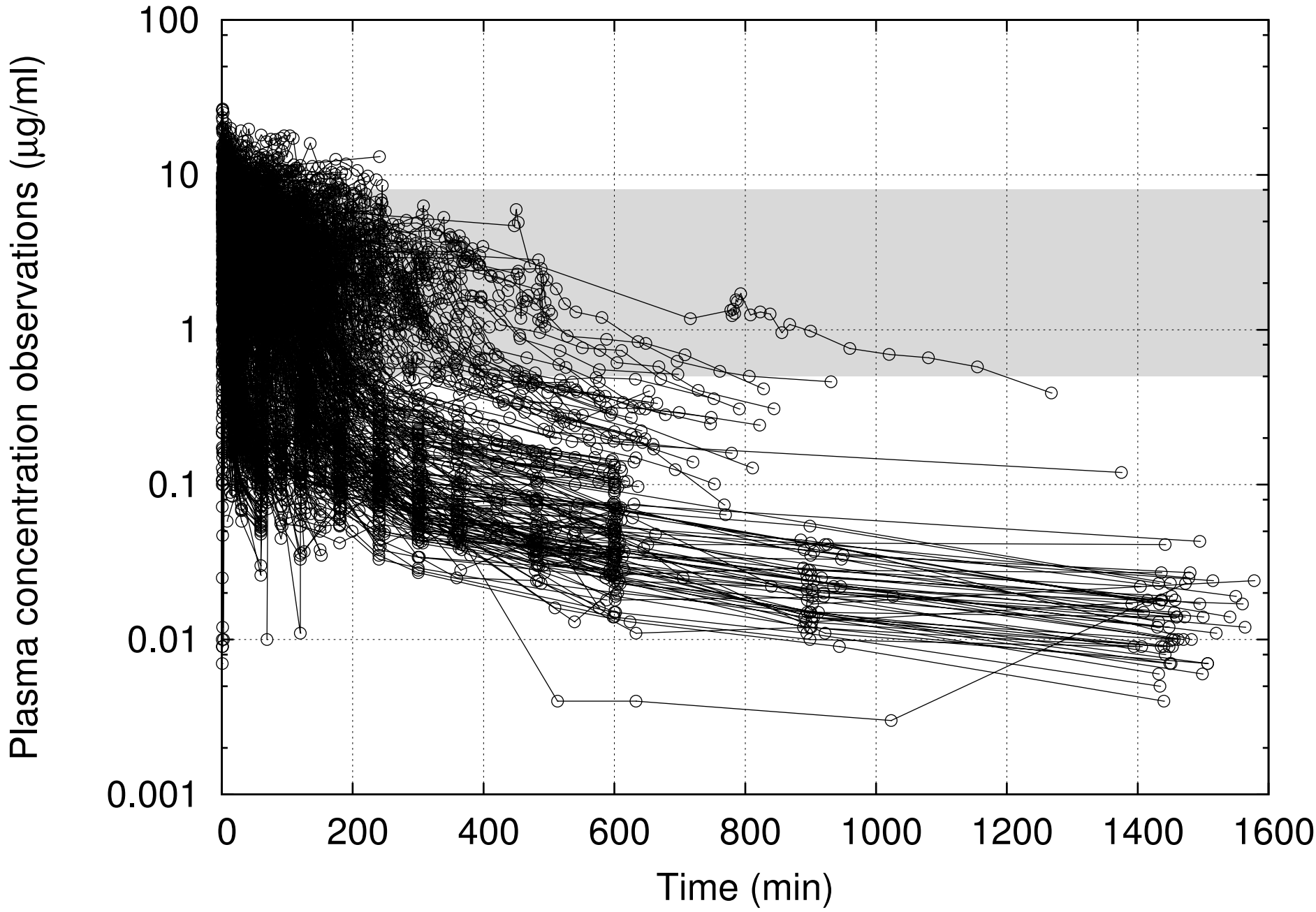
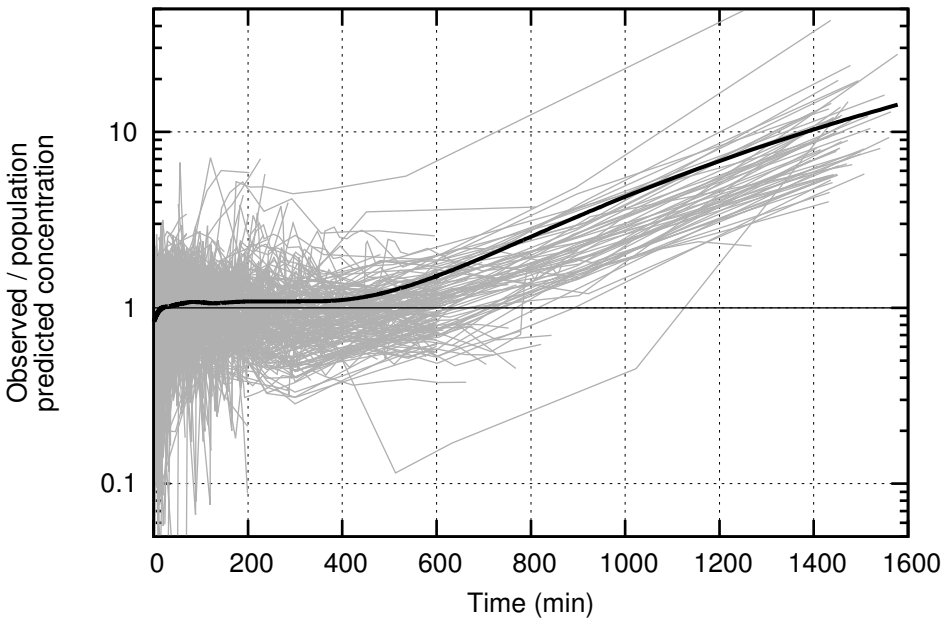
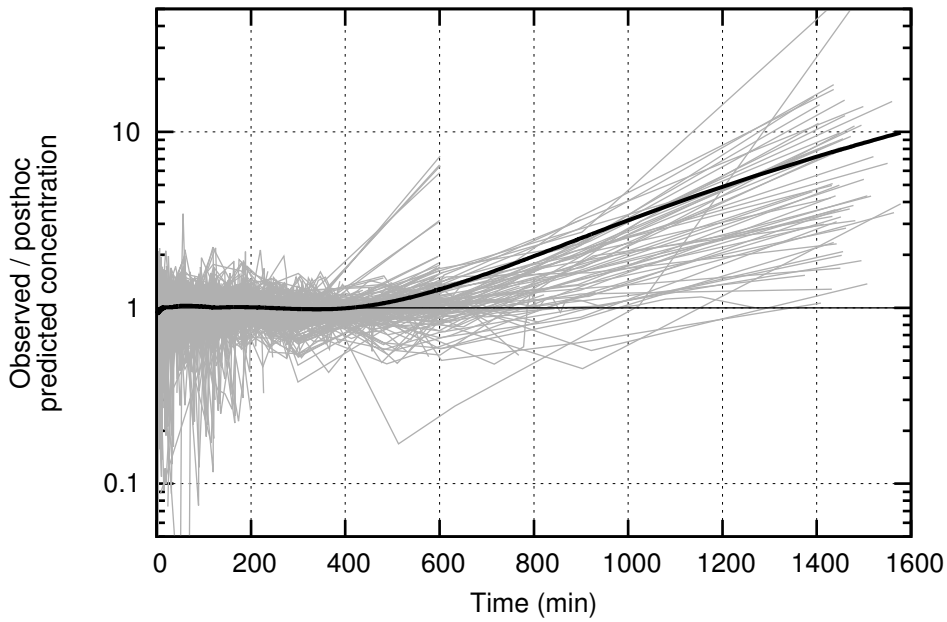
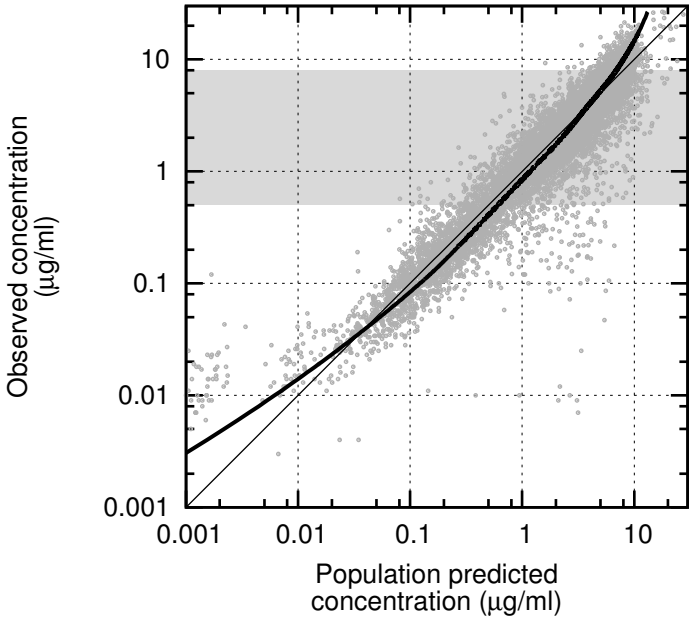
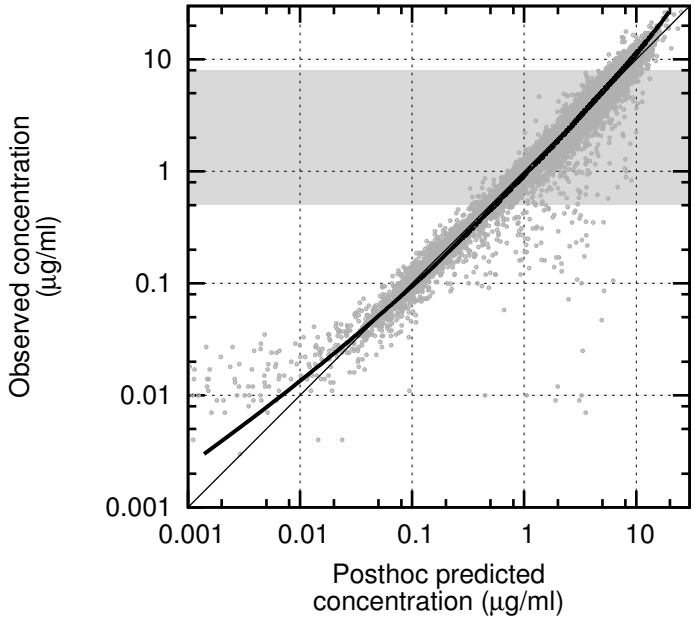

Plasma concentration observations (µg/ml)
100
10
1
0.1
0.01
0.001
0
200
400
600
800
1000
1200
1400
1600
Time (min)

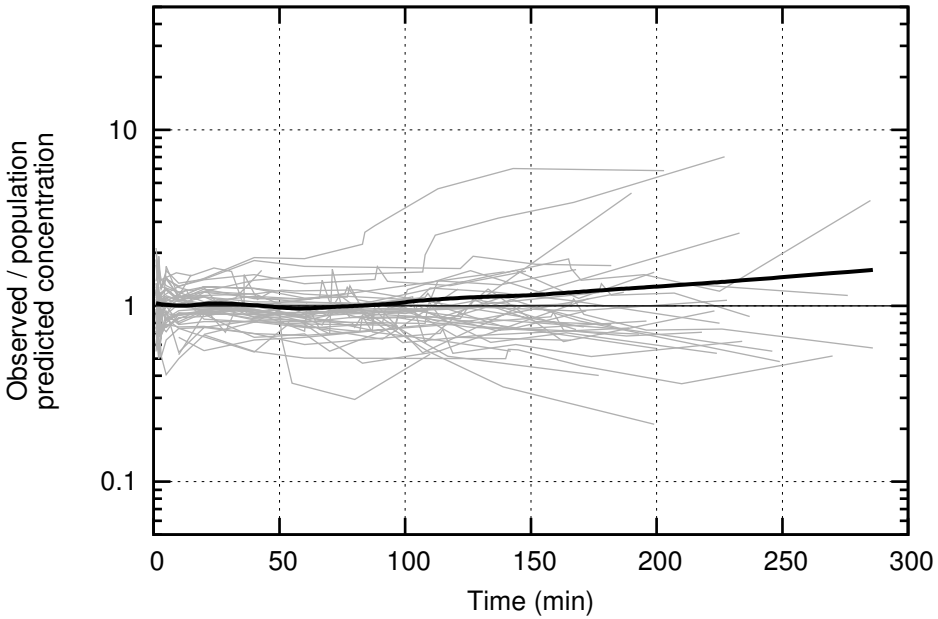

Observed / population predicted concentration
10
1
0.1
0
200
400
600
800
1000
1200
1400
1600
Time (min)

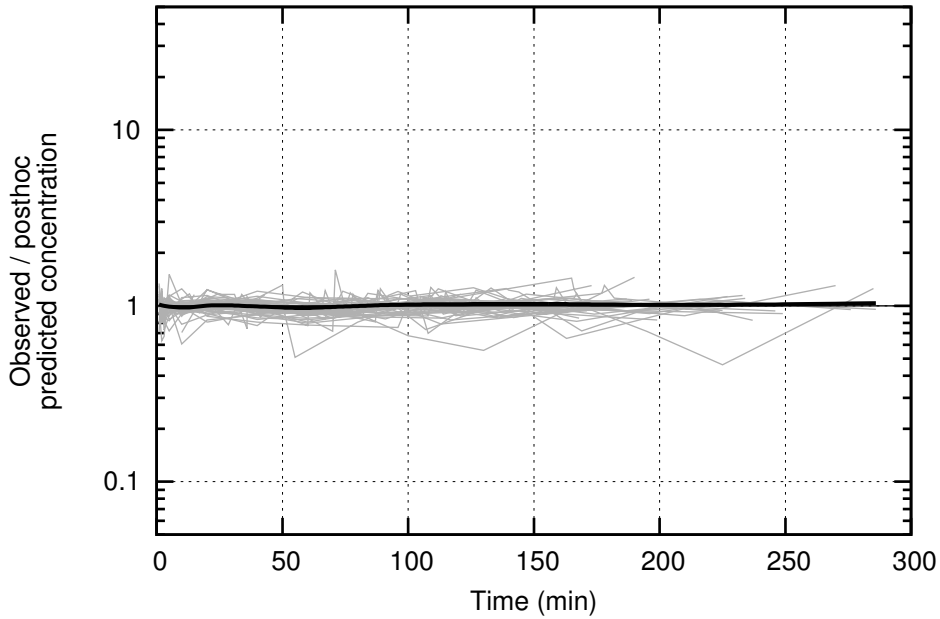

Observed / posthoc predicted concentration
10
1
0.1
0
200
400
600
800
1000
1200
1400
1600
Time (min)

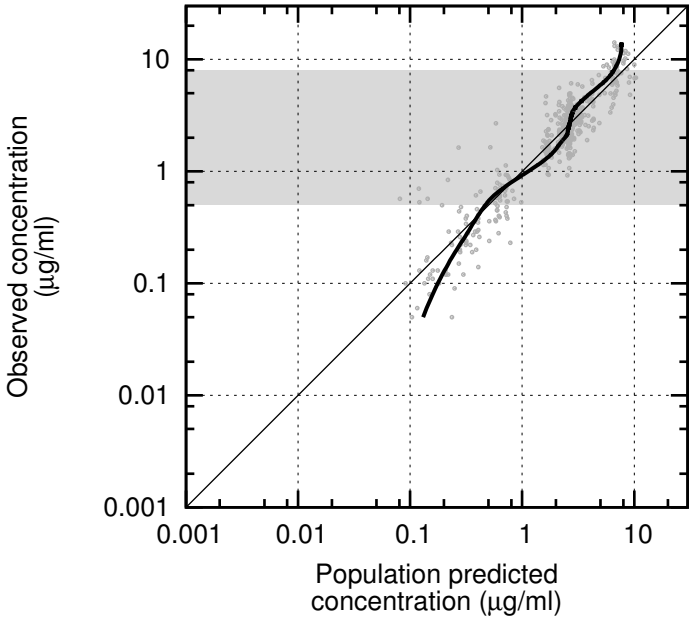

Observed concentration (µg/ml)
10
1
0.1
0.01
0.001
0.001
0.01
0.1
1
10
Population predicted concentration (µg/ml)

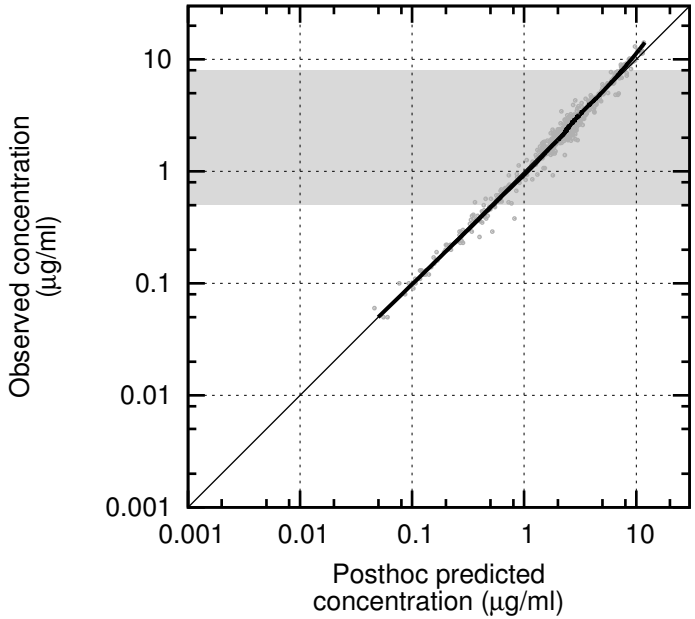

Observed concentration (µg/ml)
10
1
0.1
0.01
0.001
0.001
0.01
0.1
1
10
Posthoc predicted concentration (µg/ml)

Young children (age < 3 years)

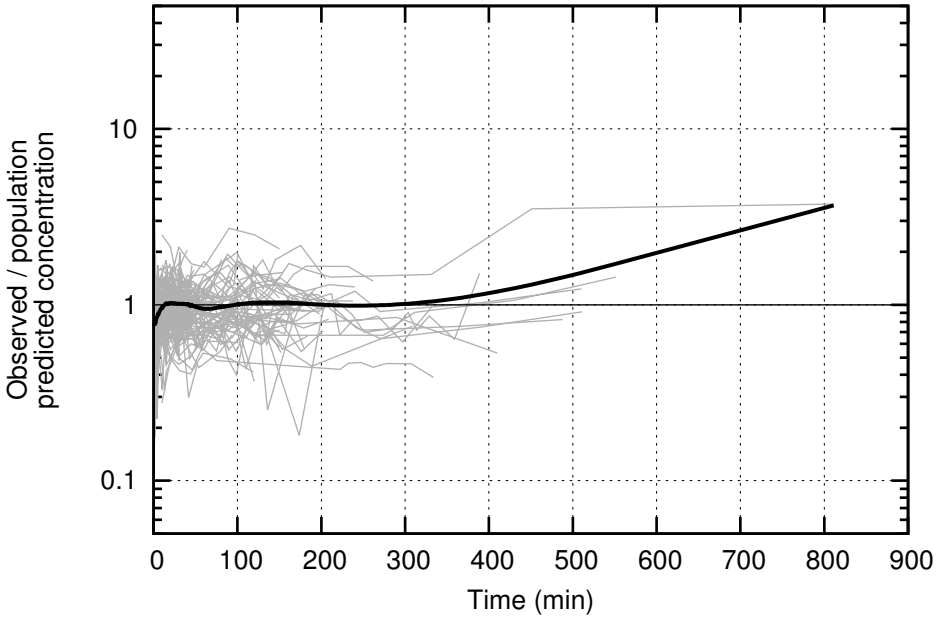


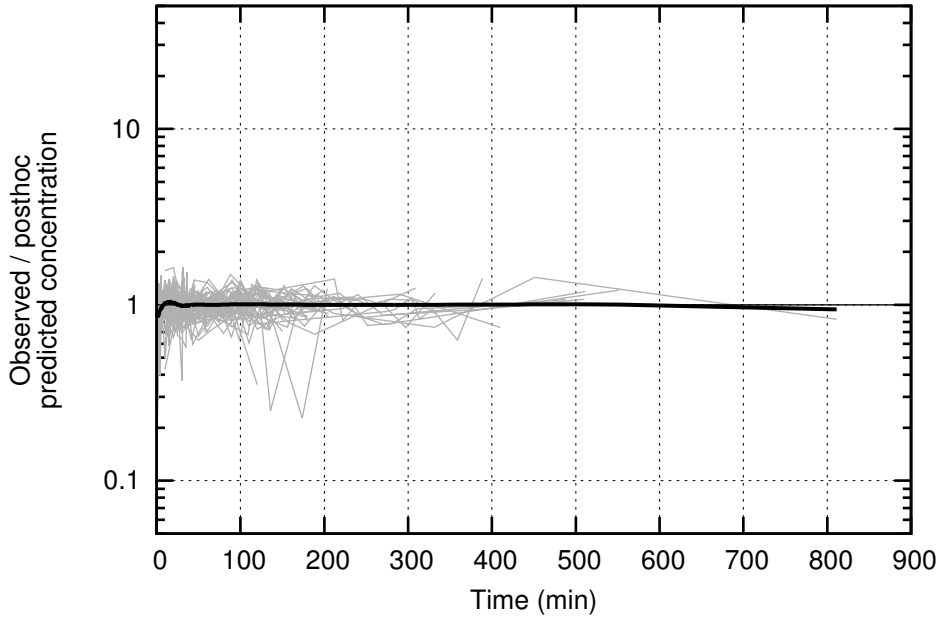


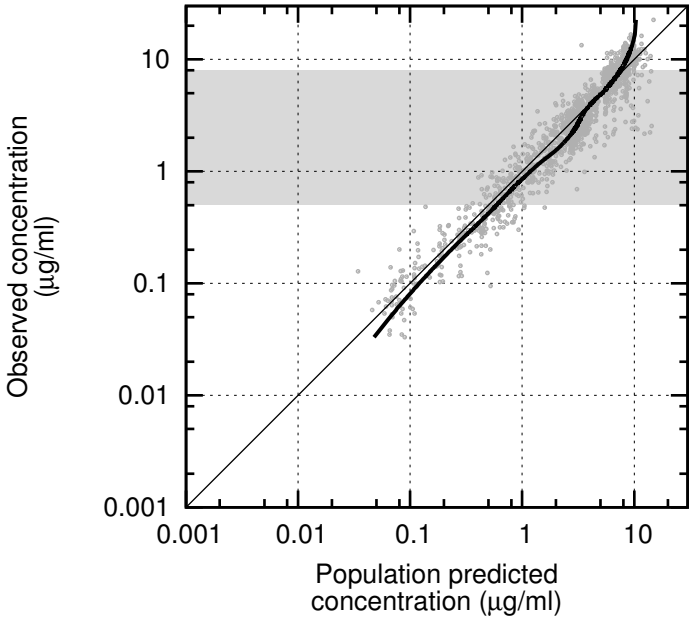


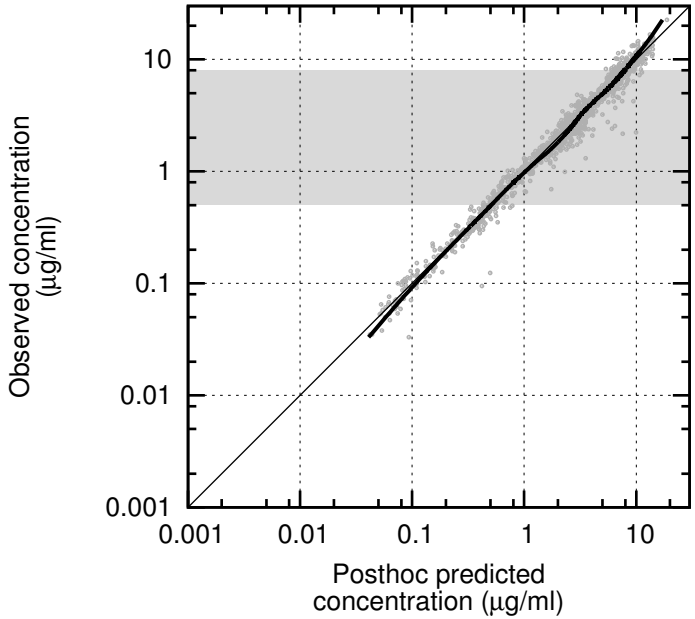


Children (3 ≤ age < 18 years)

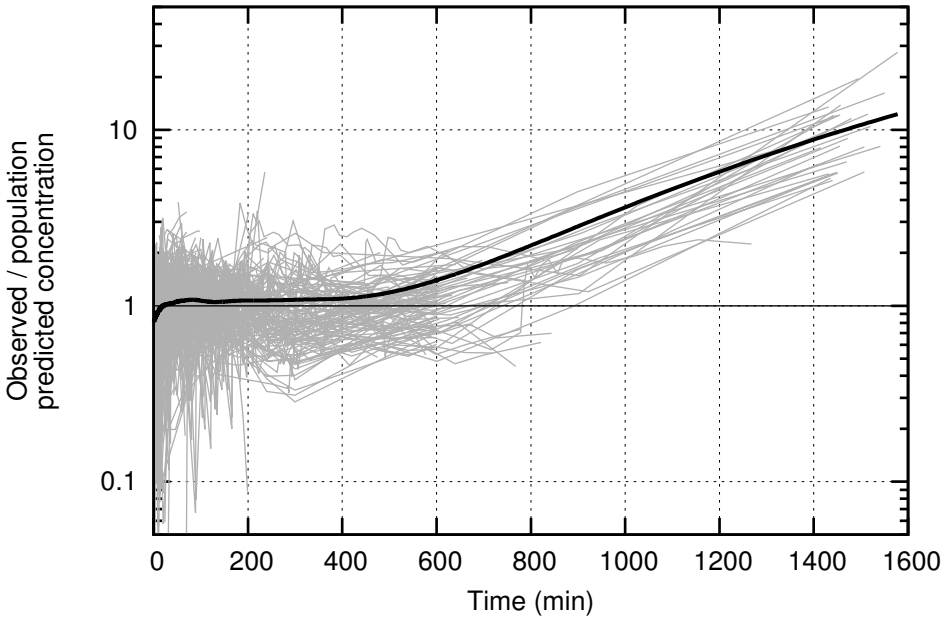


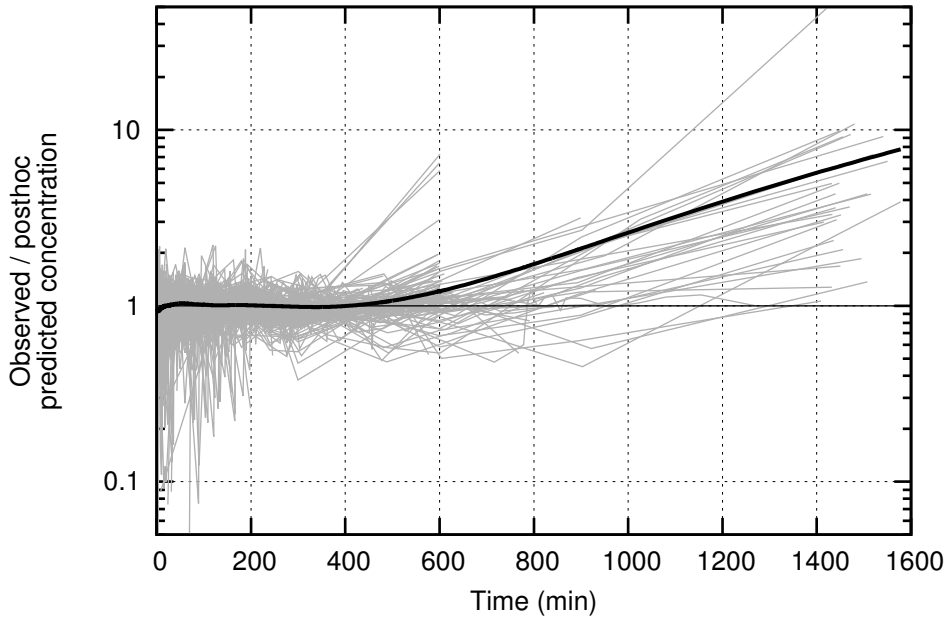


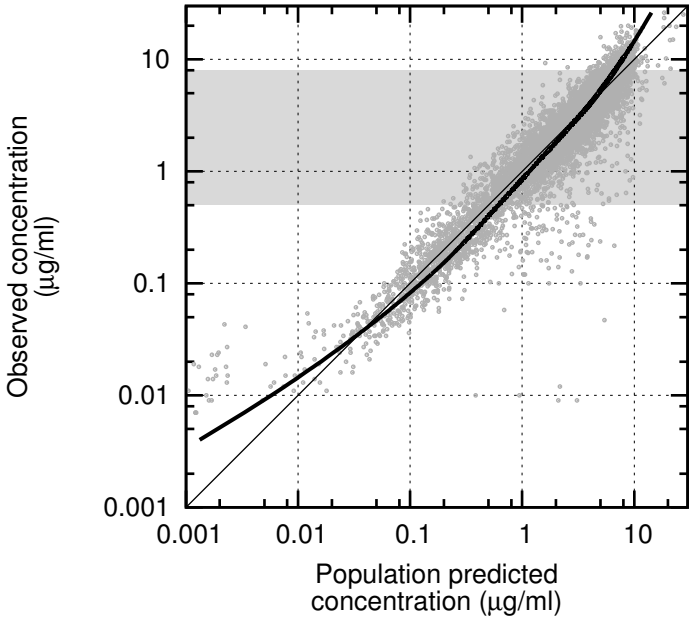


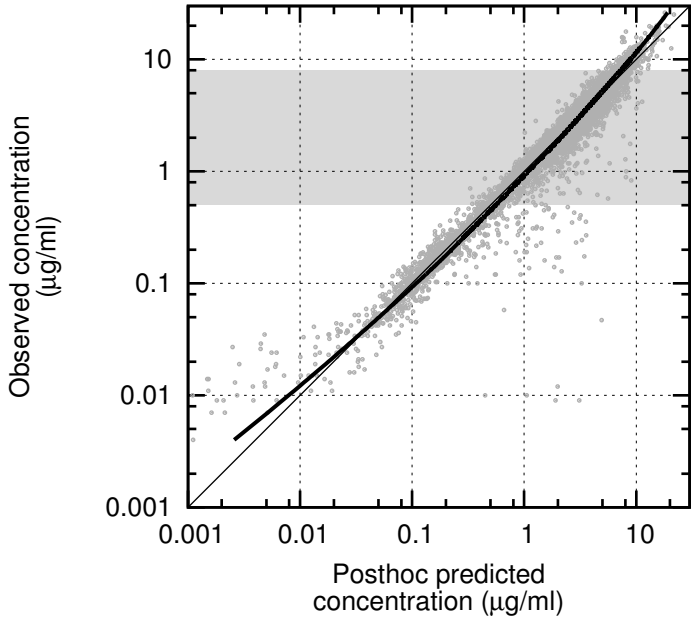


Adults (18 ≤ age < 70 years, BMI < 30)

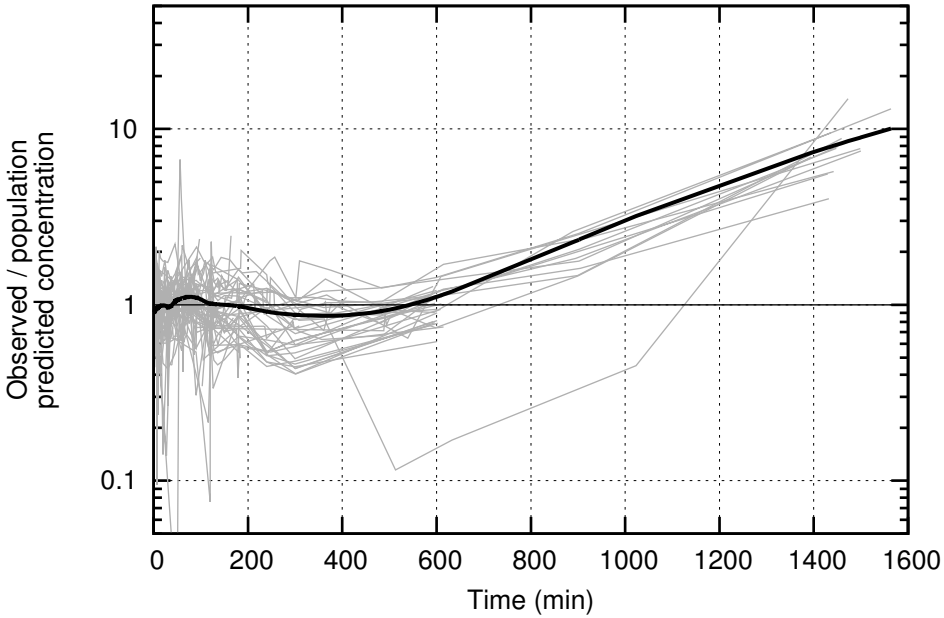


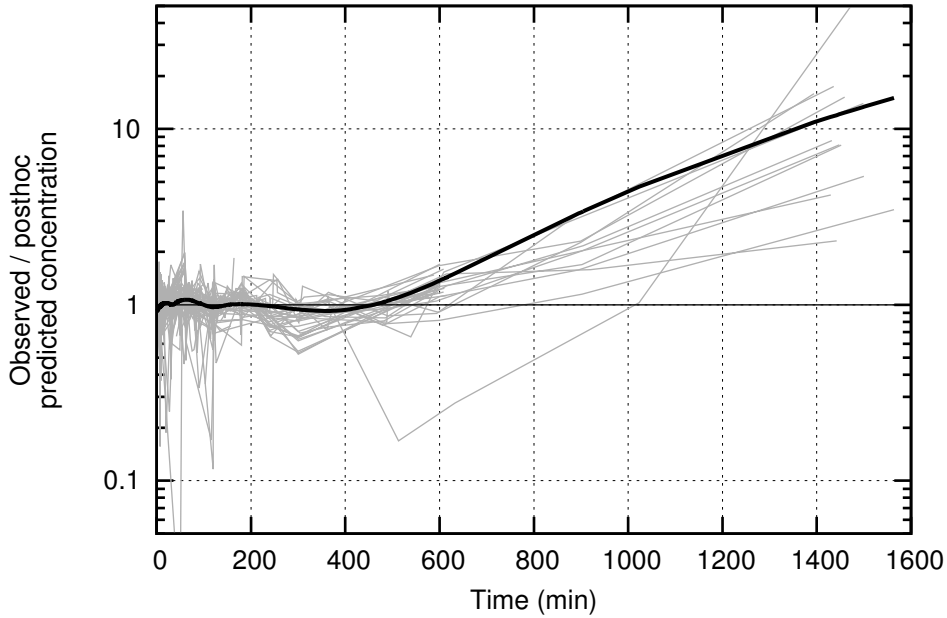


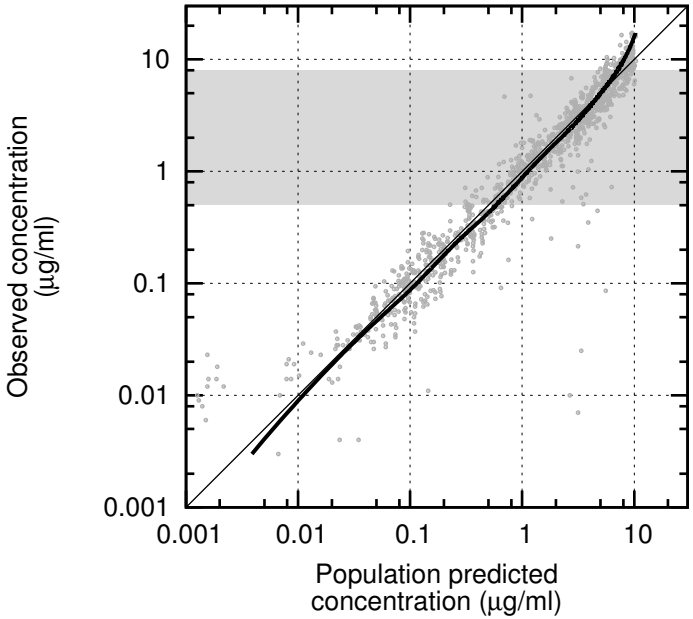


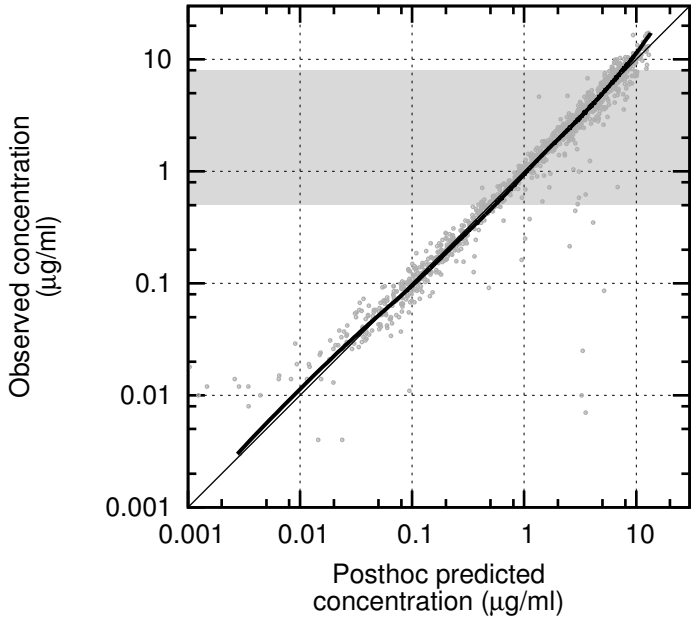


Elderly (age ≥ 70 years)

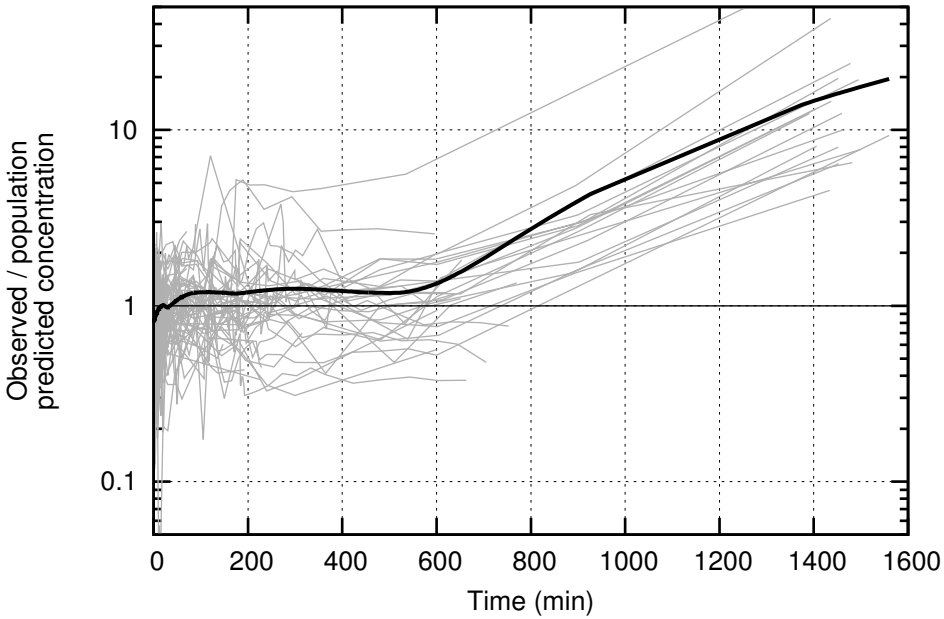


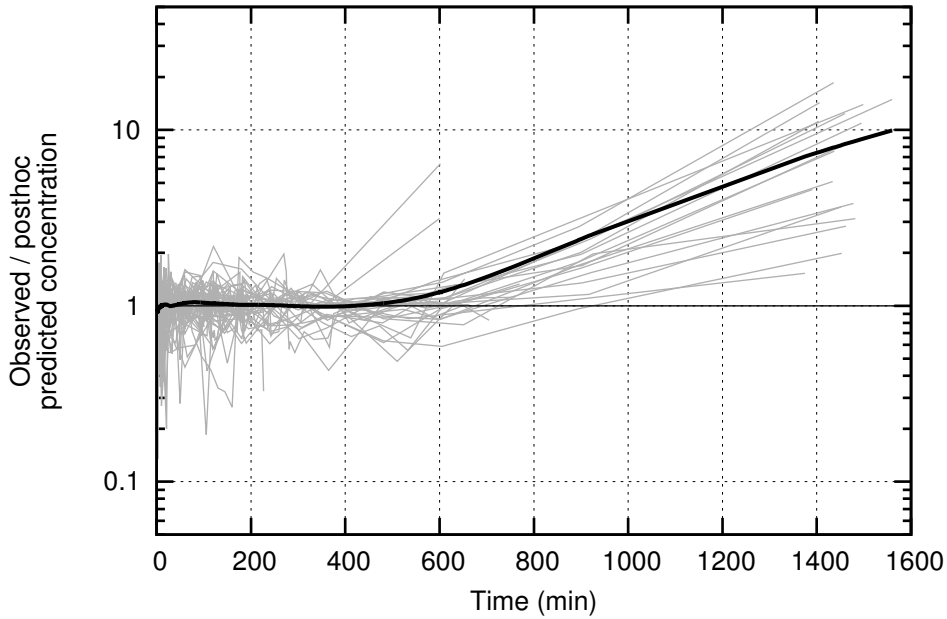


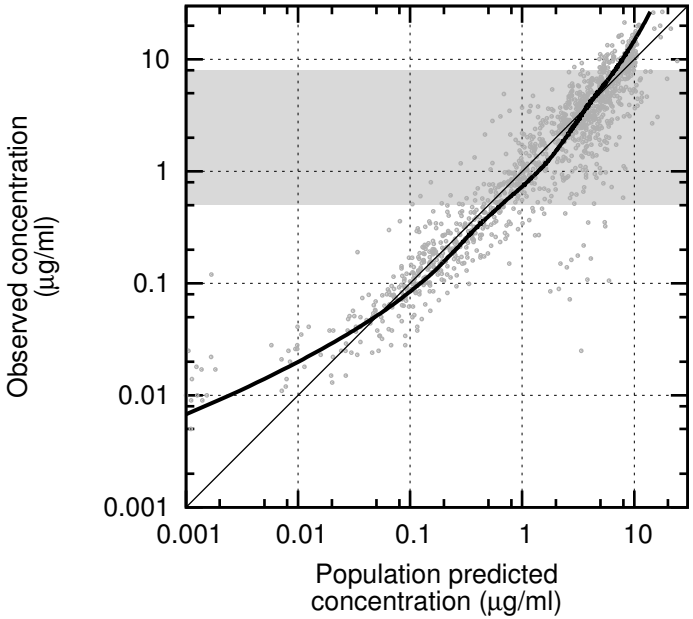


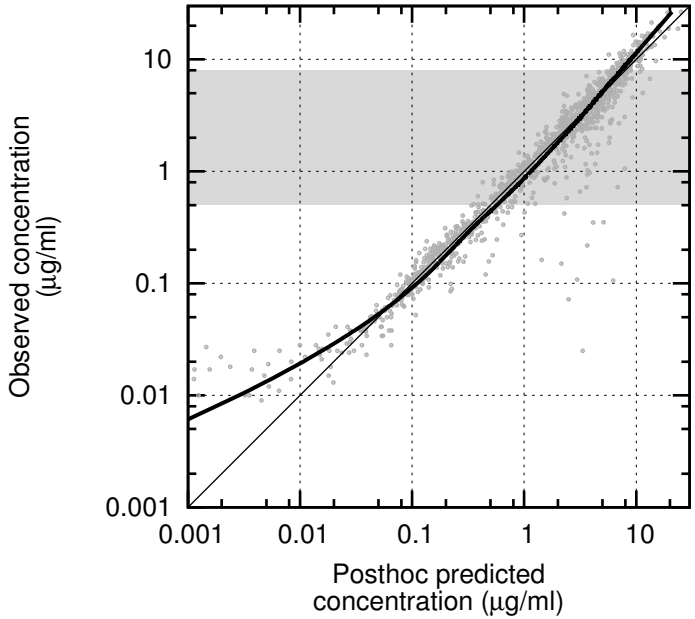


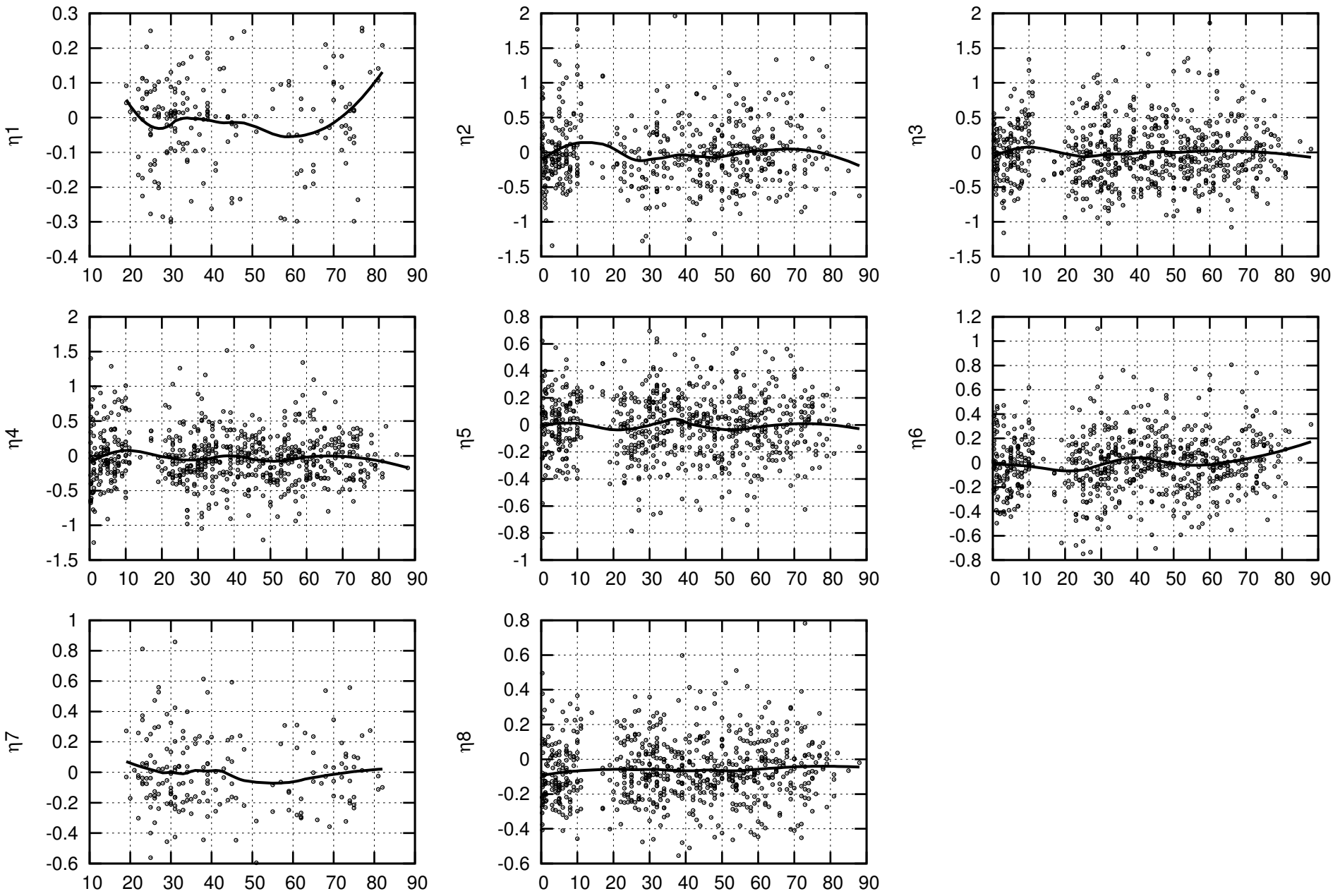
High BMI (BMI ≥ 30)

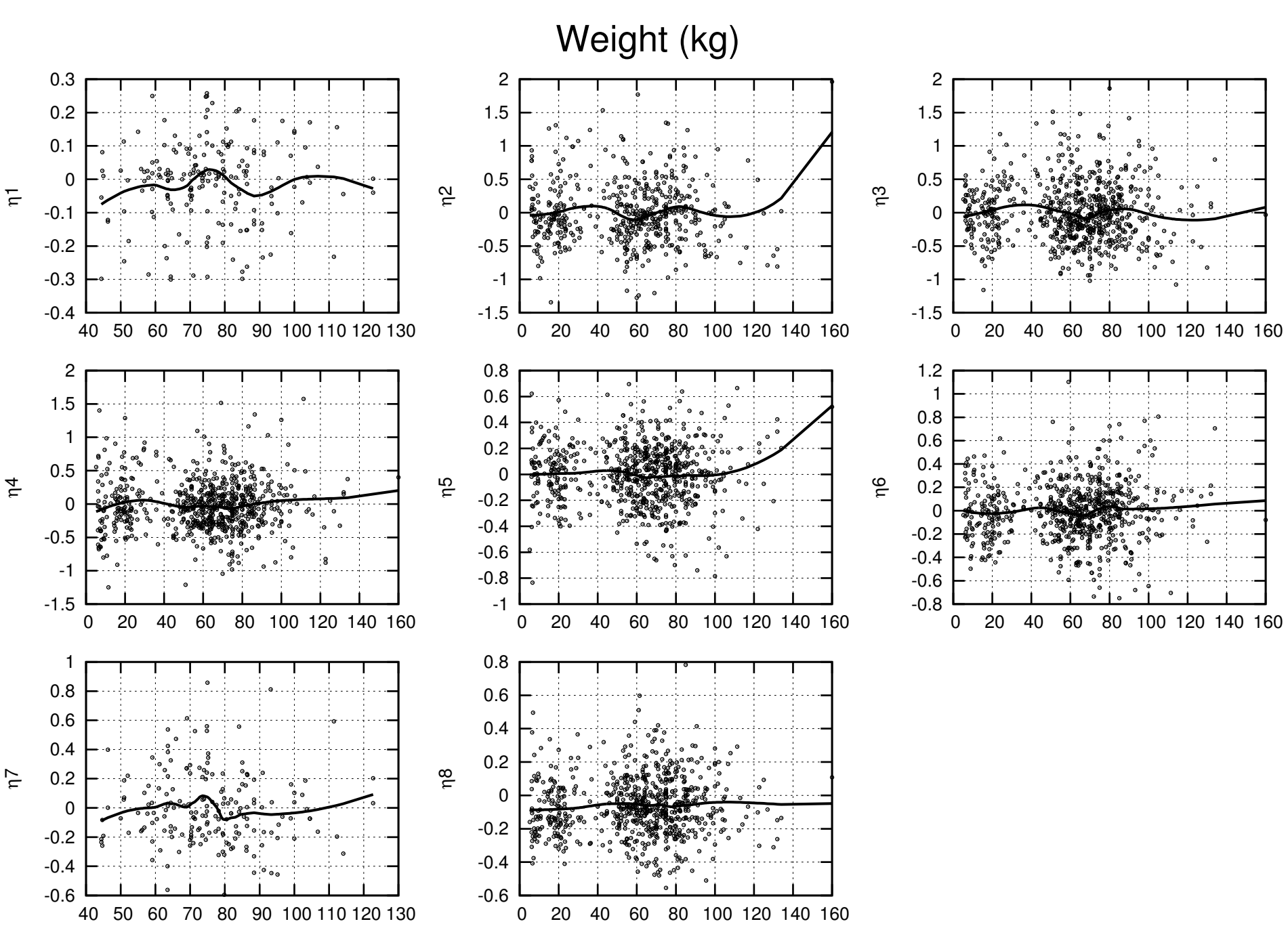


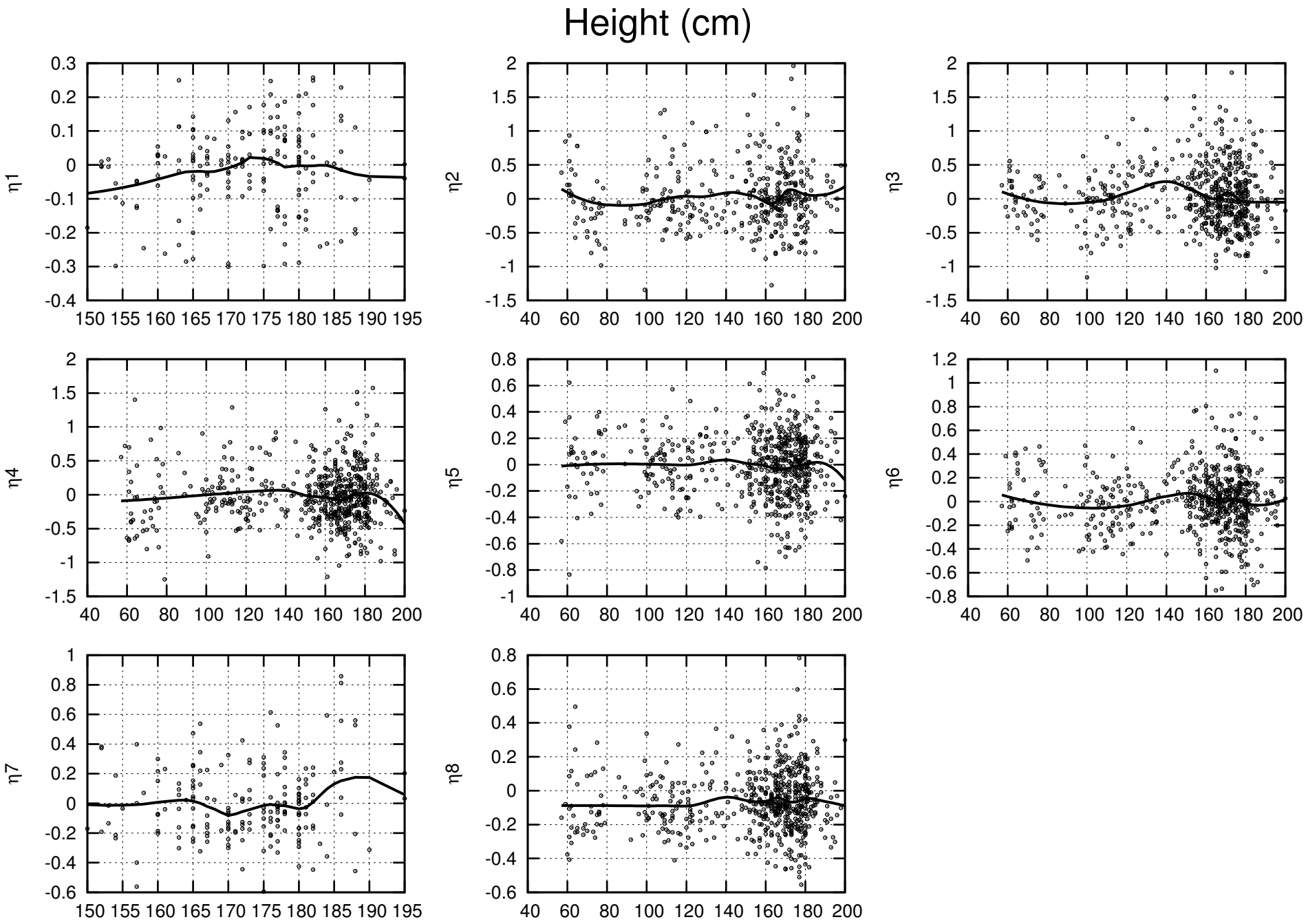




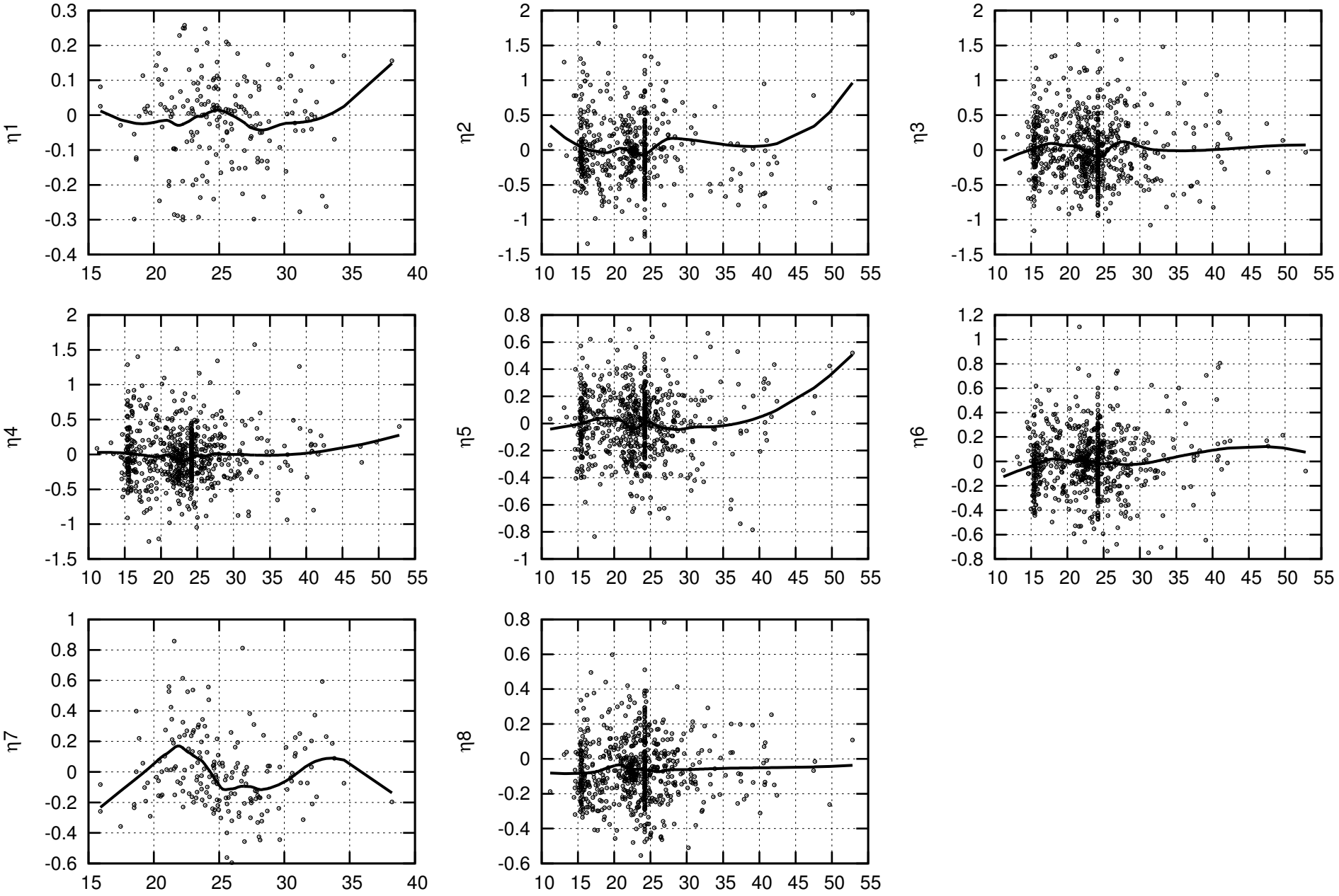



Age (years)
η1
η2
η3
η4
η5
η6
η7
η8

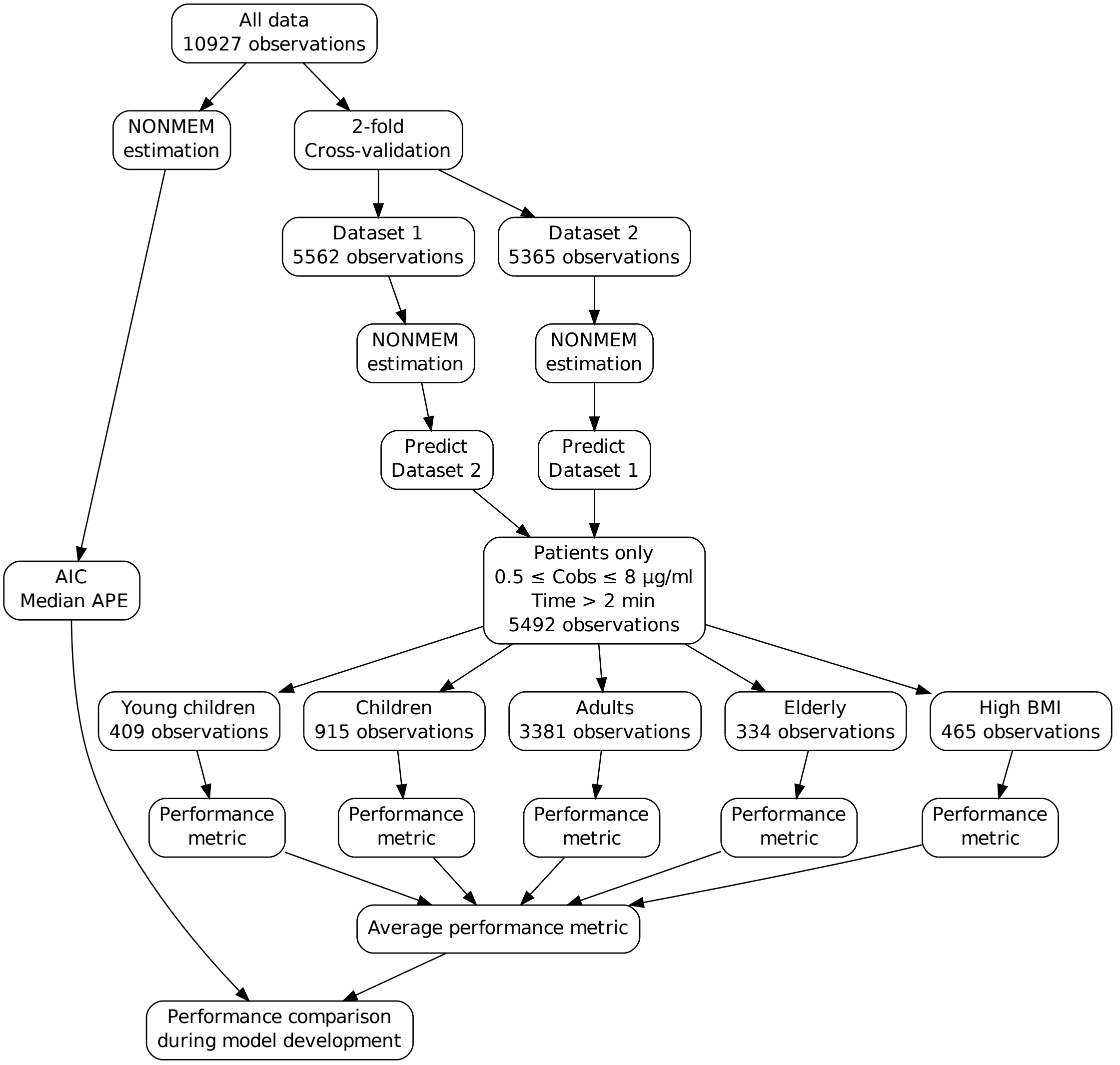

Weight (kg)
η1
η2
η3
η4
η5
η6
η7
η8


Height (cm)
η1
η2
η3
η4
η5
η6
η7
η8

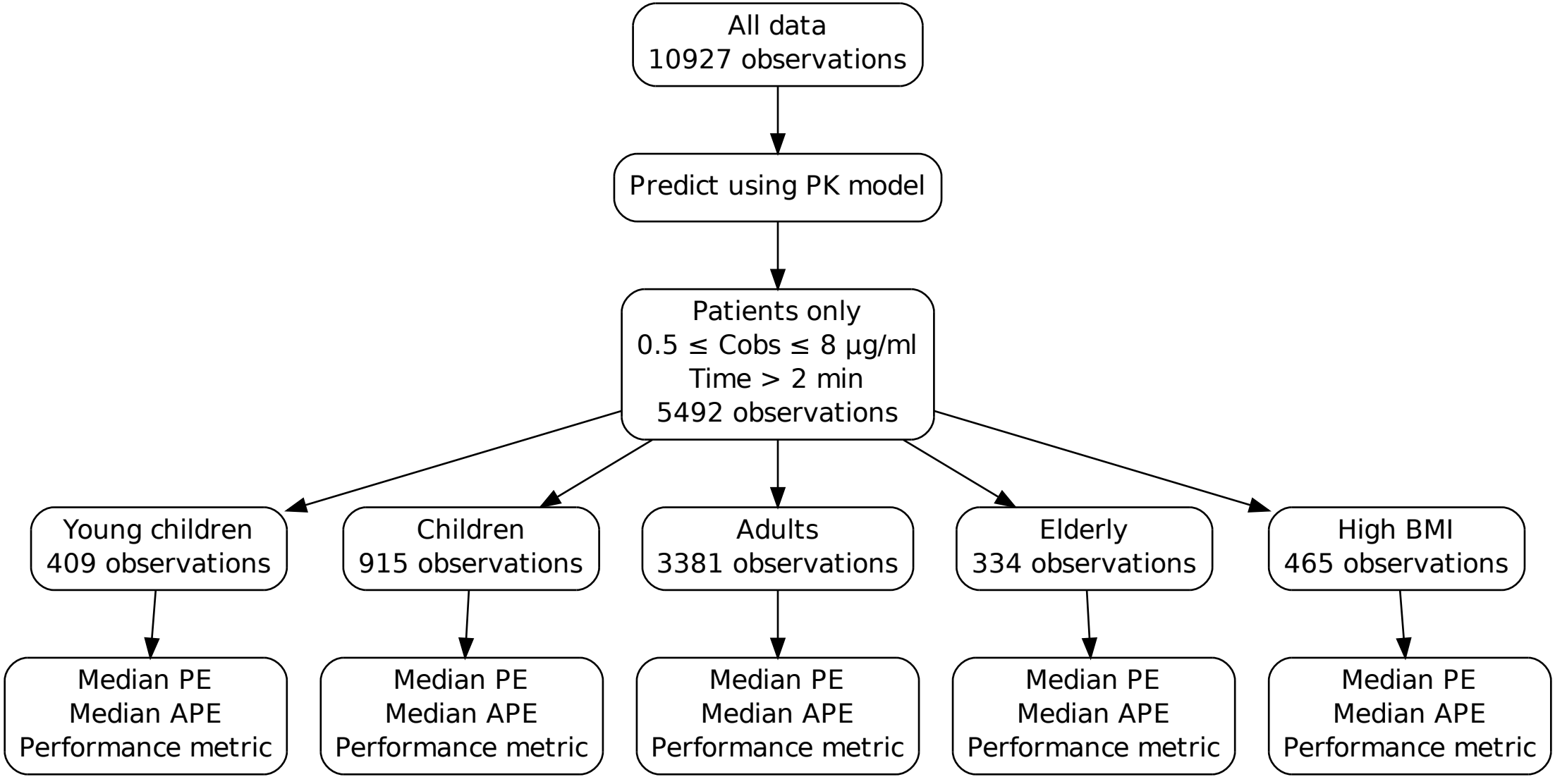
BMI

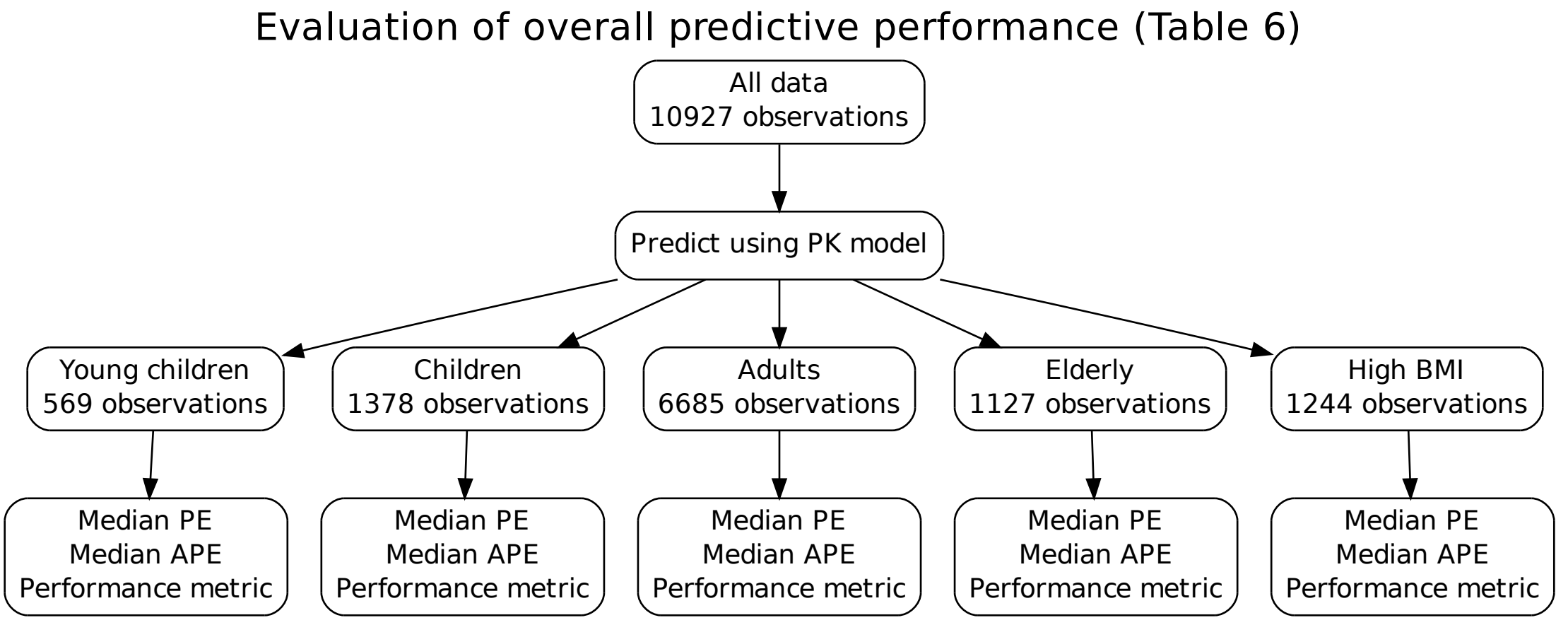


Evaluating model performance during model development



Evaluation of intra-operative predictive performance (Table 5)




Evaluation of overall predictive performance (Table 6)
All data
10927 observations
Predict using PK model
Young children
569 observations
Children
1378 observations
Adults
6685 observations
Elderly
1127 observations
High BMI
1244 observations
Median PE
Median APE
Performance metric
Median PE
Median APE
Performance metric
Median PE
Median APE
Performance metric
Median PE
Median APE
Performance metric
Median PE
Median APE
Performance metric

Bootstrap resampling and Likelihood profiles

Uncertainty in the estimated population typical parameters was evaluated using bootstrap resampling and likelihood profiles. For bootstrap resampling 350 resamples were evaluated. The results of estimations were used regardless of NONMEM termination criteria. The red line is the NONMEM estimated population typical value. In the likelihood profiles the dark shaded area indicates the p<0.05 region and the light shaded area indicates the p<0.01 region.

$$f_{sigmoid}(x,E50,\lambda) = x^{\lambda}/(x^{\lambda}+E50^{\lambda})$$

$$ADLT = f_{sigmoid}(WGT,\Theta_{13},\Theta_{14})$$

$$f_{aging}(x) = e^{-0.001\cdot(AGE-35)\cdot x}$$

$$CLAG = 1 - f_{sigmoid}(PMA,\Theta_{16},8)$$

$$PMAL = \begin{cases} f_{sigmoid}(PMA,\Theta_{15},8), & male \\ 0, & female \end{cases}$$

$$KGEN = e^{\Theta_{23}\cdot(CLAG\cdot(1-PMAL)+(1-CLAG)\cdot PMAL)\cdot ADLT}$$

$$V1(l) = \begin{cases} \Theta_1, & healthy \\ \Theta_7, & patient \end{cases} \cdot \frac{ADLT}{ADLT_{ref}} \cdot \begin{cases} 1, & male \\ \Theta_{22}, & female \end{cases} \cdot f_{aging}(\Theta_{18}) \cdot e^{\begin{cases} n1, & healthy \\ n2, & patient \end{cases}}$$

$$V2(l) = \begin{cases} \Theta_2, & healthy \\ \Theta_8, & patient \end{cases} \cdot \left(\frac{WGT}{70}\right) \cdot f_{aging}(\Theta_{19}) \cdot e^{\eta 3}$$

$$V3(l) = \begin{cases} \Theta_3, & healthy \\ \Theta_9, & patient \end{cases} \cdot \left(\frac{WGT}{70}\right)^{\Theta_{17}} \cdot \frac{ADLT}{ADLT_{ref}} \cdot e^{\eta 4}$$

$$CL(l/\min) = \begin{cases} \Theta_4, & healthy \\ \Theta_{10}, & patient \end{cases} \cdot \left(\frac{WGT}{70}\right)^{0.75} \cdot \frac{KGEN}{KGEN_{ref}} \cdot f_{aging}(\Theta_{18}) \cdot e^{\eta 5}$$

$$Q2(l/\min) = \begin{cases} \Theta_5, & healthy \\ \Theta_{11}, & patient \end{cases} \cdot \left(\frac{V2}{\Theta_8}\right)^{0.75} \cdot f_{aging}\left((1\text{-ADLT})\cdot\Theta_{20} + \text{ADLT}\cdot\Theta_{21}\right) \cdot e^{\eta 6}$$

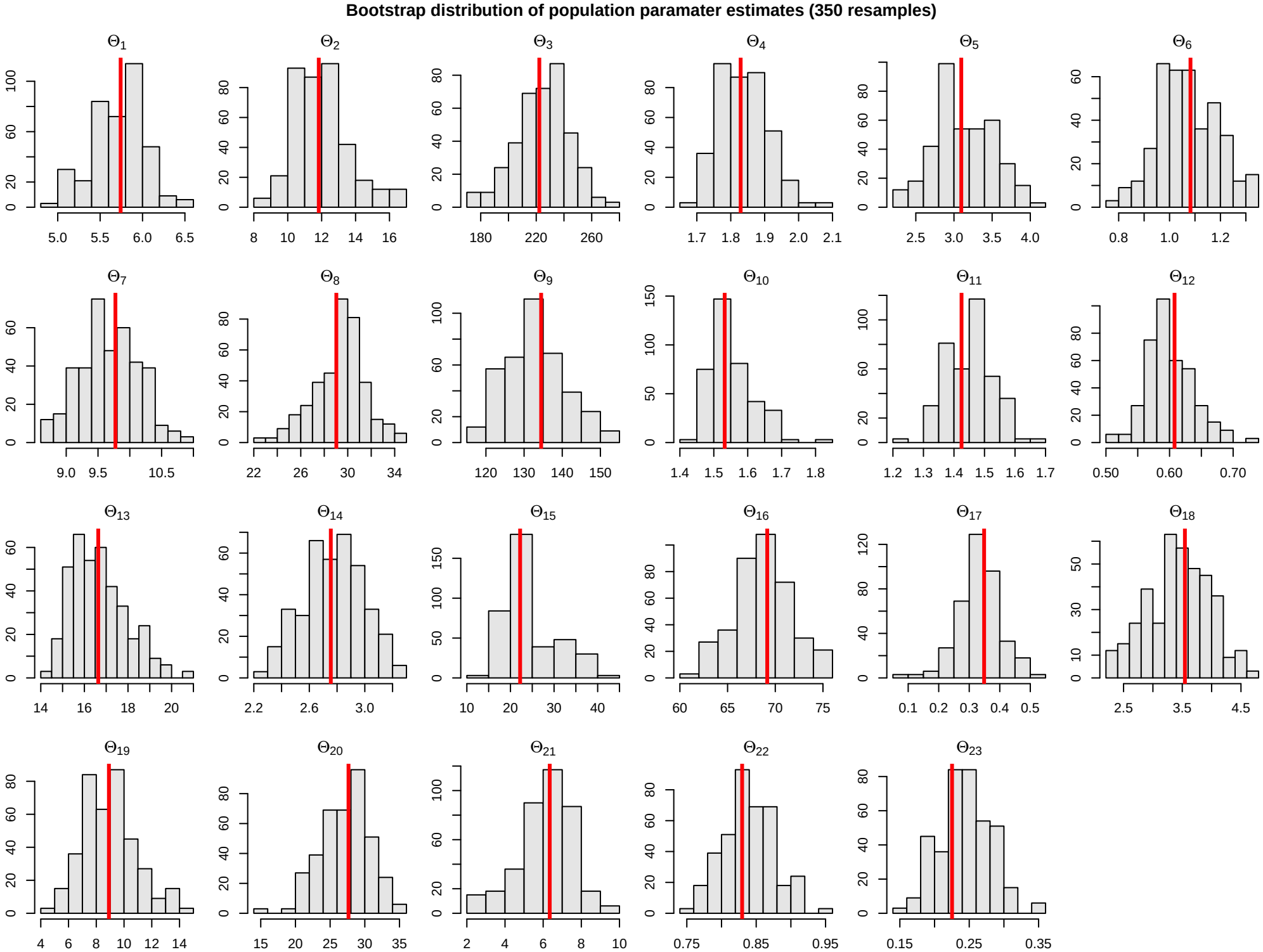
$$Q3(l/\min) = \begin{cases} \Theta_6, & healthy \\ \Theta_{12}, & patient \end{cases} \cdot \left(\frac{V3}{\Theta_9}\right)^{0.75} \cdot f_{aging}(\Theta_{21}) \cdot e^{\begin{cases} n7, & healthy \\ 0, & patient \end{cases}}$$

$$C_{observed} = C_{predicted}\left(1 + RES^2\,\varepsilon 1 \cdot e^{n8}\right) + \varepsilon 2$$

Where $\Theta_{1\text{-}23}$ are estimated parameters from the model and $\eta 1$- $\eta 8$ represent random variable of variances denoted in Table 4. *AGE*, *WGT* and *PMA* represent an individuals age in years, weight in kg and post-menstrual age in years (*AGE*+40/52), respectively. *RES* is the proportional residual error for each component dataset. Error variance $\varepsilon 1$ was fixed to a variance of 1 and $\varepsilon 2$ was estimated from the data. Constants with a subscript *ref* are calculated for the reference individual.

Table 1: Estimated model parameters compared to results from bootstrap resampling.

Parameter	**Estimated value**	**350 Bootstrap resamples**			
		Mean	**Median**	**Percentile**	
				25%	**75%**
Θ_1	5.74	5.70	5.75	5.51	5.92
Θ_2	11.8	11.8	11.8	10.6	12.9
Θ_3	222	223	225	210	238
Θ_4	1.83	1.84	1.84	1.79	1.88
Θ_5	3.10	3.14	3.11	2.84	3.39
Θ_6	1.08	1.08	1.08	0.99	1.17
Θ_7	9.77	9.65	9.66	9.32	9.97
Θ_8	29.0	29.1	29.2	27.6	30.6
Θ_9	134	133	133	128	139
Θ_{11}	1.53	1.55	1.54	1.51	1.57
Θ_{11}	1.42	1.44	1.44	1.39	1.49
Θ_{12}	0.61	0.60	0.60	0.58	0.63
Θ_{13}	16.6	16.5	16.4	15.7	17.2
Θ_{14}	2.75	2.79	2.78	2.63	2.93
Θ_{15}	22.2	24.0	22.3	20.5	25.3
Θ_{16}	69.2	68.8	68.6	66.7	71.0
Θ_{17}	0.35	0.35	0.34	0.30	0.39
Θ_{18}	3.55	3.45	3.46	3.09	3.82
Θ_{19}	8.91	9.02	8.84	7.59	10.24
Θ_{20}	27.6	27.1	27.2	24.7	29.3
Θ_{21}	6.34	6.21	6.33	5.24	7.33
Θ_{22}	0.830	0.837	0.836	0.809	0.864
Θ_{23}	0.225	0.24	0.242	0.214	0.263
Variance					
η_1	0.032	0.037	0.029	0.017	0.049
η_2	0.323	0.326	0.330	0.295	0.352
η_3	0.294	0.296	0.294	0.267	0.322
η_4	0.318	0.318	0.316	0.289	0.344
η_5	0.068	0.068	0.068	0.064	0.072
η_6	0.130	0.125	0.126	0.103	0.147
η_7	0.091	0.088	0.087	0.070	0.105
η_8	0.044	0.042	0.041	0.037	0.046


Bootstrap distribution of population paramater estimates (350 resamples)
Θ1
Θ2
Θ3
Θ4
Θ5
Θ6
Θ7
Θ8
Θ9
Θ10
Θ11
Θ12
Θ13
Θ14
Θ15
Θ16
Θ17
Θ18
Θ19
Θ20
Θ21
Θ22
Θ23