Physiologically Based Pharmacokinetic Modeling of Metformin in Children and Adolescents with Obesity: Supplemental Figures

Jennifer Lynn Ford, PhD [1], Jacqueline G. Gerhart, MS [1], Andrea N. Edginton, PhD [2], Jack A. Yanovski, MD, PhD [3], Yuen Yi Hon, PharmD, BCOP [4], and Daniel Gonzalez, PharmD, PhD [1,*]

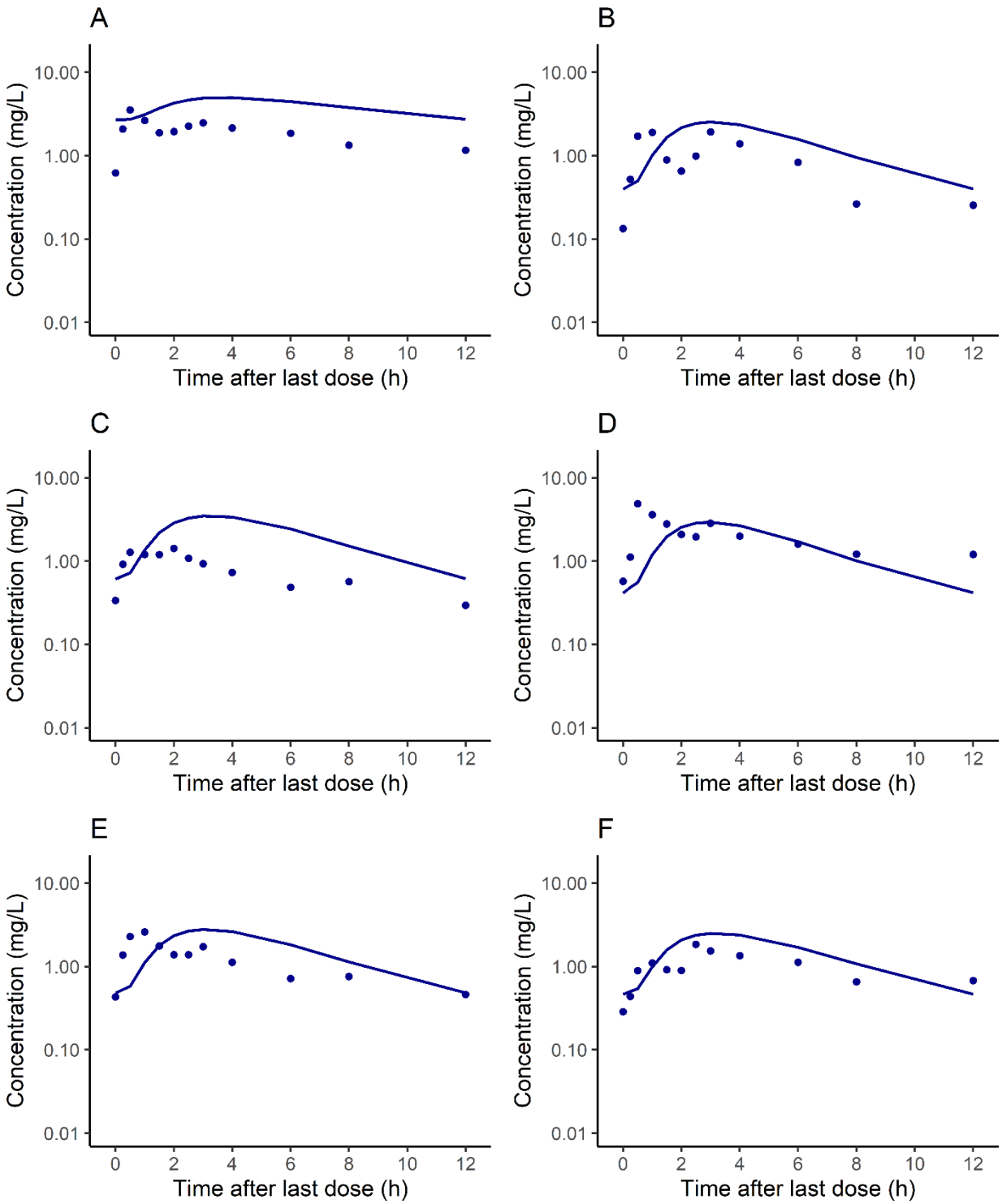
[1] Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

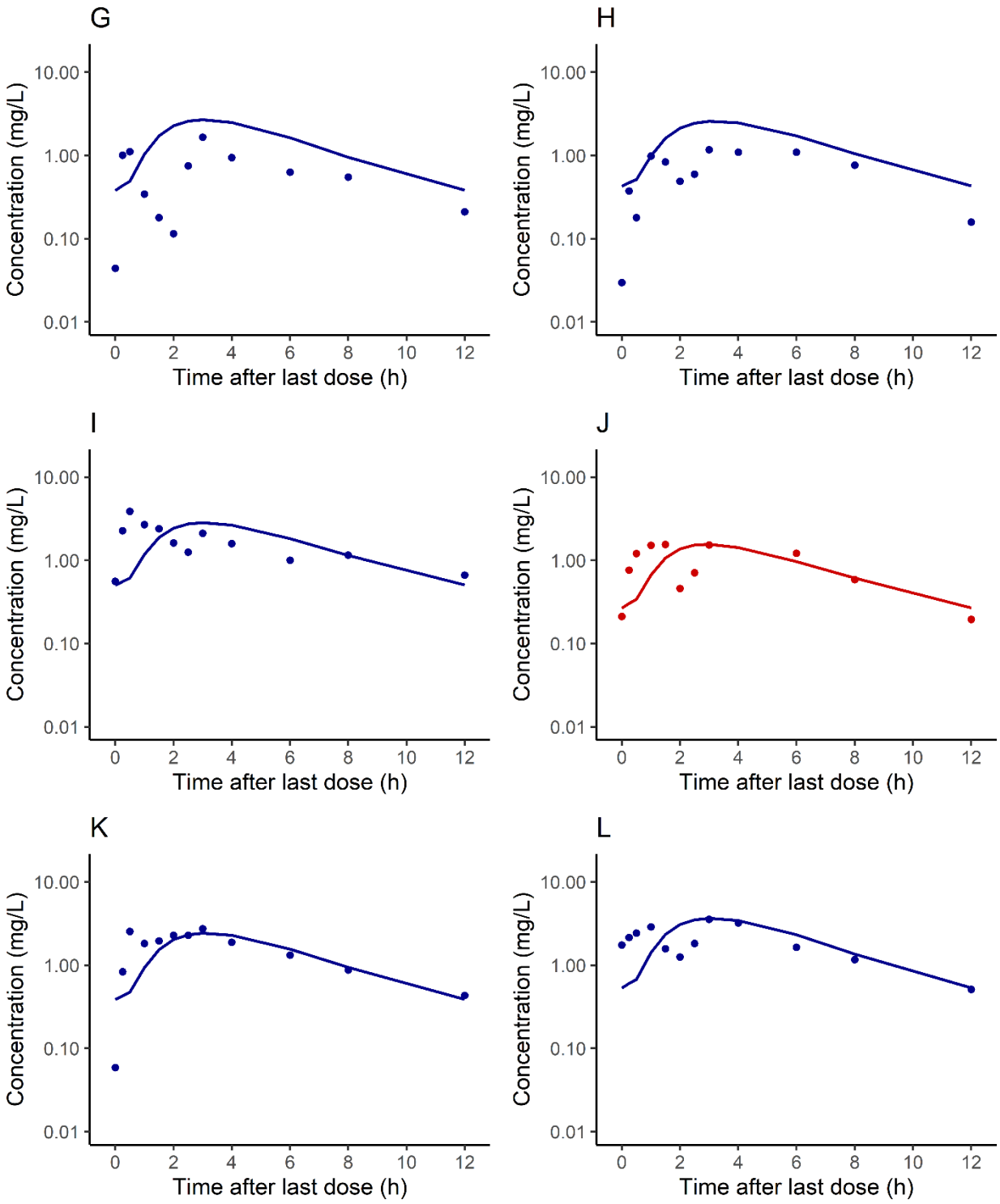
[2] School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada

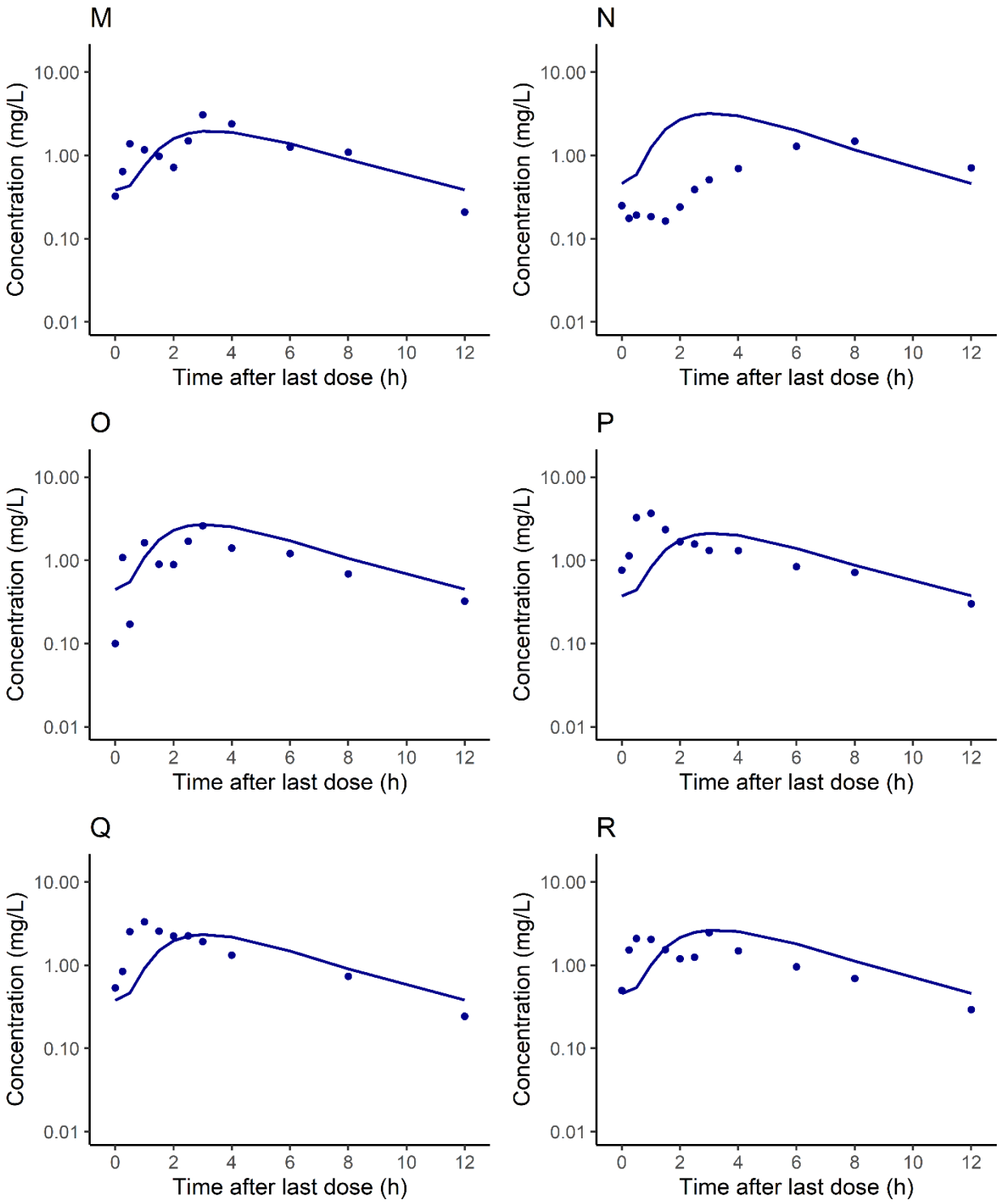
[3] Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

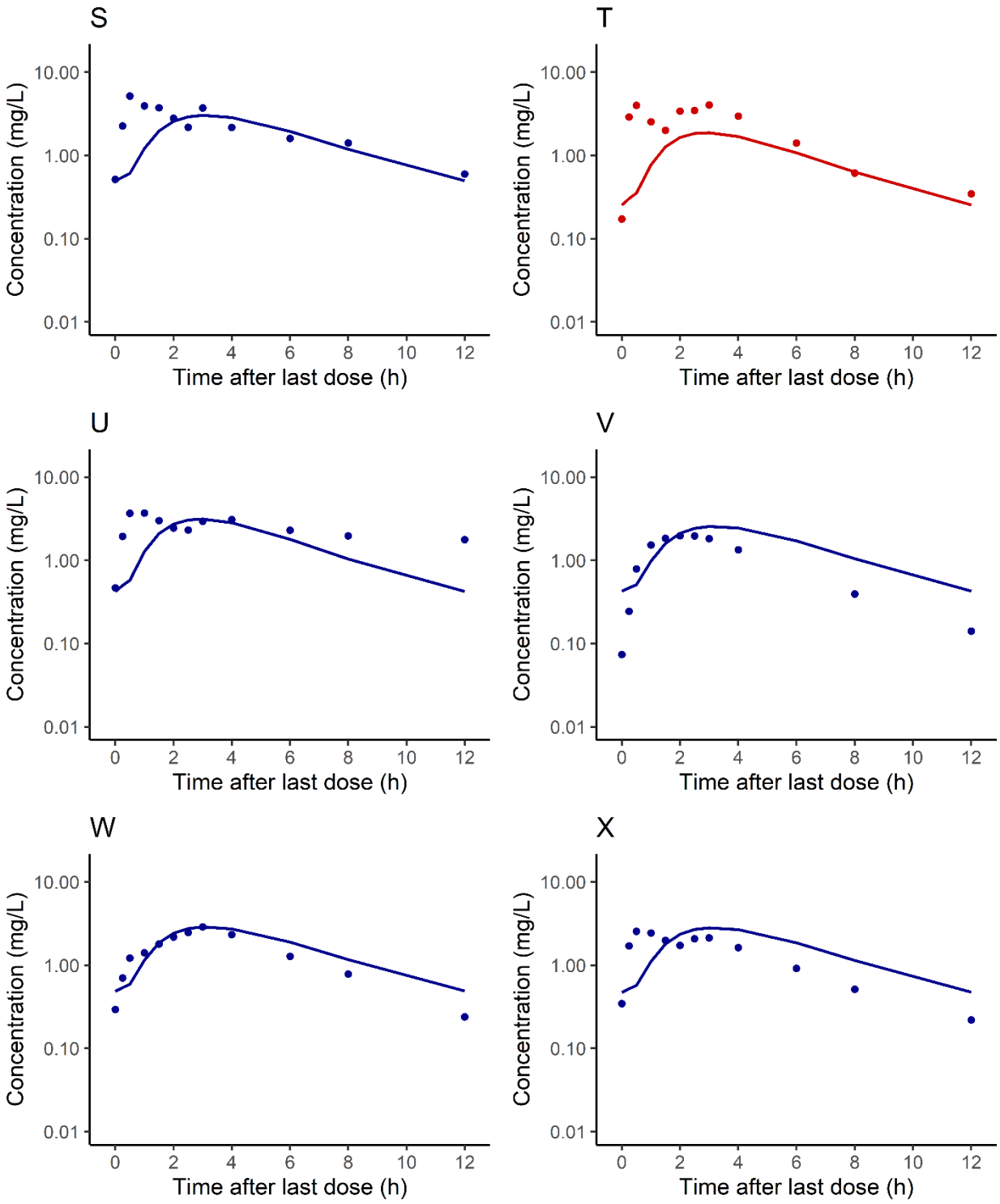
[4] Division of Rare Diseases and Medical Genetics, Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

* Correspondence should be addressed to Daniel Gonzalez; 3312 Kerr Hall, CB# 7569, Chapel Hill, NC, 27599-7569; (919) 966-9984; daniel.gonzalez@unc.edu


A
B
C
D
E
F
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


G
H
I
J
K
L
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


M
N
O
P
Q
R
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


S
T
U
V
W
X
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)

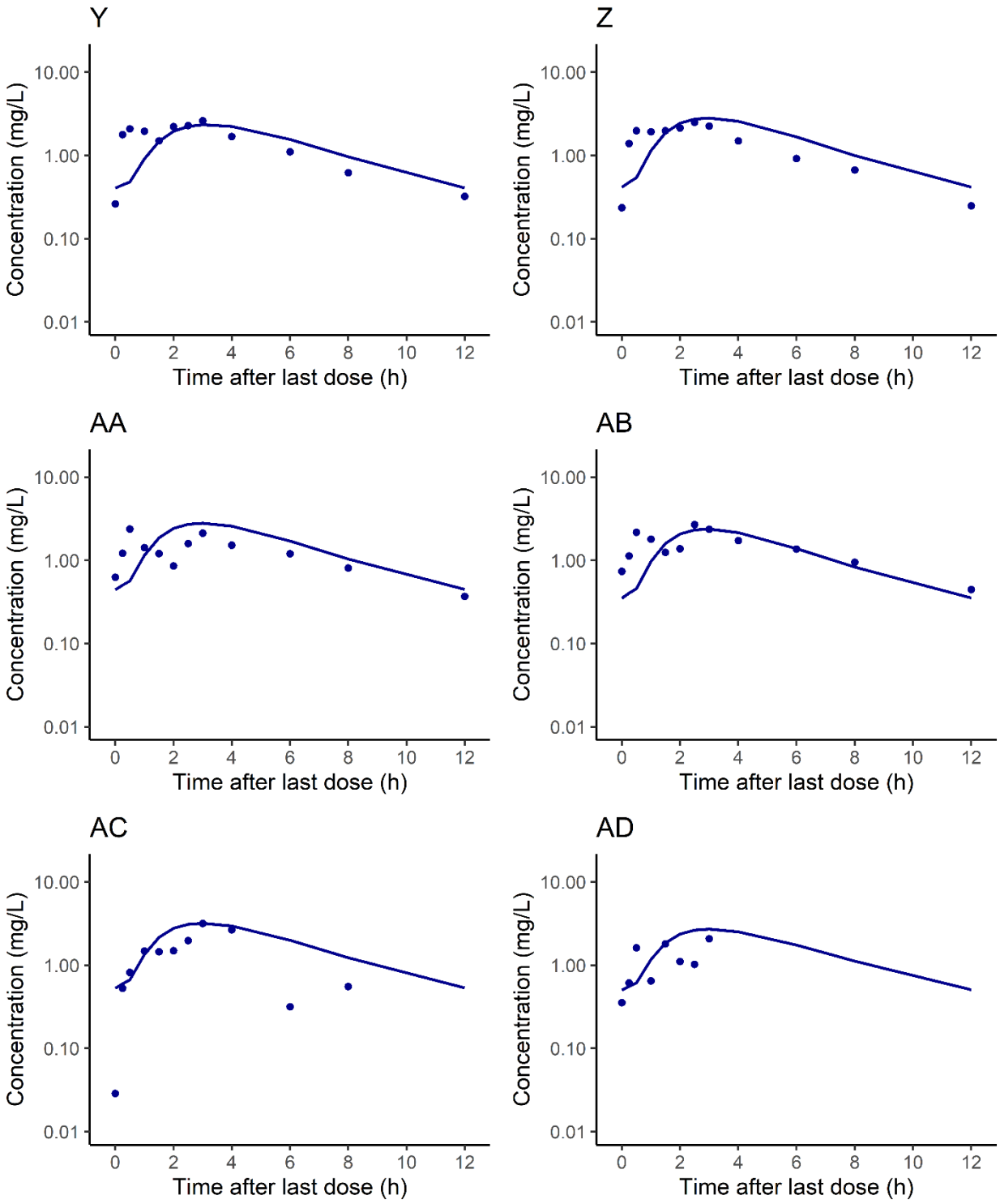
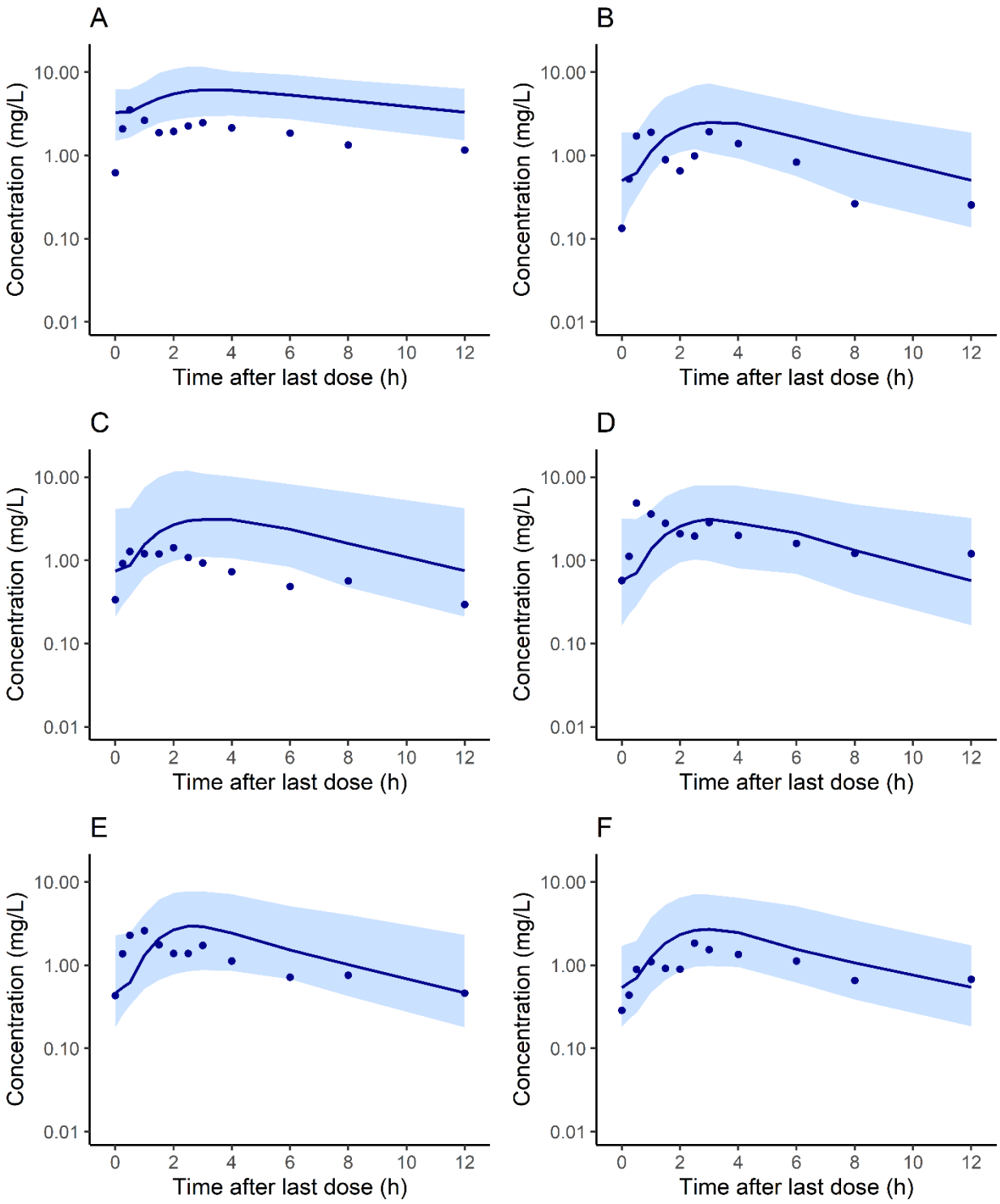
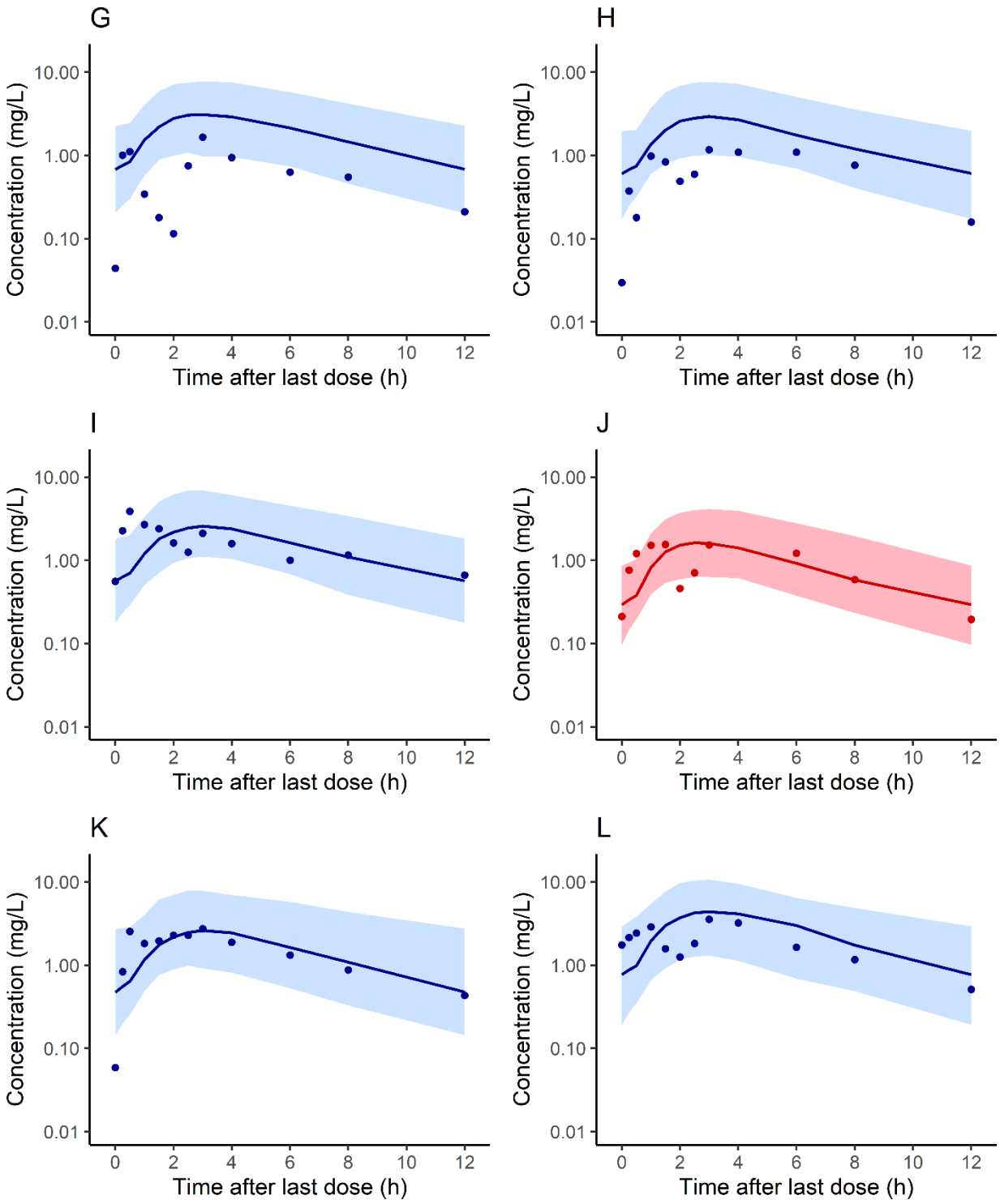
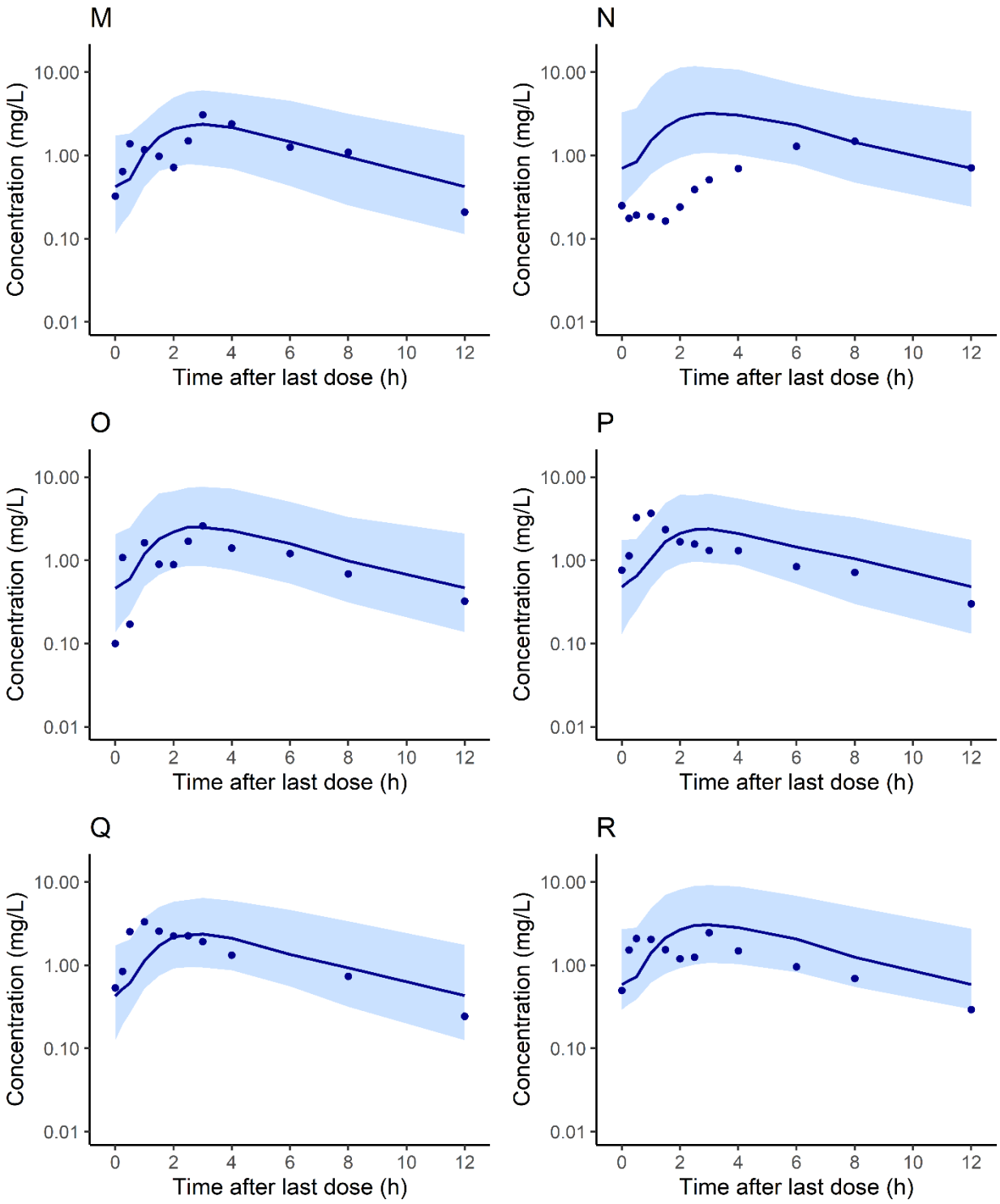
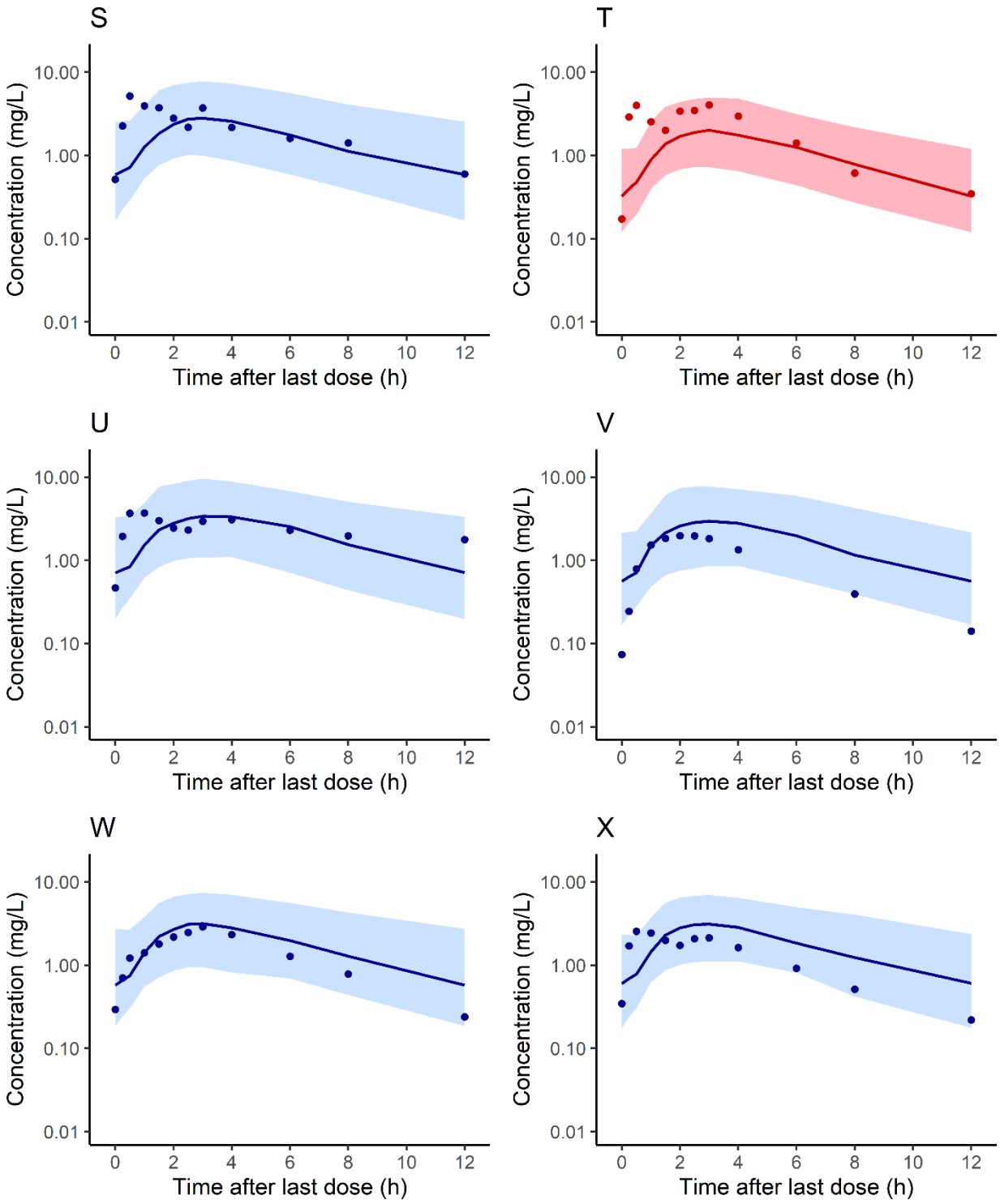


Figure S1 Observed (symbols) and simulated (solid lines) plasma concentrations at steady state in children and adolescents with severe obesity following either a 500 (J and T; red) or 1,000 mg dose of metformin (all remaining panels; blue). Each panel shows observed data for a single patient compared with simulated concentrations for a demographic-matched virtual subject. Observed data were collected over 12 h from children and adolescents with severe obesity who had been receiving 500 (n=2) or 1,000 mg (n=28) twice daily metformin therapy for 6 months.[1]


A
B
C
D
E
F
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


G
H
I
J
K
L
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


M
N
O
P
Q
R
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)


S
T
U
V
W
X
Concentration (mg/L)
10.00
1.00
0.10
0.01
0
2
4
6
8
10
12
Time after last dose (h)

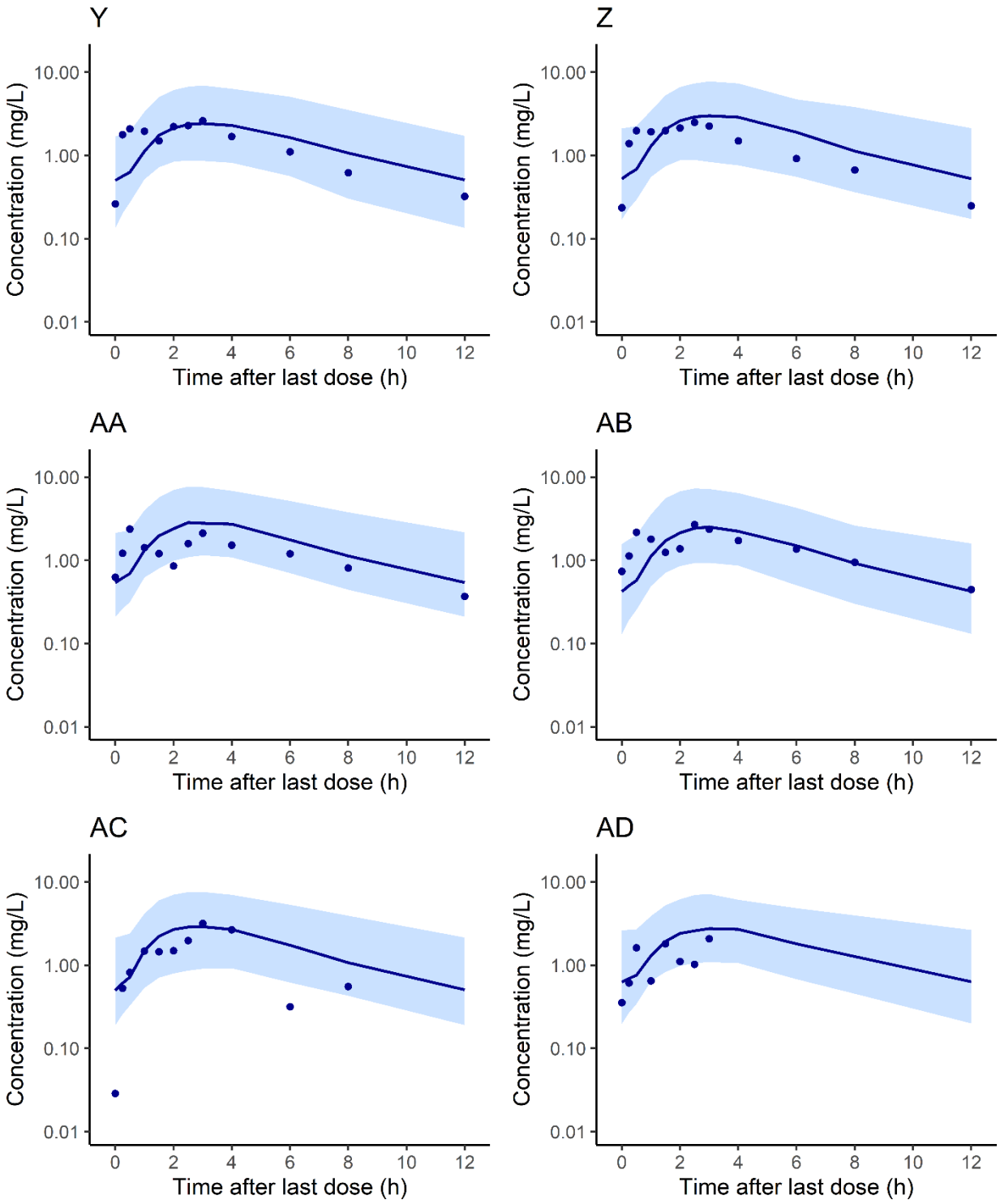


Figure S2 "Individualized" population simulations (n=100) of plasma concentration at steady state for children and adolescents with severe obesity following either a 500 (J and T; red) or 1,000 mg dose of metformin (all remaining panels; blue). Each panel shows observed data (symbols) for an individual patient compared with simulated median concentration (solid line) and the 90% prediction interval (shaded region) for a virtual population within ± 1 y of age with similar demographics. Observed data were collected over 12 h from children and adolescents with severe obesity who had been receiving 500 (n=2) or 1,000 mg (n=28) twice daily metformin therapy for 6 months.[1]

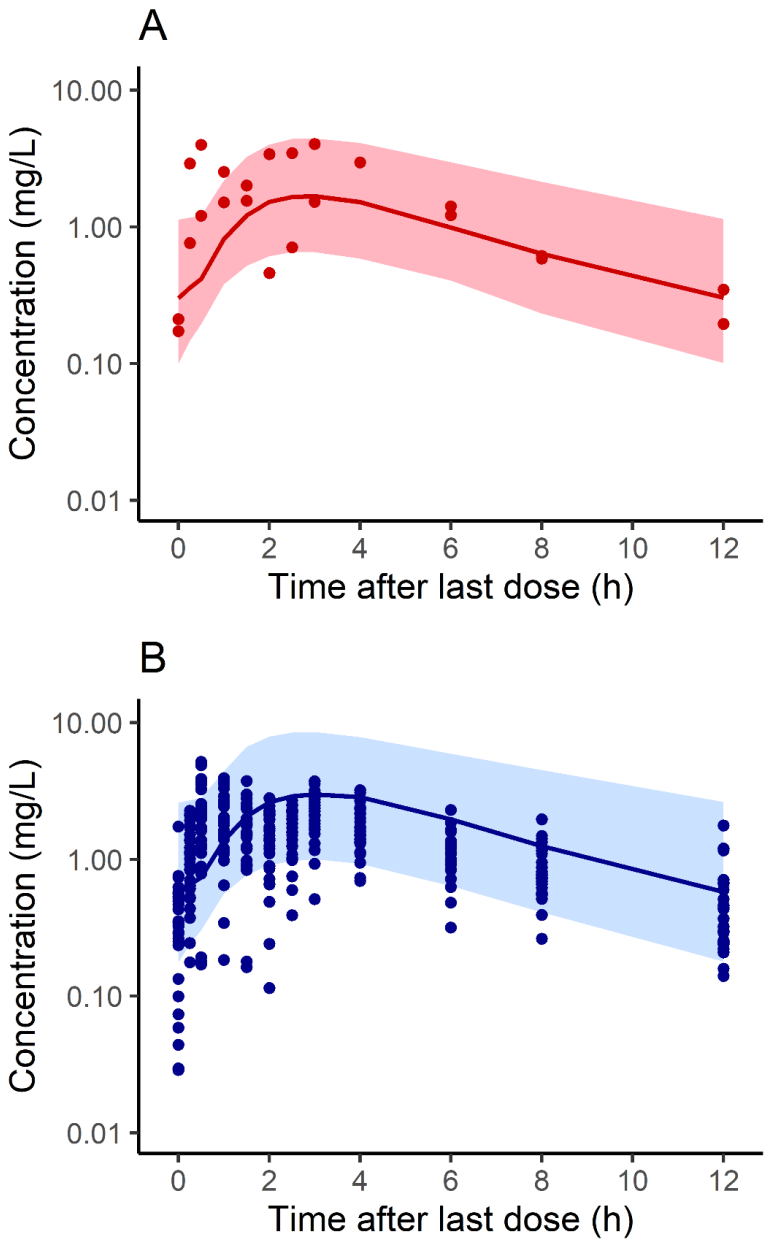


Figure S3 Population simulations (n=1,000) of plasma concentration in children and adolescents with severe obesity at steady state following either a 500 (A) or 1,000 mg (B) dose of metformin. Shown are simulated median concentration (solid line) and the 90% prediction interval (shaded region) for the population overlaid with observed data (symbols) for two subjects (A) and 28 subjects (B). The virtual population was generated using the mean demographics from the published study population.[1] In that study, observed data were collected over 12 h from patients with severe obesity who had been receiving 500 (n=2) or 1,000 mg (n=28) twice daily metformin therapy for 6 months.

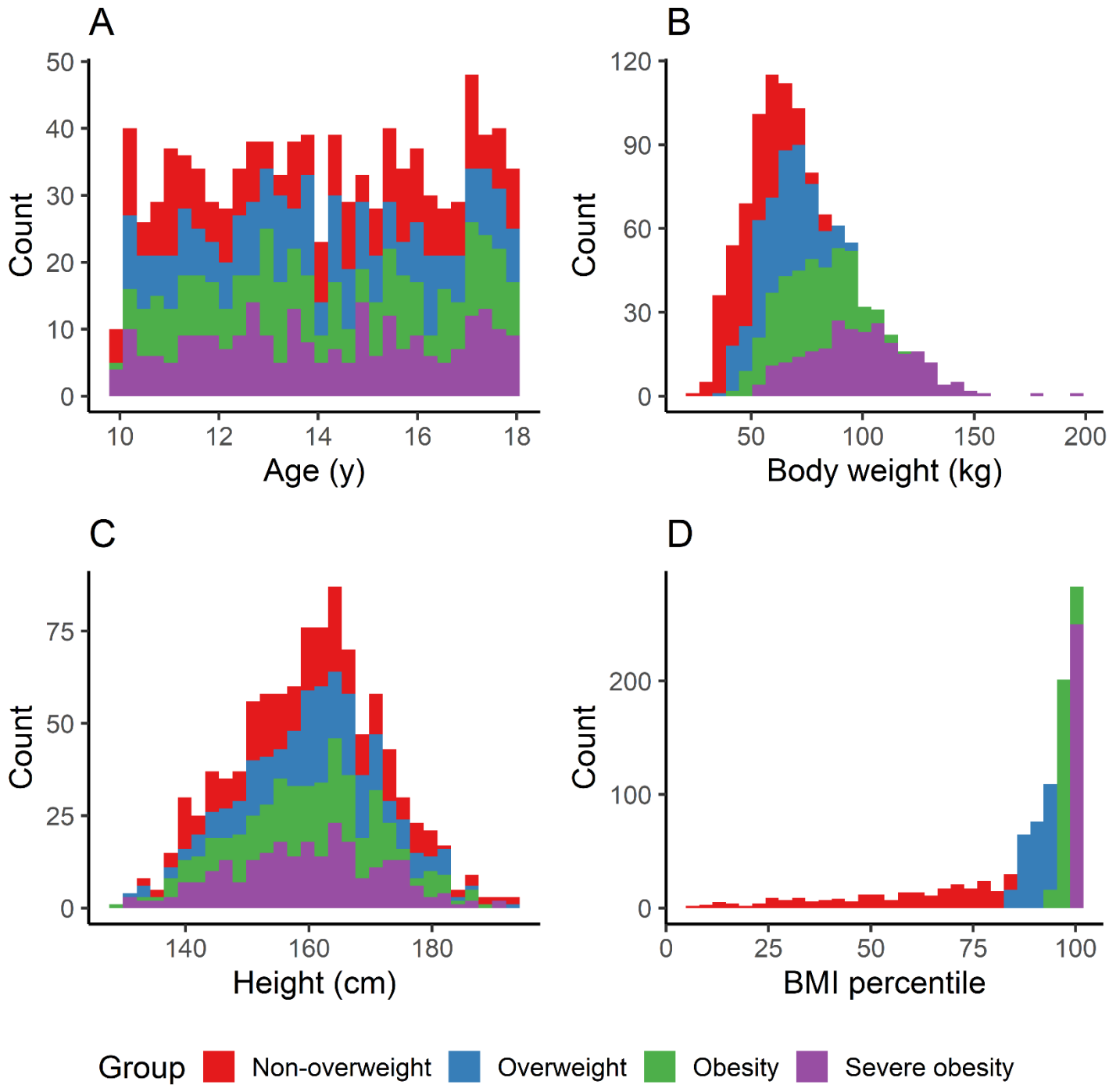


Figure S4 Demographics for a virtual population of children (n=1,000) aged 10 – 18 y grouped by BMI percentile (n=250 children/group). Groups were defined as follows: non-overweight (5 – 85th BMI percentile), overweight (85 – 95th BMI percentile), obesity (95 – 99th BMI percentile), and severe obesity (>99th BMI percentile). Panels A-D illustrate the population distribution for age, body weight, height, and BMI percentile by group as histograms. BMI, body mass index.

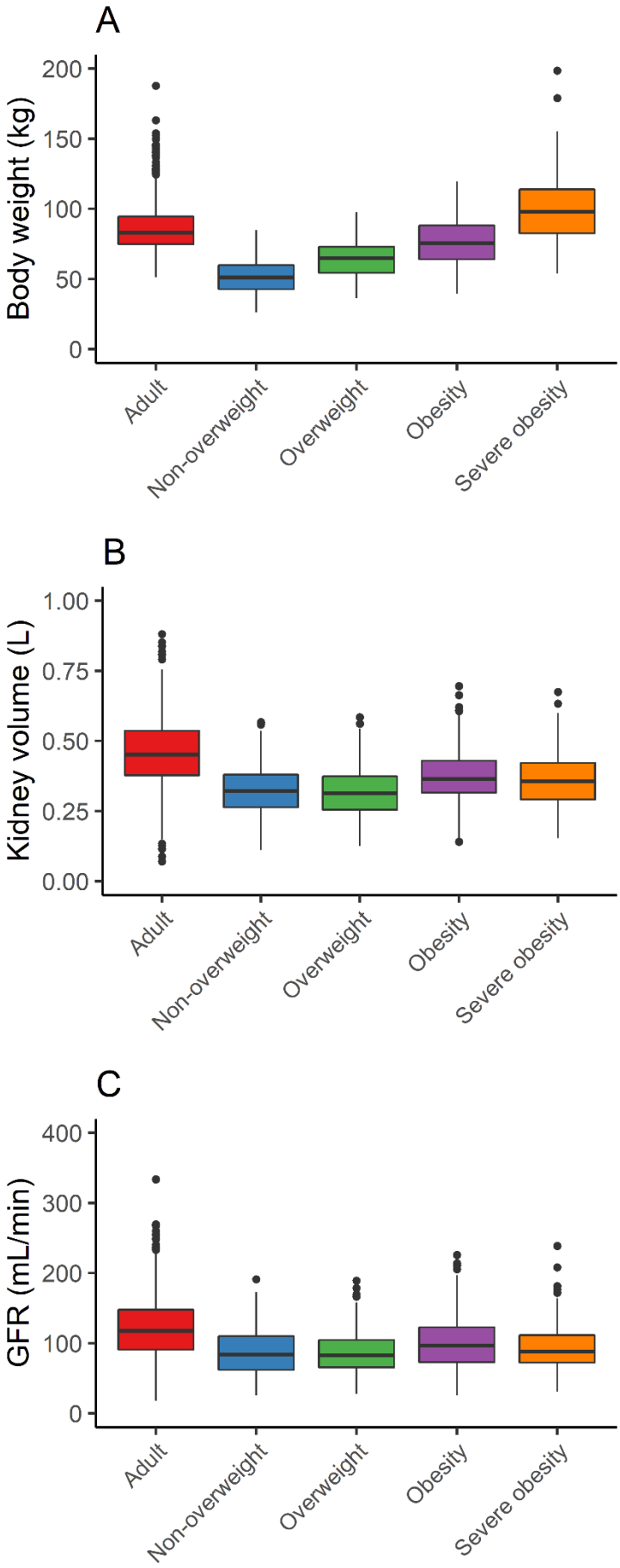


Figure S5 Relevant system related (physiological) parameters for a virtual population of older children and adolescents (n=1,000) aged 10 – 18 y grouped by BMI percentile (n=250/group); simulated values for an adult population (n=1,000) were included for comparison. Pediatric groups were defined as follows: non-overweight (5 – 85th BMI percentile), overweight (85 – 95th BMI percentile), obesity (95 – 99th BMI percentile), and severe obesity (>99th BMI percentile). Panels A-C compare body weight, kidney volume, and GFR across groups. See **Supplementary Methods** for PK-Sim® calculation of GFR. Boxplots represent median or 50th percentile (middle band), 25th and 75th percentiles (lower and upper quartiles), range (vertical line), and outliers (symbols). BMI, body mass index; GFR, glomerular filtration rate.

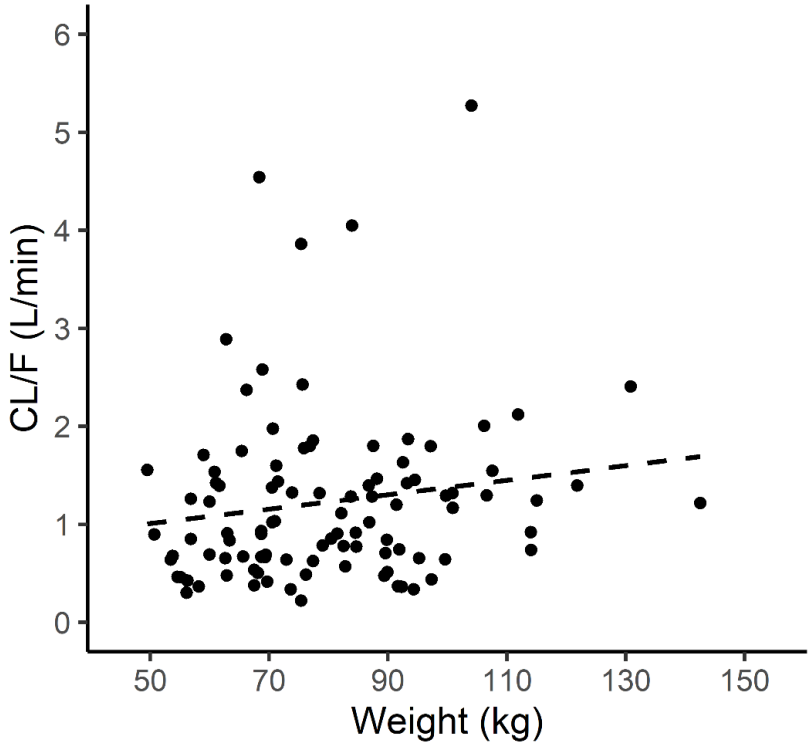


Figure S6 Simulated values for CL/F (L/min) of metformin versus body weight for a virtual population (n=100) of adolescent with overweight / obesity to replicate the comparison presented in Figure 1 of the original publication.[2] Each symbol represents an individual and the dashed line is the best fit linear regression line. Demographics and trial design for the virtual populations were matched to reflect the published study. CL/F, oral clearance (calculated as dose / area under the concentration-time curve, where dose was 1,000 mg and area under the concentration-time curve was calculated over the dosing interval at steady state).

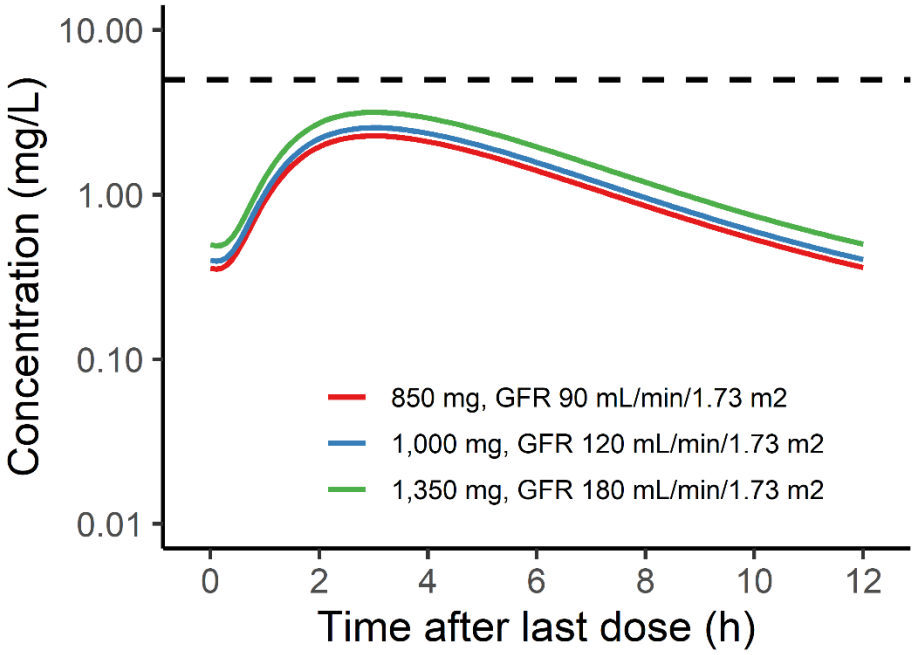


Figure S7 Simulations of steady state metformin concentrations versus time for a virtual patient with severe obesity with varying doses and GFR to replicate Figure 4 in the original publication of children and adolescents with severe obesity and insulin resistance.[1] The following scenarios were simulated: 850 mg twice daily with GFR of 90 mL/min/1.73 m^2, 1,000 mg twice daily with GFR of 120 mL/min/1.73 m^2, and 1,350 mg twice daily with GFR of 180 mL/min/1.73 m^2. The virtual individual was generated based on the mean demographics of the published population. GFR, glomerular filtration rate.

REFERENCES

1. Sam WJ, Roza O, Hon YY, et al. Effects of SLC22A1 polymorphisms on metformin-induced reductions in adiposity and metformin pharmacokinetics in obese children with insulin resistance. *J Clin Pharmacol*. 2017;57(2):219–29.
2. van Rongen A, van der Aa MP, Matic M, et al. Increased metformin clearance in overweight and obese adolescents: a pharmacokinetic substudy of a randomized controlled trial. *Pediatr Drugs*. 2018;20(4):365–74.