Supplementary file belonging to the manuscript entitled:

**The effect of neutropenia on the clinical pharmacokinetics of vancomycin in adults**

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**Modelling Results**

The rate constants describing the pharmacokinetics of vancomycin in the final model were parameterized with the following equations:

$k_{10}=CL/V_1$

$k_{12}=Q/V_1$

$k_{21}=Q/V_2$

In these equations, CL is the clearance of vancomycin from the central compartment, Q is the inter-compartmental clearance describing transport between the central and peripheral compartment. $V_1$ and $V_2$ describe the volumes of distribution of the central and peripheral compartment, respectively.

Clearance was related to creatinine clearance and neutropenia as follows:

$CL=\theta_1+(1+\theta_2\times(CL_{CR}-104))\times\theta_3^{NEUTROPENIA}$

where $\theta_1$ is the estimation for the typical vancomycin clearance (in L/h) for an individual with a creatinine clearance ($CL_{CR}$) of 104 mL/min, $\theta_2$ is the estimation for the gradient describing the change in vancomycin clearance because of a change in creatinine clearance, and $\theta_3$ is the estimation of relative change in vancomycin clearance due to neutropenia. In this equation neutropenia has a value of 1 for presence of neutropenia and a value of 0 for absence of neutropenia.

Also, Q (in L/h), which was scaled to a fat-free mass of 57.2 kg as follows:

$Q=\theta_4*(FFM/57.2)^{0.75}$

In this equation FFM is the individual calculated fat-free mass and $\theta_4$ is the estimation for Q in a typical individual with a fat-free mass of 57.2 kg.

Lastly, $V_1$ and $V_2$ were scaled to fat-free mass as follows:

$V_1=\theta_5*(FFM/57.2)$

$V_2=\theta_6*(FFM/57.2)$

In these equations $\theta_5$ and $\theta_6$ are the estimations for the central and peripheral volumes of distribution for an individual with a fat-free mass of 57.2 kg, respectively. As observed in the shrinkage, that was around 30% or lower for all random effects, the data were sufficiently informative for description of inter-individual variability and residual error. Supplementary Table 1 shows the results of the parameter estimates of the base and final model.

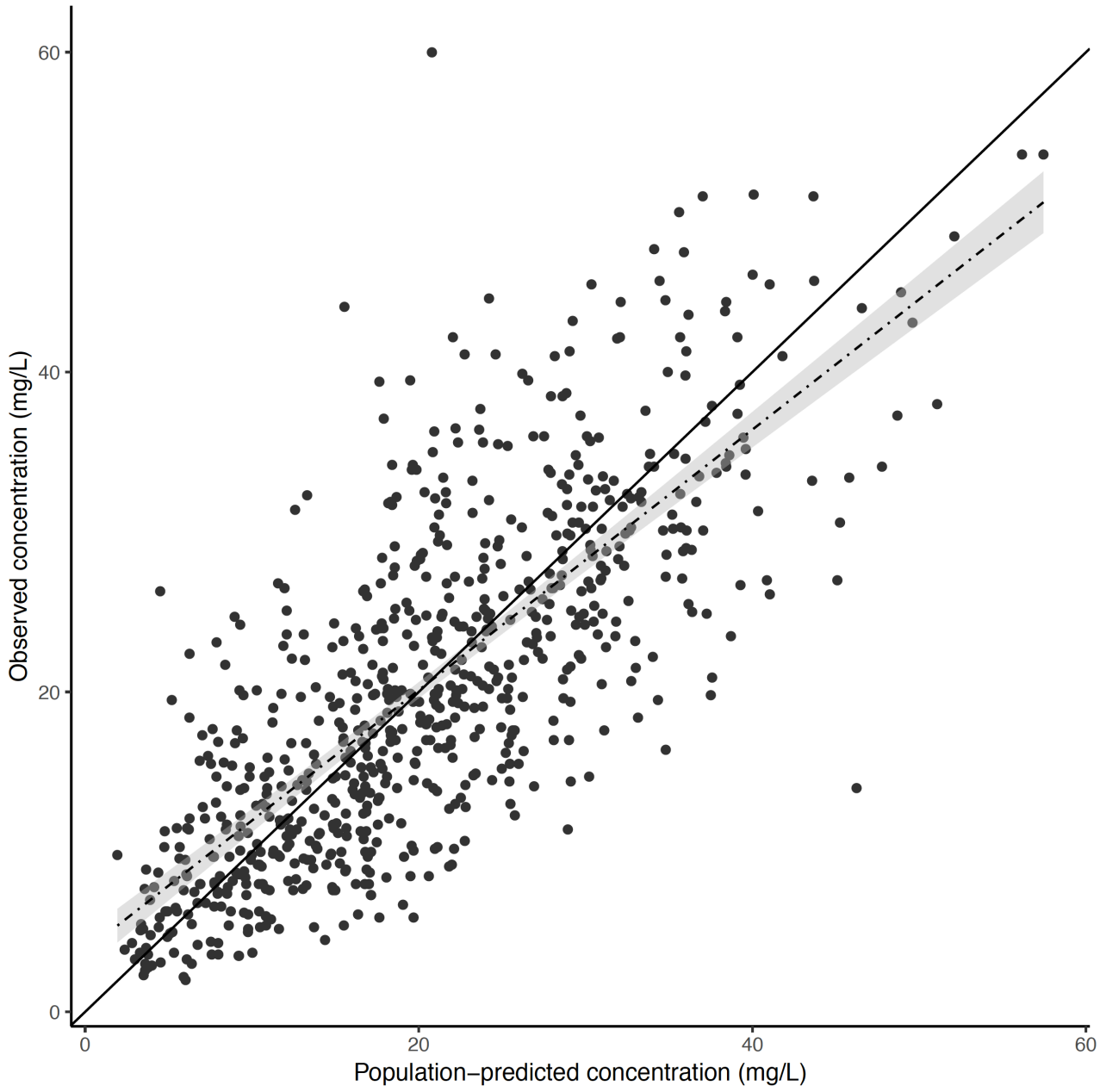
The goodness-of-fit plots are shown in Supplementary Fig 1 (panel A-F). As can be derived from these plots, the model described our data well, as the observed data in the prediction-corrected visual predictive check (Panel G) corresponded with the observed data. Although a slight over-prediction at the extremely high concentrations was observed at the population level (panel A, panel D), the individual concentrations were captured well by the model (panel B). Panel C, E and F show an even distribution of weighted residuals across the dosing interval as well as the calculated fat-free mass and creatinine clearance, indicating unbiased model predictions for the ranges of these parameters in our study.

**Supplementary table I.** Parameter estimates for the base and final model.

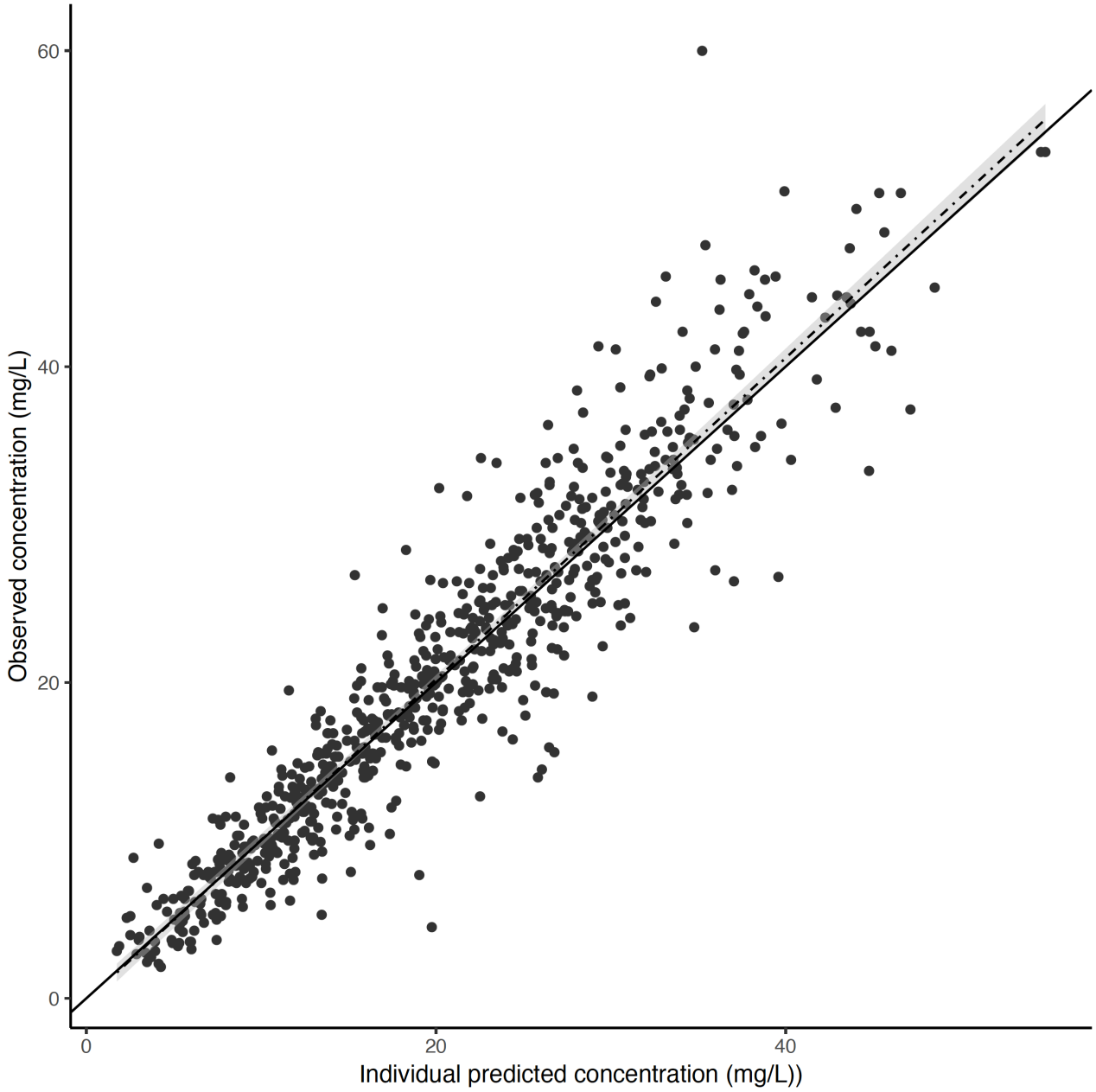
| | **Base model** | | **Final model** | |
|---|---|---|---|---|
| | Estimate (shrinkage) | 95% CI | Estimate (shrinkage) | 95% CI |
| **Clearance (CL)** | | | | |
| **$\theta_1$ (L/h)** | 3.47 | 3.20-3.73 | 3.22 | 2.97-3.48 |
| **$\theta_2$** | 0.00860 | 0.00772-0.00959 | 0.00834 | 0.00738-0.00928 |
| **$\theta_3$** | - | - | 1.277 | 1.102-1.462 |
| **Intercompartmental clearance (Q)** | | | | |
| **$\theta_4$ (L/h)*** | 4.12 | 2.88-5.19 | 4.03 | 2.81-5.22 |
| **$V_1$** | | | | |
| **$\theta_5$ (L)*** | 45.7 | 40.7-50.4 | 45.8 | 40.8-51.1 |
| **$V_2$** | | | | |
| **$\theta_6$ (L)*** | 51.0 | 37.0-64.3 | 51.7 | 37.2-66.2 |
| **Inter-individual variability** | | | | |
| **CL (%)** | 33.0 (11.1%) | 27.1-38.6 | 31.0 (8.7%) | 25.1-35.5 |
| **$V_1$ (%)** | 35.6 (29.0%) | 23.7-44.2 | 35.2 (26.1%) | 25.0-43.8 |
| **$V_2$ (%)** | 97.4 (33.6%) | 63.3-121 | 97.8 (32.5%) | 60.9-124 |
| **Residual variability** | | | | |
| **Additive (mg/L)** | 2.07 (14.2%) | 1.60-2.44 | 2.07 (19.4%) | 1.70-2.44 |
| **Proportional (%)** | 16.6 (14.2%) | 14.6-18.4 | 16.7 (13.1%) | 14.7-18.4 |
| **Objective function** | 3210.6 | | 3200.6 | |

*Scaled to a fat-free mass of 57.2 kg, corresponding with a man of1.80 m with a total body weight of 70kg. $V_1$ and $V_2$ represent the volume of distribution of the central and peripheral compartment, respectively.

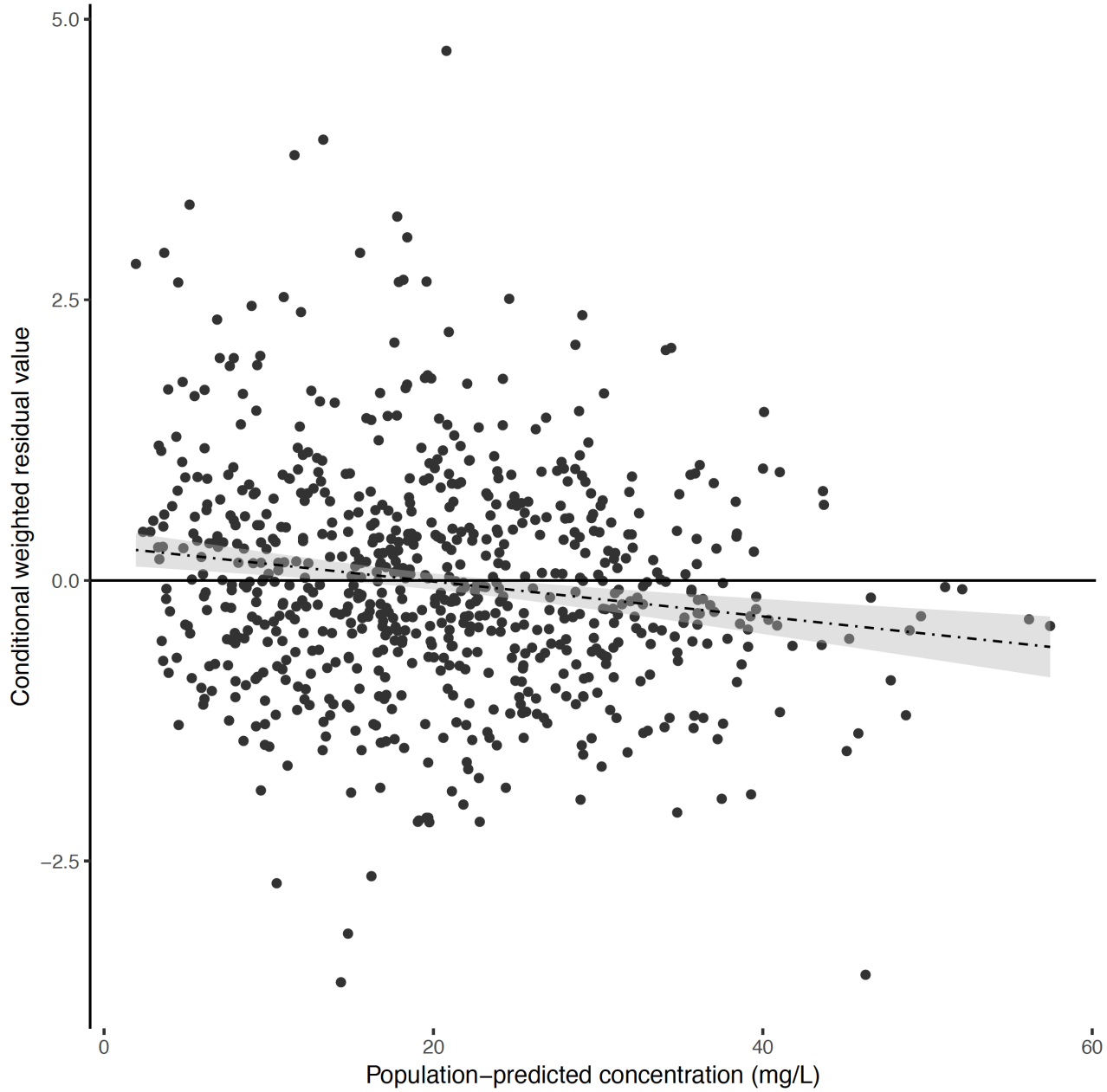
**Supplementary Figures**: Goodness-of-fit plots for the final model.



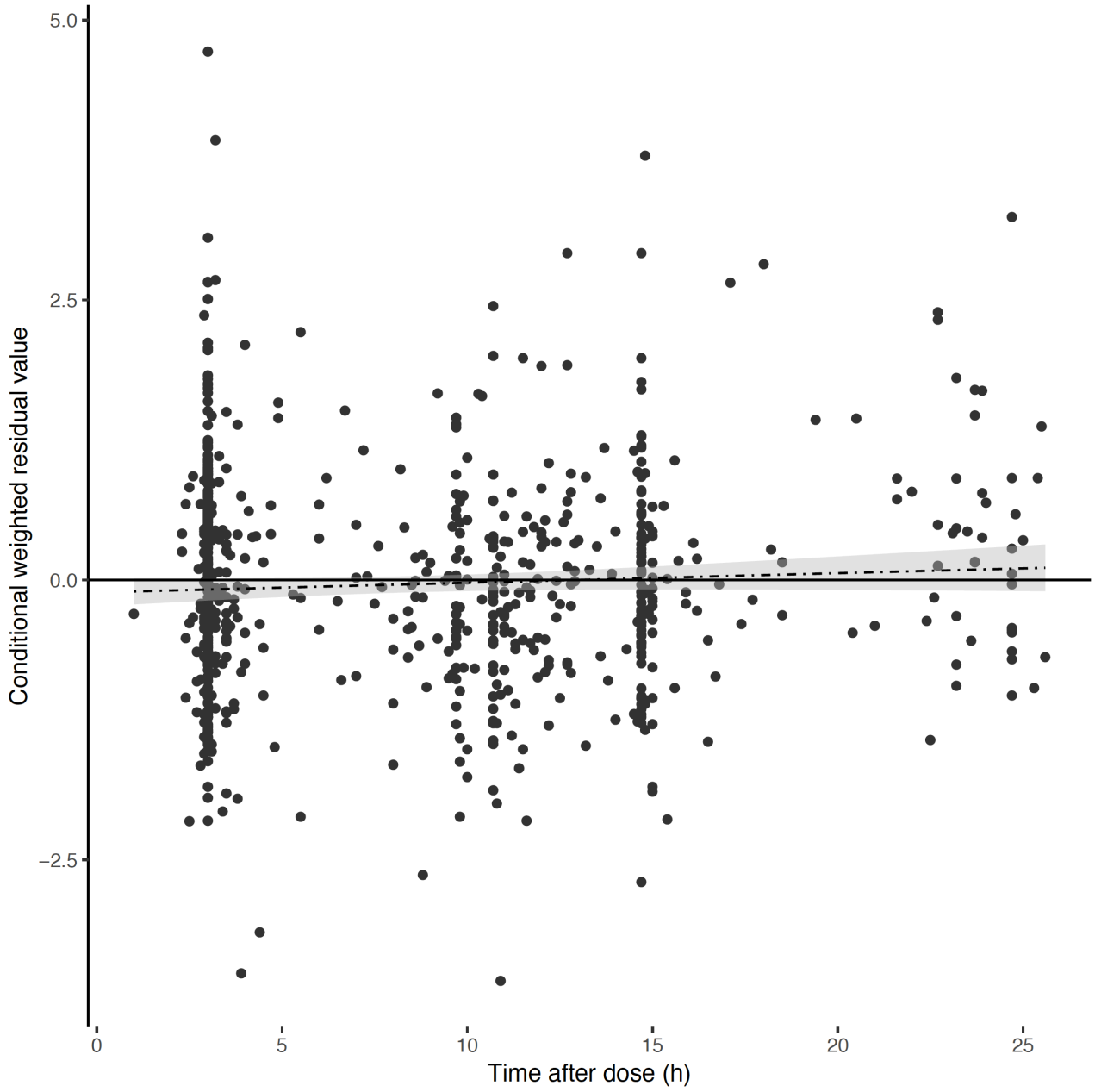

**Supplementary Fig 1A**: Observed concentration versus population-predicted concentration



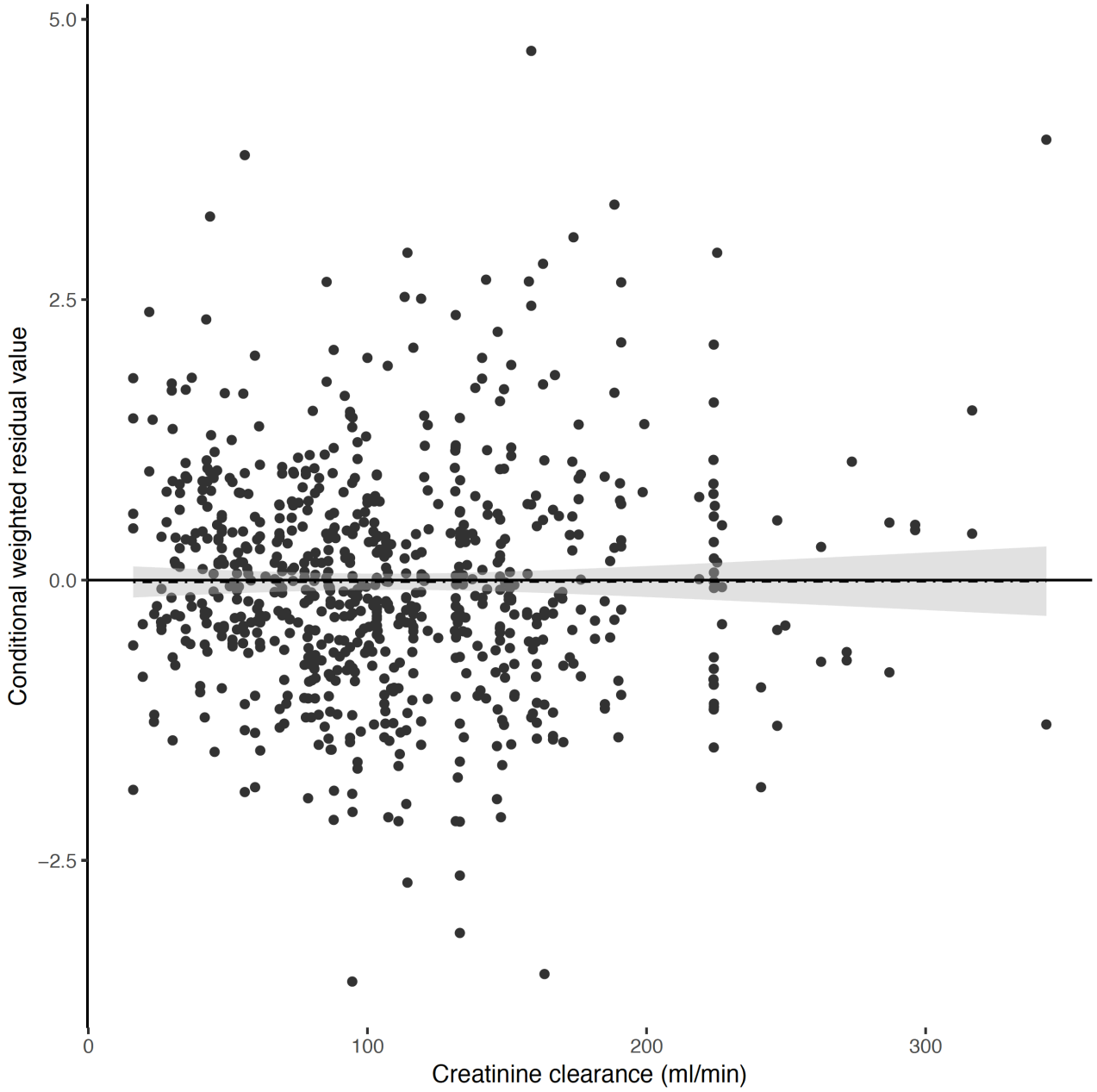

**Supplementary Fig 1B**: Observed concentration versus individual predicted concentration



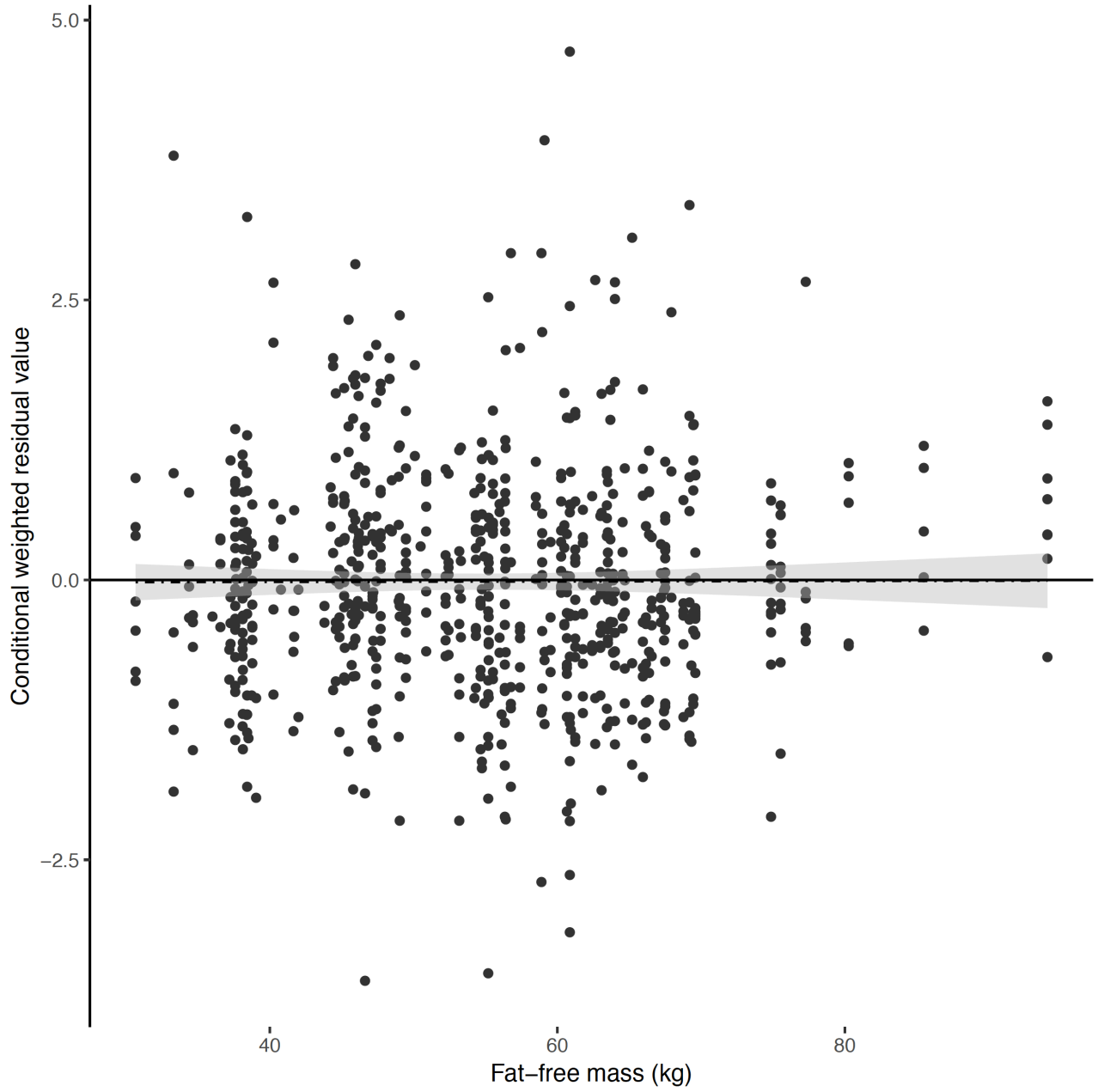

**Supplementary Fig 1C**: Conditional weighted residuals versus population-predicted concentration



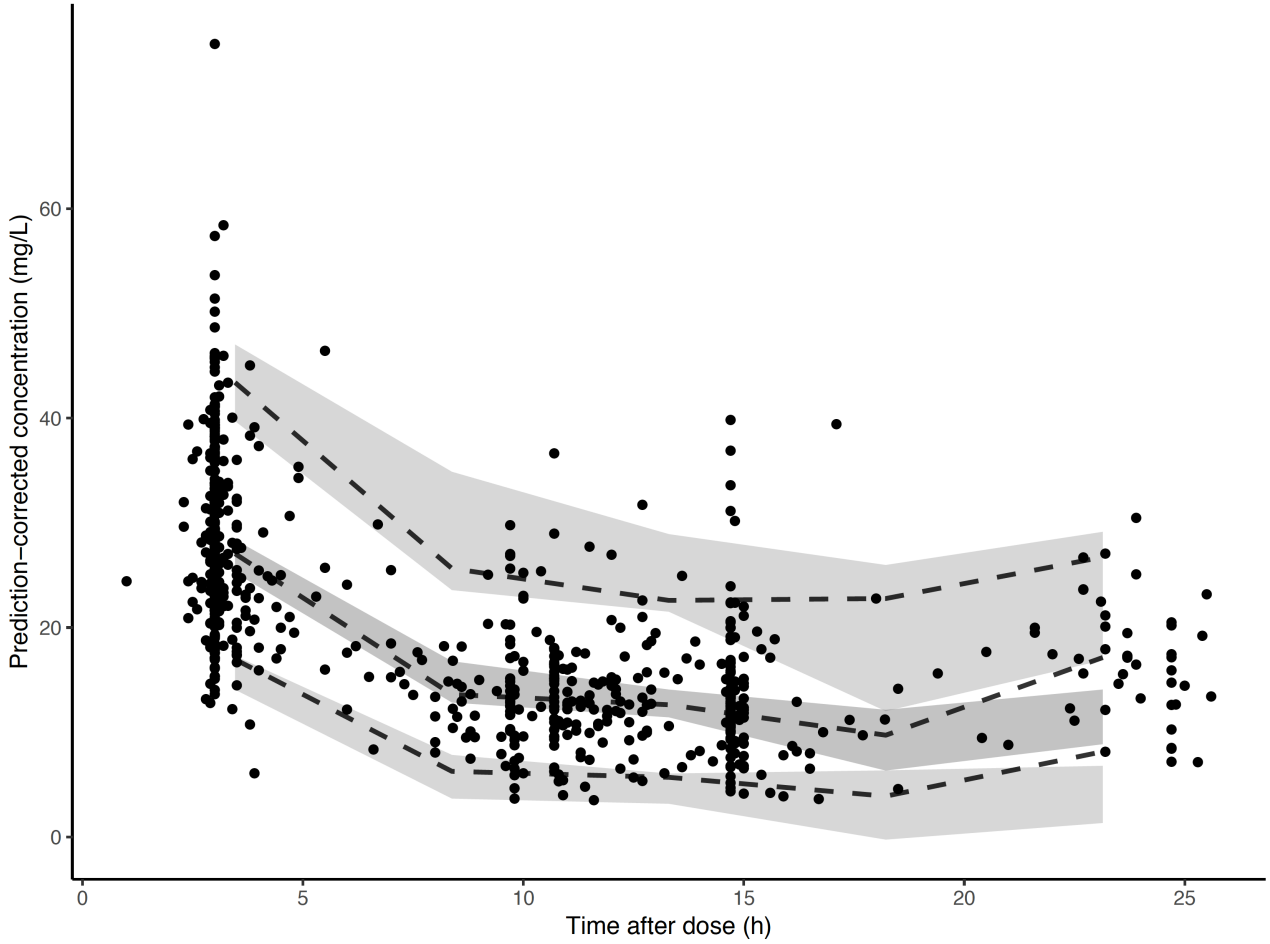

**Supplementary Fig 1D**: Conditional weighted residuals versus time after dose




**Supplementary Fig 1E**: Conditional weighted residuals versus calculated creatinine clearance




**Supplementary Fig 1F**: Conditional weighted residuals versus calculated fat-free mass




**Supplementary Fig 1G**: Prediction-corrected visual predictive check based on n=1000 simulations. Prediction-corrected simulated (shaded areas) and observed (circles and dashed lines) vancomycin concentrations versus time after dose (h). The dashed lines connect the observed median values per bin for the $5^{th}$, $50^{th}$ and $95^{th}$ percentiles. The shaded areas represent their respective predictive confidence intervals obtained from the simulations.