

Population pharmacokinetics of total and protein-unbound prednisolone in children with immune-mediated and inflammatory diseases

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Background

- High dose **prednisolone** is the mainstay treatment for **children with various (auto)immune diseases**.¹
- Standard empirical dosing regimens consist of dosages up to **2 mg/kg/day** for adequate immune suppression. This regimen is accompanied with **substantial adverse effects in the majority of patients**.²
- **Pharmacokinetic (PK) variability** may be an important **determinant for efficacy and toxicity**, but has limitedly been investigated in children.

Primary objective

Characterise the population PK and determinants of variability of protein-bound and unbound prednisolone in children with (auto)immune diseases.

Data

Two prospective studies in paediatric patients with indication for systemic prednisolone (IV and oral)

Study	PIKACHU (n=44)	CARPE DIEM (n=16)
Population	Age 0-18 years HCT	Age 6-18 years Diagnosed or relapsed AID
Indication	GvHD	e.g. SLE, uveitis and IBD
Dosages	1-2 mg/kg daily	≥0.5 mg/kg
PK sampling	Pre-dose, 0.5, 2, 4 and 7h post dosing	Pre-dose, 0.5, 2 and 4h post dosing

HCT haematopoietic cell transplantation; GvHD Graft vs. host disease; AID autoimmune disease; SLE systemic lupus erythematosus, IBD inflammatory bowel disease.

Methods

- Concentrations total (C_{pred}) and unbound prednisolone ($C_{predunb}$) in serum were quantified by liquid chromatography-tandem mass spectrometry.³

$$C_{pred} = C_{predunb} + C_{predbound}$$

- Key aspects of the structural model (**Fig. 1**)
- Allometric scaling (**Table 1**).
- Combined linear and non-linear binding to albumin and corticosteroid binding globulin (CBG), respectively (**Fig 1 en Fig 2**).
- Circadian rhythm of CBG.⁴ (**Fig. 3**)

- NONMEM v.7.5.1

Results - Table 1. parameter estimates

Parameter	Estimate (RSE%) [shr]	95% CI SIR
Structural model		
k_a (h ⁻¹)	0.68 (14.1)	0.53 – 0.89
CL_{70kg} (L/h)	155 (7.4)	137 – 182
Q_{70kg} (L/h)	105 (21.4)	68 – 155
$V_{c,70kg}$ (L)	338 (9.7)	284 – 410
$V_{p,70kg}$ (L)	170 (12.7)	130 – 215
K_{alb} (μM)	200 (11.2)	164 – 253
K_{CBG} (μM)	0.048 (5.1)	0.043 – 0.053
Covariates		
HCT-P	1.10 (7.8)	0.95 – 1.28
HCT-T	0.97 (8.3)	0.82 – 1.14
Random effects		
IIV k_a (%)	51.8 (33.7) [61]	32.6 – 67.9
IIV CL (%)	31.5 (21.3) [8]	26.0 – 38.8
IIV V_c (%)	60.4 (20.2) [22]	49.6 – 72.4
IIV V_p (%)	39.1 (34.2) [29]	27.2 – 52.3
Corr. $CL-V_c$ (%)	51.0 (27.2)	39.6 – 54.0
Corr. V_c-V_p (%)	-59.0 (30.8)	-169.0 – -15.4
Residual error		
Residual prop. err CP (%) [shr]	26.5 (9.2) [8]	24.4 – 29.0
Residual prop. err CPU (%) [shr]	33.8 (10) [10]	31.0 – 37.5

CP concentration total prednisolone in μM, CPU concentration unbound prednisolone in μM, HCT-P covariate HCTprophylaxis cohort (reference: autoimmune cohort), IIV inter individual variability.

Results - covariate relationships

$$CL = CL_{70kg} \times \left(\frac{BW}{70}\right)^{0.75} \times HCT-P^i \times HCT-T^i$$

$$Q = Q_{70kg} \times \left(\frac{BW}{70}\right)^{0.75}$$

$$V_c = V_{c,70kg} \times \left(\frac{BW}{70}\right)^1$$

$$V_p = V_{p,70kg} \times \left(\frac{BW}{70}\right)^1$$

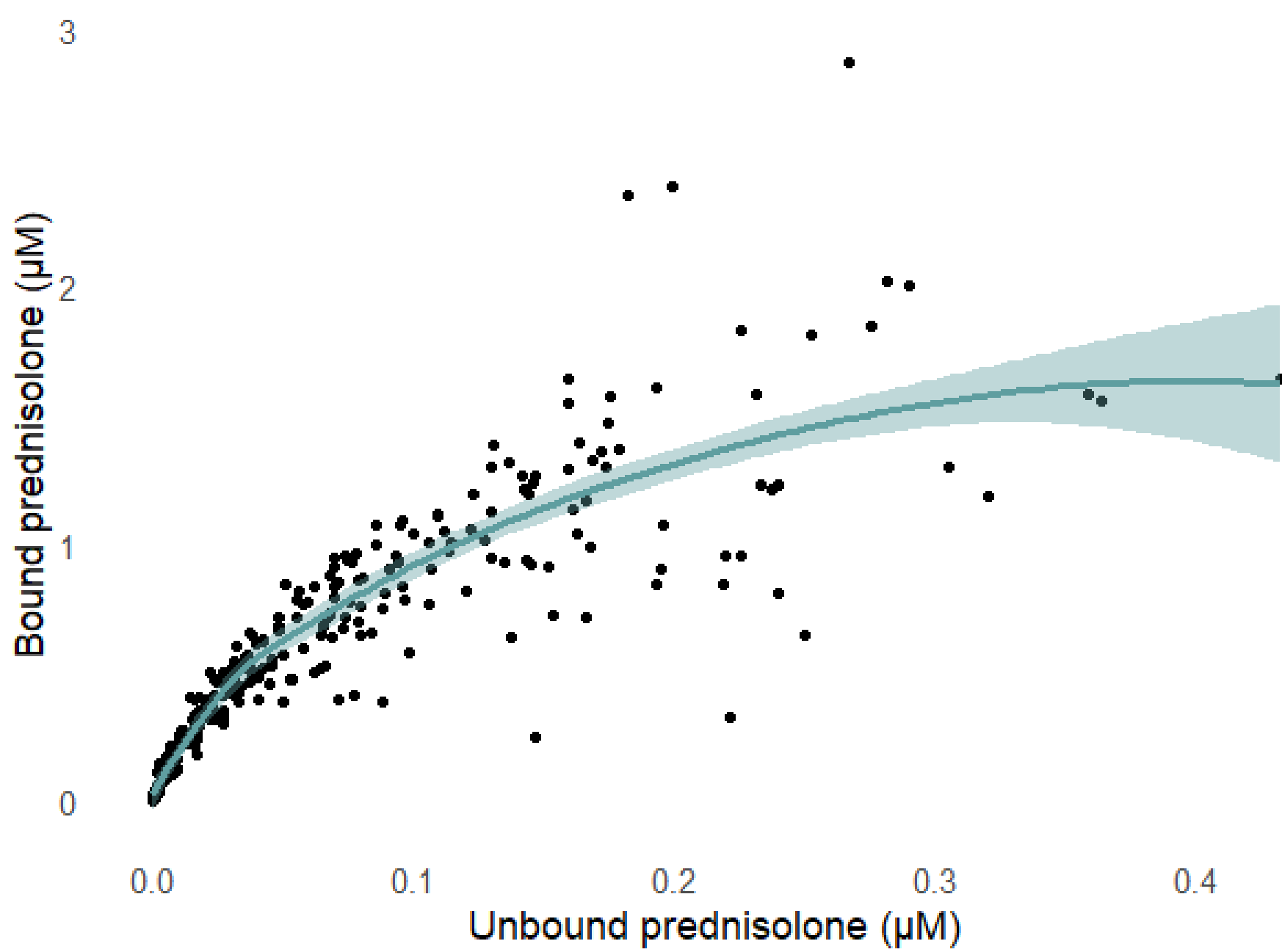


Figure 2 Concentration unbound prednisolone (x-axis) vs bound prednisolone in the lower concentration range, indicating saturable binding of prednisolone to CBG with increased serum concentrations

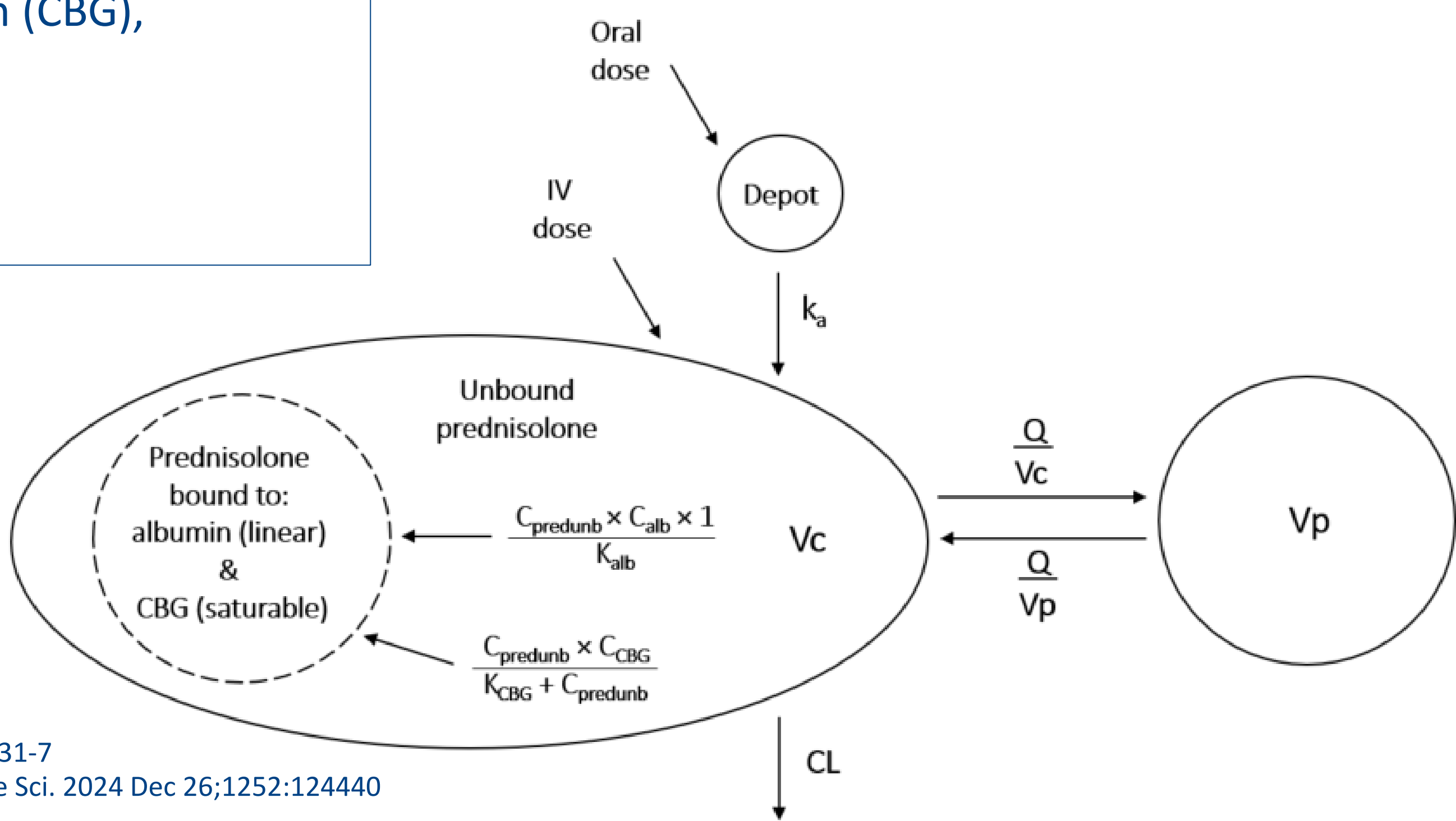


Figure 1 Model structure. CBG corticosteroid binding globulin, CL clearance, IV intravenous, k_a absorption rate constant, Q intercompartmental clearance, V_c volume of distribution central compartment, V_p volume of distribution peripheral compartment. K_{CBG} and K_{alb} affinity constants of prednisolone for CBG and albumin

References

1. Ferrara G et al. In J Mol Sci. 2019 Jan 21;20(2):444
2. McDonough AK et al. Curr Opin Rheumatol. 2008 Mar;20(2):131-7
3. Möhlmann JE et al. J Chromatogr B Analyt Technol Biomed Life Sci. 2024 Dec 26;1252:124440
4. Melin J et al. Clin Endocrinol (Oxf). 2019 Jul;91(1):33-40

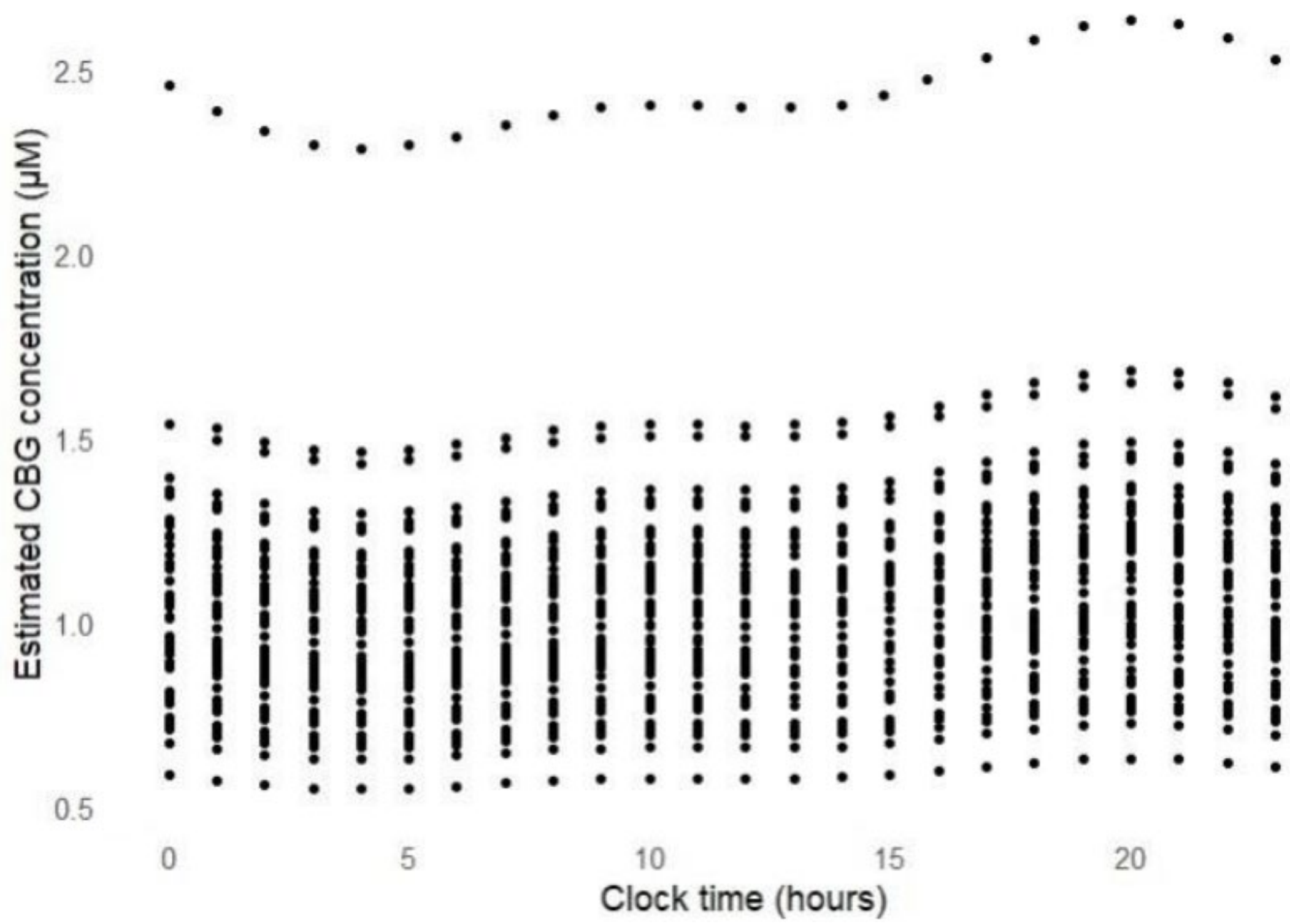


Figure 3 Predicted circadian rhythm in CBG concentrations over a 24-h time window in the study populations, based on baseline CBG sample and [4].

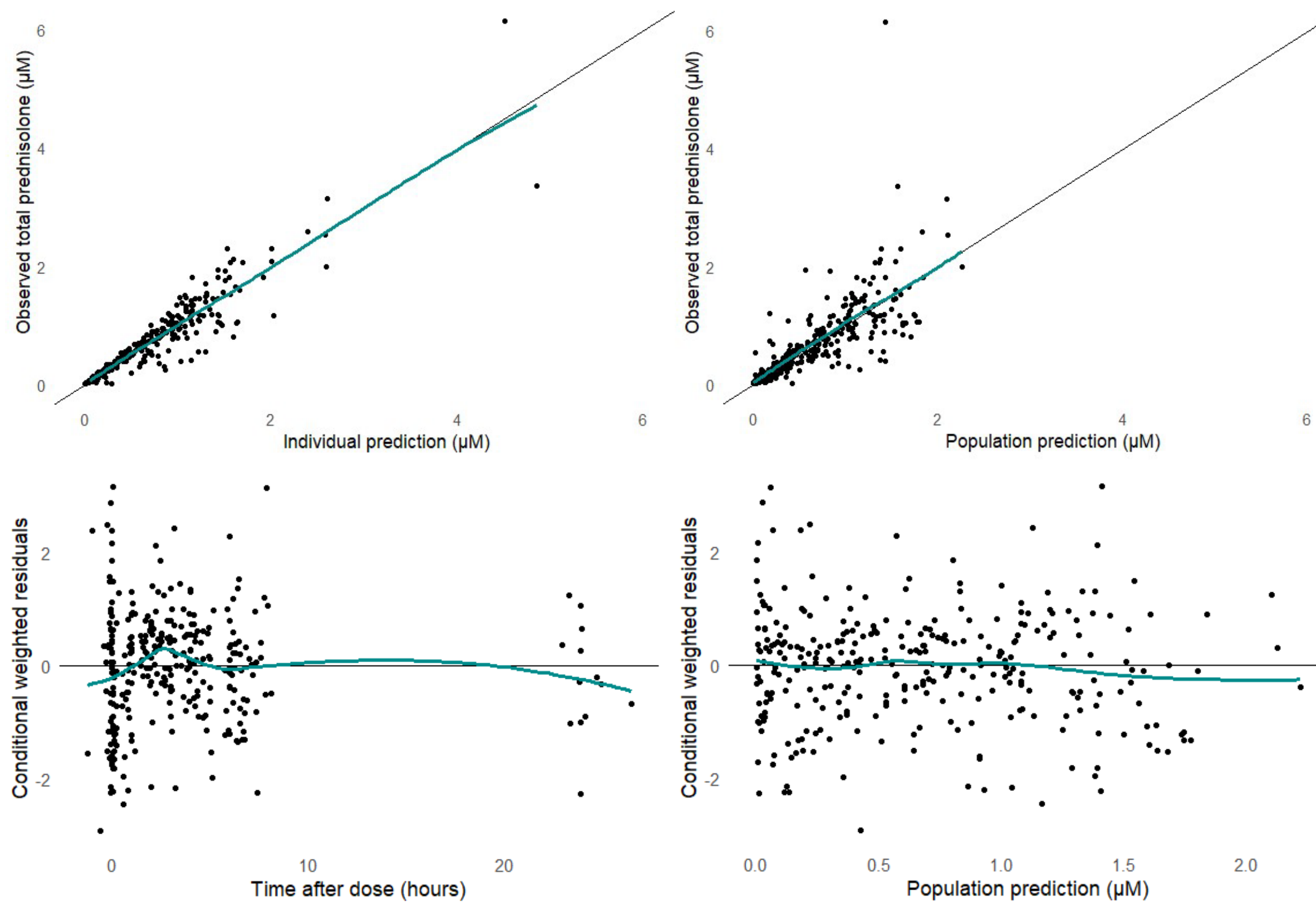


Figure 4 Goodness of fit plots total prednisolone concentration (unbound prednisolone concentrations show similar Goodness of fit, not depicted).

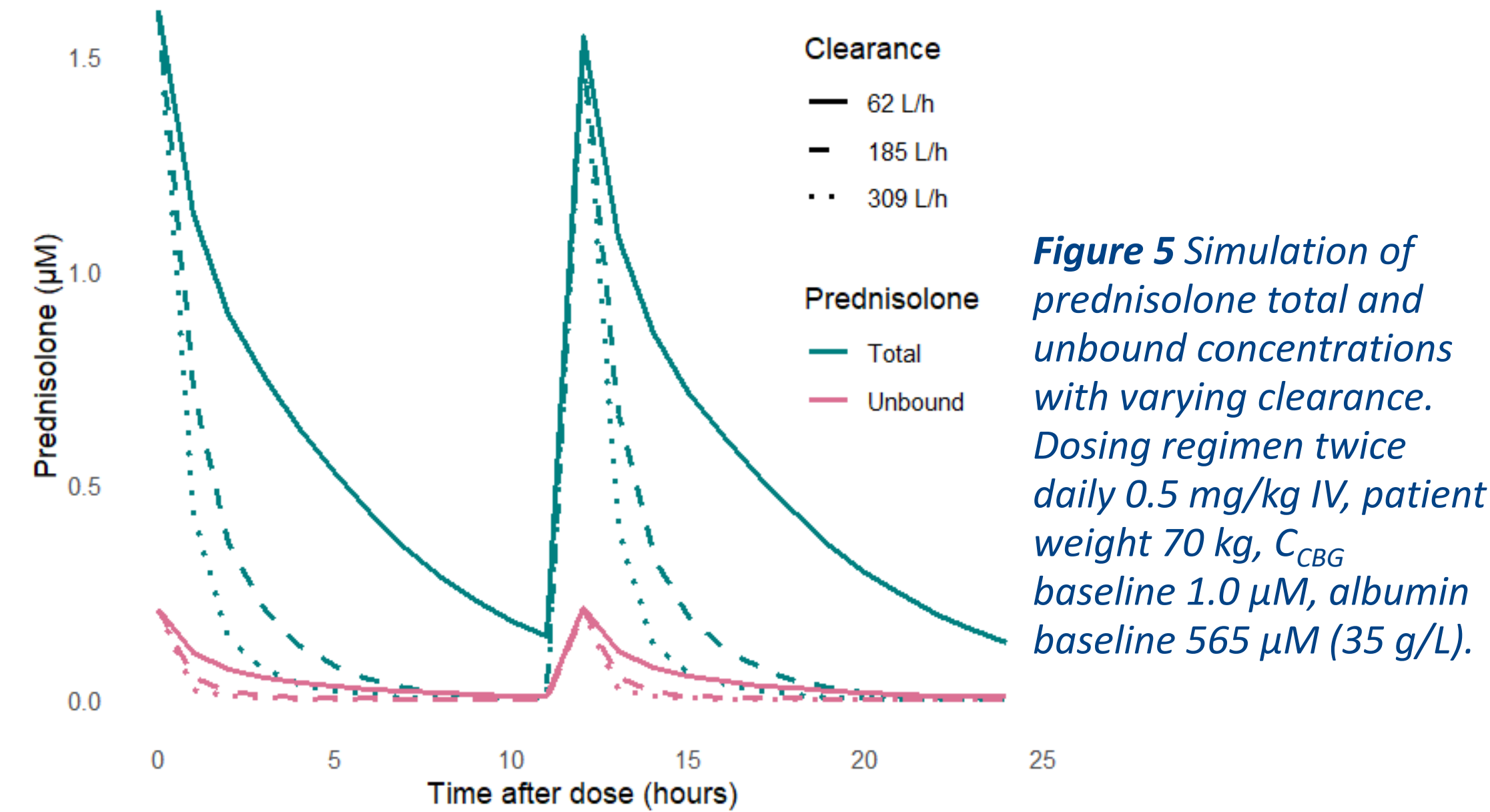


Figure 5 Simulation of prednisolone total and unbound concentrations with varying clearance. Dosing regimen twice daily 0.5 mg/kg IV, patient weight 70 kg, C_{CBG} baseline 1.0 μM, albumin baseline 565 μM (35 g/L).

Conclusions

- PK data of protein-bound and unbound prednisolone were best described by a **two-compartment model**, with **combined linear and saturable binding of prednisolone to albumin and CBG**, respectively and inclusion of the **circadian rhythm of CBG**
- Allometric scaling of PK accurately captured the effect of body size. The significant effect on prednisolone clearance implies that **current body weight-based dosing of prednisolone is not appropriate in (younger) children**, as they are relatively underdosed.