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ORIGINAL RESEARCH ARTICLE

Allometric Scaling of Clearance in Paediatric Patients: When Does the Magic of 0.75 Fade?

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Abstract Allometric scaling on the basis of bodyweight raised to the power of 0.75 (AS0.75) is frequently used to scale size-related changes in plasma clearance (CL_p) from adults to children. A systematic assessment of its applicability is undertaken for scenarios considering size-related changes with and without maturation processes. A physiologically-based pharmacokinetic (PBPK) simulation workflow was developed in R for 12,620 hypothetical drugs. In scenario one, only size-related changes in liver weight, hepatic blood flow, and glomerular filtration were included in simulations of 'true' paediatric CL_p. In a second scenario, maturation in unbound microsomal intrinsic clearance ($CL_{int,mic}$), plasma protein concentration, and haematocrit were also included in these simulated 'true' paediatric CL_p values. For both scenarios, the prediction error (PE) of AS0.75-based paediatric CL_p predictions was assessed, while, for the first scenario, an allometric exponent was also estimated based on 'true' CL_p. In the first scenario, the PE of AS0.75-based paediatric CL_p predictions reached up to 278 % in neonates, and the allometric exponent was estimated to range from 0.50 to 1.20 depending on age and drug properties. In the second scenario, the PE sensitivity to drug properties and maturation was higher in the youngest children, with AS0.75 resulting in accurate CL_p predictions above 5 years of age. Using PBPK principles, there is no evidence for one unique allometric exponent in paediatric patients, even in scenarios that only consider size-related changes. As PE is most sensitive to the allometric exponent, drug properties and maturation in younger children, AS0.75 leads to increasingly worse predictions with decreasing age.

Key Points

There is no evidence for a universal allometric exponent for scaling drug plasma clearance (CL_p) from adults to children.

When scaling CL_p to children, the prediction error (PE) is not sensitive to the allometric exponent in children above the age of 5 years, resulting in accurate CL_p predictions with allometric scaling in this age range for drugs eliminated by glomerular filtration or for drugs undergoing hepatic metabolism when enzyme activity is close to adult values.

In children below the age of 5 years, the PE in scaled CL_p becomes increasingly more sensitive to the allometric exponent, drug properties and maturation, leading to biased CL_p predictions with allometric scaling.

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1 Introduction

Allometric scaling's first main domain of application was scaling of the basal metabolic rate between species, after which a series of investigations (principally in mammals) suggested that interspecies differences in the basal metabolic rate were best described by a bodyweight-based exponential relationship with an exponent close to 0.75 [1–7]. Several theories have been developed to support the existence of a universal allometric scaling exponent [8–11]; however, these theories have been criticized, and discrepancies between the theory and observations have been reported [12–18].

The use of the allometric equation was extended to the scaling of size-related changes in clearance between species [19] and thereafter to the scaling of clearance from adults to children [20]. While different universal values [1, 21] for the allometric exponent have been proposed, a value of 0.75 is commonly applied in order to scale clearance from adults to children. While allometric scaling is applicable to both plasma and whole blood clearance, in this work we focus on allometric scaling of plasma clearance (CL_p) using an exponent of 0.75, as this is the most commonly used for clearance parameters. This scaling approach will be referred to as AS0.75 in this work. This approach is appealing because it is a simple and fast method to scale paediatric CL_p. However, this use of AS0.75 relies on two important implicit assumptions, i.e. the assumption of equivalence between basal metabolic rate and clearance, and the assumption of equivalence between inter- and intraspecies scaling. As illustrated in Fig. 1, for each of these assumptions separately, AS0.75 was found not to be supported by experimental data, challenging the belief of the strong theoretical and empirical basis of AS when applied in scaling paediatric clearance [22–31].

For the scaling of CL_p in the paediatric population, AS0.75 has been recognized as a useful tool to extrapolate CL_p from adult values to adolescents [32], while overpredictions in children younger than 5 years [33], reaching up to more than 200 and 3000 % in infants and premature neonates, respectively, have been reported [34]. The latter is often attributed to the maturational process occurring simultaneously with growth at young ages [35], similar to what was concluded for the intraspecies scaling of the basal metabolic rate [22]. To cope with this, the estimation of a maturation function (MF) in addition to AS0.75 has been proposed [35]. Because of the high correlation between age and size, and consequently the difficulty in disentangling the influence of size-related changes from the influence of age-related changes, their distinction has hitherto been mainly driven by the AS0.75 theory, according to which all changes in CL_p that are not accounted for by AS0.75 are due to maturation. Moreover, the accuracy of AS0.75 of CL_p from adults to children has been evaluated for a limited number of drugs and it is unknown how the accuracy is impacted by various drug properties.

The aim of this study was to unravel in which situations AS0.75 consistently leads to accurate paediatric CL_p predictions. To perform a systematic investigation, we developed a physiologically-based pharmacokinetic (PBPK) workflow for a wide range of hypothetical drugs cleared through hepatic metabolism or glomerular filtration (GF), and explored two scenarios—a scenario including size-related changes only, and a scenario including size-related changes as well as maturational changes. This methodology allowed for the disentanglement of the impact of drug properties, size-related changes, and maturation processes on the performance of AS0.75 in predicting paediatric CL_p from adult values.

2 Methods

A PBPK simulation workflow was developed in R version 3.0.2 (Fig. 2). This workflow was used to investigate the accuracy of AS0.75 in predicting paediatric CL_p, simulated based on PBPK principles, for a total of 12,620 hypothetical drugs (*X*).

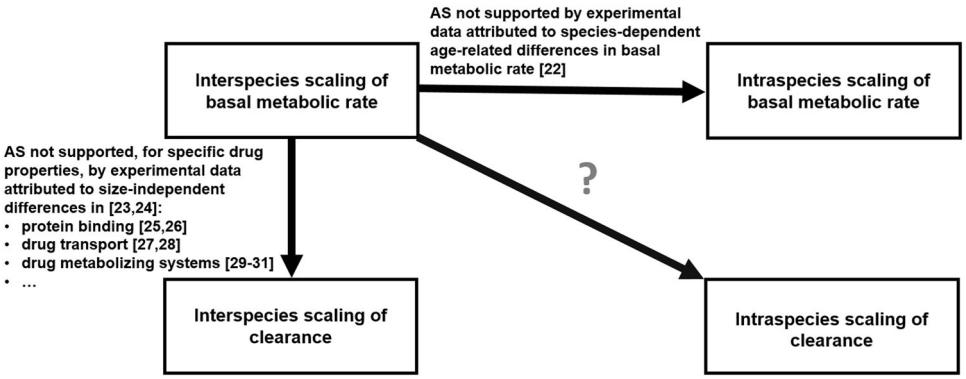


Fig. 1 Implicit assumptions underlying the use of AS to scale CL_p from adults to children. *AS* allometric scaling, *CL_p* plasma clearance

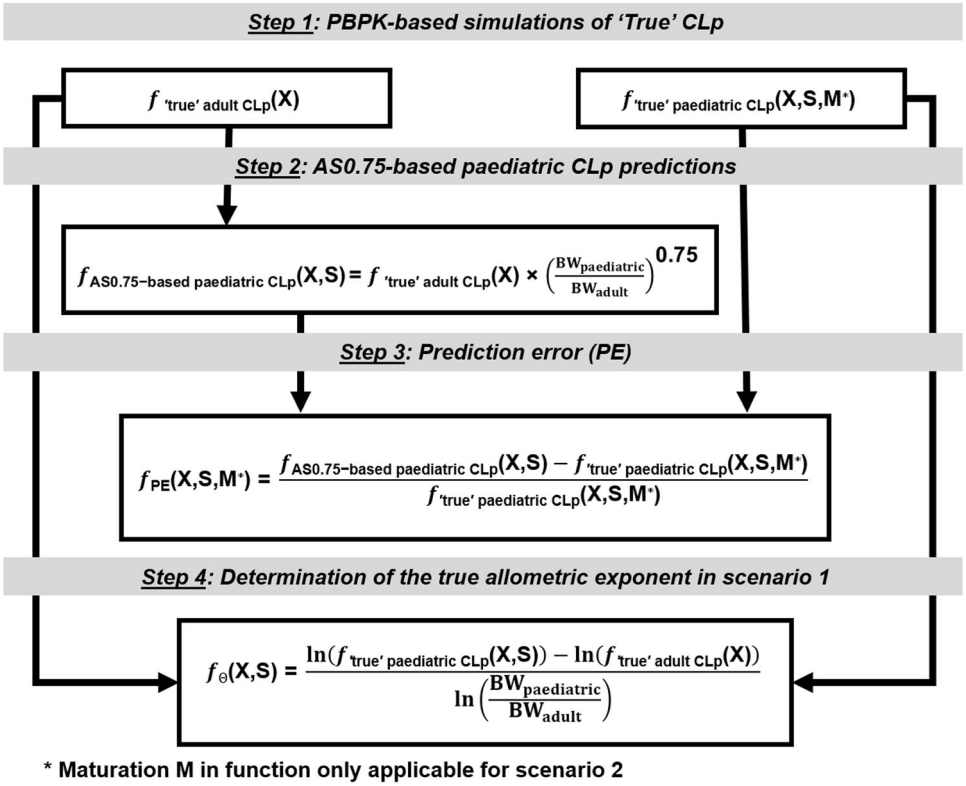


Fig. 2 PBPK simulation workflow investigating the predictive performance of AS0.75 on the basis of bodyweight to the power of 0.75, when scaling paediatric CL_p from adult CL_p values. The simulations include two scenarios: scenario 1 includes size-related changes only, while scenario 2 includes both size-related changes and maturation in the PBPK-based predictions of paediatric CL_p. Simulated CL_p values are functions of X representing drug-specific properties (i.e. f_u, type of binding plasma protein, $CL_{int,mic}$, and K_p). Paediatric CL_p predictions also depend on S representing size-related changes (changes in liver weight, hepatic blood flow, and glomerular filtration) and, in scenario 2, also on M, which represents maturational changes (changes in plasma protein concentration, haematocrit and $CL_{int,mic}$). *PBPK* physiologically-based pharmacokinetic, CL_p plasma clearance, f_u unbound drug fraction in plasma, $CL_{int,mic}$ unbound microsomal intrinsic clearance, K_p blood to plasma partition coefficient

2.1 Hypothetical Drugs (X)

In the simulations, numerous different hypothetical drugs were investigated to explore the dependence of AS0.75 predictive performance on drug properties, as drug properties have been shown to influence the predictive performance of AS0.75 in interspecies scaling of clearance (see Fig. 1). Five drug-specific properties were used to generate a wide range of hypothetical drugs (X); namely, route of elimination, type of binding plasma protein, affinity to the plasma protein, blood to plasma partition coefficient (K_p), and the unbound intrinsic clearance value of one microgram of liver microsomes ($CL_{int,mic}$). Thus, the design space was a five-dimensional hypercube, with each drug property corresponding to one dimension.

The two investigated routes of elimination were hepatic metabolism and GF. The hypothetical drugs were exclusively bound either to human serum albumin (HSA) or α1-acid glycoprotein (AGP). The affinity to plasma proteins were derived from the unbound drug fraction in plasma (f_u) in adults and the plasma concentration of the binding plasma protein in adults [36], using equations derived from Rodgers and Rowland [37]. The f_u in adults ranged from 1 to 100 %, with eight equidistant intermediate values. Because the f_u is more frequently reported than drug affinity to plasma protein, the f_u in adults, together with the type of binding plasma protein, was retained for drug categorization. K_p values of 0, 1, 2, 3 and 4 were selected, reflecting different extents of drug diffusion in the red blood cells. $CL_{int,mic}$ ranged between 0.56×10^{-3} and 0.209 L min^{-1} mg^{-1} microsomal protein [38], with 124 equidistant intermediate values. The different $CL_{int,mic}$ values reflect different affinities for and abundances of enzymes.

Hypothetical drugs undergoing hepatic metabolism were generated based on all possible combinations of the aforementioned drug properties, while hypothetical drugs undergoing GF were generated by all possible combinations of affinity to plasma protein and type of binding plasma protein only, as $CL_{int,mic}$ and K_p do not impact their clearance.

2.2 Simulation Scenarios

Two different scenarios regarding maturation (scenario 1 and scenario 2) were included in the PBPK-based simulation workflow, and an overview of these scenarios is displayed in Table 1.

The first scenario (scenario 1) was designed in order to answer the question as to whether scaling using an allometric exponent of 0.75 accounts for all size-related changes in the processes underlying CL_p in the paediatric population. Therefore, for this scenario, only size-related changes were included in the simulations of PBPK-based 'true' paediatric CL_p values. Size-related changes (*S*) included in the PBPK simulations are changes in liver weight, hepatic blood flow, and GF rate (GFR) [see step 1 of the PBPK simulation workflow for details on size-related changes]. In this scenario, for drugs undergoing hepatic metabolism, enzymes were considered to have reached maturity ($CL_{int,mic}$ was set to be 100 % of the adult value). Furthermore, for this scenario, only drugs that do not bind to plasma proteins and which are in equilibrium between plasma and red blood cells (K_p of 1) were included in order to exclude the potential influence of maturational changes on CL_p (see Eqs. 15 and 22–24 in the electronic supplementary material). This drug selection is equivalent to a selection of probe drugs for which only size-related changes would impact the clearance.

A second scenario (scenario 2) was designed to investigate how maturation processes influence the applicability of AS0.75 in the paediatric population, in order to unravel the conditions in which AS0.75 consistently leads to accurate paediatric CL_p predictions. Therefore, for this scenario, size-related changes (*S*) were included in the simulations of PBPK-based 'true' paediatric CL_p values, as well as maturation processes (*M*), which are believed not to be corrected for by AS0.75. Maturation processes included maturation in plasma protein concentration and haematocrit, as well as hepatic enzyme maturation (see step 1 of the PBPK simulation workflow for details on maturation). For this scenario, all hypothetical drugs were included.

2.3 Physiologically-Based Pharmacokinetic (PBPK) Simulation Workflow

2.3.1 Step 1: PBPK-Based Simulations of 'True' Plasma Clearance (CL_p)

For both scenarios, PBPK principles were used to simulate 'true' CL_p values for the hypothetical drugs with different properties (*X*; see the 2.1 section) in term neonates aged 1 day, infants aged 1 and 6 months, children aged 1, 2, and 5 years, adolescents aged 15 years, and adults (Fig. 2). For drugs undergoing hepatic metabolism, CL_p was computed using the dispersion model (Eqs. 1–6), with an axial dispersion number (D_N) of 0.17 [39]. The dispersion model was selected as it has been reported to better predict clearance than the well-stirred model for high-clearance drugs, which are also included in the hypothetical drugs, while both models lead to equivalent clearance predictions for the rest of the drugs [40]:

$$CLp = CL_B \times B : P \tag{1}$$

$$CL_B = Q_H \times E_H \tag{2}$$

$$E_H = 1 - F_H \tag{3}$$

$$F_H = \frac{4a}{(1+a)^2 \exp\{(a-1)/2D_N\} - (1-a)^2 \exp\{-(a+1)/2D_N\}} \tag{4}$$

Table 1 Overview of the two scenarios investigated in the PBPK-based simulation workflow. *PBPK* physiologically-based pharmacokinetic

	Scenario 1	Scenario 2
Aim and research question	Investigation of AS0.75 theory Does an allometric exponent of 0.75 account for size-related changes in paediatric CLp?	Investigation of general applicability of AS0.75 in paediatrics Under which conditions AS0.75 consistently leads to accurate paediatric CLp predictions?
PBPK-based "true" CLp	Only size-related changes (*S*) were included in the PBPK simulations of true CLp *S* include changes in liver weight, hepatic blood flow, and glomerular filtration rate	Both size-related changes (*S*) and maturation (*M*) were included in the PBPK simulations of true CLp *M* includes maturation in plasma protein concentration and in haematocrit as well as hepatic enzyme maturation
Selection of hypothetical drugs	Selection of hypothetical drugs equivalent to a selection of probe drugs for which only size-related changes would impact the clearance, by retaining drugs with: $f_u = 1$ $K_p = 1$ The number of selected drugs: undergoing GF was 1 undergoing hepatic metabolism was 126	All hypothetical drugs The number drugs: undergoing GF was 20 undergoing hepatic metabolism was 12600

$$a = (1 + 4R_N \times D_N)^{1/2} \quad (5)$$

$$R_N = (f_u/B:P) \times \mathrm{CLint}/Q_H \quad (6)$$

In these equations, CL_p is the plasma clearance, B:P is the blood to plasma ratio, CL_B is the whole blood clearance, Q_H is the hepatic blood flow, E_H is the hepatic extraction ratio, f_u is the unbound drug fraction in plasma, CL_{int} is the hepatic intrinsic clearance, and D_N is the dispersion number. For drugs undergoing GF, CL_p was computed as the product of GFR [36] and f_u.

Adult demographic values (height and weight) and adult values for cardiac output were taken from the ICRP annals [41]. CL_{int} in adults was computed as the product of $CL_{int,mic}$, amount of microsomal protein per gram of liver, and liver weight [36]. B:P in adults was derived from the K_p value, adult haematocrit [42], and f_u in adults. $CL_{int,mic}$, K_p and f_u in adults were taken from the values defined to generate the hypothetical drugs (see the 2.1 section).

Paediatric demographic values (height and weight) were taken from the CDC growth charts [43], and paediatric cardiac output values were compiled from Johnson et al. [36]. Size-related changes in CL_{int} were accounted for by changes in liver weight, and size-related changes in GF were accounted for by changes in GFR [36]. Maturation of CL_{int} was accounted for by selected extents of enzyme maturation [36]. For all hypothetical drugs undergoing hepatic metabolism, different extents of enzyme maturation, ranging between 10 and 200 % of the adult $CL_{int,mic}$ value, were investigated for each paediatric age. Additionally, scenarios were simulated with published enzyme maturation values for different hepatic isoenzymes [36, 44–47]. For these scenarios, values for enzyme maturation in neonates aged 1 day are based on values for term neonates. F_u was scaled from adults to children by accounting for maturation in plasma protein concentration (HSA and AGP) [36]. B:P was scaled from adults to children by accounting for maturation in haematocrit [42] and plasma protein concentrations [36].

The 'true' CL_ps herein simulated are a function of the properties of the hypothetical drug (X), size-related changes (S), and, in scenario 2 (*), maturation (M): f'true' $\mathrm{CLp}(X, S, M*)$. In order to allow for computation across a wide parameter space and improve interpretability of the results, single-point estimates of f'true' $\mathrm{CLp}(X, S, M*)$ were studied by transforming X, S, and M in categorical variables using typical values for the model parameters. For the same reasons, variability or uncertainty in demographic parameters or model parameters was not taken into account. Details on all equations used in the PBPK model and parameter values used in the simulations can be found in the electronic supplementary material.

2.3.2 Step 2: AS0.75-Based Paediatric CL_p Predictions

In the AS0.75 equation (Fig. 2), bodyweight (BW) is used as a descriptor of size. AS0.75-based CL_p predictions for children [fAS0.75 - based paediatric $\mathrm{CLp}(X, S)$] were performed in both scenarios for all included combinations of hypothetical drugs (X) and size-related changes (S), using the AS0.75 relationship. For scenario 1, only drugs that do not bind to plasma proteins ($f_u = 1$) and which are in equilibrium between plasma and red blood cells (K_p of 1) were included in order to exclude the potential influence of maturational changes on CL_p (see the 2.2 section, as well as Eqs. 15 and 22–24 in the electronic supplementary material).

In this AS0.75 relationship, the typical bodyweight for the different investigated paediatric ages (BWpaediatrics) was normalized to the bodyweight of a typical adult (BWadult). The typical bodyweight for the different paediatric ages and adults were kept the same as for the PBPK-based CL_p simulations (see electronic supplementary material).

2.3.3 Step 3: Prediction Error (PE)

For both scenarios, the prediction error (PE) of AS0.75 using the fixed allometric exponent of 0.75 in predicting 'true' PBPK-based paediatric CL_p was determined for all included combinations of hypothetical drugs (X) and size-related changes (S) [scenarios 1 and 2] and, where relevant, maturation (M) [scenario 2]. For scenario 1, only drugs that do not bind to plasma proteins ($f_u = 1$) and which are in equilibrium between plasma and red blood cells (K_p of 1) were included in order to exclude the potential influence of maturational changes on CL_p (see the 2.2 section, as well as Eqs. 15 and 22–24 in the electronic supplementary material). Because this workflow relies on 'true' CL_p predictions from simulations that do not take parameter uncertainty into account, predictions leading to PEs within an interval of ±30 % were considered accurate.

For both scenarios, results were categorized by age and route of elimination (hepatic metabolism or GF). For scenario 2, in which both size-related changes and maturation were included, results were also categorized by type of binding plasma protein and extent of enzyme maturation. The f_u, K_p, B:P, and extraction ratio were screened for potential additional categorization.

2.3.4 Step 4: Determination of the True Allometric Exponent in Scenario 1

To investigate patterns in potential misspecification by AS0.75, which could be useful in deriving general rules regarding the applicability of AS0.75, the true allometric

exponent (Θ) was derived for the scenario including only size-related changes (scenario 1); the true allometric exponent Θ was determined by rearranging the AS0.75 equation (Fig. 2). For each of the hypothetical drugs of this scenario, the PE obtained with AS0.75 was plotted against the true allometric exponent in order to evaluate the impact of the fixed 0.75 exponent instead of the true allometric exponent on the predictions accuracy.

3 Results

3.1 Scenario 1

Figure 3 shows the PE of AS0.75 in predicting 'true' paediatric CL_p versus the true allometric exponent for each paediatric age for the scenario including size-related changes only (scenario 1) in the simulations of PBPK-based 'true' paediatric CL_p values (see the 2.2 section). Figure 3a shows the results for 126 drugs undergoing hepatic metabolism only differing in their $CL_{int,mic}$ values, and Fig. 3b shows the results for one drug undergoing GF, as, for this scenario, only drugs that do not bind to plasma proteins ($f_u = 1$) and which are in equilibrium between plasma and red blood cells (K_p of 1) were included in order to exclude the potential influence of maturational changes in these parameters on CL_p (see the 2.1 and 2.2 sections, as well as Eqs. 15 and 22–24 in the electronic supplementary material). In this scenario, the true allometric exponent ranged from 0.52 to 0.88 for drugs undergoing hepatic metabolism, and from 0.50 to 1.20 for drugs undergoing GF. For both elimination routes, the true allometric exponent was higher in the youngest age groups. For drugs undergoing hepatic metabolism, the true allometric exponent also slightly increased with decreasing $CL_{int,mic}$ in children aged 5 years and older, with opposite results in children younger than 5 years of age.

The PE resulting from the use of the fixed allometric exponent of 0.75 instead of the true allometric exponent was higher in the youngest children. For drugs undergoing hepatic metabolism, PEs mostly remained within the ±30 % limits, with highest values reaching up to 32 % in children aged 6 months. However, for drugs undergoing GF, PE was higher than 30 % in children aged 6 months, and reached up to 278 % in neonates aged 1 day. Moreover, the absolute PE increased with decreasing $CL_{int,mic}$ in children aged 5 years and older, while it decreased with decreasing $CL_{int,mic}$ in children younger than 5 years of age. For children aged 2 years and younger, drugs undergoing hepatic metabolism with similar true allometric exponents were found to lead to increased PE with decreasing age, showing a higher sensitivity of the PE to the use of a fixed allometric exponent of 0.75 in younger children.

3.2 Scenario 2

3.2.1 PE for Hypothetical Drugs Undergoing Hepatic Metabolism

Figure 4 shows the PE for the AS0.75-based paediatric CL_p predictions in scenario 2 for drugs undergoing hepatic metabolism. Results are categorized by age, type of binding plasma protein, and extent of enzyme maturation. The extraction ratio in adults was found to be most predictive of the PE compared with f_u, K_p or *B*:*P*. For this reason, results

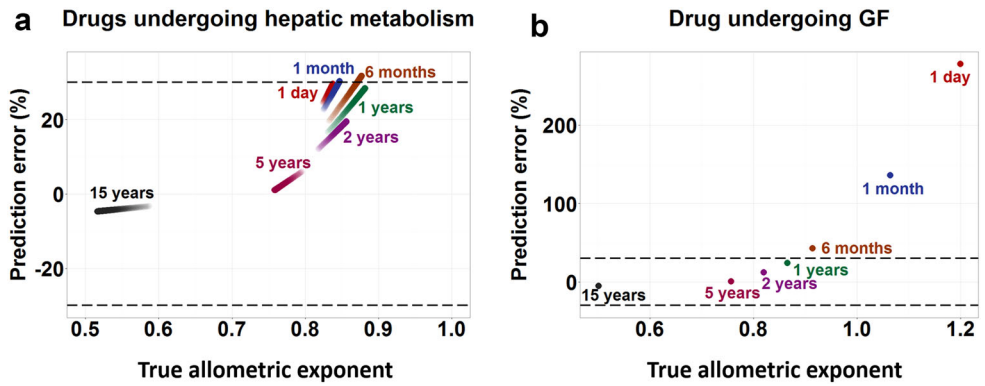


Fig. 3 PE of AS0.75 using the fixed allometric exponent of 0.75 in predicting 'true' paediatric CL_p versus the true allometric exponent for each paediatric age, for drugs undergoing (**a**) hepatic metabolism or (**b**) glomerular filtration in scenario 1, where only size-related changes were included in the PBPK-based simulations of 'true' paediatric CL_p. The values for the different ages are represented with different colours. Colour intensity increases with $CL_{int,mic}$ values of the hypothetical drugs (**a**). *Dotted black lines* indicate a PE of ±30 %. *PE* prediction error, CL_p plasma clearance, *PBPK* physiologically-based pharmacokinetic, $CL_{int,mic}$ unbound microsomal intrinsic clearance

were also categorized by adult extraction ratio in boxplots, displaying the maximum, third quartile, median, first quartile and minimum PE for each category.

The PE range increased with decreasing age and was wider for drugs binding to AGP than for drugs binding to HSA. The more the enzyme maturation differed from 100 % of the adult $CL_{int,mic}$ value, the more the PE range increased, leading to the smallest PE range for enzyme maturation of 100 %. Enzyme maturation had less effect on the PE for high extraction ratio drugs compared with low extraction ratio drugs.

For drugs undergoing hepatic metabolism, AS0.75 led to accurate predictions for all hypothetical drugs in adolescents aged 15 years and children aged 5 years when $CL_{int,mic}$ was between 75 % and 100 %, and at 100 % of the adult value, respectively. In a situation where $CL_{int,mic}$ is at 100 % of the adult value, 'true' CL_p with a PE within ±30 % for all investigated ages is predicted only in cases of drugs with a low extraction ratio and binding to HSA. For the remaining drugs, the absolute PE ranged up to 50 % in children as young as 6 months of age, and even higher in neonates. Regardless of age, AS0.75 performed poorly in predicting 'true' paediatric CL_p of drugs metabolized by enzymes for which maturation is at or below 50 % of the adult $CL_{int,mic}$ value, leading to overprediction of more than 50 % for a large part of the investigated hypothetical drugs.

Table 2 displays published $CL_{int,mic}$ maturation values for hepatic isoenzymes for each paediatric age, together with their corresponding category of PE for AS0.75-based CL_p predictions for all hypothetical drugs. Three PE categories were defined, with the PE range for all hypothetical drugs lying within ±30 % (green), within ±50 % (orange), and including absolute PE values higher than 50 % (red), with PE values rounded to the tenth (i.e 32 % was rounded to 30 %). The PE of AS0.75-based CL_p predictions for all hypothetical drugs was within ±30 % in children aged 5 years and older, except for one of the three cytochrome P450 (CYP) 1A2 enzyme maturation patterns and one of the two CYP2E1 enzyme maturation patterns published in children aged 5 years. For neonates aged 1 day and infants aged 1 month, the PE range systematically included absolute values >50 % for hypothetical substrates of all isoenzymes. Intermediate results were found for children between 6 months and 2 years of age.

3.2.2 *PE for Hypothetical Drugs Undergoing Glomerular Filtration*

Table 3 displays the PE of AS0.75-based CL_p predictions for each paediatric age and each hypothetical drug undergoing GF. Drugs undergoing GF only differed by their f_u and type of binding plasma protein. AS0.75 led to a PE within ±30 % for all these drugs in children as young as 1 year of age, with the exception of those drugs highly bound to AGP (adult f_u ≤0.12 %) in children aged 1 and 2 years. AS0.75 predictions in neonates aged 1 day and infants aged 1 month led to a PE of up to more than 100 %.

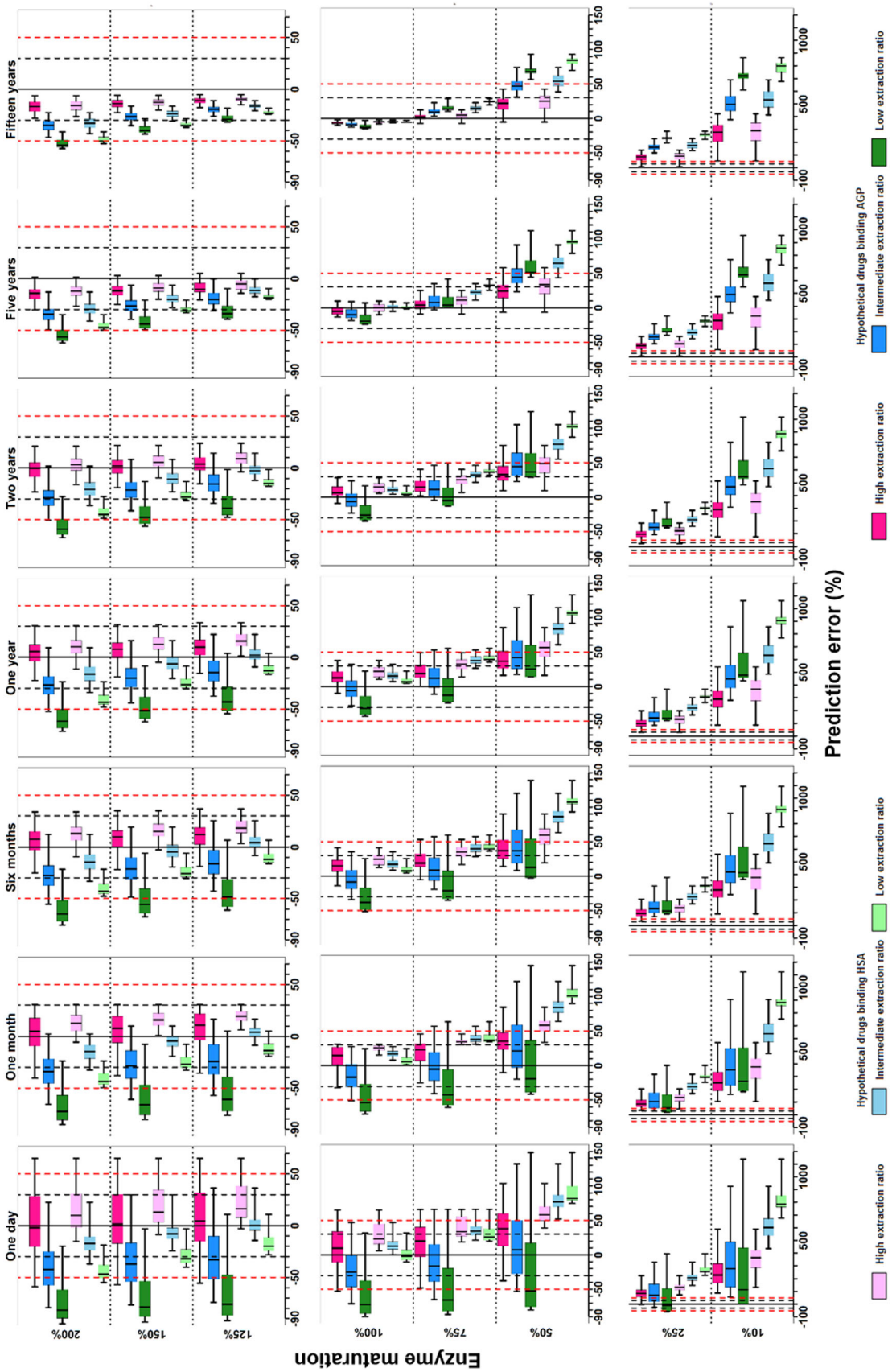
Figure 5 displays a summary of the results regarding the applicability of AS0.75 to scale CL_p from adults to children. Scenarios for which AS0.75 led to accurate CL_p predictions were defined, including ages, enzyme maturation and drug properties.

4 Discussion

In this study, a PBPK simulation workflow was developed in order to systematically investigate, for the first time, the accuracy of AS0.75-based paediatric CL_p predictions for a wide range of hypothetical drugs, undergoing hepatic metabolism or GF. The use of a systematic approach increases our current knowledge on the applicability of AS0.75 to predict paediatric CL_p based on adult values, which has, until now, been based on studies of a limited number of existing drugs and a limited number of observed concentrations. The use of PBPK principles allowed for the screening of the impact of size-related changes, maturation, and drug properties on the accuracy of AS0.75-based paediatric CL_p predictions, which is not possible with other methods. This allowed us to define scenarios, including ages, drug properties (including elimination pathways), and maturation, for which AS0.75 is likely to lead to accurate paediatric CL_p predictions (Fig. 5).

In contrast with previously proposed applications of AS0.75 theory in the paediatric population [20], but in line with more recent work [18], the current study shows that there is no universal allometric exponent that can be used to accurately scale size-related changes in CL_p from adults to children of various ages. Even when estimated in scenarios in which only size-related changes are included (scenario 1), the allometric exponent was found to vary from 0.50 to 1.20, changing with age and drug properties (Fig. 3). The corresponding PE was found to be more sensitive to the use of a fixed exponent of 0.75 among the youngest children, leading to increased bias in very young children, with values around 30 % for drugs undergoing hepatic metabolism and up to 278 % for drugs undergoing GF (Fig. 3).

The inaccurate paediatric CL_p predictions resulting from AS0.75 in the very young are often attributed to the influence of the many maturation processes that are known to occur in these children. Therefore, in model building, AS0.75 is usually used in combination with an MF that should account for these maturational changes, to describe CL_p in this population for a specific drug. However, in


Fifteen years
Five years
Two years
One year
Six months
One month
One day
Prediction error (%)
Enzyme maturation
10%
25%
50%
75%
100%
125%
150%
200%
Hypothetical drugs binding AGP
Hypothetical drugs binding HSA
High extraction ratio
Intermediate extraction ratio
Low extraction ratio

◀**Fig. 4** PE for AS0.75-based CL_p predictions of drugs undergoing hepatic metabolism in scenario 2, where both size-related changes and maturation were included in the simulations of 'true' paediatric CL_p, with enzyme maturation in $CL_{int,mic}$ ranging from 10 to 200 % of the adult value. *PE* prediction error, CL_p plasma clearance, $CL_{int,mic}$ unbound microsomal intrinsic clearance

scenario 1, which did not include maturation in the PBPK-based simulations of 'true' paediatric CL_p, the PE of the AS0.75-based CL_p predictions was still large in children aged 6 months and younger (ranging from 43 to 278 %) for drugs undergoing GF. From this it can be concluded that in these scenarios, when modelling CL_p in very young children using AS0.75 in combination with MF, the MF likely also corrects for bias introduced by the use of a fixed allometric exponent of 0.75. Therefore, while the use of AS0.75 + MF may prove to be a viable method in some cases, there is no sufficient evidence to support its scientific basis, either for predicting drug clearance between individuals of different ages or for covariate relationships in model-building procedures. Moreover, there are no grounds to reject the well-established data-driven (i.e. stepwise covariate model building) strategies for the inclusion of bodyweight in a paediatric pharmacokinetic model, which have recently been used to develop more flexible functions to accurately scale CL_p across the entire paediatric age range using only bodyweight in model development [48–51].

As similarly reported for interspecies AS0.75 of CL_p [23–31] (Fig. 1), drug properties were found to impact the accuracy of the predictions (Figs. 3 and 4). While drug properties not amenable to AS0.75 could be defined in the case of interspecies AS0.75 of CL_p [23, 24], no unique trends (in terms of direction and extent) in the impact of drug properties on the PE were observed for AS0.75 of CL_p in paediatric patients as this impact varied with maturation and size (Table 3 and Fig. 4).

We found that enzyme activity close to adult values is a requirement for accurate AS0.75-based CL_p predictions at all paediatric ages, which is in agreement with previous reports [44, 52]. However, mature enzyme activity alone is not sufficient to lead to accurate AS0.75-based CL_p predictions, as, in children younger than 5 years, AS0.75 can lead to a PE >30 %, depending on the drug properties, even when enzyme activity is close to adult values (Fig. 4). With the exception of certain publications on CYP2E1 and CYP1A2, it is commonly believed that hepatic enzymes are mature in children aged 5 years and older (Table 2), which is in line with previous reports on the use of AS0.75 to predict CL_p in children older than 5 years of age [34, 53].

Table 2 Published enzyme maturation values and their corresponding PE category of AS0.75-based CL_p predictions for drugs undergoing hepatic metabolism for scenario 2

Metabolic route	One day	One month	Six months	One year	Two years	Five years	Fifteen years
CYP1A2 [36]	0.022	3	25	47	70	90	98
CYP1A2 [44]	5	20	29	35	NA	NA	100
CYP1A2 [45]	27	41	122	153	159	152	123
CYP2B6 [36]	0.22	6	30	46	65	85	98
CYP2C8 [36]	39	88	99	100	101	101	102
CYP2C9 [36]	39	94	101	102	103	103	103
CYP2C18_19 [36]	23	30	52	66	80	95	103
CYP2D6 [36]	6	49	88	95	100	103	104
CYP2E1 [36]	11	26	41	49	57	71	90
CYP2E1 [44]	21	40	46	100	100*	100*	100
CYP3A4 [44]	20	50	110	130	130	NA	100
CYP3A4 [46]	10	NA	43	54	72	101	100
CYP3A4_5 [36]	2	29	64	76	85	92	97
UGT2B7 [44]	5	10	70	100	100*	100*	100
UGT1A6 [44]	10	16	36	50	NA	NA	100
SULT1A1 [47]	100	100	100	100	100	100	100

Age category

Numbers within cells correspond to the value of enzyme maturation, as a percentage of adult enzyme activity, for each age and isoenzyme. NA was used when no data on enzyme maturation for the corresponding age and isoenzyme were reported. * Indicates replacement of missing enzyme maturation values (NA) by 100 % when reported values in younger and older children were equal to 100 %. Colours indicate the PE category, with PE range for all hypothetical drugs lying within ±30 % in green, within ±50 % in orange, and including absolute values higher than 50 % in red. PE values were rounded to the tenth. *PE* prediction error, CL_p plasma clearance

Table 3 PE for AS0.75-based CL_p predictions for each drug binding to AGP or HSA and undergoing glomerular filtration in scenario 2, where both size-related changes and maturation were included in the simulations of 'true' paediatric CL_p. Colours indicate the prediction error categories for each drug. Three prediction error categories were defined, with PE lying within ±30 % in green, within ±50 % in orange, and including absolute values higher than 50 % in red. *PE* prediction error, *CL_p* plasma clearance, *AGP* α1-acid glycoprotein, *HSA* human serum albumin

Adult fu	Binding protein	One day	One month	Six months	One year	Two years	Five years	Fifteen years
0.01	AGP	-70	-44	-42	-39	-35	-28	-17
	HSA	172	94	25	11	3	-5	-7
0.12	AGP	-31	-24	-33	-32	-29	-25	-15
	HSA	184	99	27	13	4	-4	-7
0.23	AGP	7	-4	-23	-25	-24	-22	-14
	HSA	196	103	29	14	5	-4	-7
0.34	AGP	46	16	-14	-18	-19	-18	-13
	HSA	207	108	31	16	6	-3	-7
0.45	AGP	85	36	-4	-11	-14	-15	-11
	HSA	219	113	33	17	7	-2	-6
0.56	AGP	123	56	5	-4	-8	-12	-10
	HSA	231	117	35	19	8	-2	-6
0.67	AGP	162	76	15	3	-3	-9	-9
	HSA	243	122	37	20	9	-1	-6
0.78	AGP	201	96	24	10	2	-6	-8
	HSA	255	127	39	22	10	0	-5
0.89	AGP	239	116	33	18	7	-2	-6
	HSA	266	131	41	23	11	0	-5
1	AGP	278	136	43	25	13	1	-5
	HSA	278	136	43	25	13	1	-5

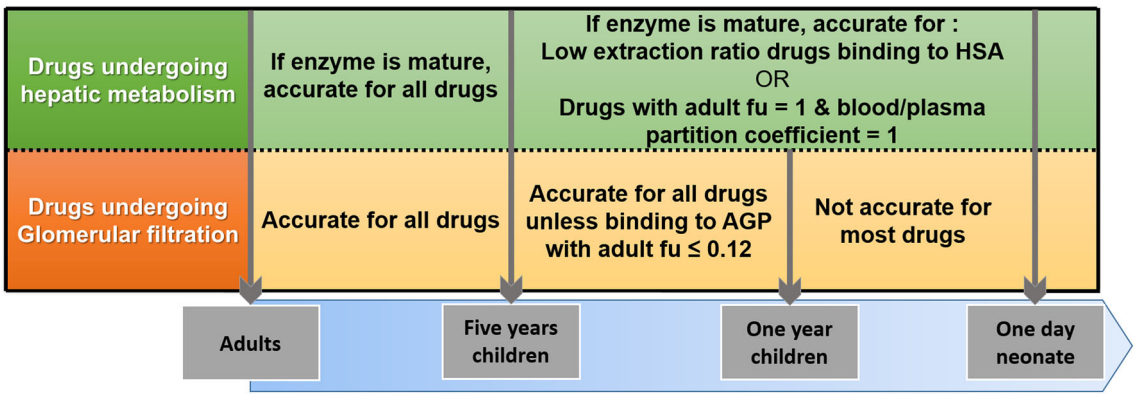


Fig. 5 Scenarios for which AS0.75-based paediatric CL_p predictions are accurate, based on a PBPK simulation workflow. *CL_p* plasma clearance, *PBPK* physiologically-based pharmacokinetic

Drugs undergoing GF were found to be amenable to AS0.75 of CL_p until a younger age, than drugs undergoing hepatic metabolism. Our results show that clearance through GF can be accurately predicted in children as young as 1 year of age for all drugs, with the exception of drugs highly bound to AGP (f_u ≤0.12) in children aged between 1 and 5 years. While this result seems in line with previous findings that GFR reaches adult values at 8–12 months of age [54], we emphasize that secretion and reabsorption processes are not yet included in the simulations.

Sethi et al. [55] recently suggested that the f_u for drugs binding to albumin was smaller than what can be predicted using MFs for albumin currently in use, in children younger than 4 years of age. The underestimated f_u in children would impact the results but would not impact our conclusion. Indeed, for children aged 3 months and younger, we found that AS0.75 led to inaccurate CL_p prediction for drugs undergoing both hepatic metabolism and GF.

The use of a PBPK approach allowed for the disentanglement of size-related changes, drug properties, and maturation processes due to its unique feature to

incorporate multiple levels of information to predict CL_p for different paediatric ages. Over the past decade, the scaling of an adult PBPK model to paediatric patients has been proven to lead to accurate CL_p predictions in children [36, 46, 56, 57]. The investigation of hypothetical drugs in the current study allowed the avoidance of bias in PBPK-based CL_p predictions due to the inaccurate measurements of drug-specific parameters, such as f_u, which can occur when studying existing drugs [58]. The parameters defining drug properties should be interpreted as apparent parameters. For instance, a drug with a K_p of 0 could translate into a drug that can enter membranes and red blood cells, but for which distribution in red blood cells is not a limiting factor for its metabolism in the hepatocytes (i.e. fast drug repartitioning compared with the residence time of blood in the capillaries [59]). This simulation workflow does not account for illness, and different results might be expected in patients for whom physiological changes, for instance in AGP concentration or organ function, can impact the drug clearance [60]. However, this allows for the investigation of AS0.75 predictive performance without confounding factors such as illness, sparse paediatric clinical data, or bias in the estimation of adult CL_p used in the AS0.75-based paediatric CL_p predictions.

The herein applied workflow is intended to give an overview of the impact of drug properties (including elimination pathways), size-related changes, and maturation on the accuracy of AS0.75-based CL_p predictions. To do so, unrealistic enzyme maturation scenarios for part of the paediatric ages, as well as uniform distribution of drug properties (equidistant values), were included in the simulations using a global sensitivity analysis with a fractional design. Indeed, keeping enzyme maturation scenarios the same for different ages allows to differentiate between the impact of age and enzyme maturation, thereby unraveling an increased sensitivity of the accuracy of AS0.75-based CLp predictions to enzyme maturation with decreasing age (see Fig. 4). Therefore, the poor predictive performance of AS0.75 in young children is not solely due to enzyme immaturity in itself, but also due to an increased sensitivity of drug clearance to enzyme maturation at that age. Because this study was intended to be systematic and not probabilistic, results were not weighted on the likelihood of the investigated drug properties. This approach can be considered a risk assessment, where rare drug properties are considered as important as frequent drug properties.

5 Conclusions

Based on current PBPK knowledge, we found no evidence for a universal allometric exponent for scaling CL_p in children. This finding holds even when only size-related changes are considered and maturation of processes underlying drug clearance are not taken into account. This work reveals that AS0.75 accurately predicts CL_p in children over 5 years of age for drugs eliminated by GF and/or undergoing hepatic metabolism, when enzyme activity is close to adult values, due to the lack of sensitivity of PE to the allometric exponent and to the drug properties in this scenario.

Compliance with Ethical Standards

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Conflict of interest Amin Rostami-Hodjegan is an employee of the University of Manchester, seconded part-time to Simcyp Limited (a Certara company) whose research is funded by a consortium of pharmaceutical companies.

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