Electronic Supplementary Material

Clinical Pharmacokinetics

The predictive value of GFR-based scaling of pediatric clearance and doses for drugs eliminated by glomerular filtration with varying protein binding properties

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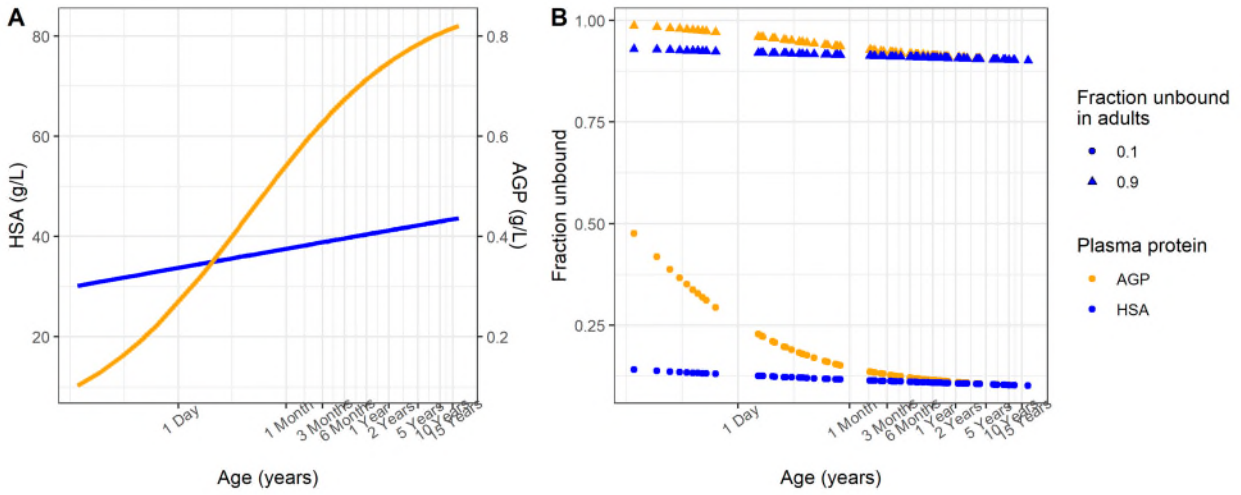

Figure S1 – Maturation profiles for plasma protein expression and plasma protein binding. Left panel (A) shows plasma concentrations of the plasma proteins human serum albumin (HSA) in blue and α-acid glycoprotein (AGP) in orange with age. Right panel (B) shows the changes in protein binding with age for each of the plasma proteins (AGP in orange, HSA in blue) when the fraction unbound measured in adults is either 0.1 (circles) and 0.9 (triangles).

Establishing the most accurate GFR maturation function in preterm neonates

As only four[7, 12, 14] of the published GFR maturation functions assessed in this manuscript were developed including data from preterm neonates and as maturation functions for physiological parameters in PBPK models are often not known in preterm neonates, the assessment of the accuracy of the published GFR maturation predictions in preterm neonates was performed separately. For this, a typical preterm neonate born at 35 weeks with a birthweight of 2330 g followed for the first 12 weeks of life was used[27]. The demographics for the typical preterm neonate were selected as they most resembled the data collected from literature[3, 5, 22]. For the remaining three[13, 15]′[16] GFR maturation functions that were not based on data from preterm neonates extrapolations were made. Furthermore, extrapolations were made for the functions used to characterize the maturation of plasma proteins concentrations and to obtain the unbound fractions in preterm neonates.

In Figure S2 we show the GFR predictions with the seven published functions for the typical preterm neonate overlaid with literature data collected for preterm neonates[3, 5, 22]. By using the demographics of the published data, we found that in preterm neonates, the prediction accuracy of the maturation function of Mahmood[12] had the lowest %RMSPE$_{GFR}$ value of 37%, but it had a similar %PE$_{GFR}$ range compared to Salem[16] and Rhodin[13](Table S1).

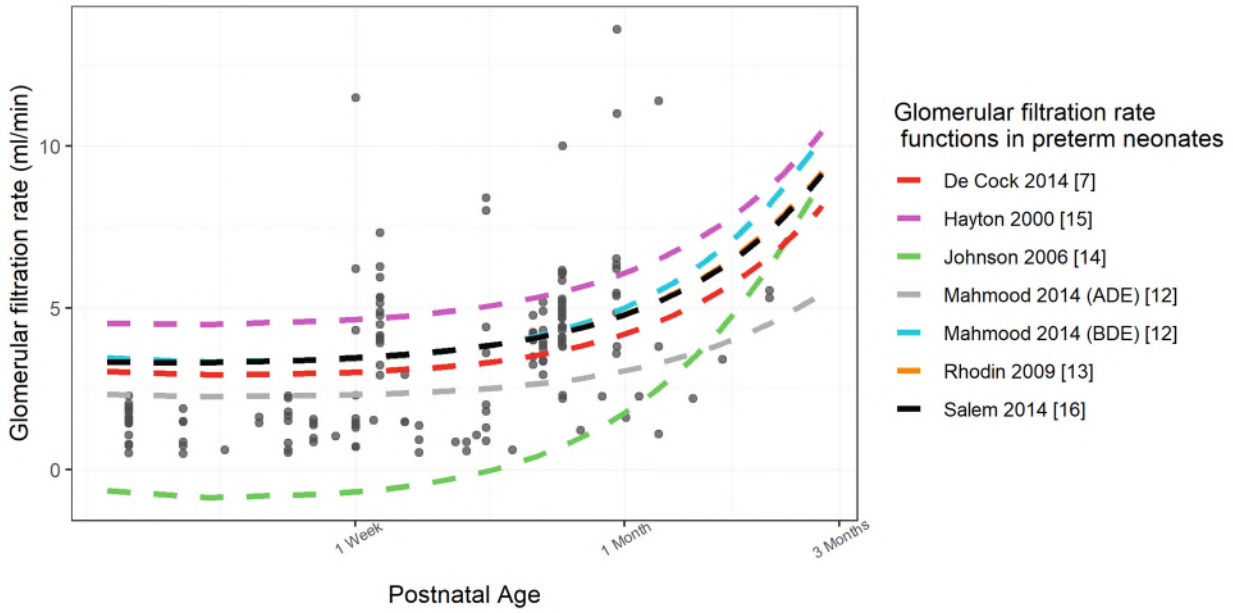

Figure S2 – GFR predictions using published maturation function [7, 12–16] *for typical preterm neonates born at 35 weeks and a weight of 2330 g during the first 12 weeks of life*[27] *(dashed lines) overlaid with observed inulin clearance measurements collected from literature*[3, 5, 22] *(dots). Rhodin[13] and Salem[16] are overlapping.*

Table S1 – Root mean square percentage error (%RMSPE$_{GFR}$) and percentage prediction error% (%PE$_{GFR}$) ranges of the GFR predictions for preterm neonates, obtained with each of the studied GFR maturation functions.

Description	Salem 2014*[16]*			Rhodin 2002*[13]*			Hayton 2000*[15]*			De Cock 2012*[7]*			Johnson 2006*[14]*			Mahmood 2016 (ADE)*[12]*			Mahmood 2016 (BDE) *[12]*		
	%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]		%RMSPE$_{GFR}$	%PE$_{GFR}$ [min-max]	
Preterm	46	-72	26	45	-72	26	60	-56	299	42	-77	39	238	-1215	-73	41	-68	48	37	-78	28