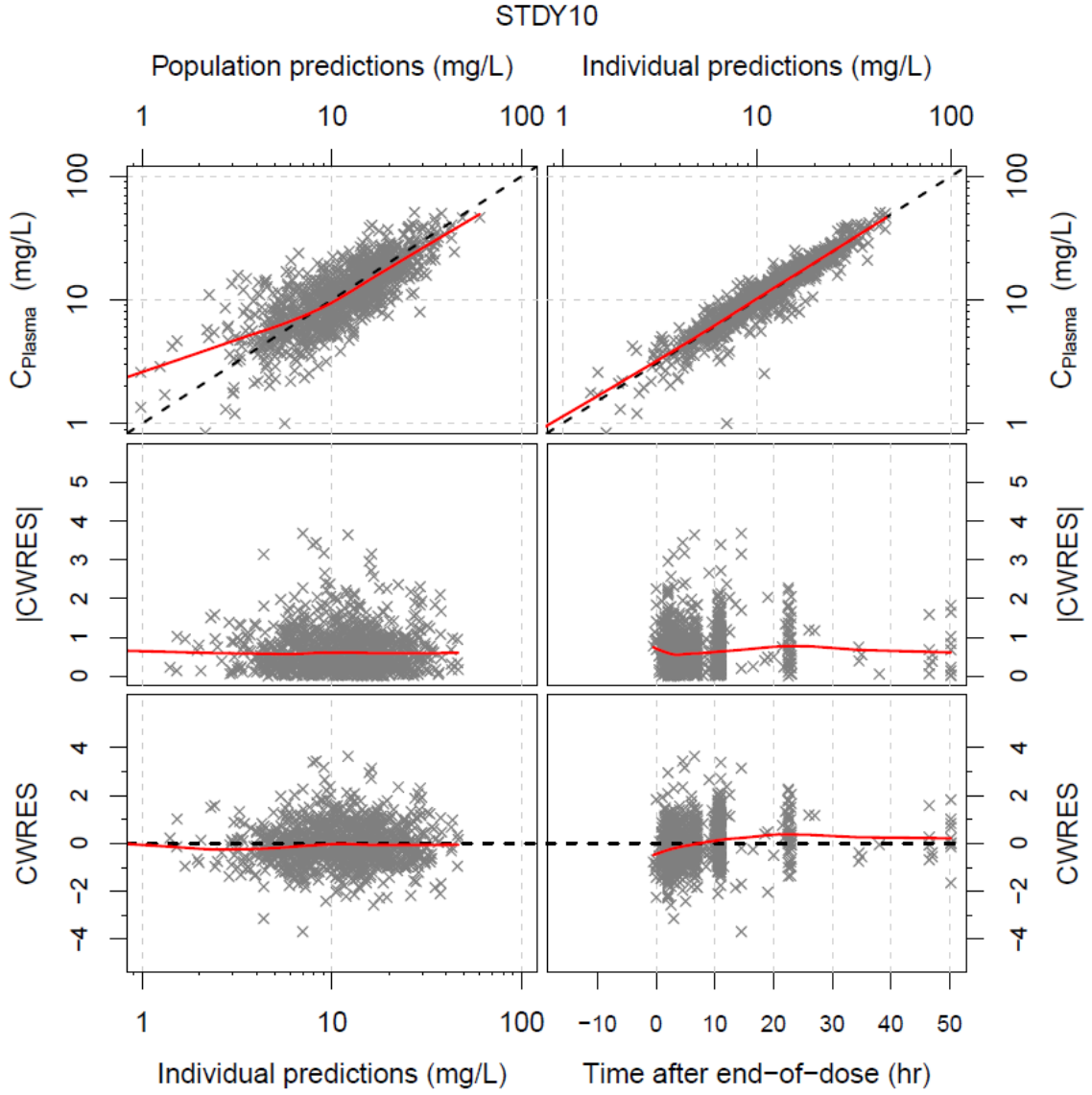

STDY5
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

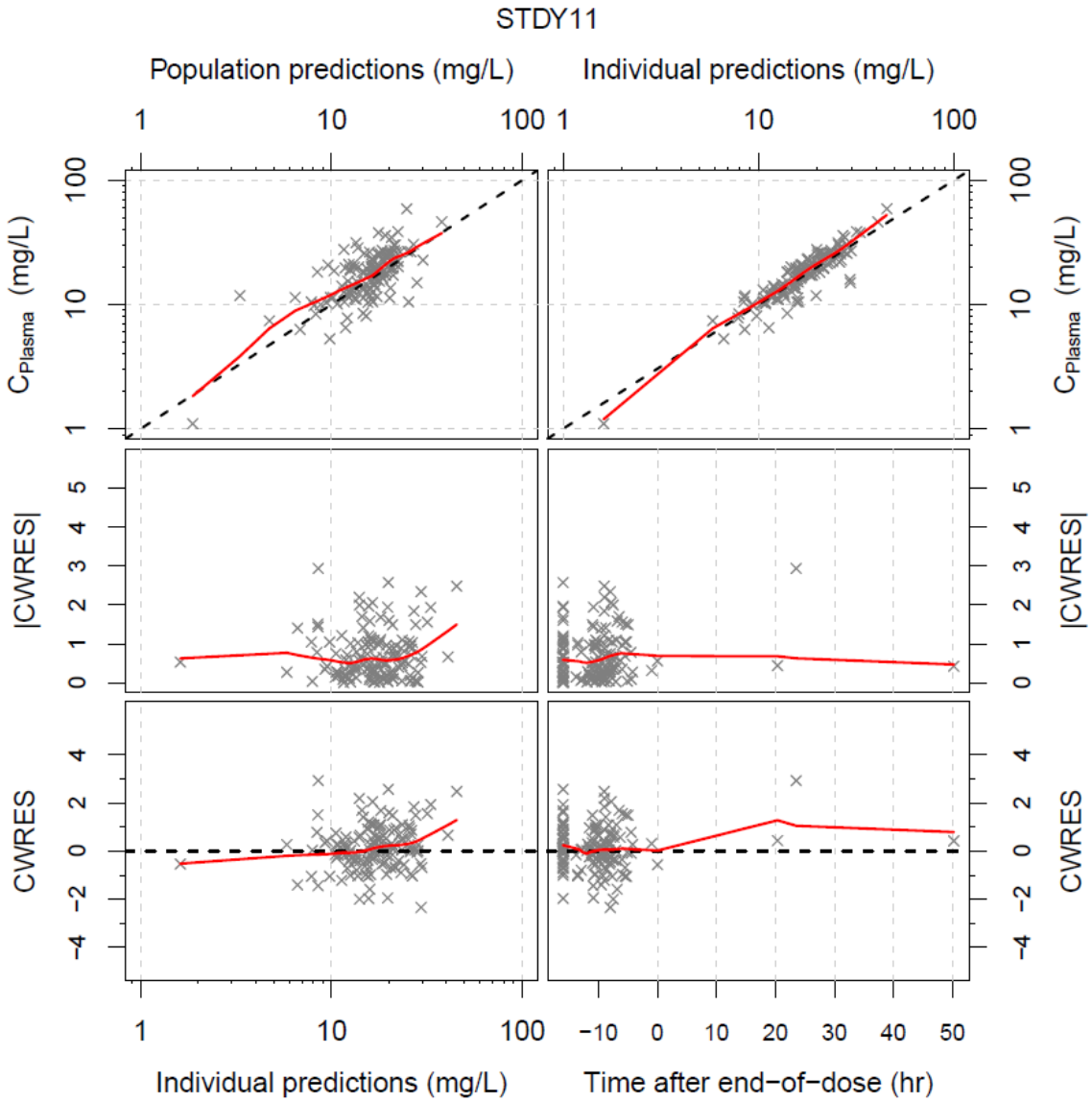

STDY6
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
−4
−2
0
2
4
0
1
2
3
4
5
−10
10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

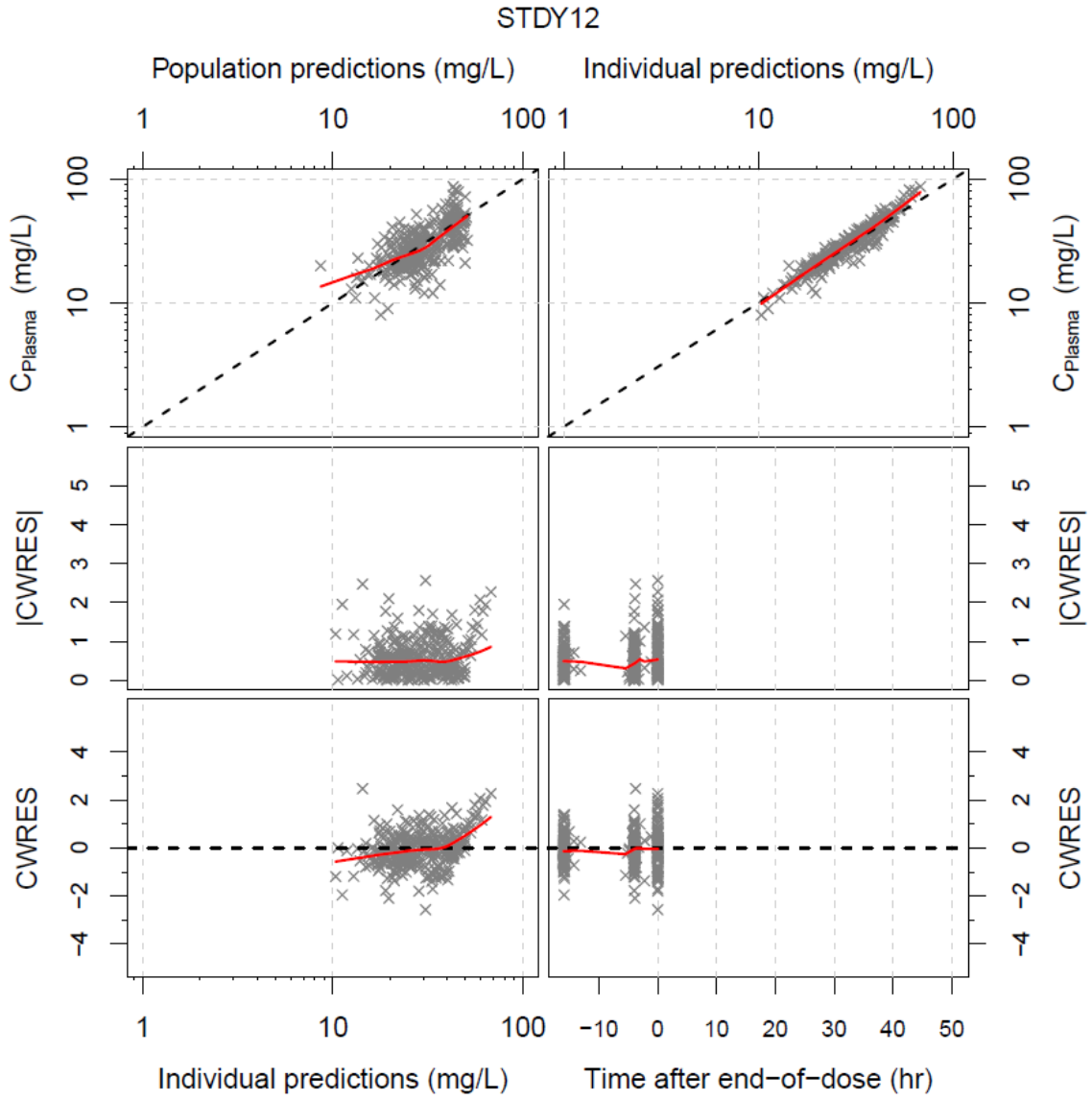

STDY7
Population predictions (mg/L)
Individual predictions (mg/L)
C_{Plasma} (mg/L)
|CWRES|
CWRES
Individual predictions (mg/L)
Time after end−of−dose (hr)

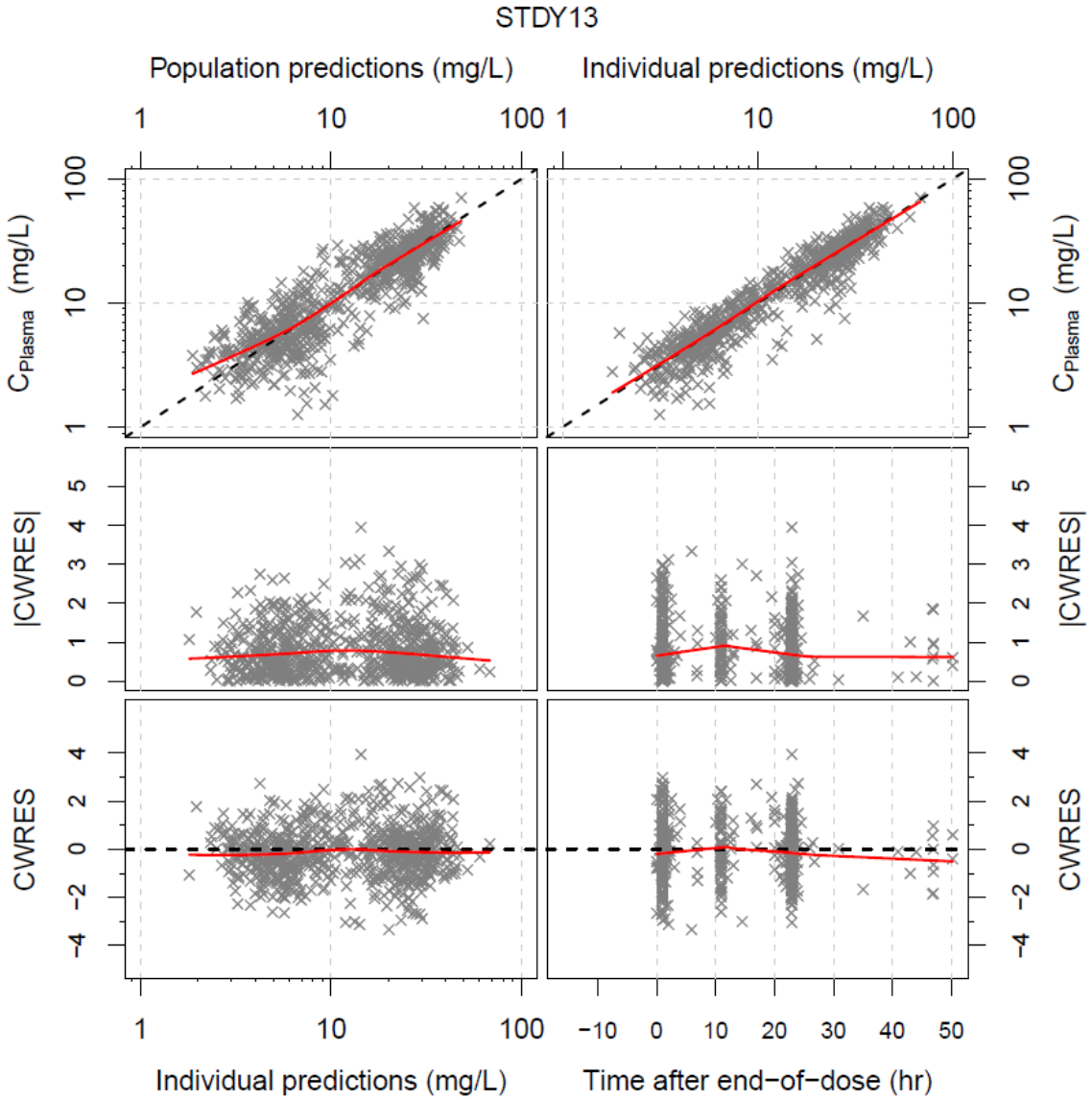

STDY8
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
−10
0
10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)


STDY9
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)


STDY10
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)


STDY11
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
−10
0
10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)


STDY12
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)


STDY13
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

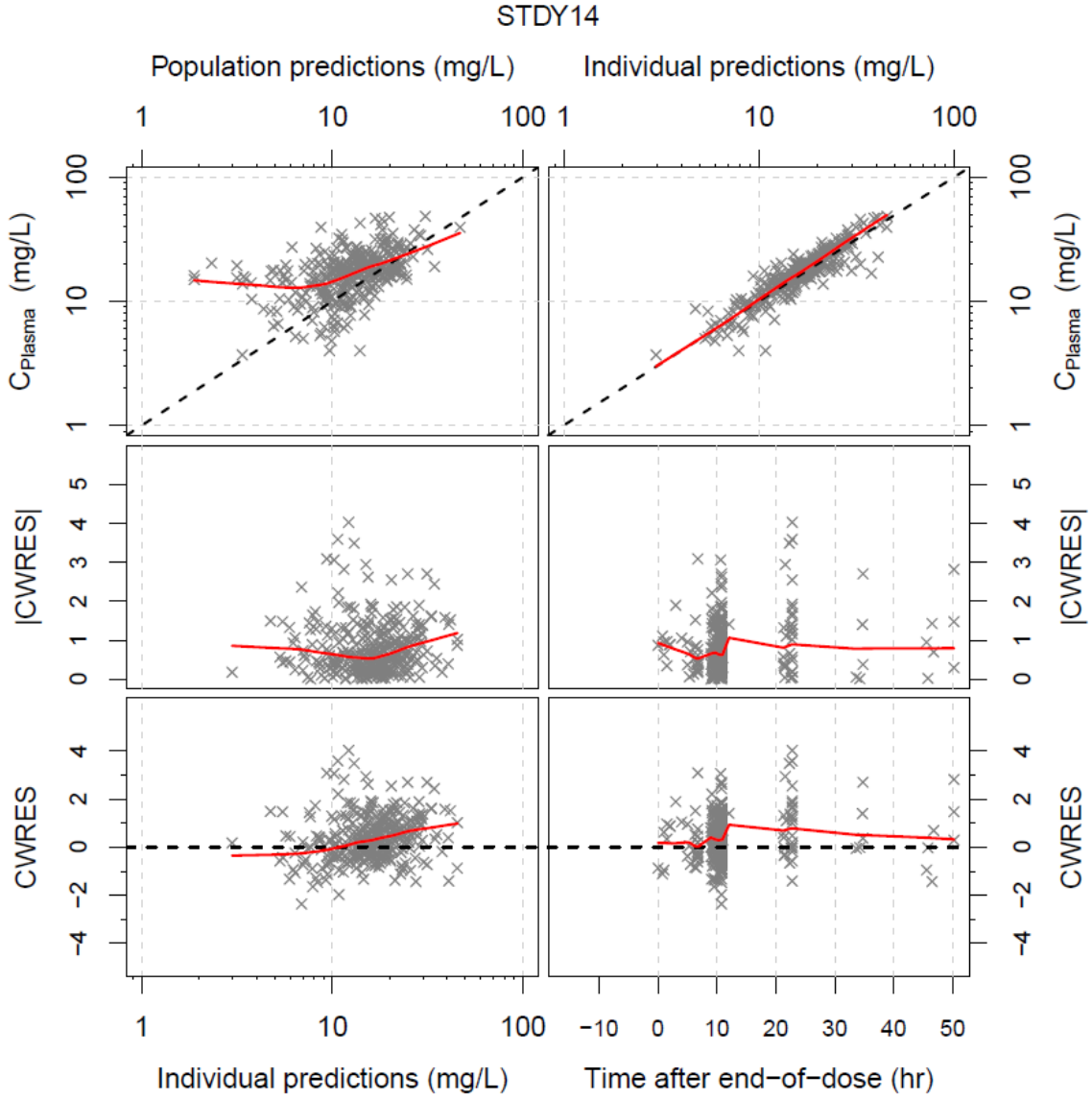

STDY14
Population predictions (mg/L)
Individual predictions (mg/L)
1
10
100
C_{Plasma} (mg/L)
|CWRES|
CWRES
0
1
2
3
4
5
−4
−2
−10
20
30
40
50
Individual predictions (mg/L)
Time after end−of−dose (hr)

Figure S4

Prediction-variance-corrected visual predictive check (pvcVPC) for the final model against time-after-end-of-last-dose (Time). Red dashed lines represent the 10th, 50th and 90th percentiles of the prediction-variance-corrected observed vancomycin concentrations (denoted by grey open circles). The grey shaded rectangles denote the 95% confidence intervals for the simulated 10th, 50th and 90th percentiles of the prediction-variance-corrected predicted vancomycin concentrations.

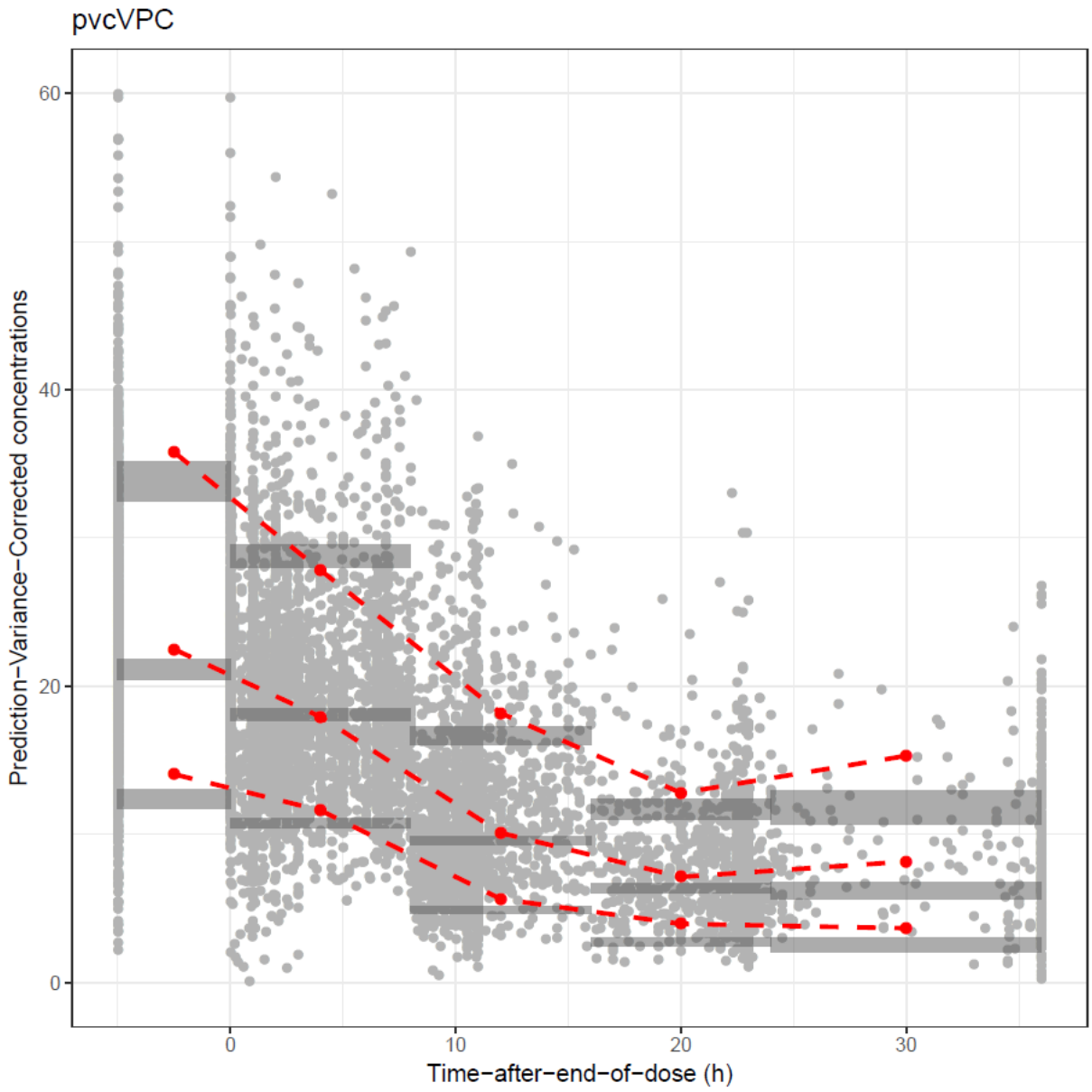
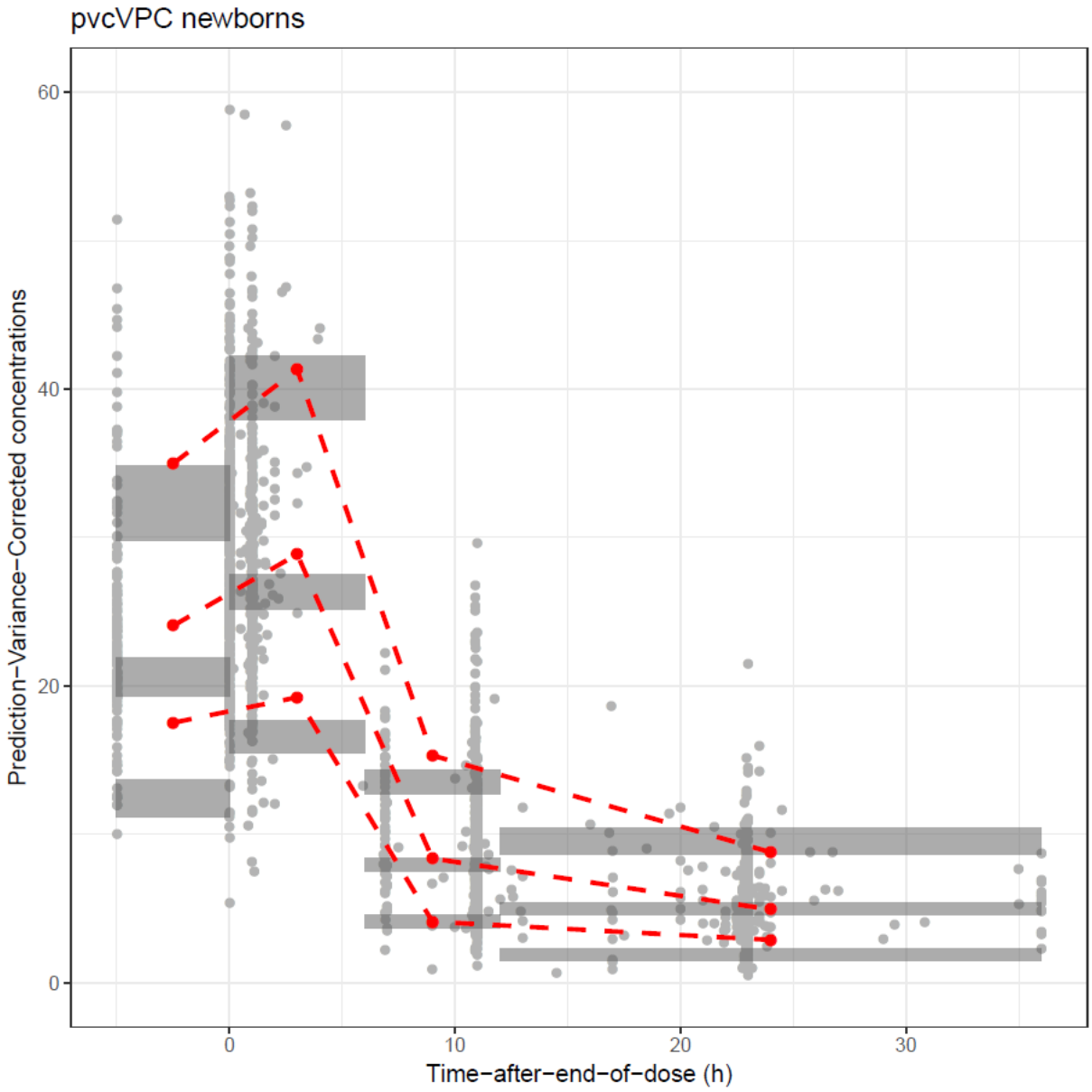
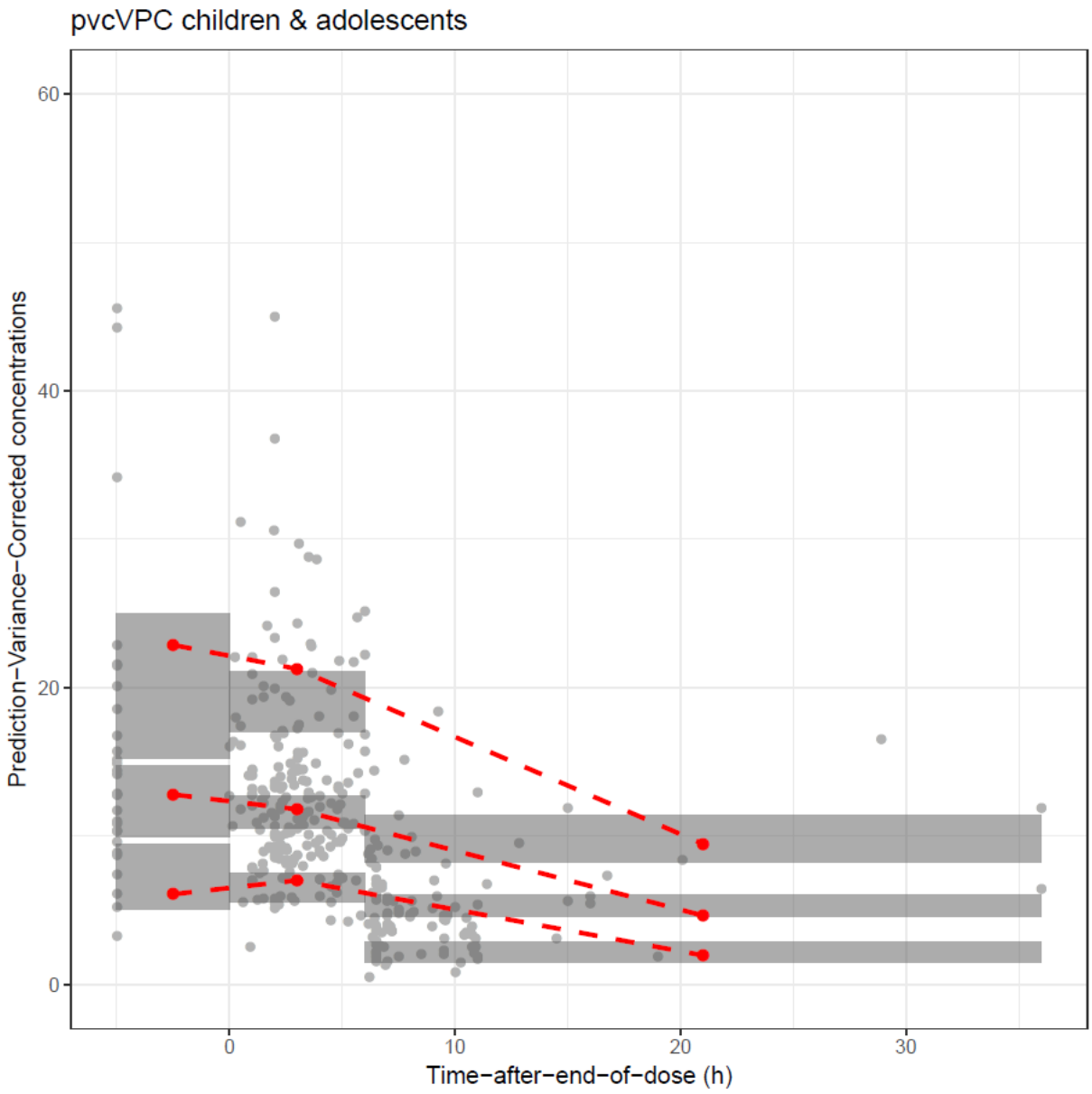
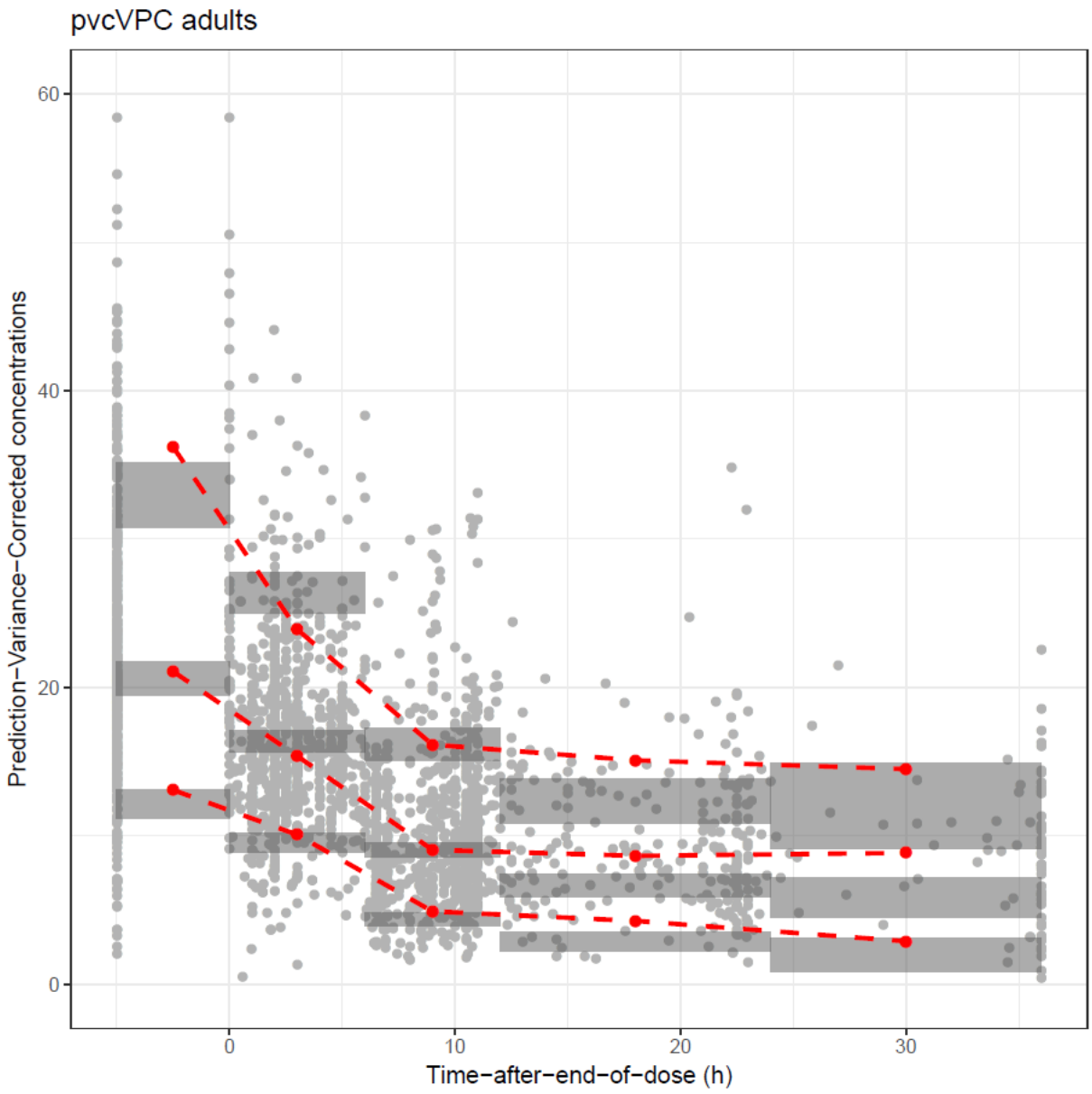


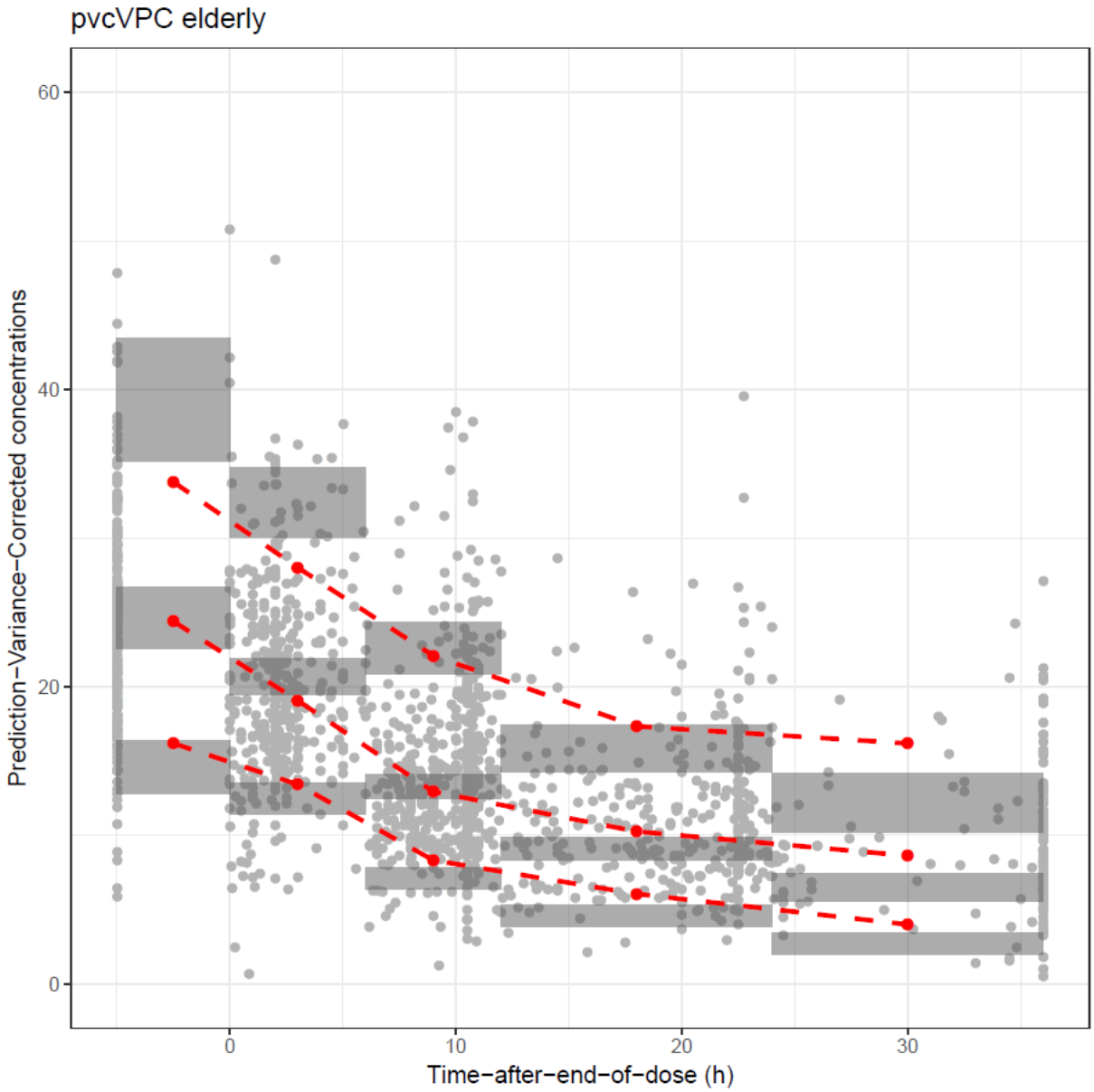
Figure S5

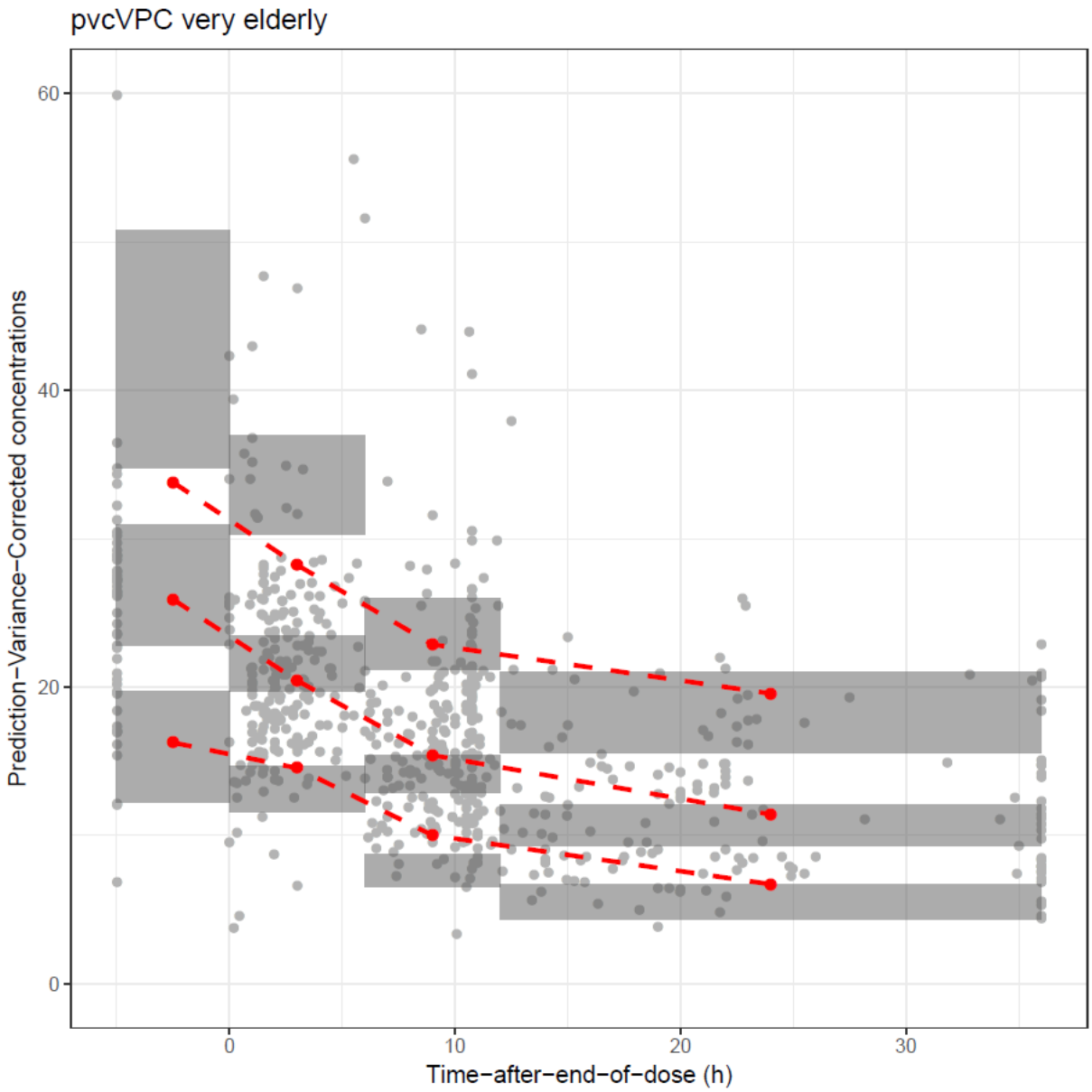
Prediction-variance-corrected visual predictive check (pvcVPC) stratified by patient category. Red dashed lines represent the 10th, 50th and 90th percentiles of the prediction-variance-corrected observed vancomycin concentrations (denoted by grey open circles). The grey shaded rectangles denote the 95% confidence intervals for the simulated 10th, 50th and 90th percentiles of the prediction-variance-corrected predicted vancomycin concentrations.

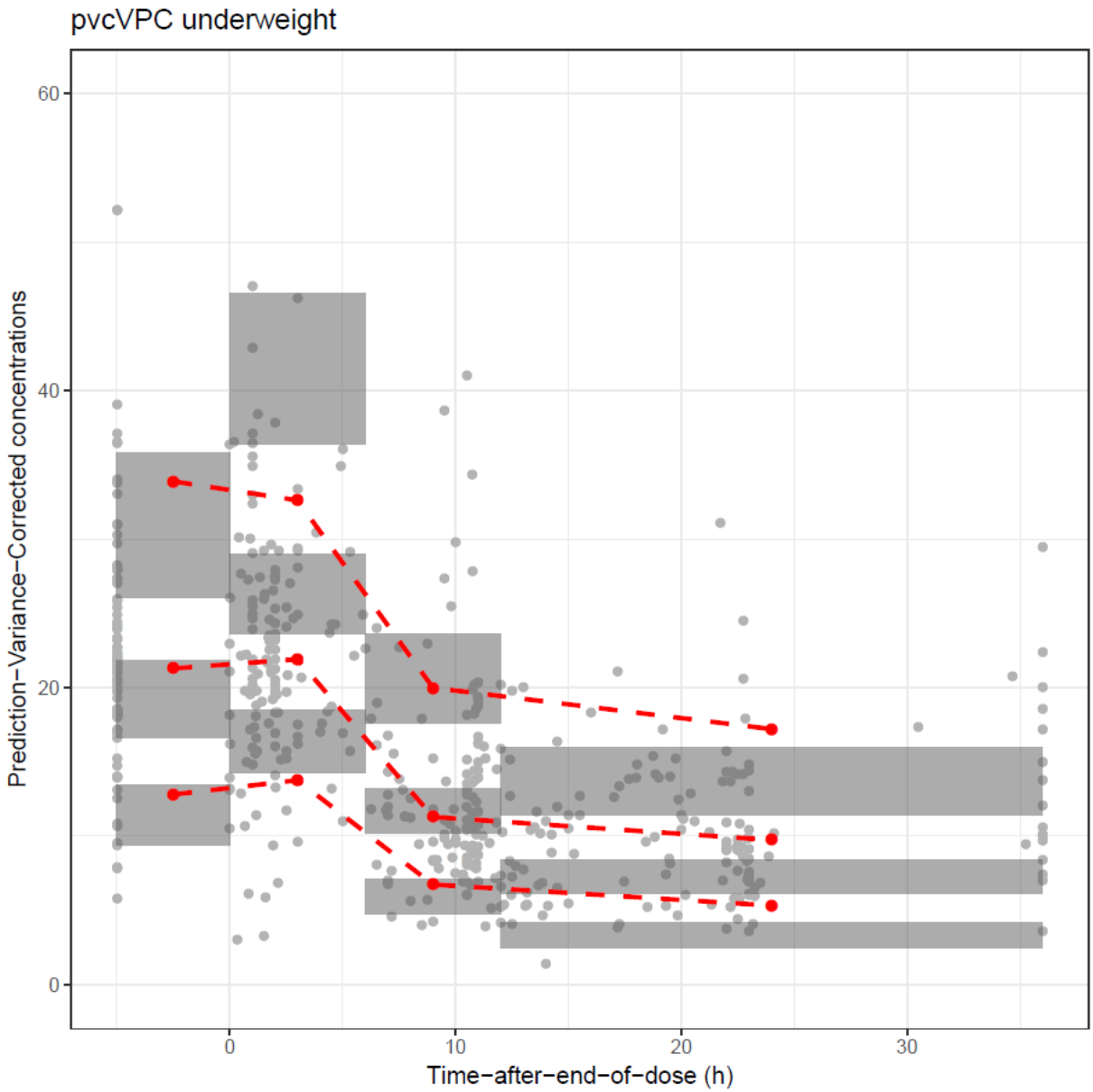



pvcVPC children & adolescents
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)


pvcVPC adults
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)


pvcVPC elderly
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)


pvcVPC very elderly
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)


pvcVPC underweight
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)

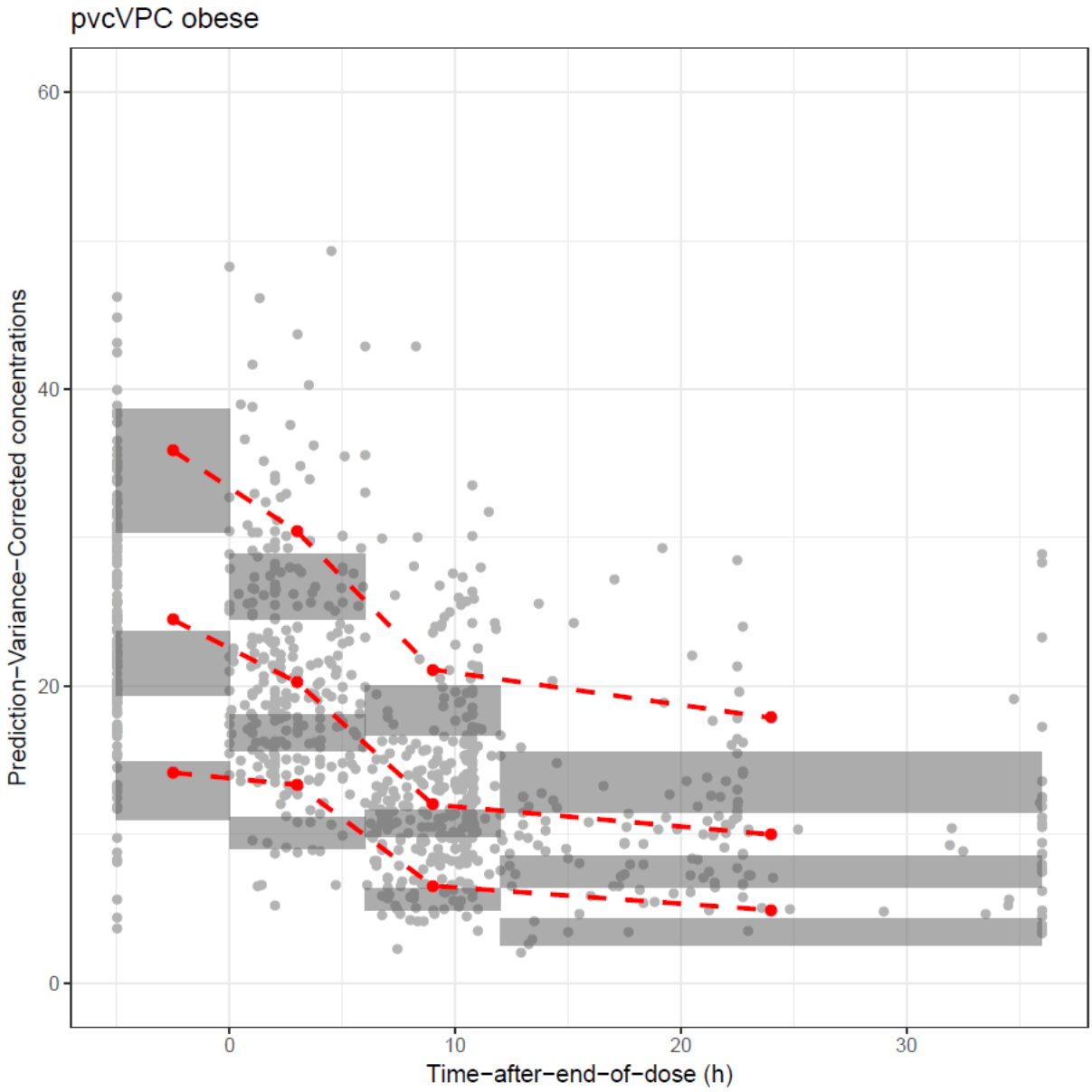

pvcVPC obese
Prediction−Variance−Corrected concentrations
60
40
20
0
0
10
20
30
Time−after−end−of−dose (h)

Figure S6

Scatterplots of the inter-individual variability in CL (ETA1), V1 (ETA2) and V2 (ETA3) for the final model for patients with (BURN 1) and without burn injuries (BURN 0).

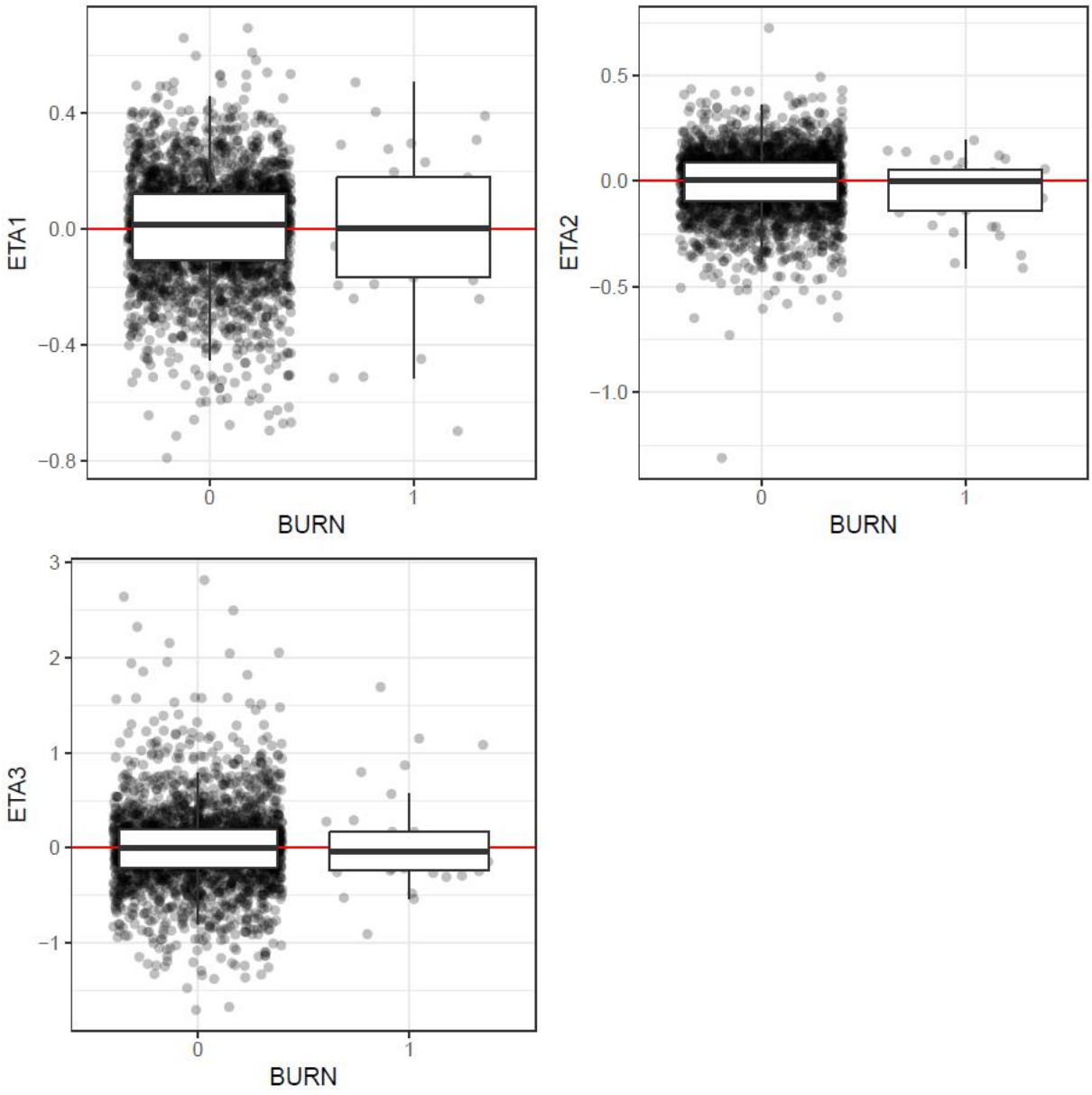


Figure S7

Scatterplots of the inter-individual variability in CL (ETA1), V1 (ETA2) and V2 (ETA3) for the final model for critically ill patients (CRIT 1) and non-critically ill patients (CRIT 0). For this figure patients from the studies by Roberts and co-workers, Revilla and co-workers and Cristallini and co-workers were considered critically ill, whereas all other patients were considered to be non-critically ill.

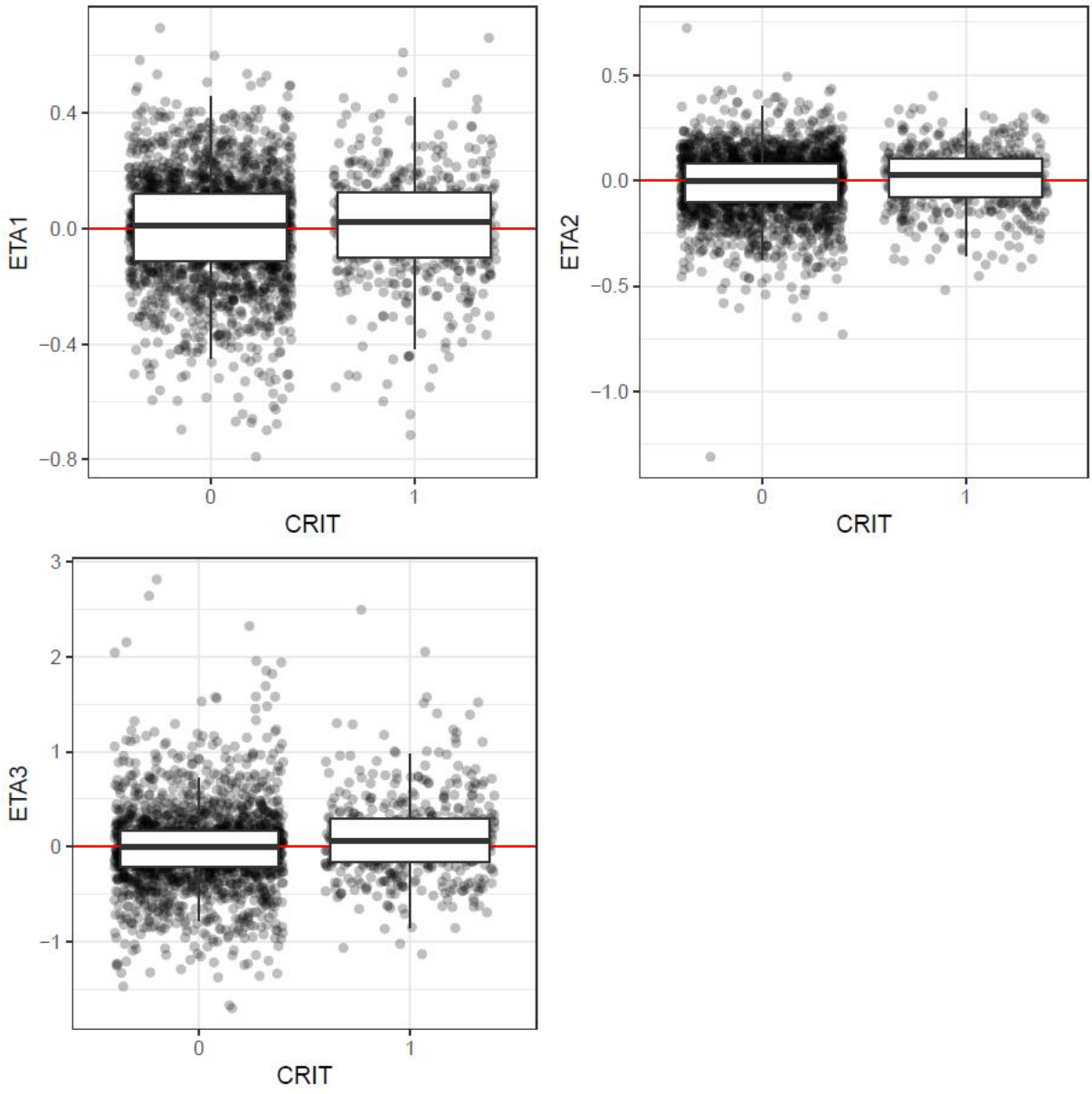


Figure S8

Scatterplots of the inter-individual variability in CL (ETA1), V1 (ETA2) and V2 (ETA3) for the final model for patients treated with continuous infusion (CONT 1) and intermittent dosing (CONT 0).

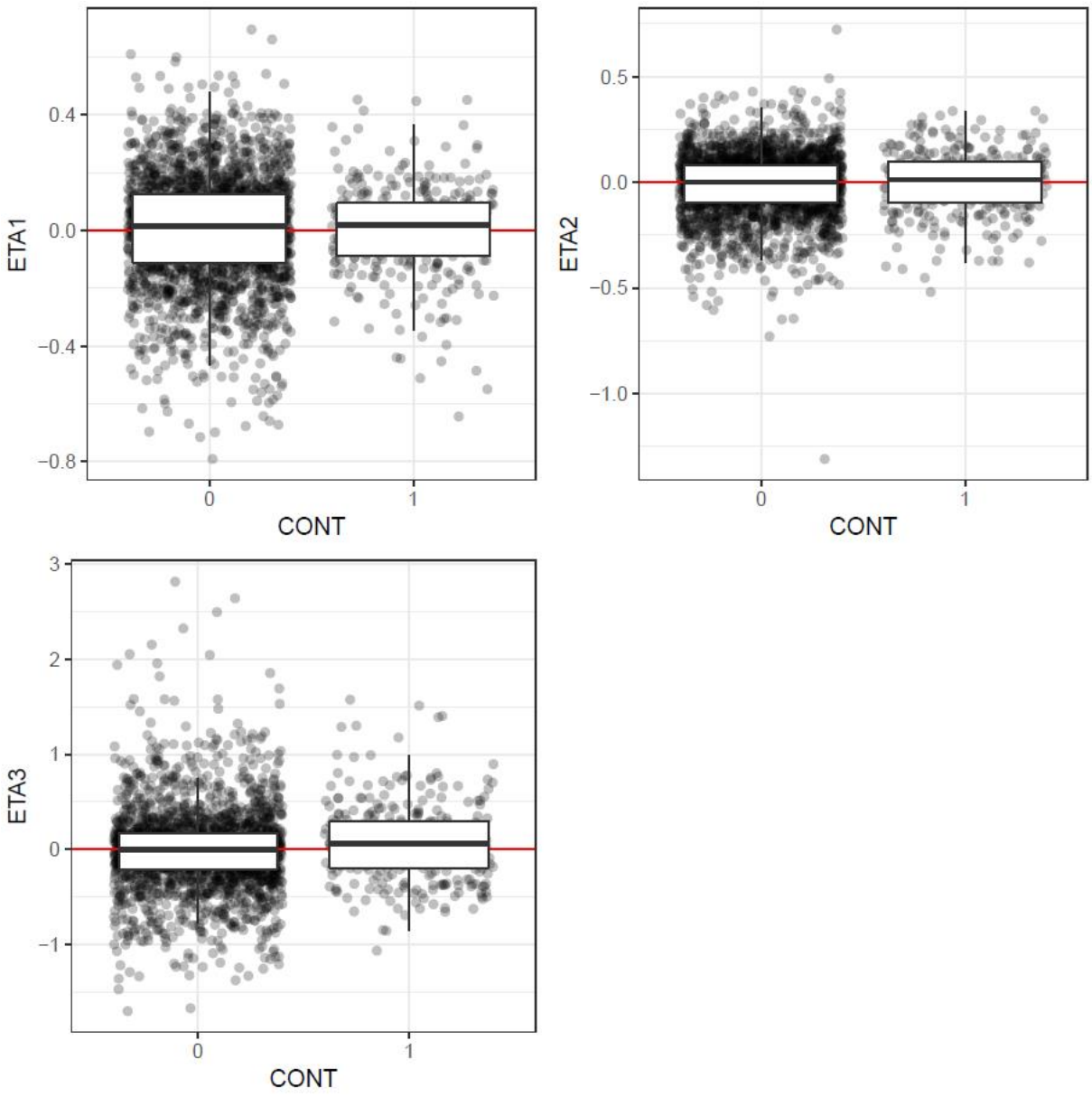


Figure S9

Scatterplots of the inter-individual variability in CL (ETA1), V1 (ETA2) and V2 (ETA3) for the final model for studies where vancomycin was measured using a turbidimetric-inhibition-based assay (PETINIA) and a fluorescence-polarization-based assay (FPIA).