

# **Physiologically-based Pharmacokinetic Modelling of Serum 25-hydroxyvitamin D concentrations in Schoolchildren Receiving Weekly Oral Vitamin D Supplementation**

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## **Supplementary Materials**

**Figure S1.** Flowchart of Mongolian children selection for model simulations.

**Figure S2.** Model diagram for models 1-8 and 11.

**Figure S3.** Model diagram for models 9 and 10.

**Figure S4.** Serum 25(OH)D concentrations after repeated weekly dosing of 250 µg vitamin D<sub>3</sub>.

**Figure S5.** Baseline serum 25(OH)D levels vs. BMI-for-age Z-score for 77 children in the treatment group.

**Figure S6.** The scatter plot for pharmacokinetic parameters for the final model and various reported covariates.

**Figure S7.** Objective function value v Kp25Im. The objective function is fitted at different Kp25Im values: 1, 2, 3, 4, 6, 8.

**Figure S8.** The fitted 77 children.

**Figure S9.** Simulation of serum 25(OH)D concentrations in 454 Cape Town children in the treatment group.

**Figure S10.** The distribution of residual error at 3 years: observation – population prediction at the 50<sup>th</sup> percentile.

**Figure S11.** The distribution of the range (i.e. 97.5<sup>th</sup> – 2.5<sup>th</sup> percentiles) at 1, 2, and 3 years.

**Figure S12.** The scatter plots between the 2.5<sup>th</sup> – 97.5<sup>th</sup> percentiles range and baseline bodyweight and ZBMI.

**Figure S13.** Comparison of the treated Mongolian children with treated Cape Town children used to fit the model.

**Figure S14.** Simulation of serum 25(OH)D concentrations in Mongolian children receiving a weekly dose of 350 µg vitamin D<sub>3</sub>.

**Figure S15.** Serum 25(OH)D in the control group of the ViDiKids safety study (n=105) changes with time.

**Figure S16:** Simulation of serum 25(OH)D concentration at 3 years with weekly 250 µg vitamin D<sub>3</sub> dosing at varying values of  $CL_{max}$  and  $C_{50}$ .

**Figure S17.** 25(OH)D clearance rate  $\frac{CL_{max} \times C_{25D}^Y}{C_{50}^Y + C_{25D}^Y} \times C_{25D}$  vs 25(OH)D.

**Table S1.** Baseline characteristics of the study population.

**Table S2.** Physiological parameters used for paediatric compartmental lumping.

**Table S3.** Physiological parameters of the PBPK model for paediatrics after compartments are lumped together.

**Table S4.** Drug-specific parameters for model development.

**Table S5.** Model development for 25(OH)D paediatric pharmacokinetics.

**Table S6.** 25(OH)D model fitting results.

## Supplementary Figures

**Figure S1.** Flowchart of Mongolian children selection for model simulations. Schoolchildren aged 6 to 13 years from participating schools in Ulaanbaatar, Mongolia, were recruited from September 2015 to March 2017 to the randomised controlled trials of vitamin D supplementation to prevent tuberculosis infection. Over the 3-year study period, each child randomised to the intervention arm received a weekly oral capsule containing 350µg (14,000 IU) vitamin D<sub>3</sub> or a placebo. Blood samples were collected at baseline and at the end of the third year. Serum 25(OH)D<sub>3</sub> concentrations were determined using an enzyme-linked fluorescent assay [16]. The participants in the treatment group with 25(OH)D concentrations above the lower limit of quantification (14.2 nmol/L) at both baseline and follow-up were included in the model simulation using the final model

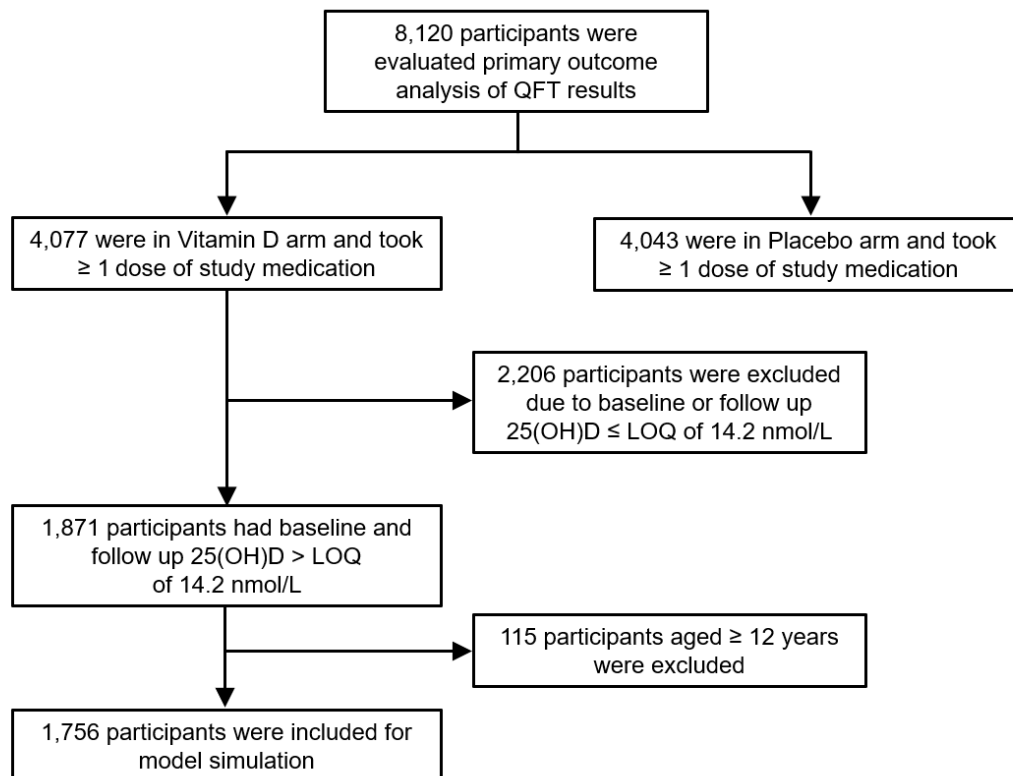
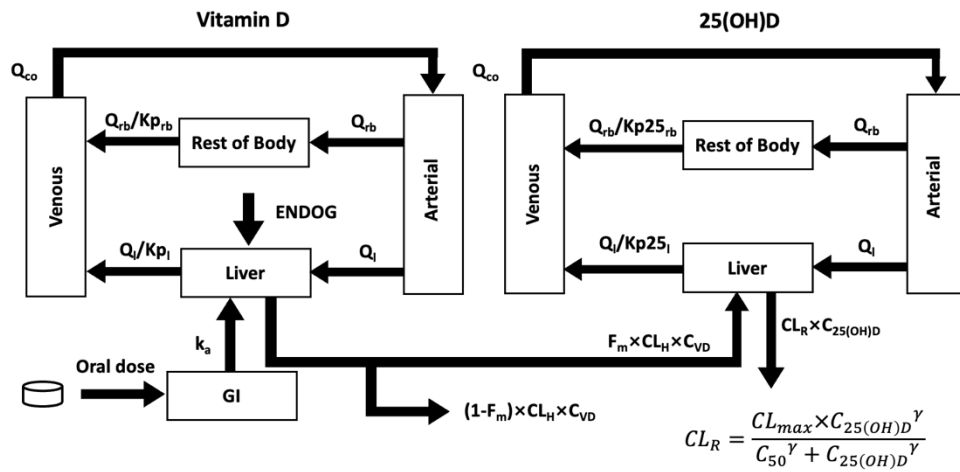


**Figure S2.** Model diagram for models 1-8 and 11, adapted from our previous publication [13]. The model considers 5 compartments for vitamin D including venous blood, arterial blood, liver, and the rest of body (i.e. all non-eliminating organs) and 4 compartments for 25(OH)D, including venous blood, arterial blood, liver, and the rest of body (i.e. all non-eliminating organs). Vitamin D<sub>3</sub> supplement enters the body via gastrointestinal tract (GI) and passes through the liver to either enter the venous blood or to be metabolised into 25(OH)D<sub>3</sub>. Endogenously synthesised vitamin D<sub>3</sub> is assumed to enter the liver at a constant rate ENDOG, which varies for each person. The equation of 25(OH)D<sub>3</sub> clearance (CL<sub>R</sub>) is listed in the bottom right corner. GI: gastrointestinal tract. Q<sub>co</sub>: Cardiac output (L/h). Q<sub>rb</sub>: blood flow into and out of the rest of body. Q<sub>l</sub>: blood flow into and out of the liver. K<sub>prb</sub> and K<sub>p25rb</sub>: distribution coefficient between venous blood and the rest of body for vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub>, respectively. K<sub>pl</sub> and K<sub>p25l</sub>: distribution coefficient between venous blood and the liver for vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub>, respectively. F<sub>m</sub>: fraction of vitamin D<sub>3</sub> metabolised into 25(OH)D<sub>3</sub>. CL<sub>H</sub>: hepatic clearance rate (L/h). C<sub>VD</sub>: concentration of hepatic vitamin D<sub>3</sub>.



$$ENDOG = \frac{CL_{max} \times D25_{BASE}^\gamma}{C_{50}^\gamma + D25_{BASE}^\gamma} \times D25_{BASE} \times 3$$

$$\frac{dA_{dep}}{dt} = -k_a \times A_{dep}$$

$$\frac{dA_{ven}}{dt} = \frac{Q_l \times A_l}{V_l} \times \frac{1}{K_{pl}} + \frac{Q_{rb} \times A_{rb}}{V_{rb}} \times \frac{1}{K_{prb}} - \frac{Q_{co} \times A_{ven}}{V_{ven}}$$

$$\frac{dA_l}{dt} = -\frac{Q_l \times A_l}{V_l} \times \frac{1}{K_{pl}} + \frac{Q_l \times A_{art}}{V_{art}} - \frac{MCL_H \times A_l}{V_l} \times \frac{1}{K_{pl}} + ENDOG + k_a \times A_{dep}$$

$$\frac{dA_{25ven}}{dt} = \frac{Q_l \times A_{25l}}{V_l} \times \frac{1}{K_{p25l}} + \frac{Q_{rb} \times A_{25rb}}{V_{rb}} \times \frac{1}{K_{p25rb}} - \frac{Q_{co} \times A_{25ven}}{V_{ven}}$$

$$\begin{aligned} \frac{dA25_l}{dt} = & -\frac{Q_l \times A25_l}{V_l} \times \frac{1}{K_{p25l}} + \frac{Q_l \times A25_{art}}{V_{art}} + \frac{MCL_H \times A_l}{V_l} \times \frac{1}{K_{pl}} \times \frac{1}{3} \\ & - \frac{CL_{max} \times \left( \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \right)^y}{C_{50}^y + \left( \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \right)^y} \times \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \end{aligned}$$

$$\frac{dA25_{rb}}{dt} = \frac{Q_{rb} \times A25_{art}}{V_{art}} - \frac{Q_{rb} \times A25_{rb}}{V_{rb}} \times \frac{1}{K_{p25rb}}$$

$$\frac{dA25_{art}}{dt} = \frac{Q_{co} \times A25_{ven}}{V_{ven}} - \frac{Q_l \times A25_{art}}{V_{art}} - \frac{Q_{rb} \times A25_{art}}{V_{art}}$$

**Initial conditions:**

$$A_{art} = \frac{\frac{Q_{co} \times A_{ven}}{V_{ven}}}{\frac{Q_l + Q_{rb}}{V_{art}}}$$

$$A_{rb} = \frac{A_{art} \times K_{prb} \times V_{rb}}{V_{art}} = \frac{\frac{\frac{Q_{co} \times A_{ven}}{V_{ven}}}{\frac{Q_l + Q_{rb}}{V_{art}}} \times K_{prb} \times V_{rb}}{V_{art}}$$

$$A_{dep}(0) = 0$$

$$A_{ven}(0) = ENDOG \times \frac{V_{ven}}{MCL_H}$$

$$A_l(0) = ENDOG \times \frac{V_l}{MCL_H} \times K_{pl}$$

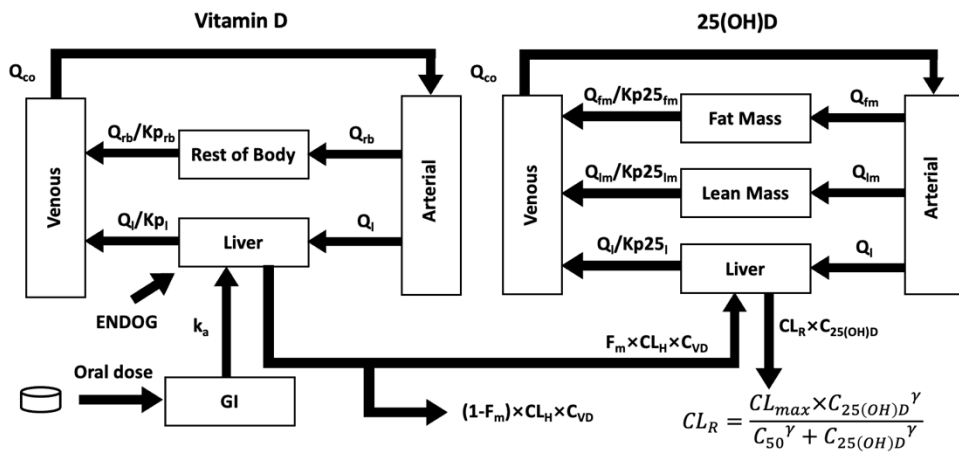
$$A25_{ven}(0) = D25_{BASE} \times V_{ven}$$

$$A25_l(0) = D25_{BASE} \times V_l \times K_{p25l}$$

$$A25_{rb}(0) = D25_{BASE} \times V_{rb} \times K_{p25rb}$$

$$A25_{art}(0) = D25_{BASE} \times V_{art}$$

**Figure S3.** Model diagram for models 9-10, adapted from our previous publication [13]. The model considers 5 compartments for vitamin D (same as models 1-8 and 11) and 5 compartments 25(OH)D, including the arterial blood, venous blood, liver, fat mass and lean mass. Vitamin D<sub>3</sub> supplement enters the body via gastrointestinal tract (GI) and passes through the liver to either enter the venous blood or to be metabolised into 25(OH)D<sub>3</sub>. Endogenously synthesised vitamin D<sub>3</sub> is assumed to enter the liver at a constant rate ENDOG, which varies for each person. The equation of 25(OH)D<sub>3</sub> clearance (CL<sub>R</sub>) is listed in the bottom right corner. GI: gastrointestinal tract. Q<sub>co</sub>: Cardiac output (L/h). Q<sub>rb</sub>: blood flow into and out of the rest of body. Q<sub>l</sub>: blood flow into and out of the liver. Q<sub>fm</sub>: blood flow into and out of the fat mass. Q<sub>lm</sub>: blood flow into and out of the lean mass. K<sub>pb</sub> and K<sub>p25rb</sub>: distribution coefficient between venous blood and the rest of body for vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub>, respectively. K<sub>pl</sub> and K<sub>p25l</sub>: distribution coefficient between venous blood and the liver for vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub>, respectively. K<sub>pfm</sub>: distribution coefficient between venous blood and the fat mass for 25(OH)D<sub>3</sub>. K<sub>plm</sub>: distribution coefficient between venous blood and the lean mass for 25(OH)D<sub>3</sub>. F<sub>m</sub>: fraction of vitamin D<sub>3</sub> metabolised into 25(OH)D<sub>3</sub>. CL<sub>H</sub>: hepatic clearance rate (L/h). C<sub>VD</sub>: concentration of hepatic vitamin D<sub>3</sub>.



$$ENDOG = \frac{CL_{max} \times D25_{BASE}^{\gamma}}{C_{50}^{\gamma} + D25_{BASE}^{\gamma}} \times D25_{BASE} \times 3$$

$$\frac{dA_{dep}}{dt} = -k_a \times A_{dep}$$

$$\frac{dA_{ven}}{dt} = \frac{Q_l \times A_l}{V_l} \times \frac{1}{K_{pl}} + \frac{Q_{rb} \times A_{rb}}{V_{rb}} \times \frac{1}{K_{prb}} - \frac{Q_{co} \times A_{ven}}{V_{ven}}$$

$$\frac{dA_l}{dt} = -\frac{Q_l \times A_l}{V_l} \times \frac{1}{K_{pl}} + \frac{Q_l \times A_{art}}{V_{art}} - \frac{MCL_H \times A_l}{V_l} \times \frac{1}{K_{pl}} + ENDOG + k_a \times A_{dep}$$

$$\frac{dA25_{ven}}{dt} = \frac{Q_l \times A25_l}{V_l} \times \frac{1}{K_{p25l}} + \frac{Q_{fm} \times A25_{fm}}{V_{fm}} \times \frac{1}{K_{p25fm}} + \frac{Q_{lm} \times A25_{lm}}{V_{lm}} \times \frac{1}{K_{p25lm}} - \frac{Q_{co} \times A25_{ven}}{V_{ven}}$$

$$\begin{aligned} \frac{dA25_l}{dt} = & -\frac{Q_l \times A25_l}{V_l} \times \frac{1}{K_{p25l}} + \frac{Q_l \times A25_{art}}{V_{art}} + \frac{MCL_H \times A_l}{V_l} \times \frac{1}{K_{pl}} \times \frac{1}{3} \\ & - \frac{CL_{max} \times \left( \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \right)^y}{C_{50}^y + \left( \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \right)^y} \times \frac{A25_l}{V_l} \times \frac{1}{K_{p25l}} \end{aligned}$$

$$\frac{dA25_{fm}}{dt} = \frac{Q_{fm} \times A25_{art}}{V_{art}} - \frac{Q_{fm} \times A25_{fm}}{V_{fm}} \times \frac{1}{K_{p25fm}}$$

$$\frac{dA25_{lm}}{dt} = \frac{Q_{lm} \times A25_{art}}{V_{art}} - \frac{Q_{lm} \times A25_{lm}}{V_{lm}} \times \frac{1}{K_{p25lm}}$$

$$\frac{dA25_{art}}{dt} = \frac{Q_{co} \times A25_{ven}}{V_{ven}} - \frac{Q_l \times A25_{art}}{V_{art}} - \frac{(Q_{fm} + Q_{lm}) \times A25_{art}}{V_{art}}$$

**Initial conditions:**

$$A_{art} = \frac{\frac{Q_{co} \times A_{ven}}{V_{ven}}}{\frac{Q_l + Q_{rb}}{V_{art}}}$$

$$A_{rb} = \frac{A_{art} \times K_{prb} \times V_{rb}}{V_{art}} = \frac{\frac{\frac{Q_{co} \times A_{ven}}{V_{ven}}}{\frac{Q_l + Q_{rb}}{V_{art}}} \times K_{prb} \times V_{rb}}{V_{art}}$$

$$A_{dep}(0) = 0$$

$$A_{ven}(0) = ENDOG \times \frac{V_{ven}}{MCL_H}$$

$$A_l(0) = ENDOG \times \frac{V_l}{MCL_H} \times K_{pl}$$

$$A25_{ven}(0) = D25_{BASE} \times V_{ven}$$

$$A25_l(0) = D25_{BASE} \times V_l \times K_{p25l}$$

$$A25_{fm}(0) = D25_{BASE} \times V_{fm} \times K_{p25fm}$$

$$A25_{lm}(0) = D25_{BASE} \times V_{lm} \times K_{p25lm}$$

$$A25_{art}(0) = D25_{BASE} \times V_{art}$$

**Allometric weight scaling on volume of distribution and clearance**

$$V_T = TV_T \times \frac{WT_{cur}}{30}$$

$$V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$$

$$V_{fm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$$

$$CL_{MAX} = e^{TCL_{MAX} + \eta_{CL_{MAX}}} \times \left( \frac{WT_{cur}}{30} \right)^{0.75}$$

$$K_{p25fm} = e^{TKp25_{fm}}$$

Where  $V_T$  is the volume of distribution of compartment T,  $TV_T$  is typical value for compartment T determined from paediatric bodyweight as presented in **Table S3**, WT is bodyweight,  $CL_{MAX}$  is maximum clearance,  $TCL_{MAX}$  is typical value of  $CL_{MAX}$ ,  $\eta_{CL_{MAX}}$  is the inter-individual variability of  $CL_{MAX}$ .

**Figure S4** Serum 25(OH)D concentrations after repeated weekly dosing of 250 µg vitamin D<sub>3</sub>.

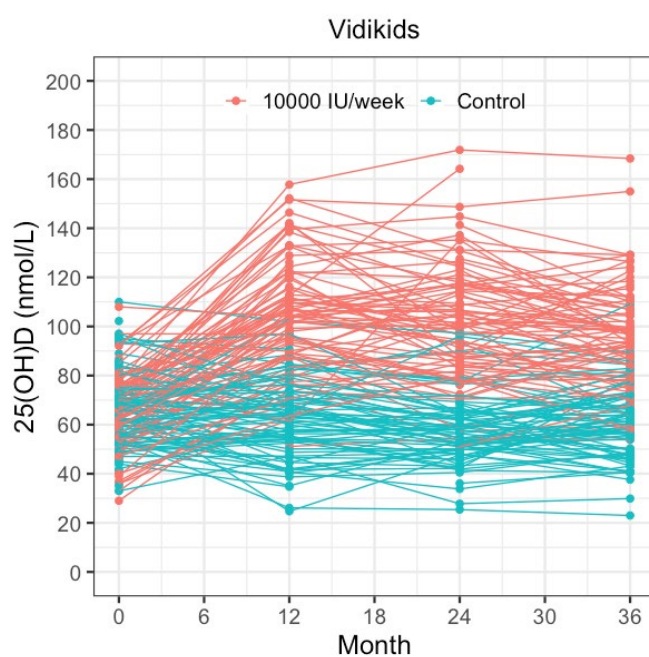


**Figure S5.** Baseline serum 25(OH)D levels vs. BMI-for-age Z-score for 77 children in the treatment group. The slope of the regression line: -2.644 nmol/L.

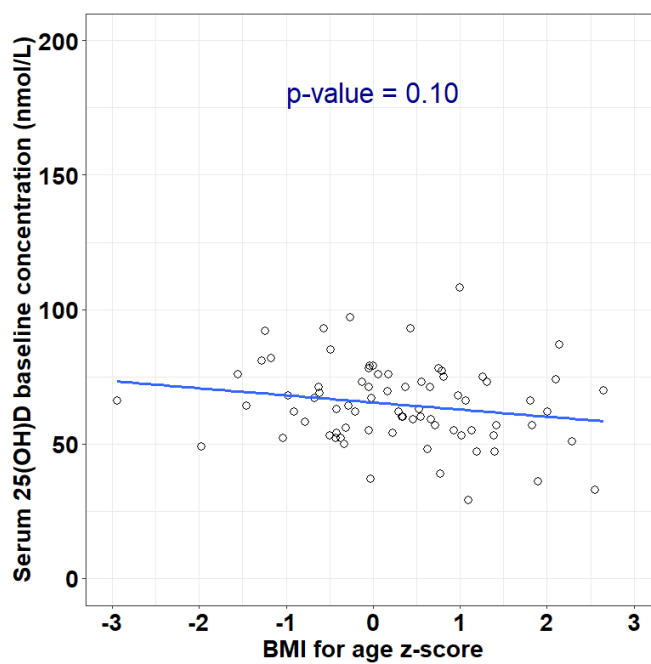
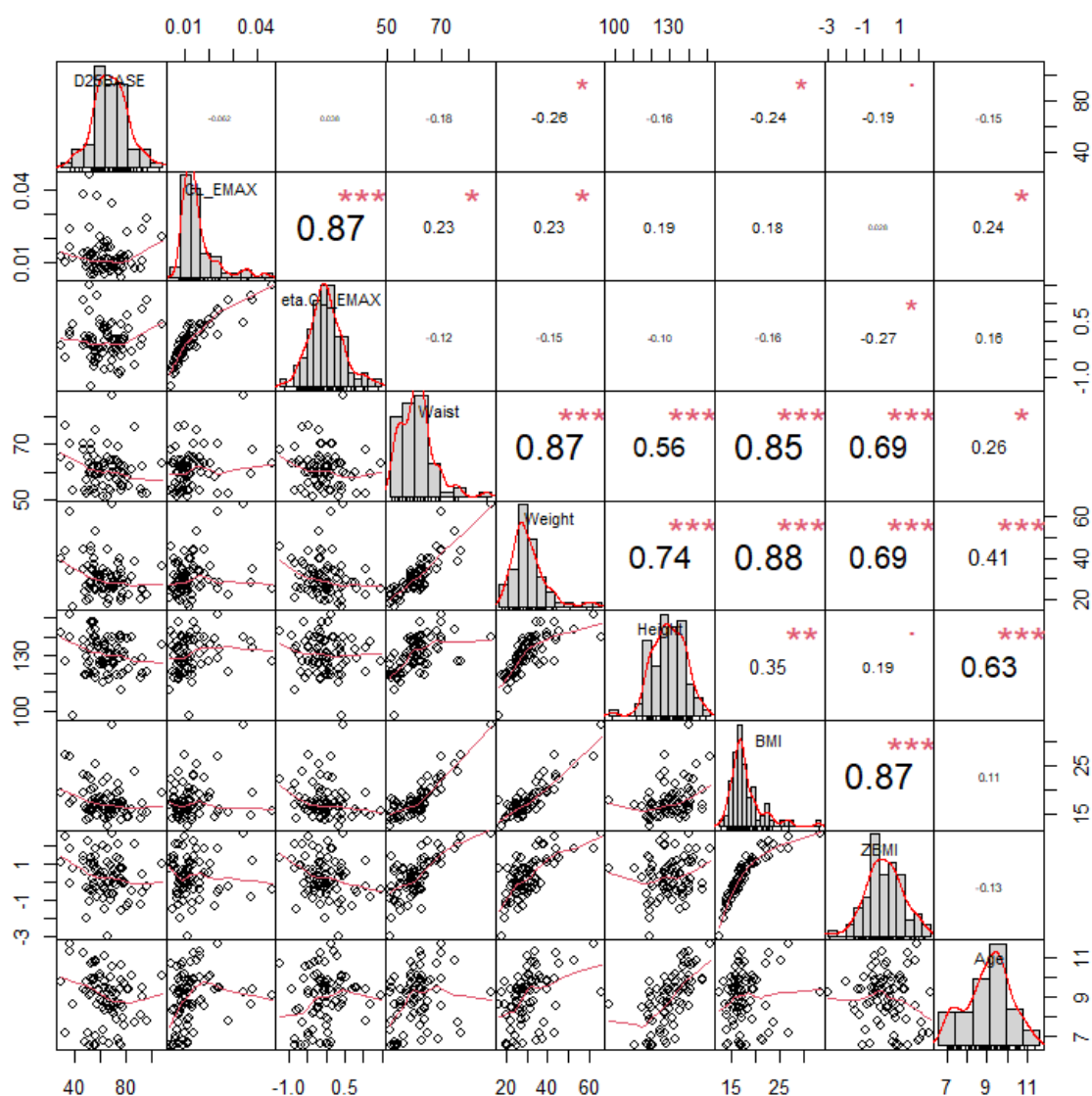


**Figure S6.** The scatter plot for pharmacokinetic parameters for the final model and various reported covariates.



#### Parameters:

**D25BASE**, baseline 25OHD; **CL\_EMAX**, Maximum clearance ( $CL_{MAX}$  in the text); **eta.CL\_EMAX**, Between-subject variability of  $CL_{MAX}$  ( $\eta_{CL_{MAX}}$  in the text); **BMI**, Body Mass Index ( $kg/m^2$ ); **ZBMI**, BMI-for-age Z-score; **Weight**, Bodyweight in kg; **Waist**, Waist circumference in cm; **Height**, Height in cm; **Age**: Age in years.

**Figure S7.** Objective function value v Kp25Im. The objective function is fitted at different Kp25Im values: 1, 2, 3, 4, 6, 8.

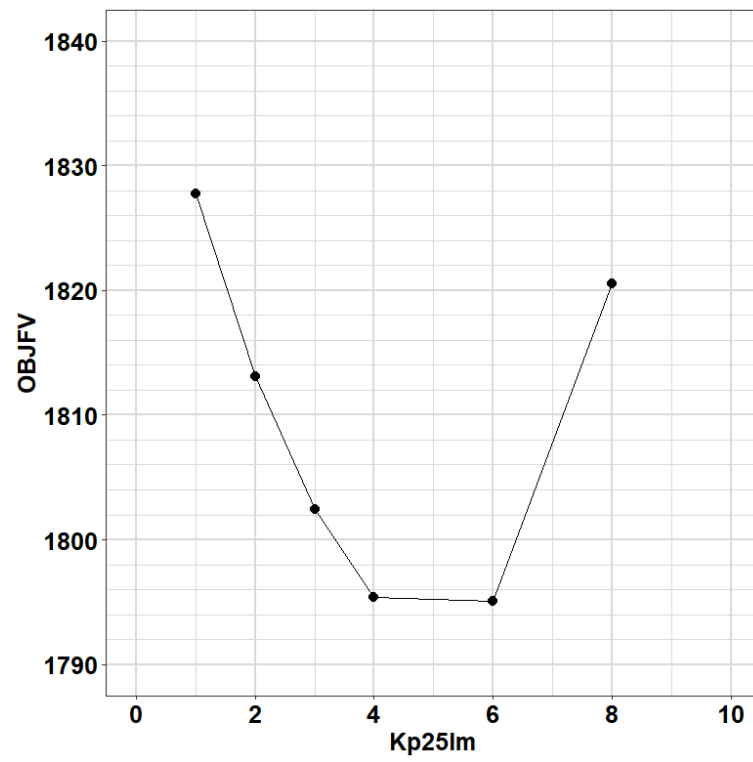


**Figure S8.** The fitted 77 children. Black solid lines: population predictions. Black dashed lines: individual predictions. Blue dots: observations. Vertical lines: doses.

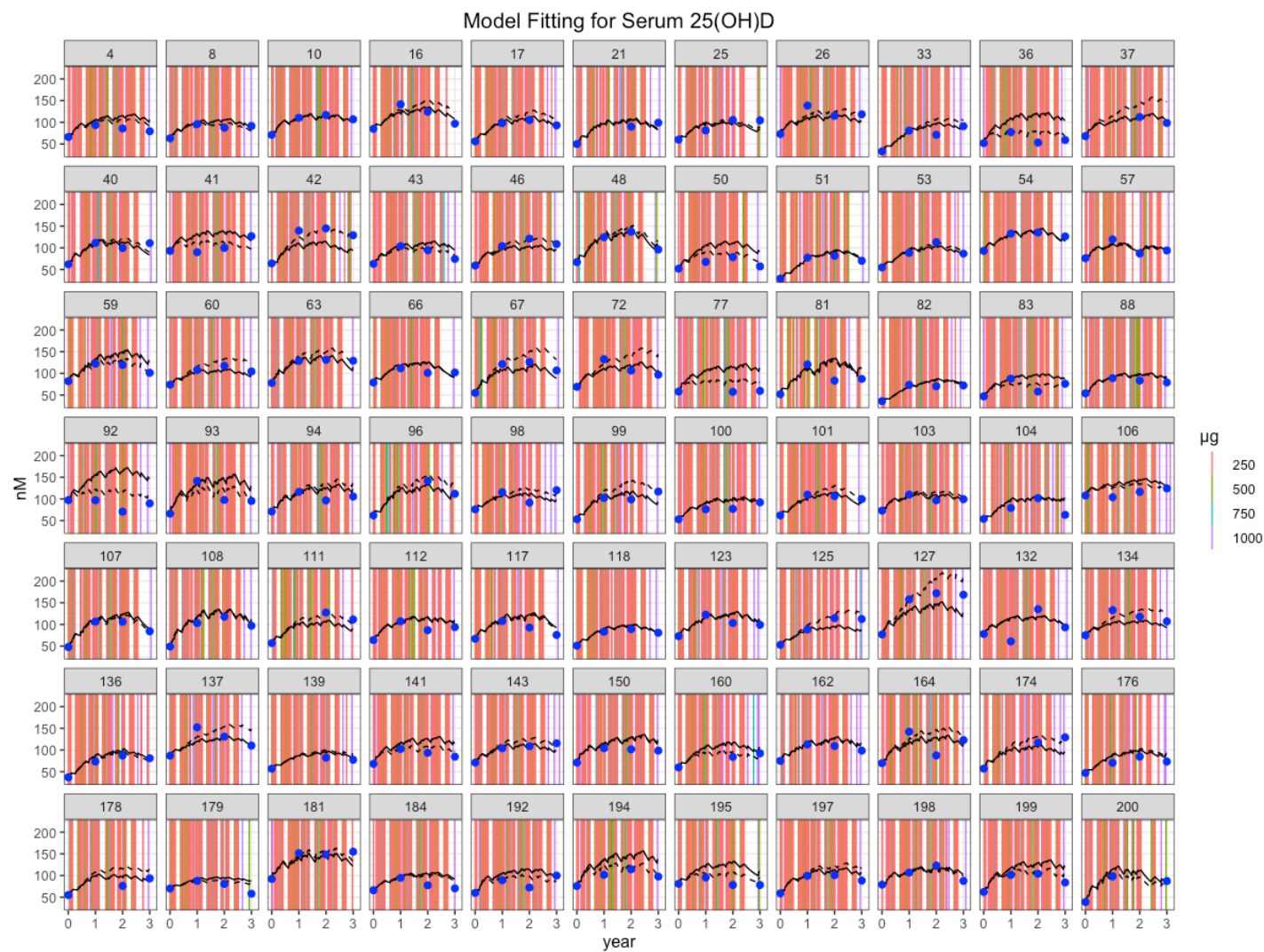
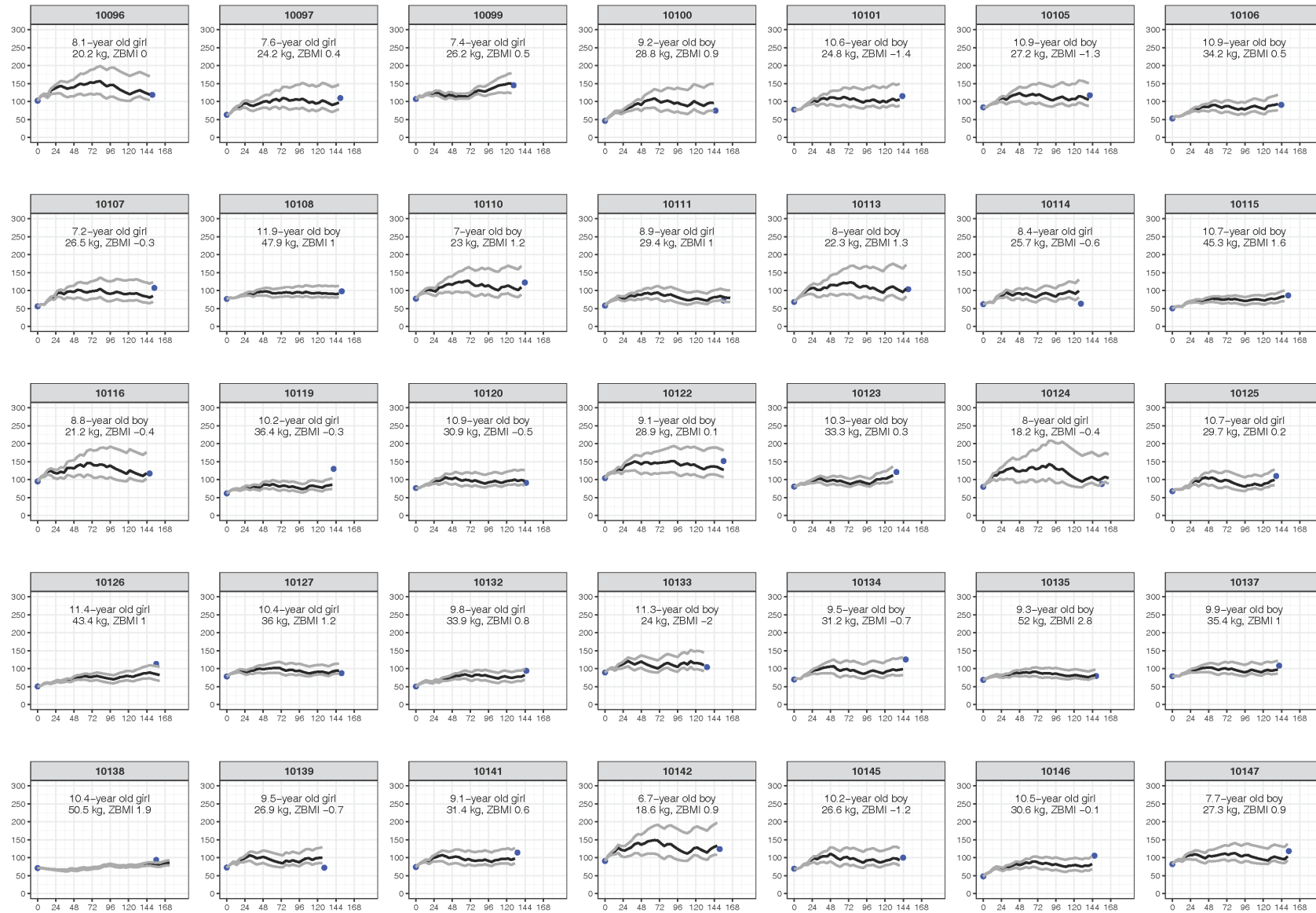
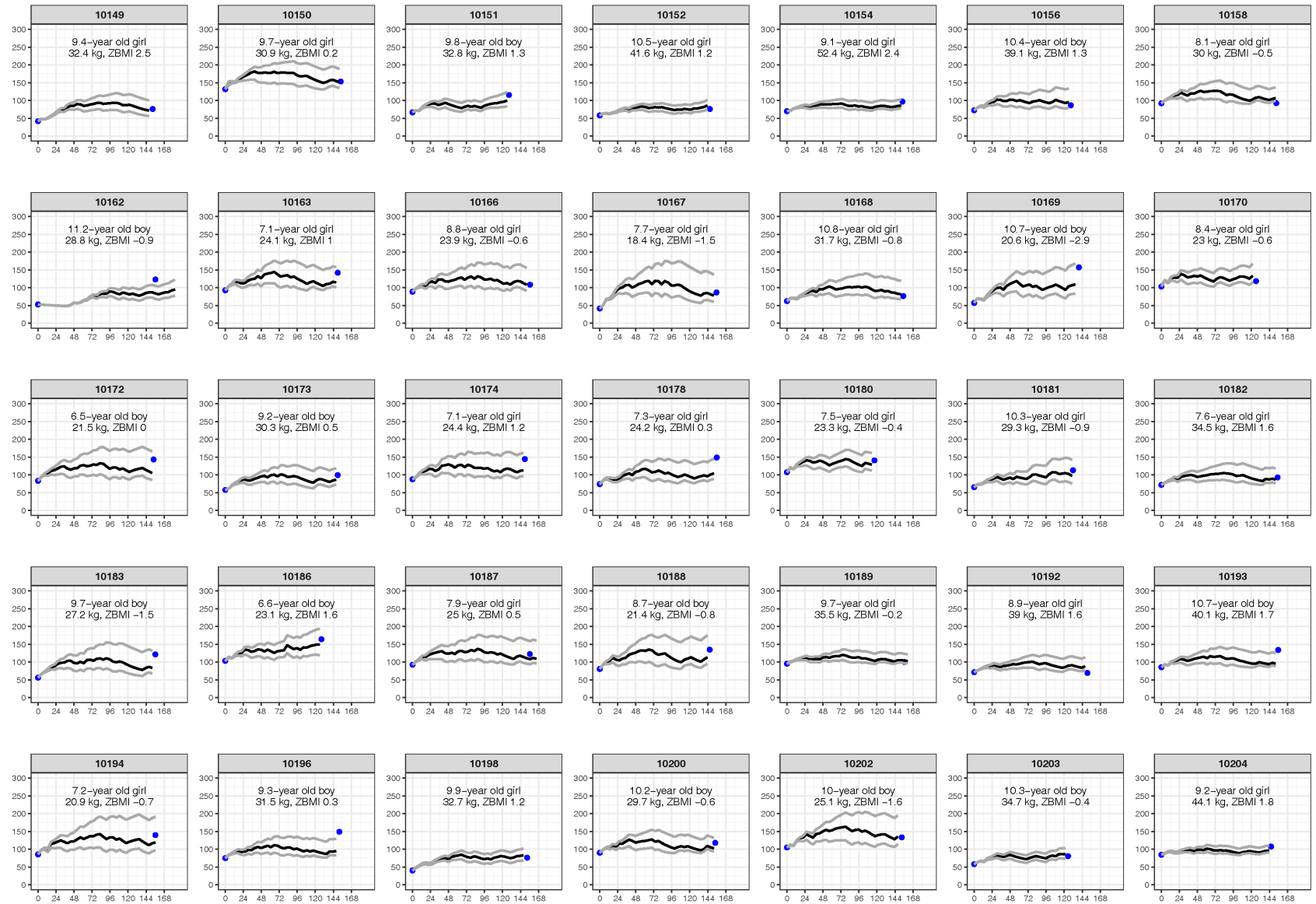
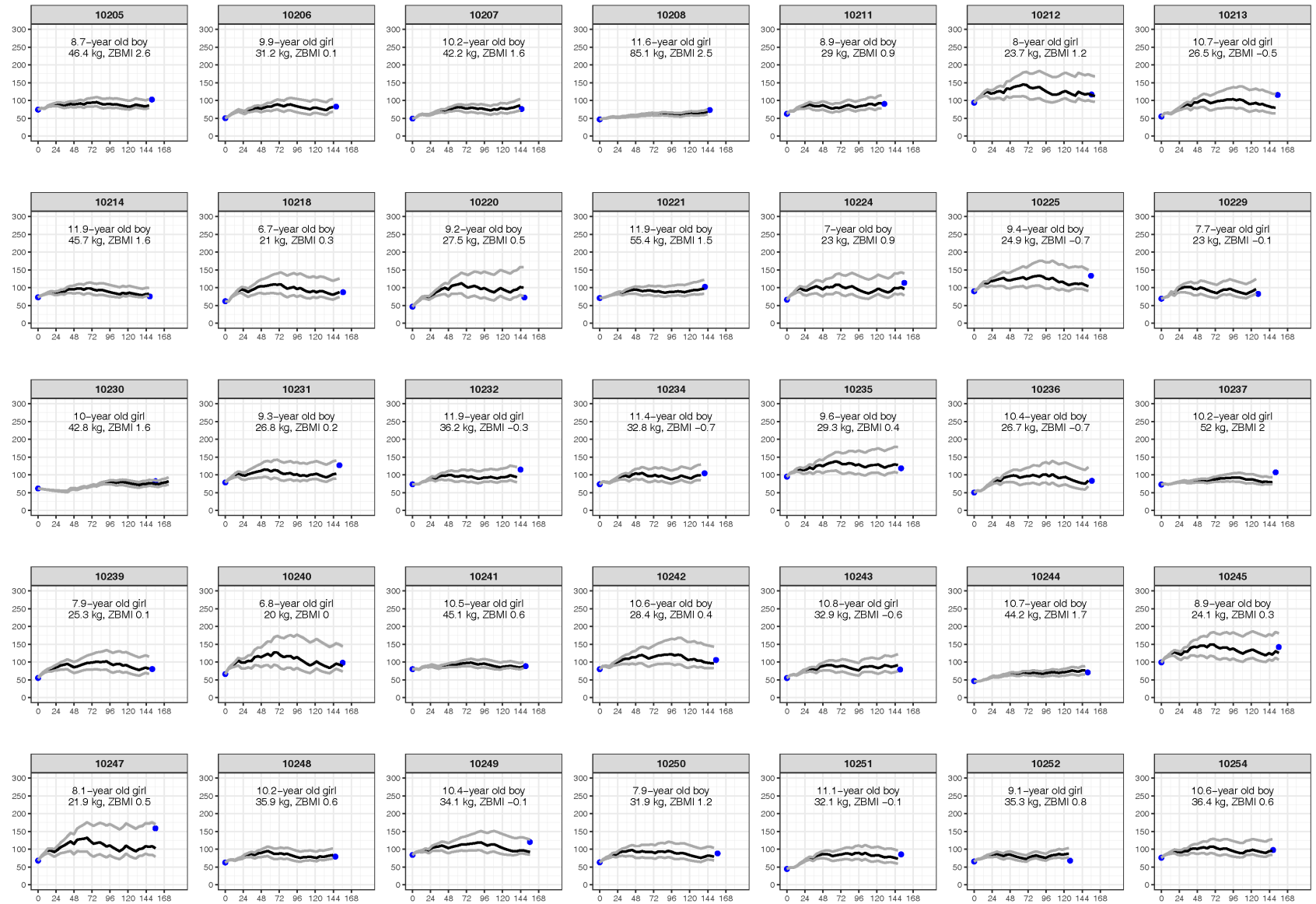
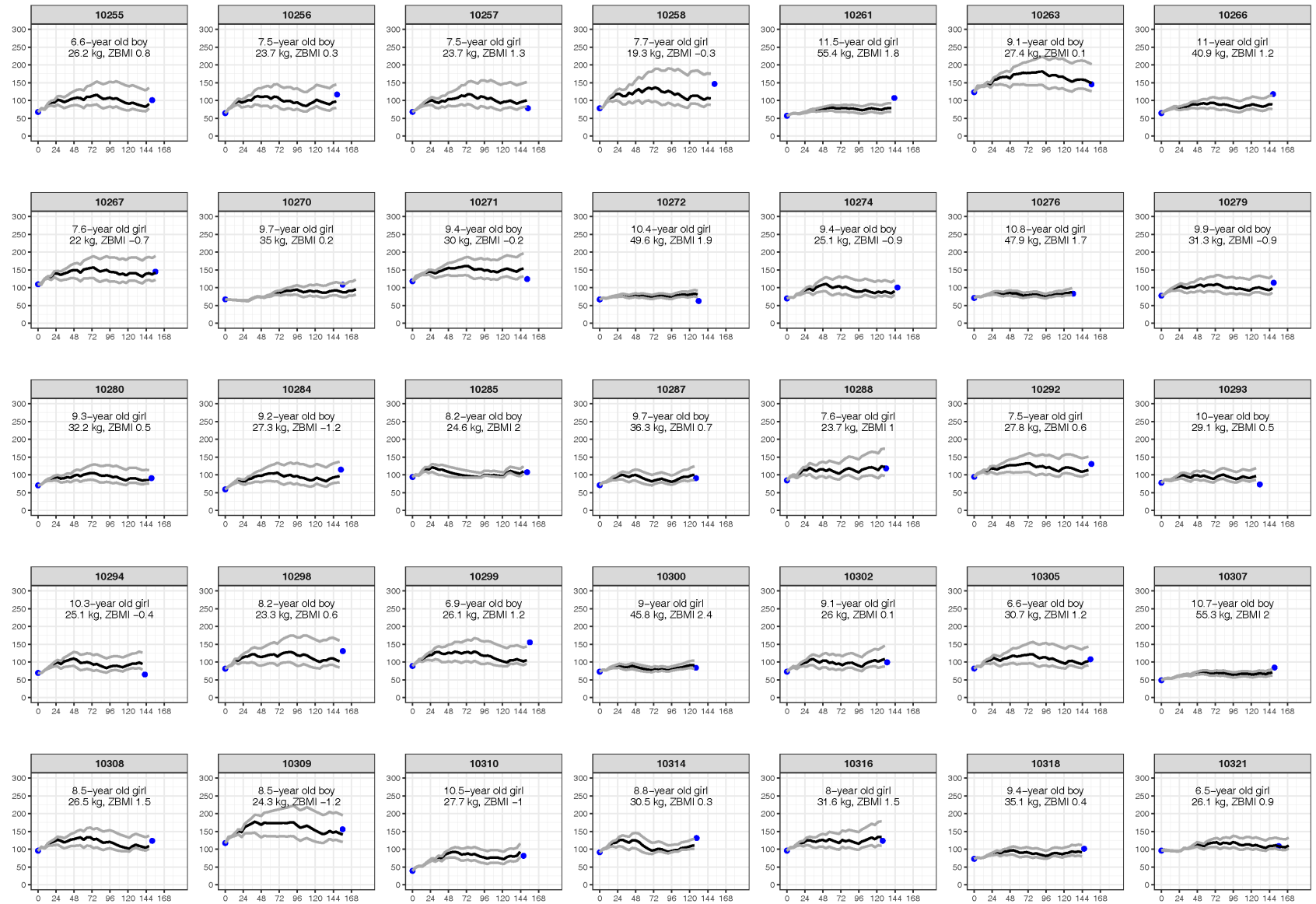


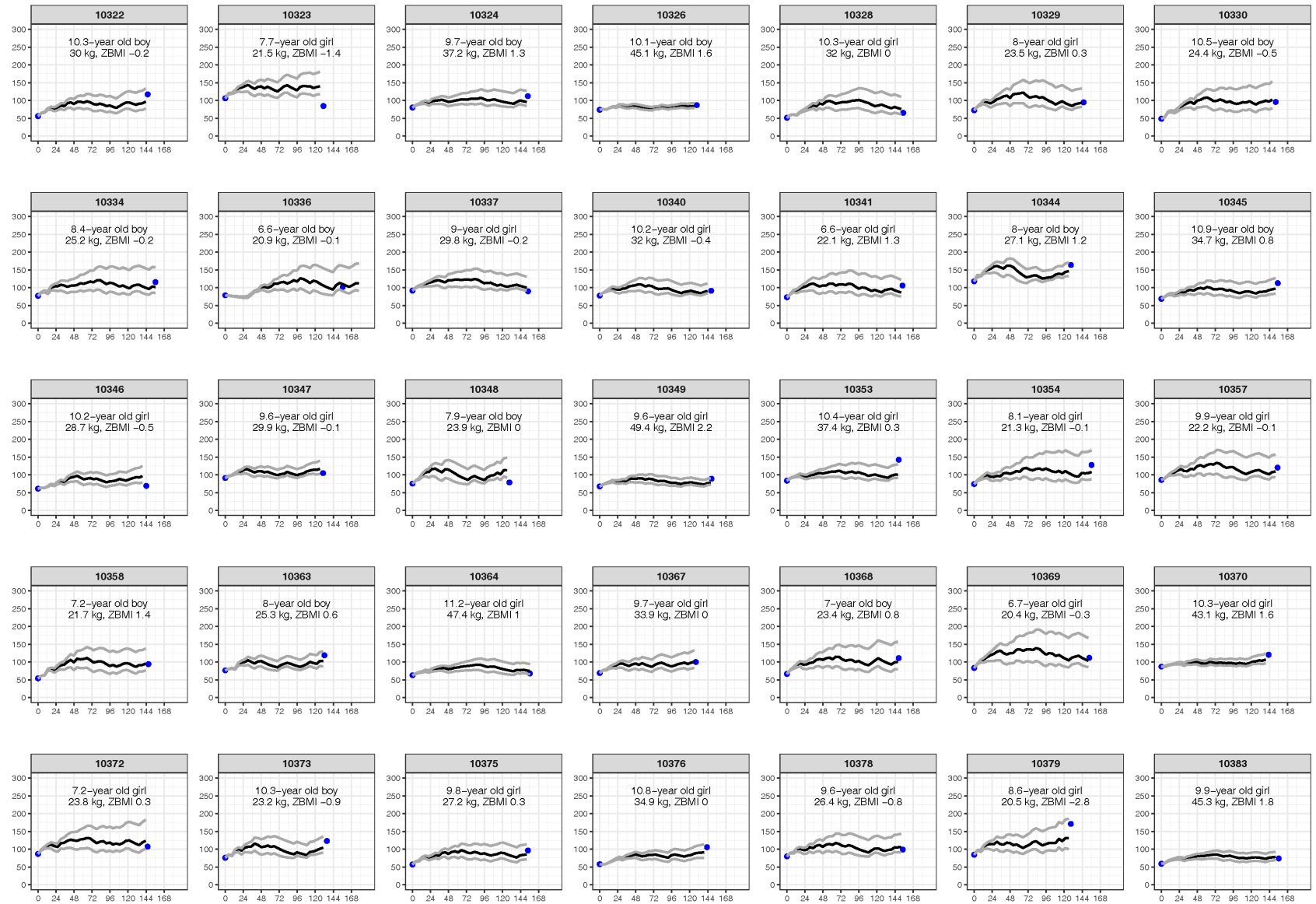
**Figure S9.** Simulation of serum 25(OH)D concentrations in 454 Cape Town children in the treatment group.

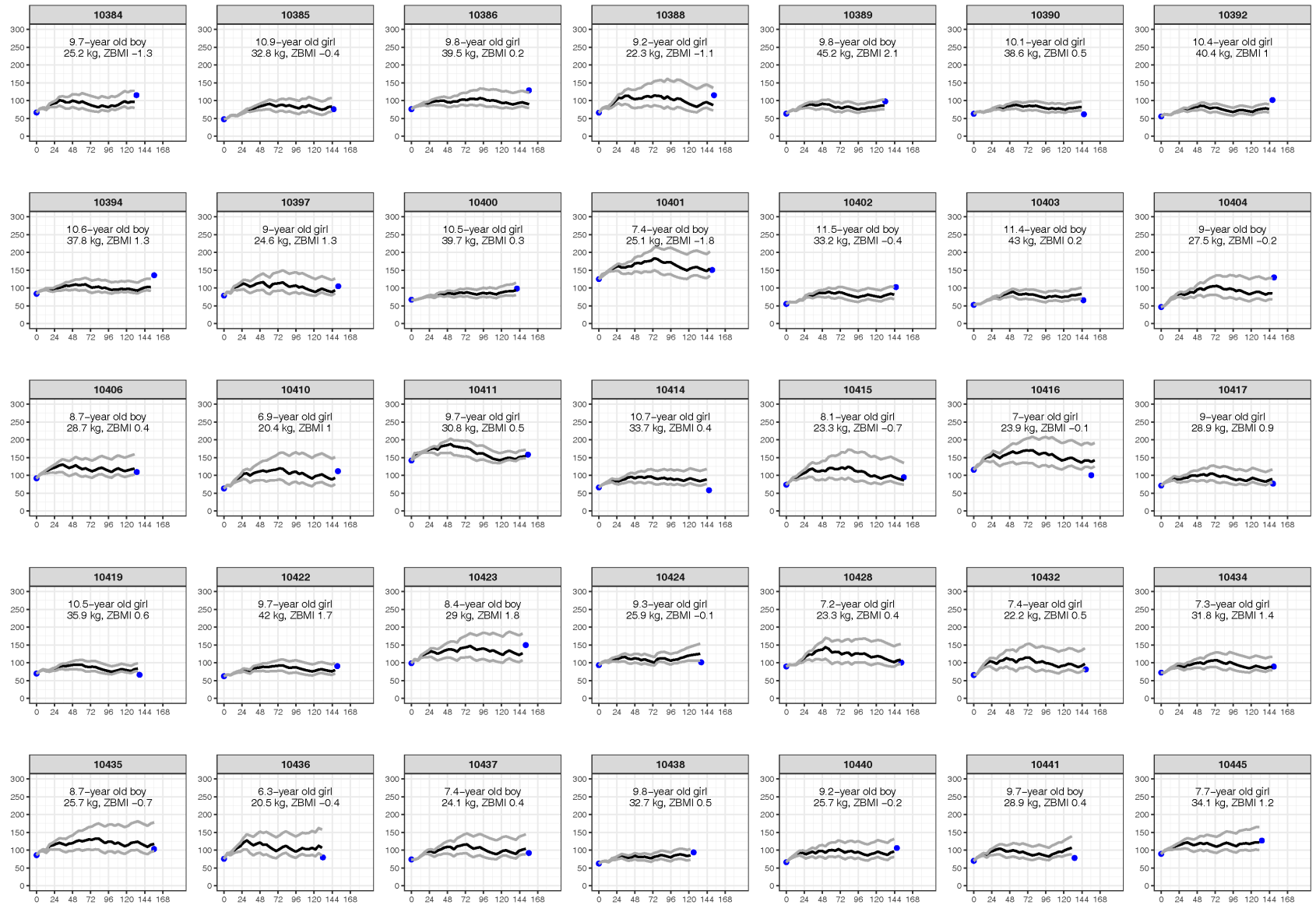


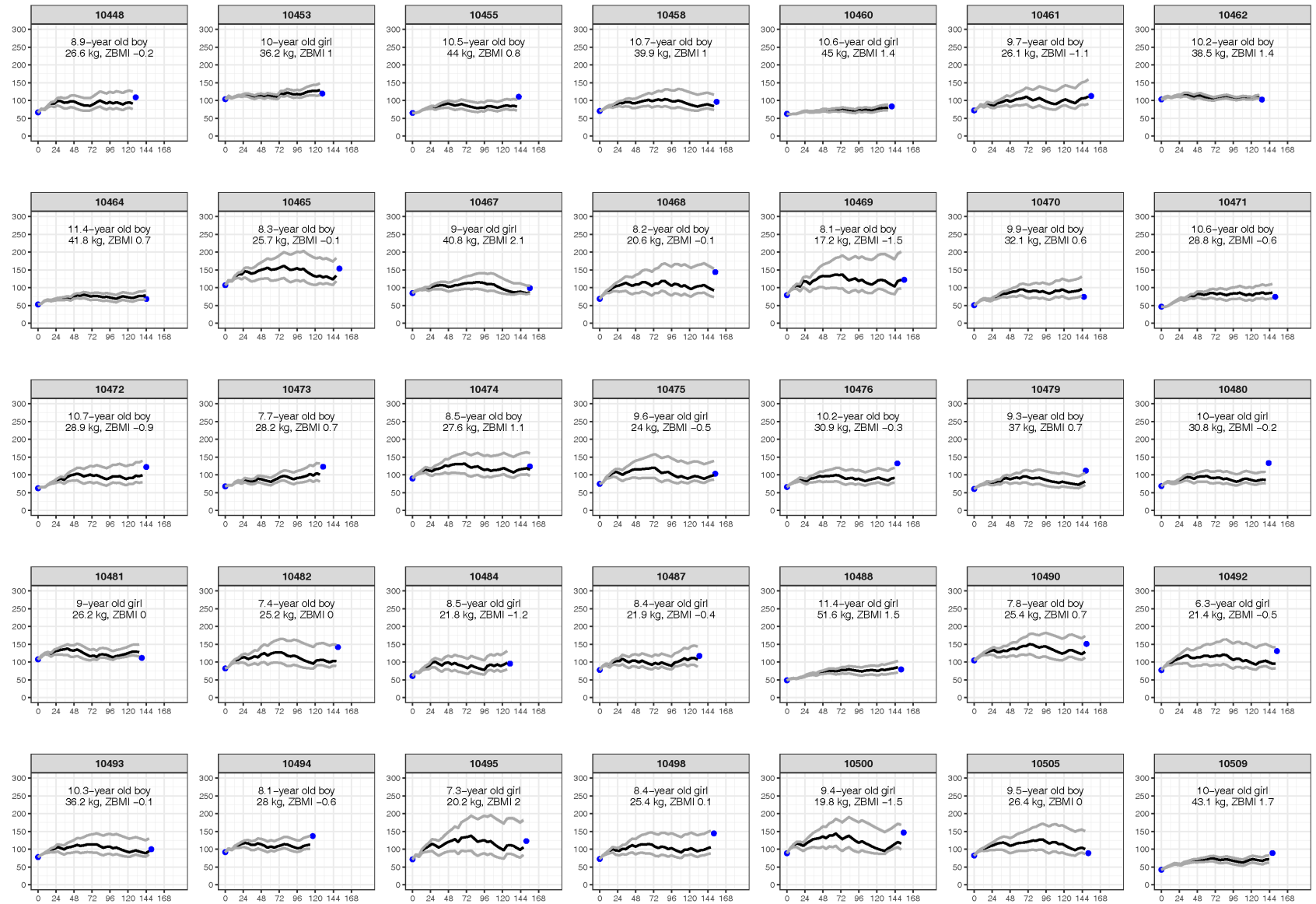


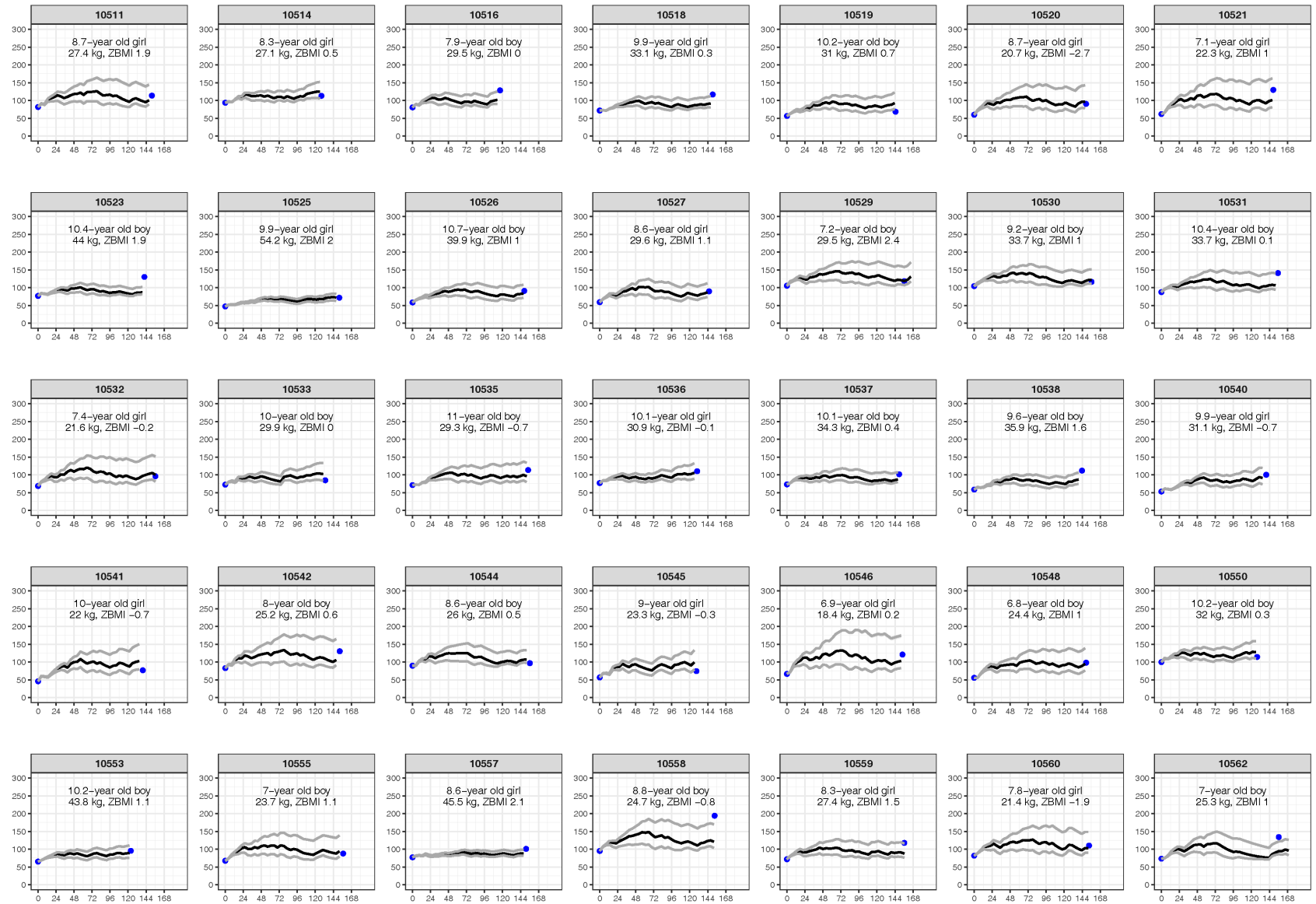


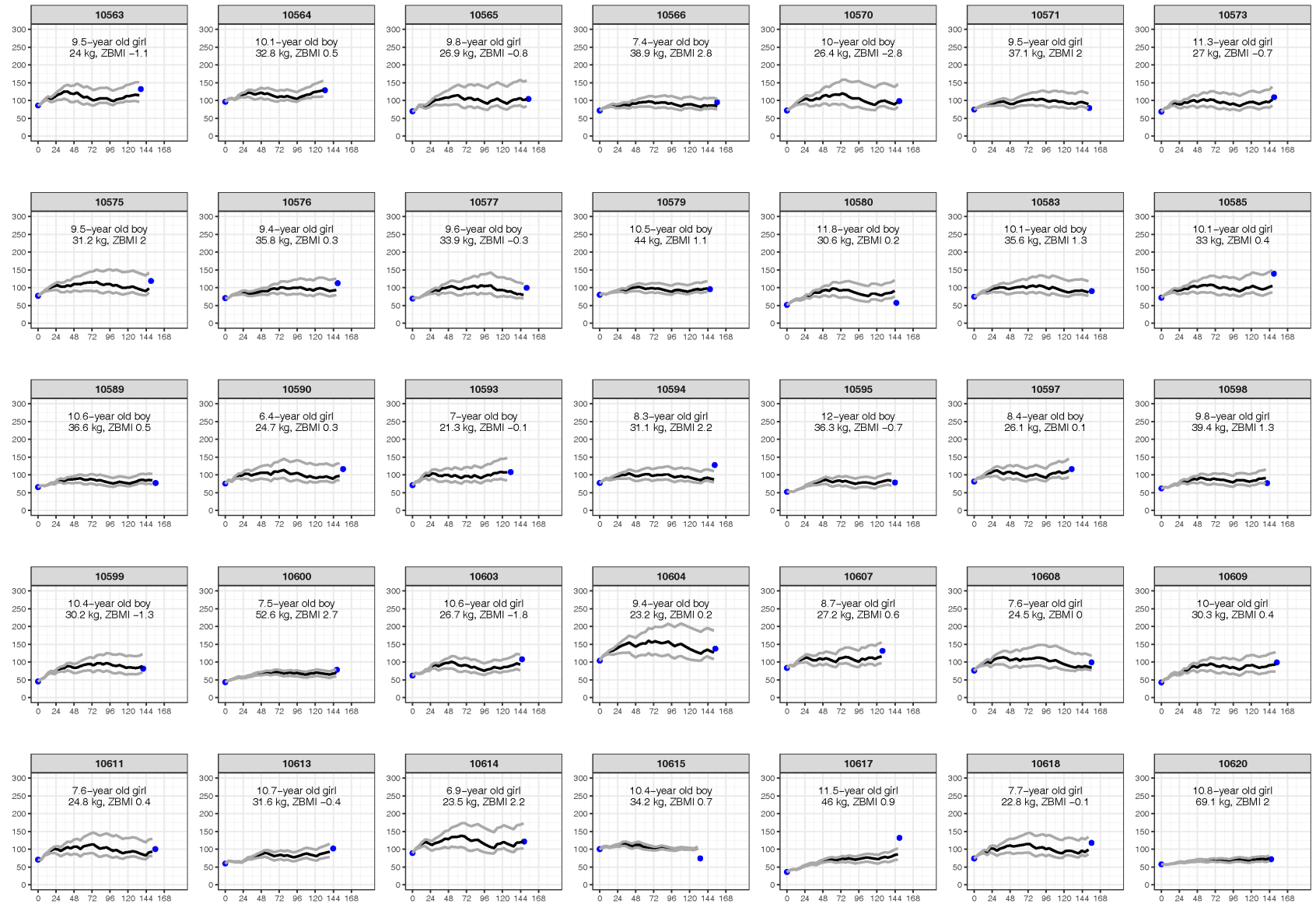


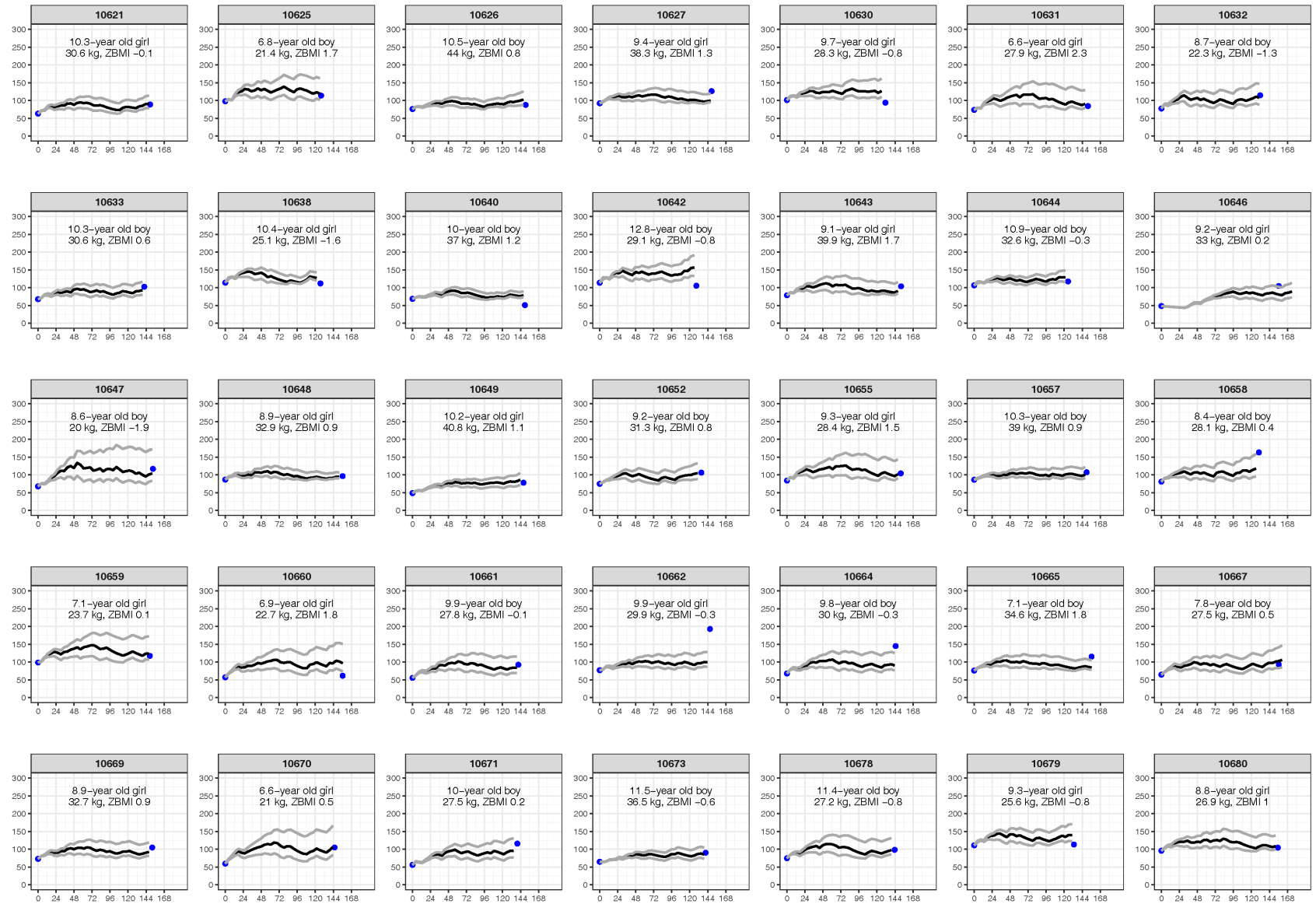


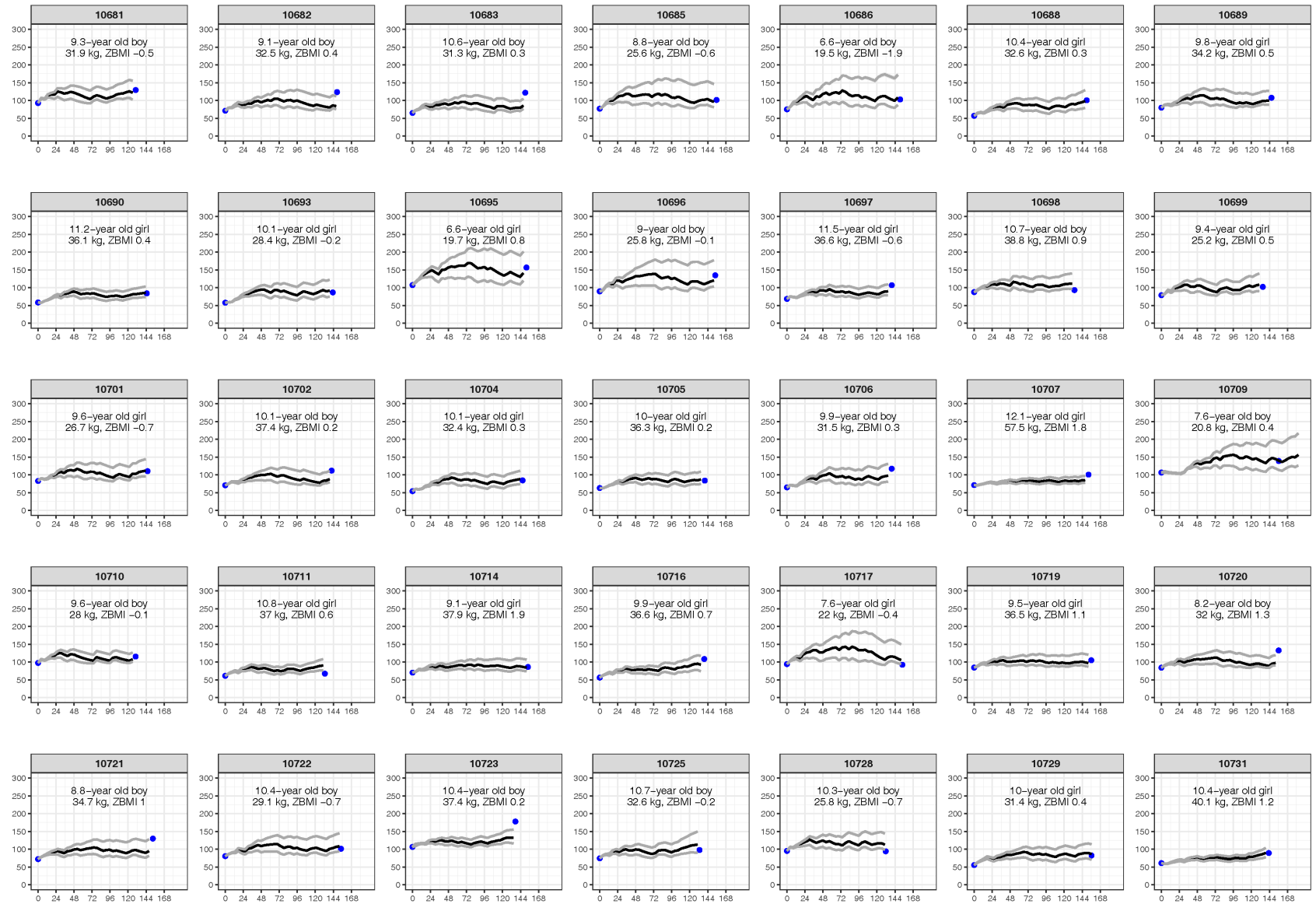


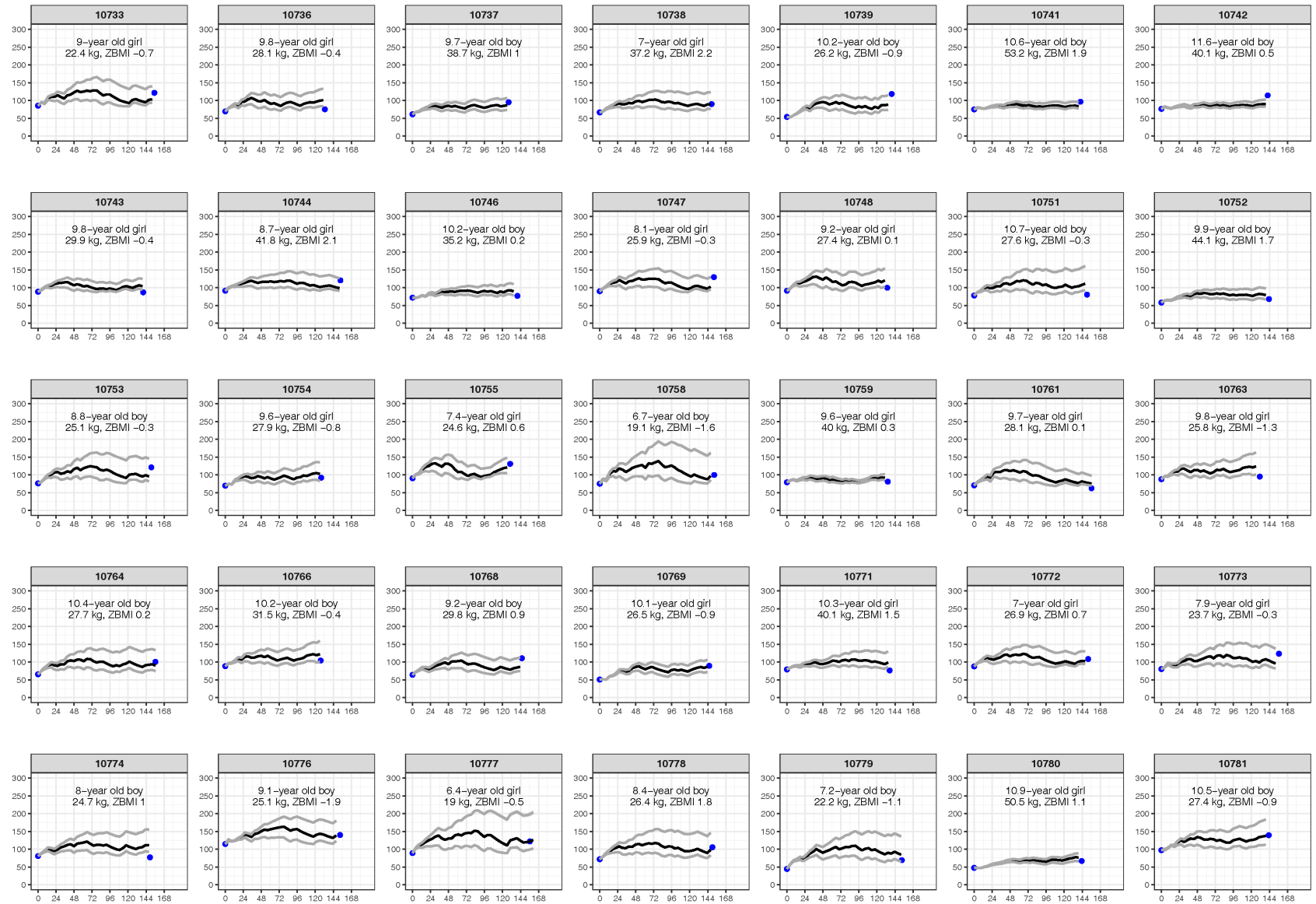












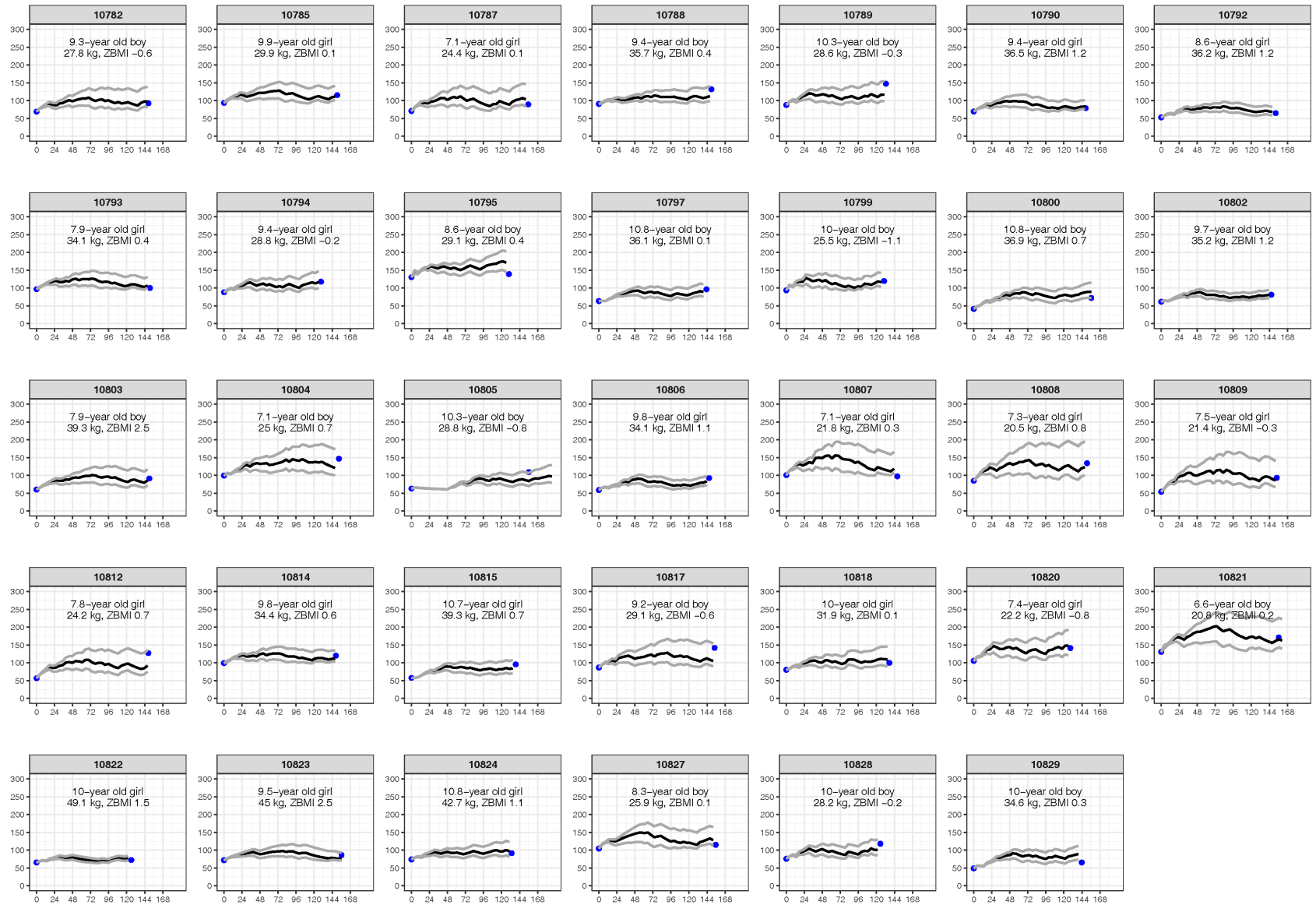


**Figure S10.** The distribution of residual error at 3 years: observation – population prediction at the 50<sup>th</sup> percentile. Red vertical line: 50<sup>th</sup> percentile = 5.4 nmol/L. Dashed vertical lines: 5<sup>th</sup> and 95<sup>th</sup> percentiles (-26.2 and 39.5 nmol/L, respectively).

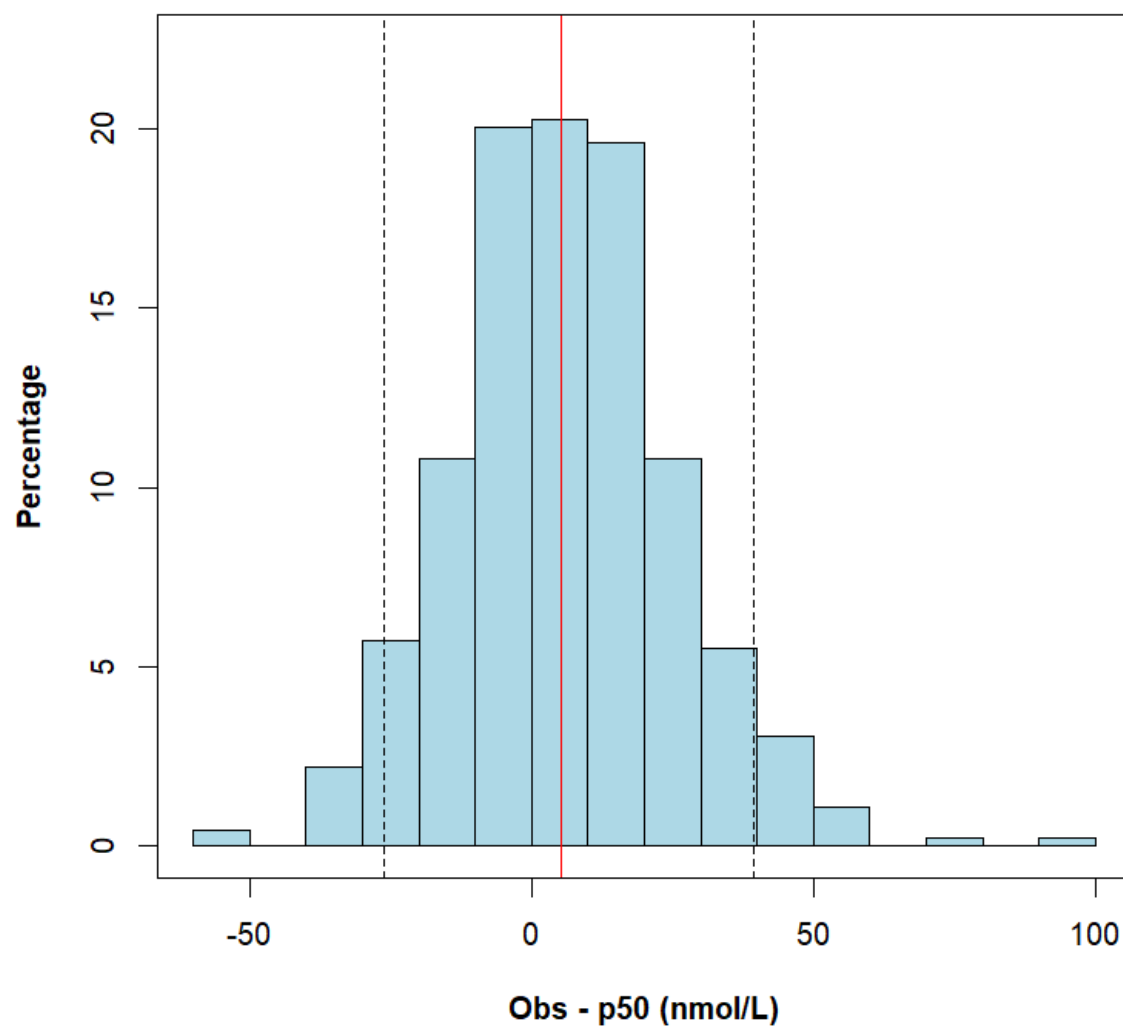


**Figure S11.** The distribution of the range (i.e. 97.5<sup>th</sup> – 2.5<sup>th</sup> percentiles) at 1, 2, and 3 years. Red vertical line: 50<sup>th</sup> percentile of the range. Dashed vertical lines: 5<sup>th</sup> and 95<sup>th</sup> percentiles of the range.

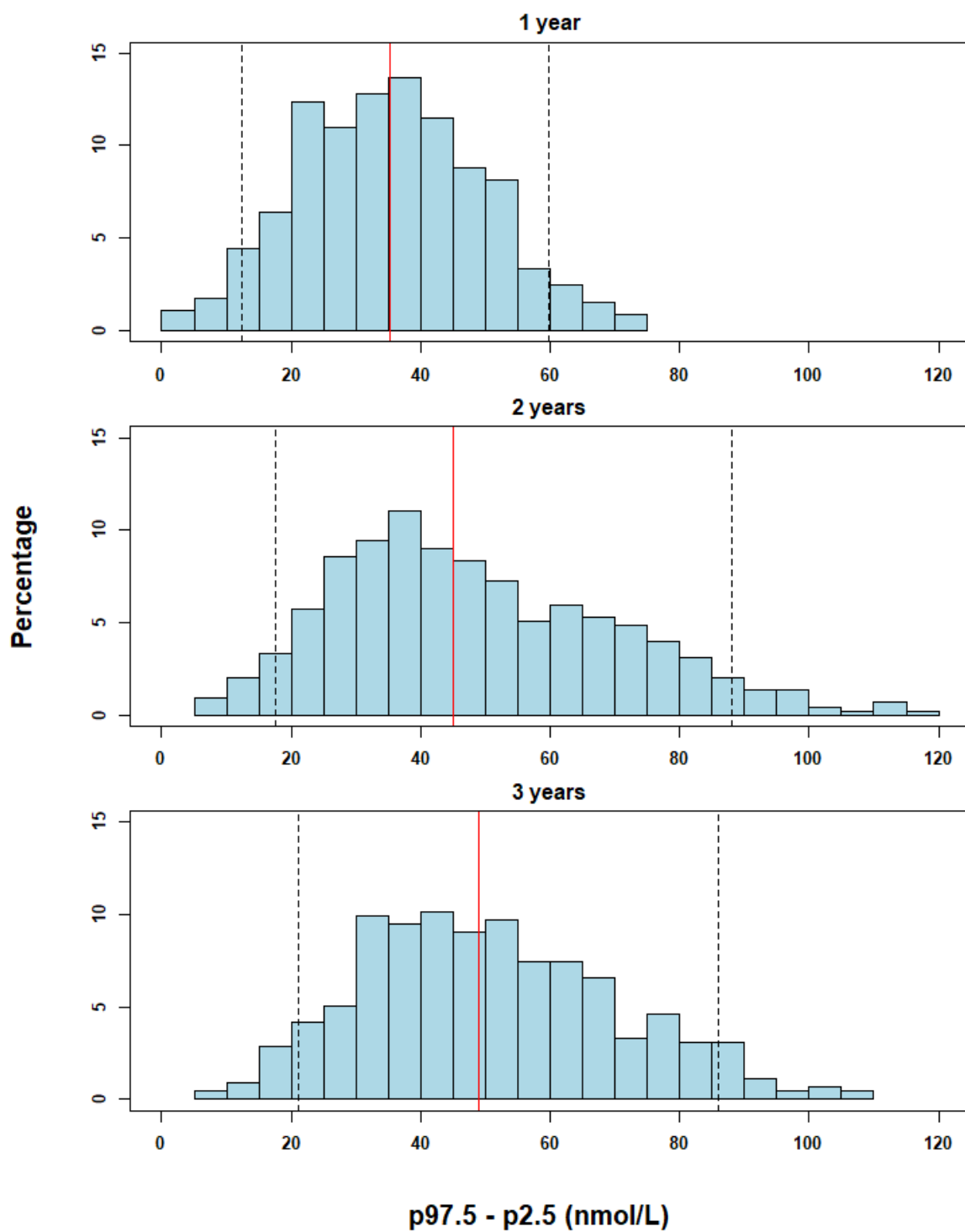


**Figure S12.** The scatter plots between the 2.5th – 97.5th percentiles range and baseline bodyweight and ZBMI.

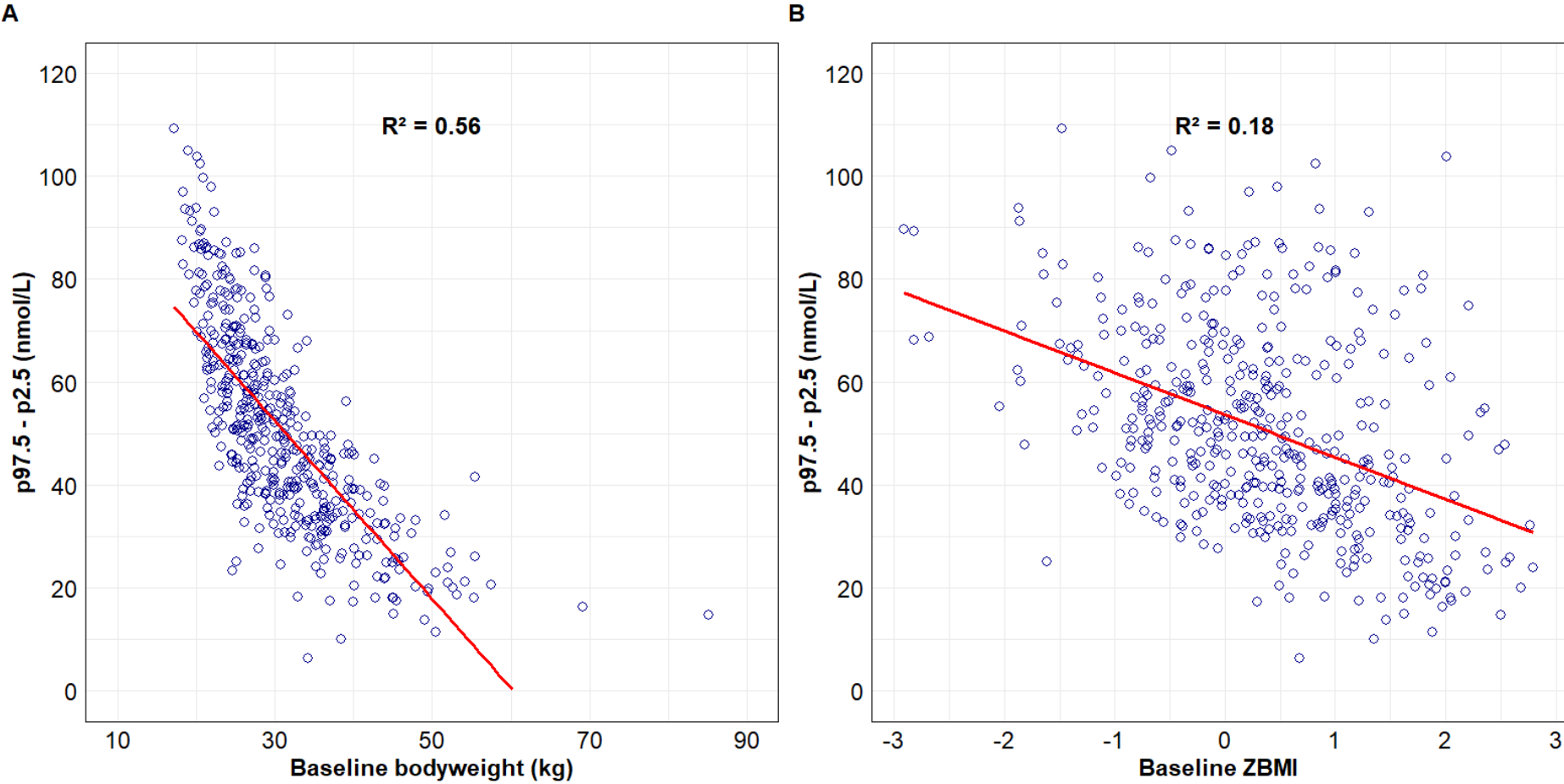


**Figure S13.** Comparison of the treated Mongolian children (A-E: n = 1756) with treated Cape Town children used to fit the model (F-J: n = 77). For the Mongolian trial, we selected those children (less than 12-year-old) with both baseline and 3-year serum 25(OH)D, gated at the limit of quantification (14.2 nmol/L). Compliance is defined as the ratio between the total number of received doses (Cape Town: 250 $\mu$ g; Mongolia: 350 $\mu$ g) and the number of weeks. It is normalised to 100%. Dashed vertical lines: mean. Salmon: baseline. Cyan: final. For the Mongolian trial, weight was only measured at baseline.

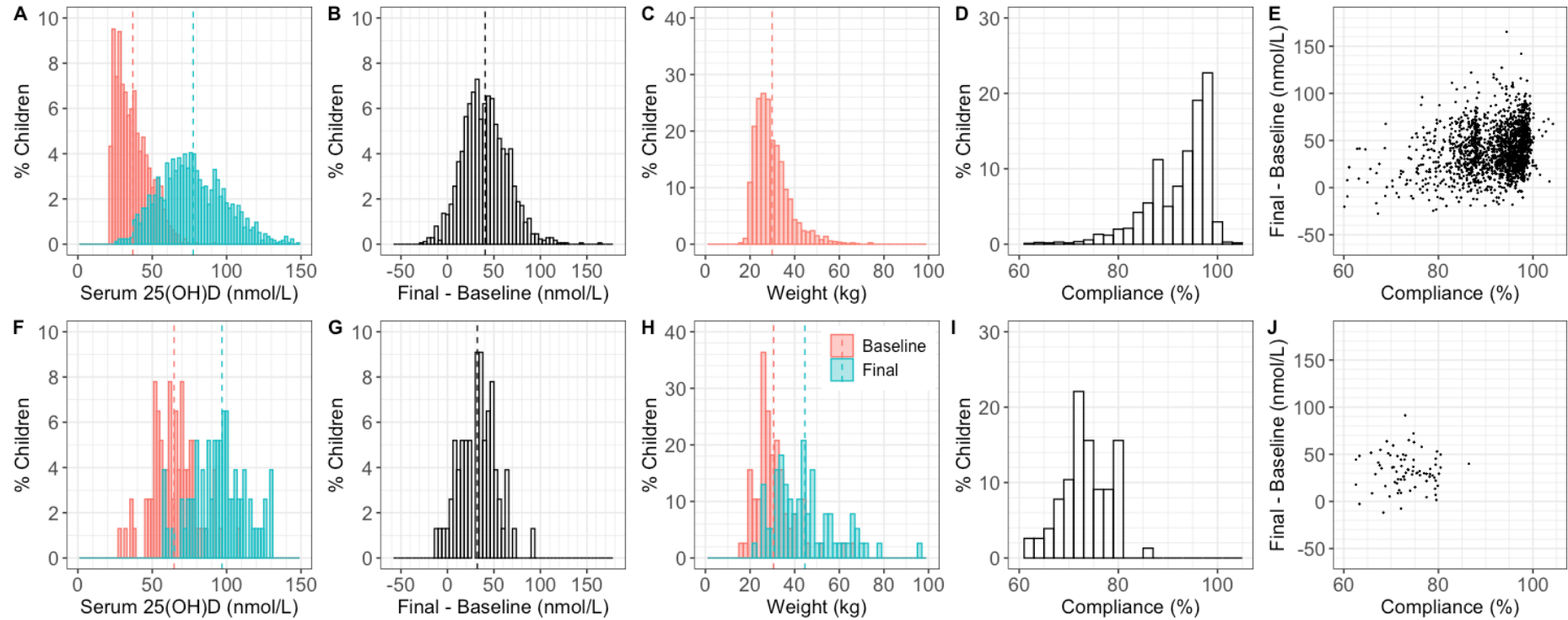


**Figure S14.** Simulation of serum 25(OH)D concentrations in Mongolian children receiving weekly dose of 350 µg vitamin D<sub>3</sub>. Simulated participants were under 12 years at baseline and had both baseline and follow up 25(OH)D<sub>3</sub> above the lower limit of quantification: 1756 children in total (Figures S1 and S13): A) the Cape Town model with typical values:  $CL_{max} = 0.012 \text{ h}^{-1}$ ,  $C_{50} = 86.3 \text{ nmol/L}$ ; B)  $CL_{max} = 0.048 \text{ h}^{-1}$ ; C)  $C_{50} = 30 \text{ nmol/L}$ ; D)  $C_{50} = 10 \text{ nmol/L}$ ; E)  $CL_{max} = 0.048 \text{ h}^{-1}$ ;  $C_{50} = 30 \text{ nmol/L}$ ; F)  $CL_{max} = 0.048 \text{ h}^{-1}$ ;  $C_{50} = 110 \text{ nmol/L}$ . f: girls; m: boys.

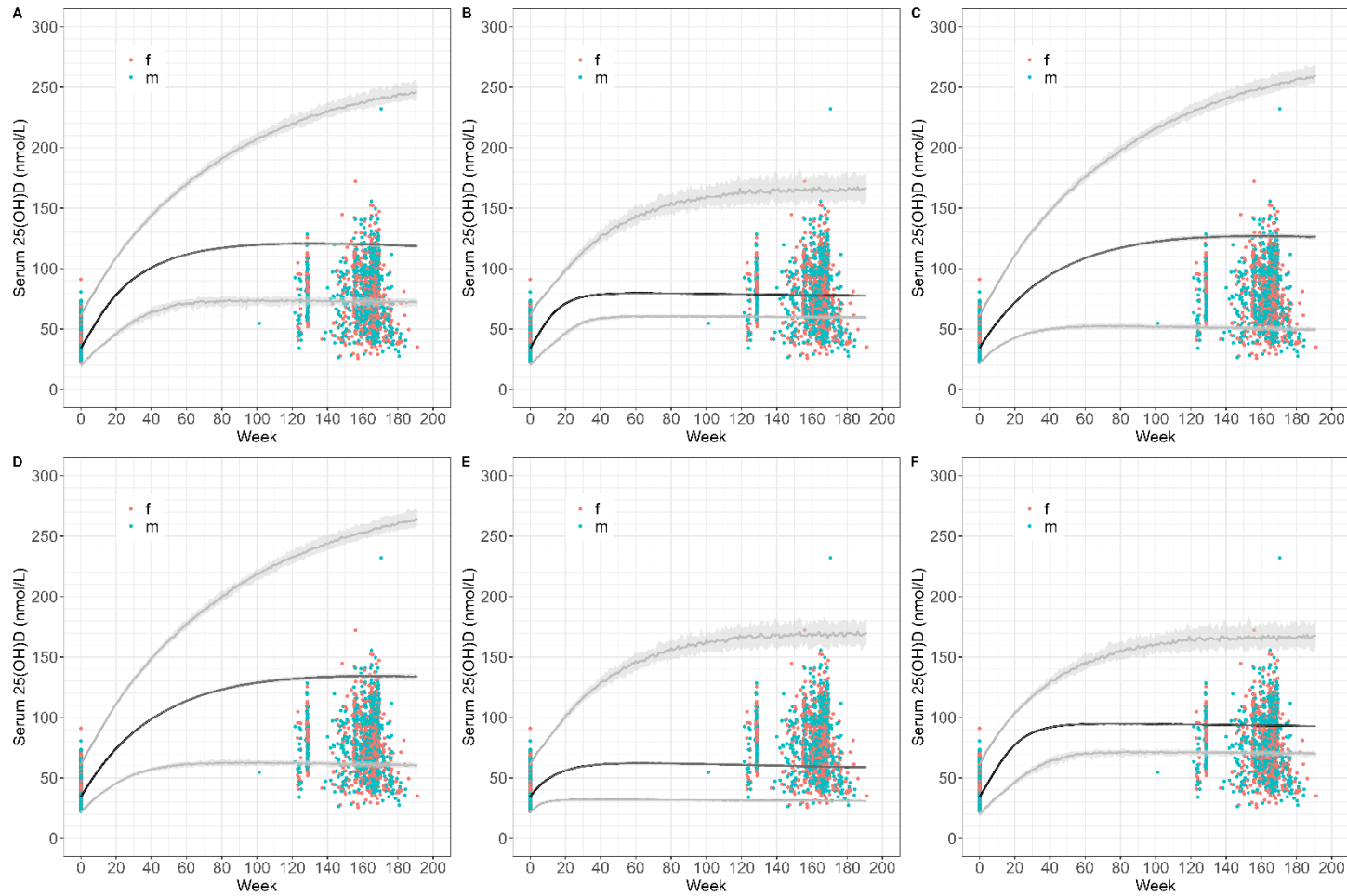


**Figure S15.** Serum 25(OH)D in the control group of the ViDiKids safety study (n=105) changes with time. A sinusoidal curve was fitted to the data. Amplitude: 11.5 nmol/L.

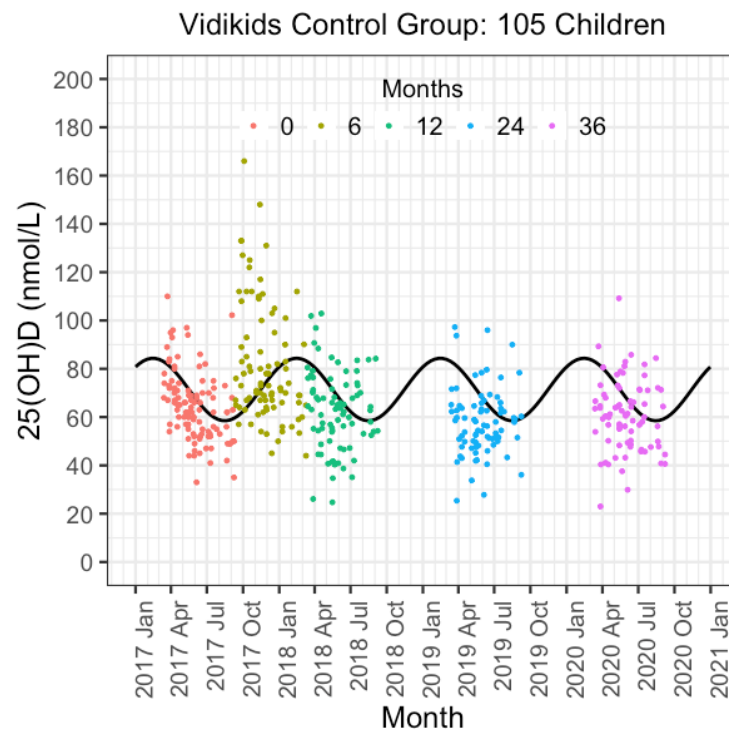


**Figure S16.** Simulation of serum 25(OH)D concentration at 3 years with weekly 250µg vitamin D<sub>3</sub> dosing at varying values of  $CL_{max}$  and  $C_{50}$ . A)  $CL_{max} = 0.012h^{-1}$ ,  $C_{50} \in [10,200] \text{ nmol/L}$ ; B)  $CL_{max} = 0.01248$ ,  $C_{50} \in [10,200] \text{ nmol/L}$ ; C)  $C_{50} = 30, 86.3, 110 \text{ nmol/L}$ ,  $CL_{max} \in [0.001, 0.06]h^{-1}$ . All plots in semi-log scale. Red dashed line marks the typical value for a Cape Town child. At baseline, weight = 30kg; 25(OH)D = 50 nmol/L. Weight increases by 3.16 kg/year.

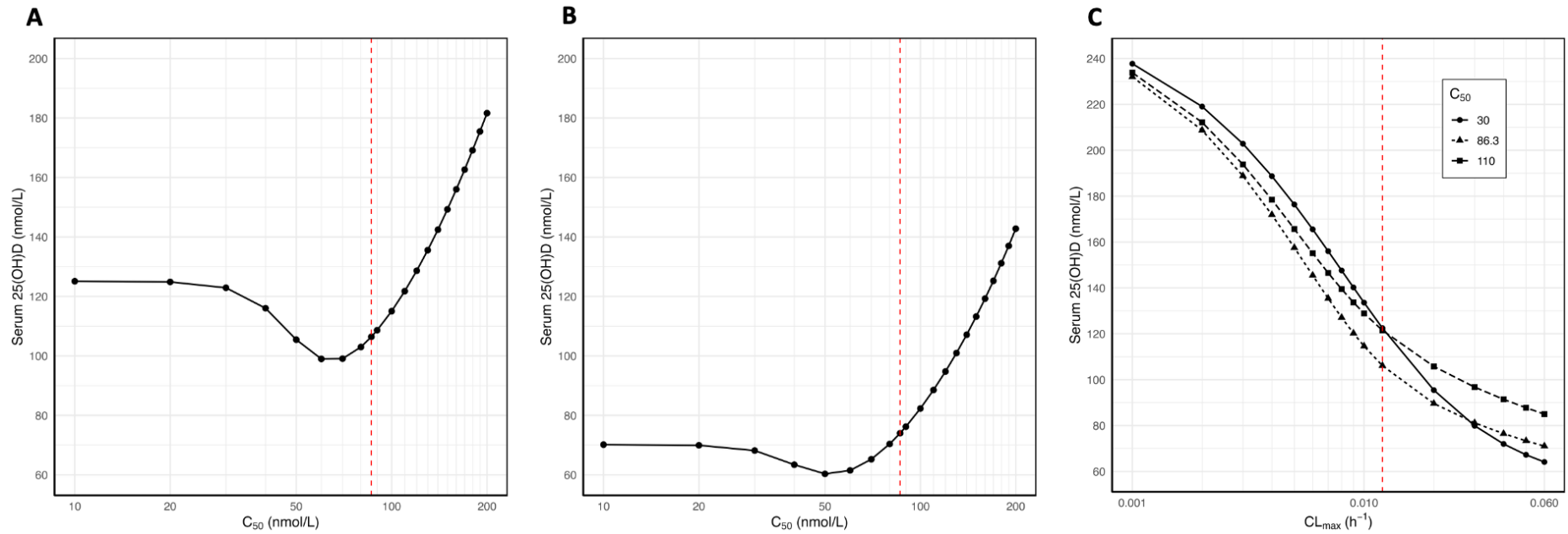
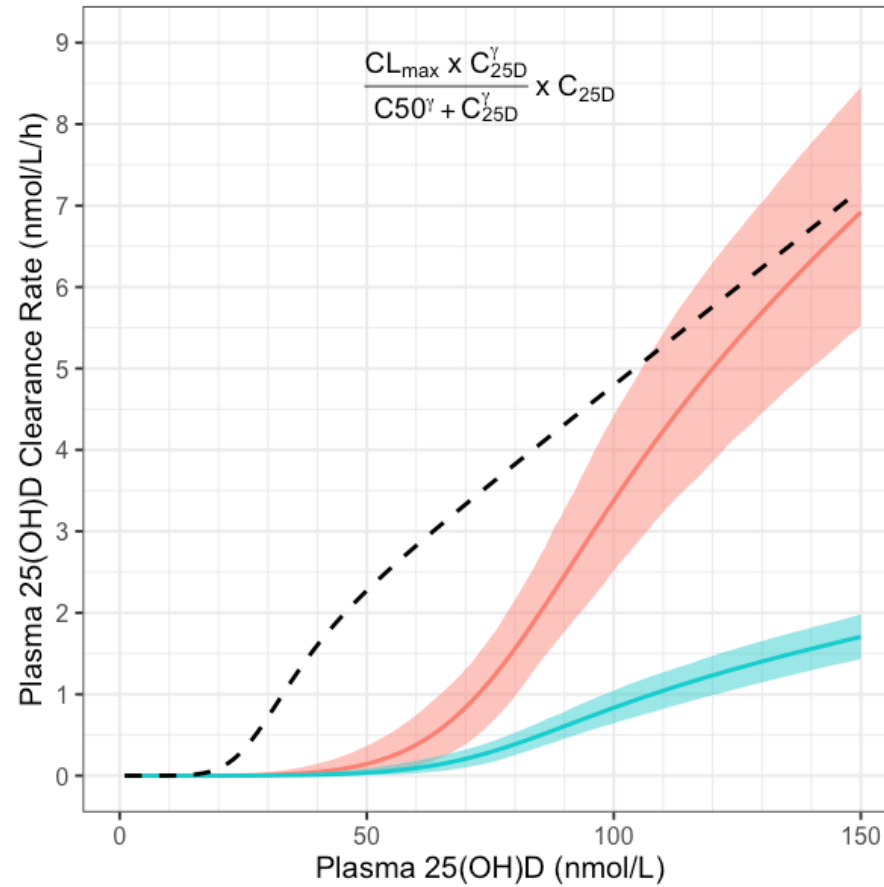


**Figure S17.** 25(OH)D clearance rate  $\frac{CL_{max} \times C_{25D}^\gamma}{C_{50}^\gamma + C_{25D}^\gamma} \times C_{25D}$  vs 25(OH)D. Salmon: healthy adults [14]. Cyan: Cape Town children (mean and 95% CI of  $CL_{max}$ : Table 2). Black dashed line:  $CL_{max} = 0.048 \text{ h}^{-1}$ ;  $C_{50} = 30 \text{ nmol/L}$ . For healthy adults (salmon) and Cape Town children (cyan): 1000 samples were generated using Latin Hypercube method for  $CL_{max}$ ,  $C_{50}$  and  $\gamma$ ; line: expected mean; band: 5% – 95% confidence interval.



## Supplementary Tables

**Table S1.** Baseline characteristics of the study population.

| Participants ( <i>n</i> = 77)    |             |
|----------------------------------|-------------|
| Age, y (Mean±SD)                 | 8.94±1.29   |
| Male, n (%)                      | 30(38.96)   |
| Weight, kg (Mean±SD)             | 30.57±8.99  |
| Height, cm (Mean±SD)             | 149±10.91   |
| BMI, kg/m <sup>2</sup> (Mean±SD) | 17.75±3.46  |
| ZBMI, n (%)                      |             |
| -3 to -2                         | 1 (1.30)    |
| -2 to -1                         | 7 (9.09)    |
| -1 to +1                         | 49 (63.64)  |
| +1 to +2                         | 14 (18.18)  |
| +2 to +3                         | 6 (7.79)    |
| 25(OH)D, nmol/L (Mean±SD)        | 64.67±14.85 |

Data are presented as number with percentage in parenthesis or as mean and standard deviation.

**Abbreviation:** BMI, body mass index; ZBMI, BMI for age z-score.

**Table S2.** Physiological parameters used for paediatric compartmental lumping.

| Compartment                         | Blood flow (%) * | Blood flow (L/h) # | Volume (%) | Volume (L) § | Source                      |
|-------------------------------------|------------------|--------------------|------------|--------------|-----------------------------|
| Lung                                | 100              | 273                | 0.76       | 0.23         | Brown1997 and Edginton 2006 |
| Heart                               | 4                | 10.92              | 0.47       | 0.14         | Brown1997                   |
| Kidney                              | 17.5             | 47.78              | 0.44       | 0.13         | Brown1997                   |
| Liver, total                        | 22.7             | 61.97              | 2.57       | 0.77         | Brown1997                   |
| Liver, hepatic artery               | 4.6              | 12.56              | -          | -            | Brown1997                   |
| GI                                  | 15.1             | 41.22              | 1.71       | 0.51         | adjusted                    |
| Spleen                              | 3                | 8.19               | 0.26       | 0.08         | adjusted                    |
| Brain                               | 11.4             | 31.12              | 2          | 0.60         | Brown1997                   |
| Adipose                             | 5.2              | 14.20              | 21.42      | 6.43         | Brown1997                   |
| Skin                                | 5.8              | 15.83              | 3.71       | 1.11         | Brown1997                   |
| Muscle                              | 19.1             | 52.14              | 40         | 12           | Brown1997                   |
| Bone                                | 4.2              | 11.47              | 14.29      | 4.29         | Brown1997                   |
| Venous                              | 100              | 273                | 6          | 1.80         | Brown1997                   |
| Arterial                            | 100              | 273                | 2          | 0.60         | Brown1997                   |
| Splanchnic organ                    | 18.1             | 49.413             | na         |              | Brown1997                   |
| Rest of the body (all other organs) | 10.1             | 27.57              | 4.37       | 1.31         | Brown1997                   |

\* Blood flow (%) comes from (Brown *et al*, 1997)

# Edginton (2006) reported mean cardiac output for boys (4.8 L/min) and girls (4.3 L/min) aged between 7 and 9 years. We take the average of 4.55 L/min (273 L/h). Subsequently, blood flow to each organ was calculated by multiplying the first column (blood flow %) with the total mean cardiac output.

§ We assumed an apparent density of 1 kg/L. For a 30 kg bodyweight, total volume is 30L.

Brown RP, Delp MD, Lindstedt SL, Rhomberg LR and Beliles RP (1997) Physiological parameter values for physiologically based pharmacokinetic models. *Toxicology and industrial health* **13**:407-484.

Edginton AN, Schmitt W and Willmann S (2006) Development and Evaluation of a Generic Physiologically Based Pharmacokinetic Model for Children. *Clinical Pharmacokinetics* **45**:1013-1034.

**Table S3.** Physiological parameters of the PBPK model for paediatrics after compartments are lumped together.

| Parameters  | Definition                         | Units | Value  |
|-------------|------------------------------------|-------|--------|
| <b>Qco</b>  | Cardiac output                     | L/h   | 273.00 |
| <b>Ql</b>   | Blood flow to liver                | L/h   | 61.97  |
| <b>Qrb</b>  | Blood flow to rest of body         | L/h   | 211.03 |
| <b>Vven</b> | Volume of venous compartment       | L     | 1.80   |
| <b>VI</b>   | Volume of liver compartment        | L     | 0.77   |
| <b>Vrb</b>  | Volume of rest of body compartment | L     | 26.83  |
| <b>Vart</b> | Volume of arterial compartment     | L     | 0.6    |

**Note:** Lumping: Assume apparent density = 1kg/L.  $V_{rb} = 30L - V_I - V_{ven} - V_{art}$ ;  $Q_{rb} = Q_{co} - Q_l$ .

**Table S4.** Drug-specific parameters for model development.

| Parameter        | Description                                | Unit          | Value |
|------------------|--------------------------------------------|---------------|-------|
| <b>Vitamin D</b> |                                            |               |       |
| $K_a$            | Absorption rate                            | $h^{-1}$      | 0.19  |
| $K_{p_l}$        | Partition coefficient for liver            | Dimensionless | 1     |
| $K_{p_{rb}}$     | Partition coefficient for rest of the body | Dimensionless | 0.09  |
| MCLH             | Hepatic clearance after repeated dose      | $h^{-1}$      | 0.222 |
| <b>25(OH)D</b>   |                                            |               |       |
| $K_{p25_l}$      | Partition coefficient for liver            | Dimensionless | 1     |
| $C_{50}$         | Concentration at half maximum clearance    | nmol/L        | 86.3  |
| $\gamma$         | Exponent                                   | Dimensionless | 5.64  |

**Table S5.** Model development for 25(OH)D paediatric pharmacokinetics.

|   | Fixed Effects                           | Random Effects                                                                                                                                                                                  | Covariate                                                                                                                                                                                                                                            | AIC  | BIC  | OBJFV | Comments                                                                                                                                                      |
|---|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$\text{cor}(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = 0.204$                                      | -                                                                                                                                                                                                                                                    | 2408 | 2434 | 1846  | Base model                                                                                                                                                    |
| 2 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$\text{cor}(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.668$                                     | $V_{art} = TV_{art} \times \frac{WT}{30}$<br>$V_{ven} = TV_{ven} \times \frac{WT}{30}$<br>$V_{rb} = TV_{rb} \times \frac{WT}{30}$<br>$V_l = TV_l \times \frac{WT}{30}$                                                                               | 2400 | 2426 | 1838  | Baseline weight is used to predict the volume of distribution.<br><br>The objective function value is improved compared to model 1.                           |
| 3 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}} \times (\frac{WT}{30})^{0.75}}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$\text{cor}(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.754$       | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}} \times (\frac{WT}{30})^{0.75}}$                                                                                                                                                                           | 2388 | 2413 | 1826  | Baseline weight is used to predict clearance.<br><br>The objective function value is improved compared to model 2.                                            |
| 4 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}} \times (\frac{WT_{cur}}{30})^{0.75}}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$\text{cor}(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.781$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}} \times (\frac{WT}{30})^{0.75}}$<br>$V_{art} = TV_{art} \times \frac{WT}{30}$<br>$V_{ven} = TV_{ven} \times \frac{WT}{30}$<br>$V_{rb} = TV_{rb} \times \frac{WT}{30}$<br>$V_l = TV_l \times \frac{WT}{30}$ | 2387 | 2413 | 1825  | Baseline weight is used to predict the volume of distribution and clearance.<br><br>The objective function value is not significantly different from model 3. |
| 5 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}} \times (\frac{WT_{cur}}{30})^{0.75}}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$\text{cor}(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.731$ | $WT_{cur} = WT + 3.0836 \times (\frac{\text{time}}{24 \times 365 \times 3})$ for boy<br><br>$WT_{cur} = WT + 3.2282 \times (\frac{\text{time}}{24 \times 365 \times 3})$ for girl                                                                    | 2527 | 2552 | 1965  | A changing weight is used to predict the volume of distribution and clearance in a sex-dependent manner.                                                      |

|   | Fixed Effects                           | Random Effects                                                                                                                                                                                                                                 | Covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                 |
|---|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                                         |                                                                                                                                                                                                                                                | $CL_{\max} = e^{TCL_{\max} + \eta_{CL_{\max}}} \times \left(\frac{WT_{\text{cur}}}{30}\right)^{0.75}$ $K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$ $V_{\text{art}} = TV_{\text{art}} \times \frac{WT_{\text{cur}}}{30}$ $V_{\text{ven}} = TV_{\text{ven}} \times \frac{WT_{\text{cur}}}{30}$ $V_{\text{rb}} = TV_{\text{rb}} \times \frac{WT_{\text{cur}}}{30}$ $V_l = TV_l \times \frac{WT_{\text{cur}}}{30}$                                                                                                                                                                                                                                                               |      |      |       | The objective function value is higher than model 4.                                                                                                                                                                                                     |
| 6 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{\max} = e^{TCL_{\max} + \eta_{CL_{\max}}} \times \left(\frac{WT_{\text{cur}}}{30}\right)^{0.75}$ $K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}} + (ZBMI \times K_{p25rb} ZBMI)}$ $\text{cor}(\eta_{CL_{\max}}, \eta_{K_{p25rb}}) = -0.758$ | $WT_{\text{cur}} = WT + 3.0836 \times \left(\frac{\text{time}}{24 \times 365 \times 3}\right) \text{ for boy}$ $WT_{\text{cur}} = WT + 3.2282 \times \left(\frac{\text{time}}{24 \times 365 \times 3}\right) \text{ for girl}$ $CL_{\max} = e^{TCL_{\max} + \eta_{CL_{\max}}} \times \left(\frac{WT_{\text{cur}}}{30}\right)^{0.75}$ $K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}} + (ZBMI \times K_{p25rb} ZBMI)}$ $V_{\text{art}} = TV_{\text{art}} \times \frac{WT_{\text{cur}}}{30}$ $V_{\text{ven}} = TV_{\text{ven}} \times \frac{WT_{\text{cur}}}{30}$ $V_{\text{rb}} = TV_{\text{rb}} \times \frac{WT_{\text{cur}}}{30}$ $V_l = TV_l \times \frac{WT_{\text{cur}}}{30}$ | 2535 | 2564 | 1971  | <p>A changing weight is used to predict the volume of distribution and clearance in a sex-dependent manner. ZBMI is used as a covariate for the partition coefficient of the rest of the body.</p> <p>The objective function value is higher than 4.</p> |
| 7 | CL <sub>MAX</sub><br>Kp25 <sub>rb</sub> | $CL_{\max} = e^{TCL_{\max} + \eta_{CL_{\max}}} \times \left(\frac{WT_{\text{cur}}}{30}\right)^{0.75}$ $K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$ $\text{cor}(\eta_{CL_{\max}}, \eta_{K_{p25rb}}) = -0.760$                                | $WT_{\text{cur}} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$ $CL_{\max} = e^{TCL_{\max} + \eta_{CL_{\max}}} \times \left(\frac{WT_{\text{cur}}}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2401 | 2426 | 1839  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated</p>                                                                                                                                             |

|    | Fixed Effects                                  | Random Effects                                                                                                                                                                                      | Covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                                                                                                                                    |
|----|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                |                                                                                                                                                                                                     | $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$                                                                                                                                                                                                                                                                                                                                                                                                                 |      |      |       | <p>linearly between the baseline and final time points.</p> <p>The objective function value is higher than model 4.</p>                                                                                                                                                                                                                                                     |
| 8  | $CL_{MAX}$<br>$Kp25_{rb}$                      | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$cor(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.204$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$ $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$ $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $cp = \frac{A25_{ven}}{V_{ven}} - 1.9; \text{ time} = 24 \times 365$ $cp = \frac{A25_{ven}}{V_{ven}} - 6.6; \text{ time} = 24 \times 365 \times 2$ $cp = \frac{A25_{ven}}{V_{ven}} - 4.1; \text{ time} = 24 \times 365 \times 3$ | 3078 | 3104 | 2516  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated linearly between the baseline and final time points.</p> <p>Plasma concentration is calculated at a specific time point ("cp") subtracting the mean value of the control group at each time point.</p> <p>The objective function value is higher than model 4.</p> |
| 9a | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 1)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TK_{p25fm}}$                                                                         | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$ $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                                                                                                                                                                        | 2385 | 2404 | 1828  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated</p>                                                                                                                                                                                                                                                                |

|           | Fixed Effects                                  | Random Effects                                                                                                              | Covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                                                                      |
|-----------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           |                                                |                                                                                                                             | $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$                                                                                                                                                                                      |      |      |       | <p>linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value is marginally higher than model 4, while the AIC and BIC are improved.</p>                                                                                |
| <b>9b</b> | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 2)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ | 2371 | 2389 | 1813  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value, AIC and BIC are improved compared to model 9a.</p> |
| <b>9c</b> | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 3)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                                                                                                                    | 2360 | 2379 | 1802  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated</p>                                                                                                                                                                                                  |

|           | Fixed Effects                                  | Random Effects                                                                                                              | Covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                                                                                               |
|-----------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           |                                                |                                                                                                                             | $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$                                                                                                                                                                                      |      |      |       | <p>linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value, AIC and BIC are improved compared to model 9b.</p>                                                                                                                                |
| <b>9d</b> | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 4)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{\text{time}}{24 \times 365 \times 3}$ | 2353 | 2372 | 1795  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value, AIC and BIC are improved compared to model 9c.</p> <p><b>Best model</b></p> |
| <b>9e</b> | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 6)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{\text{time}}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                                                                                                                    | 2353 | 2371 | 1795  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated</p>                                                                                                                                                                                                                           |

|    | Fixed Effects                                  | Random Effects                                                                                                              | Covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                                                                   |
|----|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                |                                                                                                                             | $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{time}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{time}{24 \times 365 \times 3}$                                                                                                                                                                               |      |      |       | <p>linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value, AIC and BIC are similar to model 9d.</p>                                                                                                              |
| 9f | $CL_{MAX}$<br>$Kp25_{fm}$<br>$(Kp25_{lm} = 8)$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{time}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$ $V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$ $V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$ $V_l = TV_l \times \frac{WT_{cur}}{30}$ $V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{time}{24 \times 365 \times 3}$ $V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{time}{24 \times 365 \times 3}$ | 2378 | 2397 | 1821  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.*</p> <p>The objective function value, AIC and BIC are worse compared to model 9d.</p> |
| 10 | $CL_{MAX}$<br>$Kp25_{fm}$<br>$Kp25_{lm}$       | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$<br>$K_{p25fm} = e^{TKp25_{fm}}$ | $WT_{cur} = WT + (WT_{3Y} - WT) \times \frac{time}{24 \times 365 \times 3}$<br>$CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT_{cur}}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                                                                                                      | 2409 | 2435 | 1847  | <p>A changing weight is used to predict the volume of distribution and clearance. Weight is interpolated</p>                                                                                                                                                                                               |

|    | Fixed Effects                           | Random Effects                                                                                                                                                                                | Covariate                                                                                                                                                                                                                                                                                                                                                        | AIC  | BIC  | OBJFV | Comments                                                                                                                                                                                                                                                           |
|----|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                         | $K_{p25lm} = e^{TK_{p25lm}}$                                                                                                                                                                  | $V_{art} = TV_{art} \times \frac{WT_{cur}}{30}$<br>$V_{ven} = TV_{ven} \times \frac{WT_{cur}}{30}$<br>$V_{rb} = TV_{rb} \times \frac{WT_{cur}}{30}$<br>$V_l = TV_l \times \frac{WT_{cur}}{30}$<br>$V_{fm} = FM_0 + (FM_{3Y} - FM_0) \times \frac{time}{24 \times 365 \times 3}$<br>$V_{lm} = LM_0 + (LM_{3Y} - LM_0) \times \frac{time}{24 \times 365 \times 3}$ |      |      |       | <p>linearly between the baseline and final time points.</p> <p>ZBMI is used to predict fat mass and lean mass.</p> <p>One more fixed and random effects than Model 9: Kp25lm.</p> <p>The objective function value, AIC and BIC are worse compared to model 9d.</p> |
| 11 | $CL_{MAX}$<br>$K_{p25rb}$<br>$CL_{C50}$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT}{30}\right)^{0.75}$<br>$K_{p25rb} = e^{TK_{p25rb} + \eta_{K_{p25rb}}}$<br>$cor(\eta_{CL_{max}}, \eta_{K_{p25rb}}) = -0.266$ | $CL_{max} = e^{TCL_{max} + \eta_{CL_{max}}} \times \left(\frac{WT}{30}\right)^{0.75}$                                                                                                                                                                                                                                                                            | 2372 | 2401 | 1808  | <p>Weight is used to predict clearance.</p> <p>The objective function value, AIC and BIC are worse compared to model 9d.</p>                                                                                                                                       |

\*Fat mass and lean mass are calculated from ZBMI using the following equations:

$$f_{FM} = \begin{cases} \max\left(\frac{28.61 + 7.82 \times ZBMI - 0.91 \times ZBMI^2 + 0.03 \times ZBMI^3}{100}, 0.05\right), & \text{if } ZBMI \leq 6.19 \\ 0.49, & \text{if } ZBMI > 6.19 \end{cases}$$

$$FM_0 = WT \times f_{FM}(0)$$

$$FM_{3Y} = WT_{3Y} \times f_{FM}(3Y)$$

$$LM_0 = WT \times (1 - f_{FM}(0)) - (1.80 + 0.77 + 0.6) \times \frac{WT}{30}$$

$$LM_{3Y} = WT \times (1 - f_{FM}(3Y)) - (1.80 + 0.77 + 0.6) \times \frac{WT}{30}$$

**Table S6.** 25(OH)D model fitting results.

| 25(OH)D Model 1: "fit.s1.25OHD.rds" |         |        |       |                         |          |             |
|-------------------------------------|---------|--------|-------|-------------------------|----------|-------------|
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -4.01   | 0.0736 | 1.83  | 0.0181 (0.0156, 0.0209) | 63.4     | 6.54%<      |
| TKp25rb                             | 1.51    | 0.0919 | 6.07  | 4.54 (3.8, 5.44)        | 32.7     | 34.3%>      |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.00249 |        |       | 0.00249                 |          |             |
| prop.err                            | 0.106   |        |       | 0.106                   |          |             |
| 25(OH)D Model 2: "fit.s2.25OHD.rds" |         |        |       |                         |          |             |
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -4.01   | 0.0794 | 1.98  | 0.0181 (0.0155, 0.0212) | 70.3     | 2.05%<      |
| TKp25rb                             | 1.4     | 0.0869 | 6.2   | 4.06 (3.43, 4.82)       | 37.0     | 25.6%=      |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.00249 |        |       | 0.00249                 |          |             |
| prop.err                            | 0.104   |        |       | 0.104                   |          |             |
| 25(OH)D Model 3: "fit.s3.25OHD.rds" |         |        |       |                         |          |             |
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -4      | 0.0779 | 1.95  | 0.0184 (0.0158, 0.0214) | 68.3     | 5.93%<      |
| TKp25rb                             | 1.15    | 0.114  | 9.93  | 3.16 (2.52, 3.95)       | 69.7     | 9.53%<      |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.00252 |        |       | 0.00252                 |          |             |
| prop.err                            | 0.102   |        |       | 0.102                   |          |             |
| 25(OH)D Model 4: "fit.s4.25OHD.rds" |         |        |       |                         |          |             |
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -3.99   | 0.0715 | 1.79  | 0.0186 (0.0161, 0.0214) | 60.6     | 1.69%<      |
| TKp25rb                             | 1.32    | 0.0857 | 6.47  | 3.76 (3.18, 4.45)       | 34.1     | 10.5%<      |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.00249 |        |       | 0.00249                 |          |             |
| prop.err                            | 0.106   |        |       | 0.106                   |          |             |
| 25(OH)D Model 5: "fit.s5.25OHD.rds" |         |        |       |                         |          |             |
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -3.99   | 0.0759 | 1.9   | 0.0185 (0.0159, 0.0215) | 66.4     | 7.64%<      |
| TKp25rb                             | 1.28    | 0.0999 | 7.77  | 3.61 (2.97, 4.39)       | 53.6     | 11.9%<      |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.0025  |        |       | 0.0025                  |          |             |
| prop.err                            | 0.102   |        |       | 0.102                   |          |             |
| 25(OH)D Model 6: "fit.s6.25OHD.rds" |         |        |       |                         |          |             |
|                                     | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
| TCL_EMAX                            | -3.99   | 0.0741 | 1.86  | 0.0185 (0.016, 0.0214)  | 63.7     | 3.21%<      |
| TKp25rb                             | 1.35    | 0.0941 | 6.94  | 3.88 (3.22, 4.66)       | 36.2     | 16.2%<      |
| Kp25rb_ZBMI                         | 0.0137  | 0.073  | 533   | 0.0137 (-0.129, 0.157)  |          |             |
| C50                                 | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ                                   | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err                             | 0.0025  |        |       | 0.0025                  |          |             |
| prop.err                            | 0.104   |        |       | 0.104                   |          |             |

25(OH)D Model 7: "fit.s7.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI)  | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|--------------------------|----------|-------------|
| TCL_EMAX | -4.59   | 0.0785 | 1.71  | 0.0102 (0.00873, 0.0119) | 64.3     | 17.8%<      |
| TKp25rb  | 1.2     | 0.124  | 10.3  | 3.33 (2.61, 4.25)        | 113.     | 15.9%<      |
| C50      | FIXED   | FIXED  | FIXED | 86.3                     |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                     |          |             |
| add.err  | 0.00247 |        |       | 0.00247                  |          |             |
| prop.err | 0.0936  |        |       | 0.0936                   |          |             |

25(OH)D Model 8: "fit.s8.25OHD.rds"

|          | Est.     | SE    | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|----------|-------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -4.37    | 0.107 | 2.44  | 0.0127 (0.0103, 0.0156) | 9.79     | 38.9%>      |
| TKp25rb  | 0.944    | 0.296 | 31.4  | 2.57 (1.44, 4.59)       | 48.6     | 45.8%>      |
| C50      | FIXED    | FIXED | FIXED | 86.3                    |          |             |
| γ        | FIXED    | FIXED | FIXED | 5.64                    |          |             |
| add.err  | 37.8     |       |       | 37.8                    |          |             |
| prop.err | 0.000353 |       |       | 0.000353                |          |             |

25(OH)D Model 9a: "fit.s9a.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -4.42   | 0.0795 | 1.8   | 0.012 (0.0103, 0.014)   | 61.6     | 9.01%<      |
| TKp25fm  | 2.34    | 0.0632 | 2.7   | 10.4 (9.16, 11.7)       |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 1                       |          |             |
| add.err  | 0.00251 |        |       | 0.00251                 |          |             |
| prop.err | 0.111   |        |       | 0.111                   |          |             |

25(OH)D Model 9b: "fit.s9b.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -4.43   | 0.0781 | 1.76  | 0.0119 (0.0102, 0.0139) | 61.0     | 9.85%<      |
| TKp25fm  | 2.13    | 0.0771 | 3.62  | 8.4 (7.22, 9.77)        |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 2                       |          |             |
| add.err  | 0.00265 |        |       | 0.00265                 |          |             |
| prop.err | 0.11    |        |       | 0.11                    |          |             |

25(OH)D Model 9c: "fit.s9c.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -4.41   | 0.0778 | 1.76  | 0.0121 (0.0104, 0.0141) | 61.8     | 10.9%<      |
| TKp25fm  | 1.81    | 0.104  | 5.74  | 6.14 (5, 7.53)          |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 3                       |          |             |
| add.err  | 0.00249 |        |       | 0.00249                 |          |             |
| prop.err | 0.11    |        |       | 0.11                    |          |             |

25(OH)D Model 9d: "fit.s9d.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -4.43   | 0.0786 | 1.77  | 0.0119 (0.0102, 0.0139) | 62.7     | 13.1%<      |
| TKp25fm  | 1.54    | 0.138  | 8.96  | 4.66 (3.56, 6.11)       |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                    |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 4                       |          |             |
| add.err  | 0.00282 |        |       | 0.00282                 |          |             |
| prop.err | 0.109   |        |       | 0.109                   |          |             |

25(OH)D Model 9e: "fit.s9e.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI)  | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|--------------------------|----------|-------------|
| TCL_EMAX | -4.49   | 0.0814 | 1.81  | 0.0112 (0.00957, 0.0132) | 65.3     | 13.7%<      |
| TKp25fm  | 0.694   | 0.311  | 44.8  | 2 (1.09, 3.68)           |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                     |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                     |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 6                        |          |             |
| add.err  | 0.00251 |        |       | 0.00251                  |          |             |
| prop.err | 0.11    |        |       | 0.11                     |          |             |

25(OH)D Model 9f: "fit.s9f.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI)  | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|--------------------------|----------|-------------|
| TCL_EMAX | -4.65   | 0.0909 | 1.96  | 0.0096 (0.00803, 0.0115) | 74.9     | 16.8%<      |
| TKp25fm  | 0.121   | 0.204  | 169   | 1.13 (0.756, 1.68)       |          |             |
| C50      | FIXED   | FIXED  | FIXED | 86.3                     |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                     |          |             |
| Kp25lm   | FIXED   | FIXED  | FIXED | 8                        |          |             |
| add.err  | 0.00265 |        |       | 0.00265                  |          |             |
| prop.err | 0.119   |        |       | 0.119                    |          |             |

25(OH)D Model 10: "fit.s9a.25OHD.rds"

|             | Est.    | SE     | %RSE  | Back-transformed(95%CI)  | IIV(CV%) | Shrink(SD)% |
|-------------|---------|--------|-------|--------------------------|----------|-------------|
| TCL_EMAX    | -4.46   | 0.0779 | 1.75  | 0.0116 (0.00996, 0.0135) | 59.3     | 7.77%<      |
| TKp25lm     | 1.36    | 0.104  | 7.68  | 3.89 (3.17, 4.77)        |          |             |
| TKp25fm     | 1.6     | 0.118  | 7.34  | 4.96 (3.94, 6.25)        |          |             |
| C50         | FIXED   | FIXED  | FIXED | 86.3                     |          |             |
| γ           | FIXED   | FIXED  | FIXED | 5.64                     |          |             |
| add.err     | 0.00245 |        |       | 0.00245                  |          |             |
| prop.err    | 0.107   |        |       | 0.107                    |          |             |
| eta.FM_frac |         |        |       |                          | 1.36     | 39.8%>      |

25(OH)D Model 11: "fit.s9a.25OHD.rds"

|          | Est.    | SE     | %RSE  | Back-transformed(95%CI) | IIV(CV%) | Shrink(SD)% |
|----------|---------|--------|-------|-------------------------|----------|-------------|
| TCL_EMAX | -3.24   | 0.32   | 9.89  | 0.0392 (0.021, 0.0735)  | 105.     | 1.11%<      |
| TKp25rb  | 1.37    | 0.119  | 8.69  | 3.95 (3.12, 4.98)       | 44.1     | 37.4%>      |
| C50      | 4.76    | 0.0841 | 1.77  | 117 (98.8, 137)         |          |             |
| γ        | FIXED   | FIXED  | FIXED | 5.64                    |          |             |
| add.err  | 0.00252 |        |       | 0.00252                 |          |             |
| prop.err | 0.0995  |        |       | 0.0995                  |          |             |