

Current Methods to Characterize Drug Disposition and Optimize Dosing in Children with Obesity

Daniel Gonzalez, Pharm.D., Ph.D.

Associate Professor

Division of Pharmacotherapy and Experimental Therapeutics

UNC Eshelman School of Pharmacy

The University of North Carolina at Chapel Hill

daniel.gonzalez@unc.edu

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- I serve as a consultant for Tellus Therapeutics
- I will present examples that evaluate off label dosing of approved medications

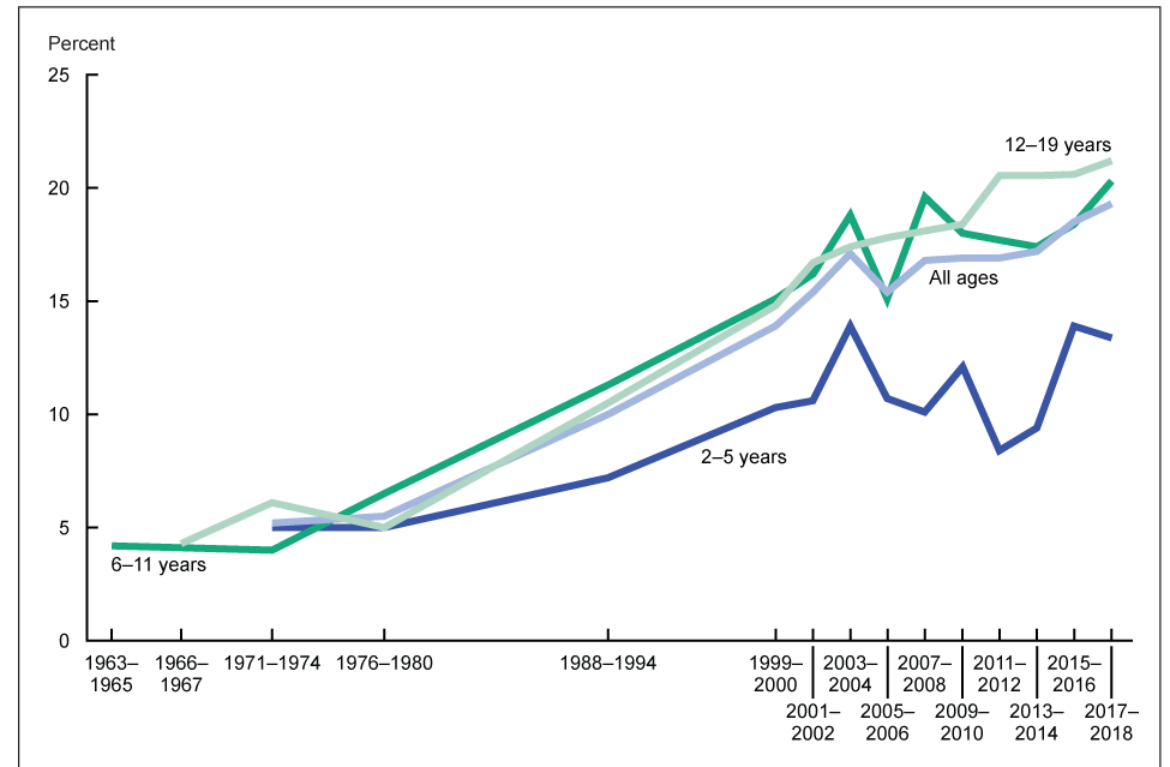
Objectives

- Discuss differences in pharmacokinetics between children with and without obesity
- Discuss the application of population pharmacokinetic modeling to characterize drug disposition and optimize dosing in children with obesity
- Review the development and application of a virtual population of children with obesity for physiologically-based pharmacokinetic modeling

The Prevalence of Obesity in Children Continues to Increase

- The overall prevalence of 19.7%
- 14.7 million children and adolescents with obesity
- Since the 1970s, the percentage of children and adolescents with obesity has tripled

Figure. Trends in the prevalence of obesity among youth aged 2–19 years in the United States (1963–1965 through 2017–2018).

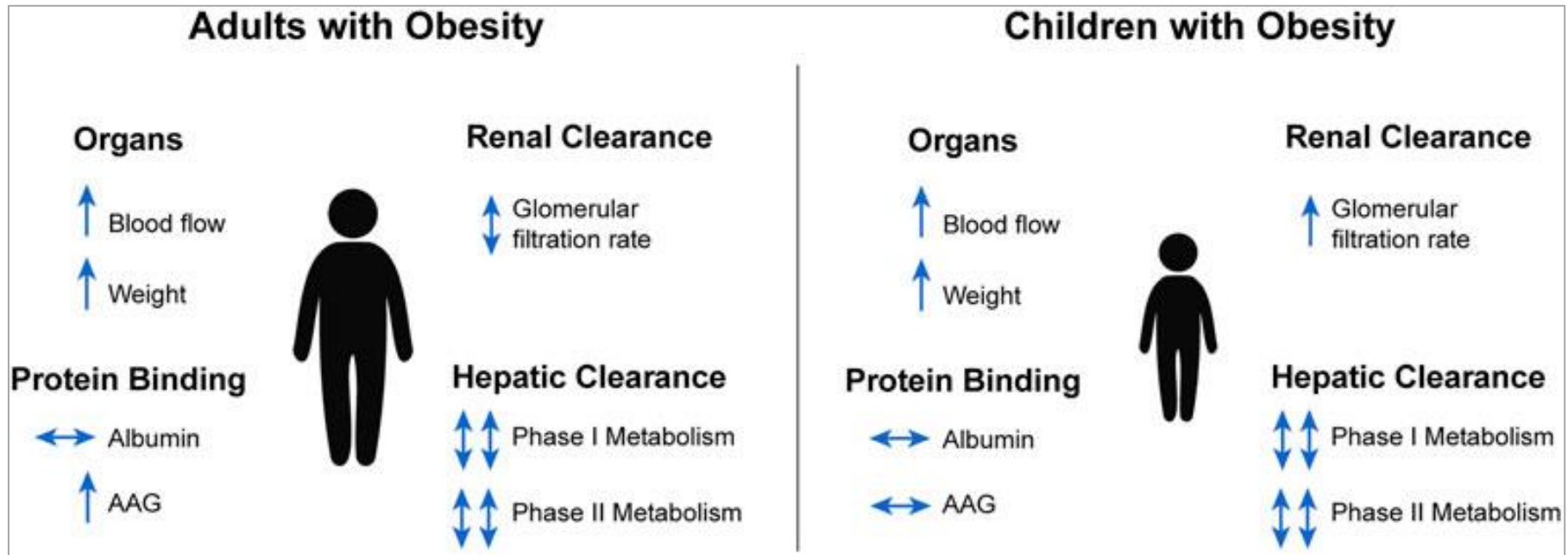


NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: National Center for Health Statistics, National Health Examination Surveys II (ages 6–11), III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018.

Why Study Drugs in Children with Obesity?

- Important age- and size-dependent physiological changes
- Potentially altered dose-exposure and/or exposure-response relationships
- Lack of available drug dosing recommendations for children with obesity in the product labeling
- Federal legislation to expand pediatric drug development

Physiological Changes with Obesity



PK Studies Have Demonstrated Alterations in Children with Obesity

- Systematic literature review for studies in children with obesity
- 20 studies of 21 drugs identified
- Clinically significant PK alterations were observed in 65% of drugs studied in children with obesity

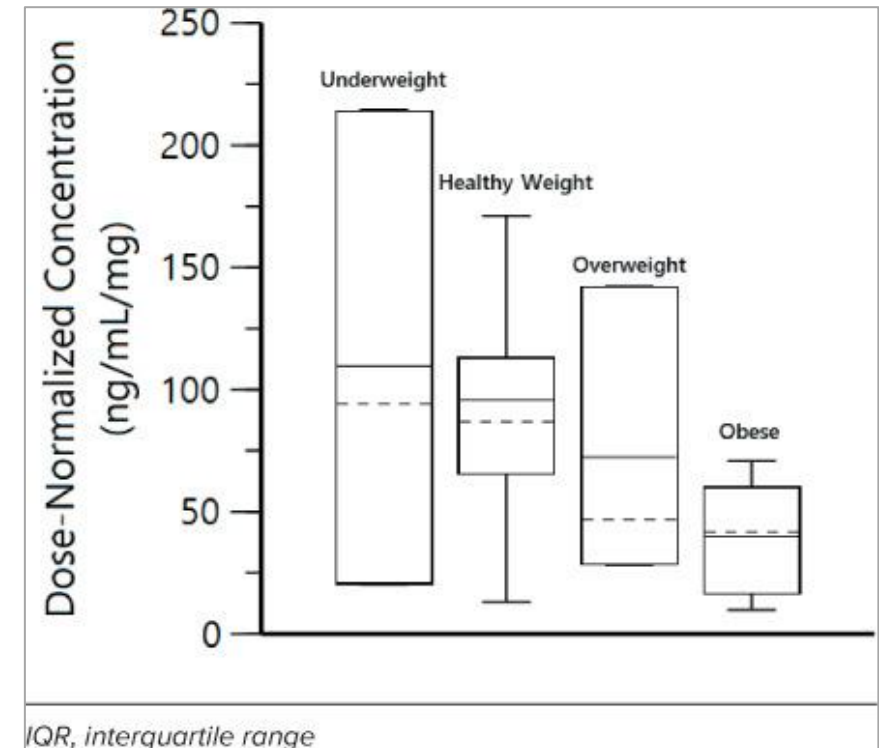
Table. Changes in weight-normalized clearance and volume of distribution.

Drug	Volume of distribution	Clearance
Analgesics/anesthetics		
Acetaminophen	↓ (83%)	↔
Antipyrine	↓ (76%)	↓ (50%)
Antibiotics		
Cefazolin	↔	↔
Gentamicin	↓ (71%)	
Tobramycin	↓ (75%)	↔
Vancomycin	↓ (81%)	↓ (80%)
Anticonvulsants		
Carbamazepine	↓ (89%)	↓ (63%)
Midazolam		↔
Antineoplastics		
Busulfan		↓ (84%)
Cytarabine		↔
Doxorubicin	↑ (113%)	↔
Etoposide		↔
Mercaptopurine	↑ (166%)	↑ (222%)
Methotrexate		↔
Teniposide		↔
Respiratory stimulants		
Caffeine	↓ (65%)	↓ (30%)
Theophylline	↓ (69%)	

Reduced Etanercept Concentrations in Children with Obesity

- Observational study in children receiving etanercept for juvenile idiopathic arthritis
- 29 children with a median (range) age of 10 years (2-18)
 - A single concentration measurement per child
- Dose-normalized concentrations were significantly lower in children with obesity (40.1 ± 23.3 vs. 94.4 ± 55 ng/mL/ mg, $P=0.01$)

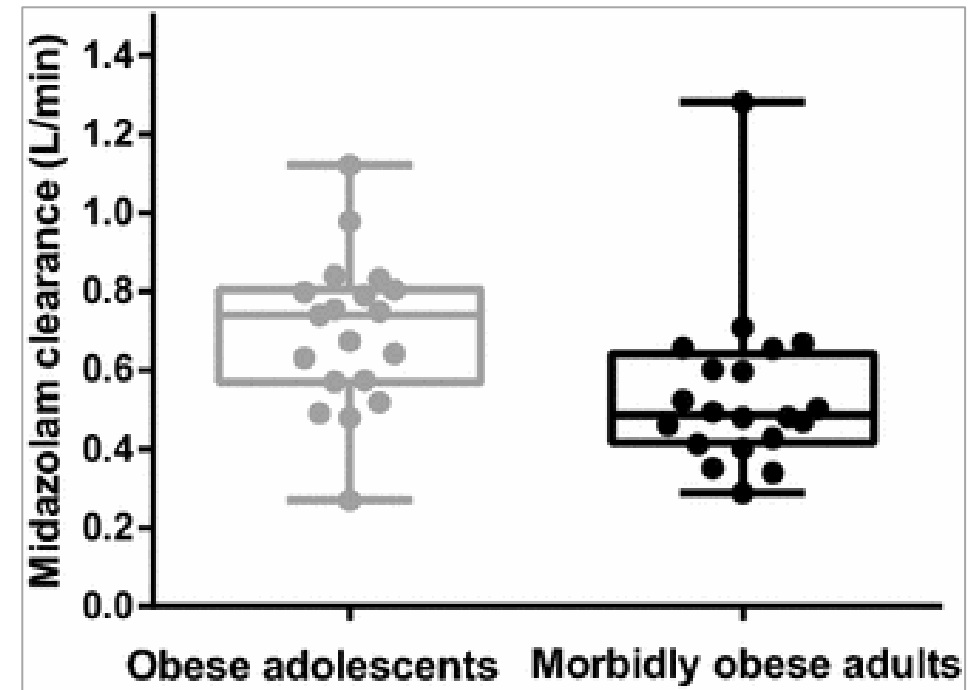
Table. Dose normalized etanercept concentrations by weight category.



PK Changes with Obesity Can Differ Between Adults and Children

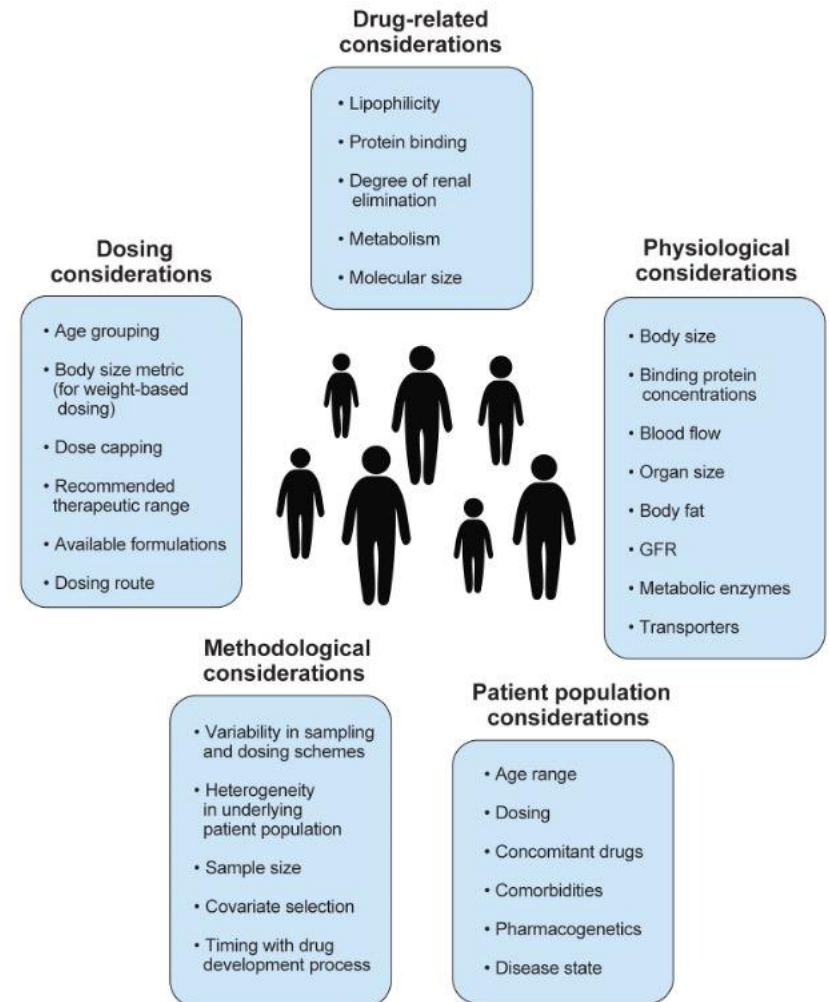
- Data from 19 adolescents with obesity and 20 adults with morbid obesity
- The population mean midazolam clearance was higher in adolescents with obesity (0.71 vs. 0.44 L/min, $p < 0.01$)
- The authors hypothesized that the difference is due to less obesity-induced suppression of CYP3A activity in adolescents

Figure. Midazolam clearance in obese adolescents and morbidly obese adults.



Factors to Consider When Evaluating PK in Children with Obesity

- Evaluating the effect of obesity requires considering drug, patient population, physiological, and methodological variables
- A sufficient number of children across BMIs and ages need to be enrolled
- When performing dose optimization, factors such as the optimal body size metric and the need for dose capping should be considered



Direct and Indirect Measures of Body Size

<p>Total body weight (TBW)</p> $TBW [kg] = \text{Measured weight of child} [kg]$	<p>Fat-free mass (FFM) ³</p> $FFM(\text{boys}) [kg] = \left[0.88 + \left(\frac{1 - 0.88}{1 + \left(\frac{Age [y]}{13.4} \right)^{-12.7}} \right) \right] \left[\frac{9270 * TBW [kg]}{6680 + \left(216 * BMI \left[\frac{kg}{m^2} \right] \right)} \right]$ $FFM(\text{girls}) [kg] = \left[1.11 + \left(\frac{1 - 1.11}{1 + \left(\frac{Age [y]}{7.1} \right)^{-1.1}} \right) \right] \left[\frac{9270 * TBW [kg]}{8780 + \left(244 * BMI \left[\frac{kg}{m^2} \right] \right)} \right]$
<p>Body mass index (BMI)</p> $BMI \left[\frac{kg}{m^2} \right] = \frac{TBW [kg]}{Height [m]^2}$	
<p>Body surface area (BSA) ¹</p> $BSA [m^2] = 0.024265 * TBW [kg]^{0.5378} * Height [cm]^{0.3964}$	
<p>Ideal body weight (IBW) ²</p> $IBW [kg] = BMI_{50} \left[\frac{kg}{m^2} \right] * Height [m]^2$ $BMI_{50}(\text{boys}) \left[\frac{kg}{m^2} \right] = 24.27 - \frac{8.91}{1 + \left(\frac{Age [y]}{15.78} \right)^{4.40}}$ $BMI_{50}(\text{girls}) \left[\frac{kg}{m^2} \right] = 22.82 - \frac{7.51}{1 + \left(\frac{Age [y]}{13.46} \right)^{4.44}}$	<p>Body fat percent (BFP) ⁴</p> $BFP(\text{boys}) [\%] = \frac{0.647 * 0.0598 * e^{2.050 * BMI_{95} \left[\frac{kg}{m^2} \right]}}{0.647 + 0.0598 * \left(e^{2.050 * BMI_{95} \left[\frac{kg}{m^2} \right]} - 1 \right)} + 0.1140 - 0.00890 * Age [y]$ $BFP(\text{girls}) [\%] = \frac{1.080 * 0.1930 * e^{0.897 * BMI_{95} \left[\frac{kg}{m^2} \right]}}{1.080 + 0.1930 * \left(e^{0.897 * BMI_{95} \left[\frac{kg}{m^2} \right]} - 1 \right)} - 0.0856 + 0.00682 * Age [y]$

¹ See (Haycock et al., 1978), n = 81 subjects.

³ See (Janmahasatian et al., 2005; Al-Sallami et al., 2015), n = 1,011 subjects

² See (Pai and Paloucek, 2000; Callaghan and Walker, 2015), n = 108 subjects

⁴ See (Green et al., 2021), n = 4,274 subjects

Use of PopPK to Characterize the Effect of Obesity

$$\left[\frac{Size_i}{Size_{std}} \right]^{\theta_{exp}}$$

Includes evaluation of body size descriptors (e.g., total body weight, fat free mass, lean body weight)

$$PK_i = PK_{standard} * f_{size} * f_{age} * f_{function} * Random\ effects$$

Typical value of the PK parameter

Body size effect

Ontogeny early in life

Organ function effect

Clindamycin PK Studies in Children with Obesity Performed by the Pediatric Trials Network

- Clindamycin is a widely prescribed antibiotic for community-acquired methicillin-resistant *S. aureus* (MRSA)
- Clindamycin PK data collected by the Pediatric Trials Network from children with and without obesity through two studies

	POP01 ¹	CLIN01 ²
Phase	I	I
Number of Sites	27	6
Age Groups	<21 years of age	2 to <18 years
Clindamycin Dosing	Standard of care	30 to 40 mg/kg/day IV every 6 or 8 h

POP01: Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care.

CLIN01: Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin Pediatric Subjects With BMI \geq 85th Percentile.

Clindamycin PK studies in children with obesity

$$CL \text{ (liters/hour)} = 13.8 \times (TBW/70)^{0.75} \times \left[PMA^{2.83} / (39.5^{2.83} + PMA^{2.83}) \right]$$

$$V \text{ (liters)} = 63.6 \times (TBW/70) \times (ALB/3.3)^{-0.83} \times (AAG/2.4)^{-0.25}$$

Parameter	Median (range) for age category ^a					
	>2-6 yrs ^b		>6-12 yrs		>12 yrs ^c	
	Nonobese (n = 8)	Obese (n = 12)	Nonobese (n = 15)	Obese (n = 20)	Nonobese (n = 26)	Obese (n = 44)
CL (liters/h)	4.17 (0.90-9.10)	5.69 (1.84-8.27)	12.50 (3.55-34.40)	10.70 (4.71-26.70)	14.25 (5.56-37.40)	19.15 (3.92-33.70)
CL (liters/h/kg)	0.23 (0.082-0.78)	0.28 (0.11-0.40)	0.33 (0.13-0.78)	0.22 (0.092-0.64)	0.23 (0.064-0.53)	0.18 (0.041-0.65)
CL (liters/h/70 kg)	10.64 (3.59-35.03)	14.83 (5.49-20.32)	20.67 (7.08-48.48)	14.69 (5.94-39.16)	15.82 (4.72-34.68)	13.97 (3.12-37.89)
V (liters)	15.25 (7.58-19.70)	17.60 (8.39-25.20)	29.0 (17.50-57.40)	46.90 (32.90-85.80)**	60.10 (22.50-94.60)	85.75 (28.50-160.0)**
V (liters/kg)	0.81 (0.69-1.26)	0.86 (0.66-1.03)	0.90 (0.67-1.06)	1.03 (0.66-1.29)	0.89 (0.70-1.34)	0.89 (0.62-1.58)
Half-life (h)	2.41 (1.12-5.85)	2.15 (1.53-4.36)	2.15 (0.95-5.77)	3.03 (1.19-6.26)**	2.84 (1.17-7.60)	3.55 (0.90-11.30)

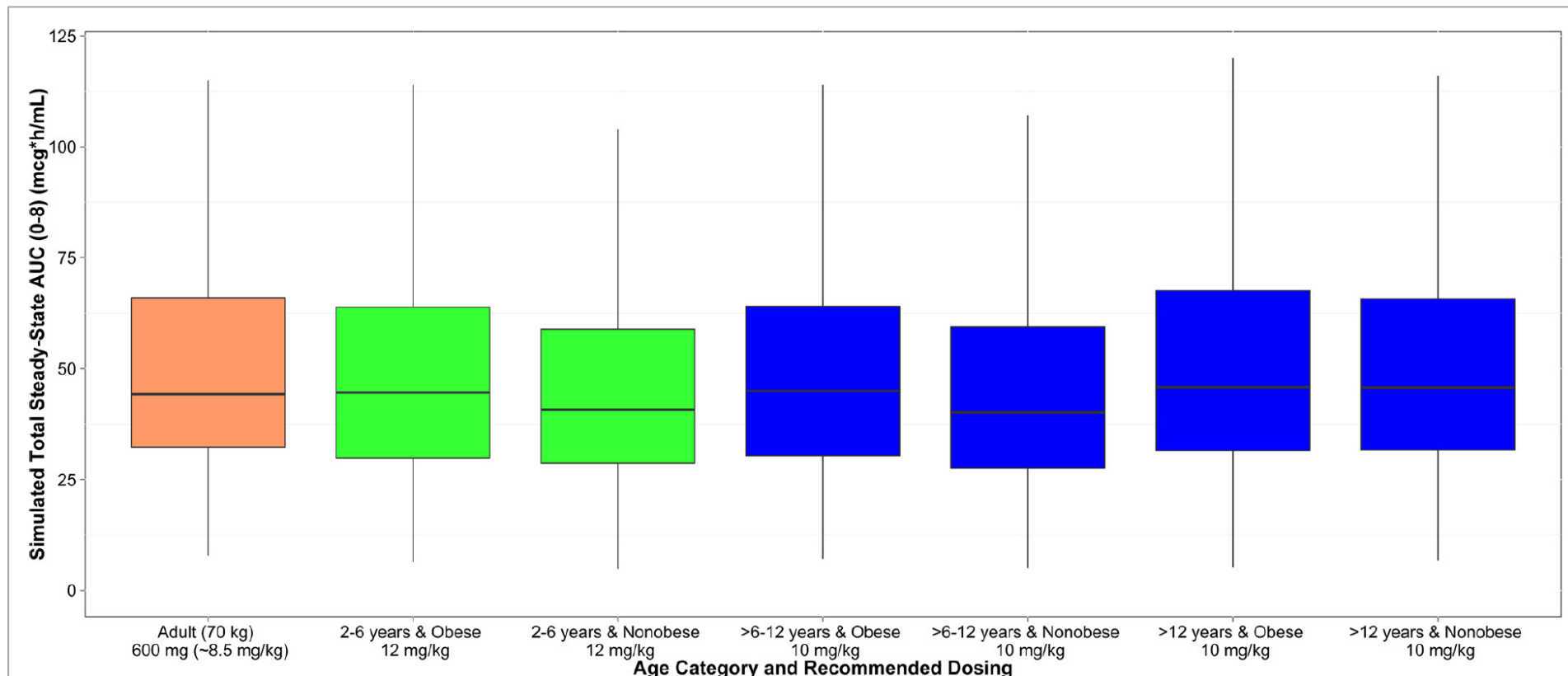
^aStatistically significant differences (**) were observed using a rank sum test.

^bThree participants with missing height (and BMI) were not included in this parameter summary.

^cTen participants (6 nonobese and 4 obese) who were >18 years of age were included in the parameter summary.

Clindamycin PopPK Model Dosing Simulations

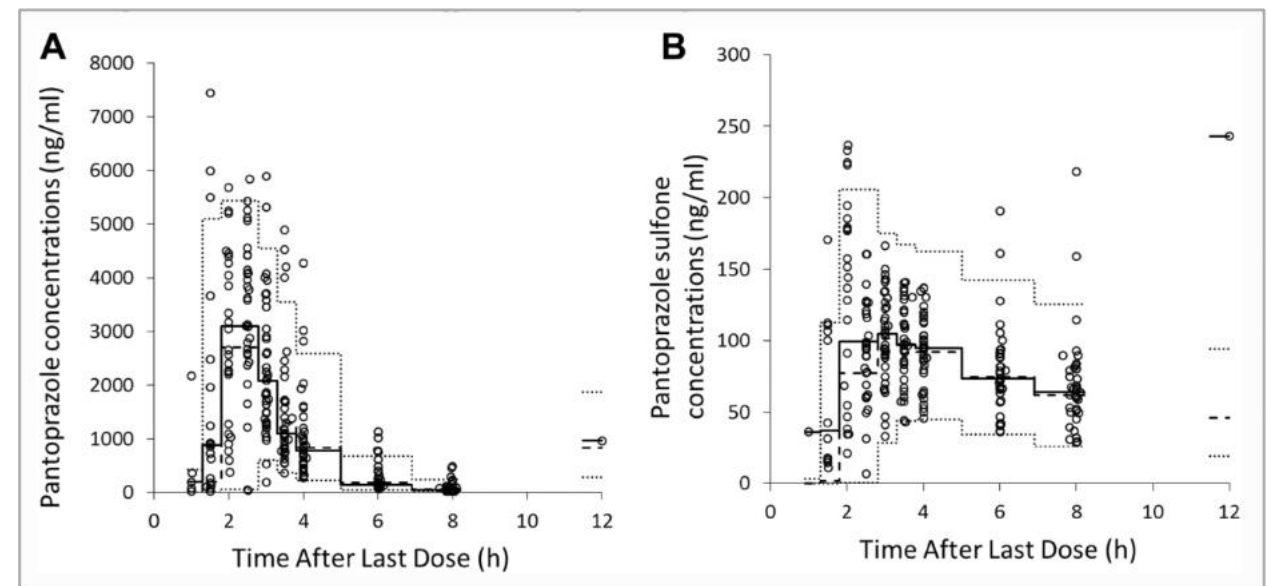
Total body weight-based dosing with a max adult dosage (900 mg IV every 8 hours) was found to match adult exposure



Pantoprazole PopPK in Children with Obesity

- Pantoprazole is a proton pump inhibitor used in children with gastroesophageal reflux disease (GERD)
- Data from 40 children with obesity (aged 6–17 years; $n = 40$) were used to perform a population PK analysis (273 pantoprazole and 256 pantoprazole-sulfone plasma concentrations)
- Two-compartment models for pantoprazole and pantoprazole-sulfone provided the best fit of the data
- *CYP2C19* genotype and total body weight were covariates for pantoprazole CL

Figure. Visual predictive check for pantoprazole (A) and pantoprazole-sulfone (B). The lines represent the 97.5th, 50th, and 2.5th percentiles for the simulated data.



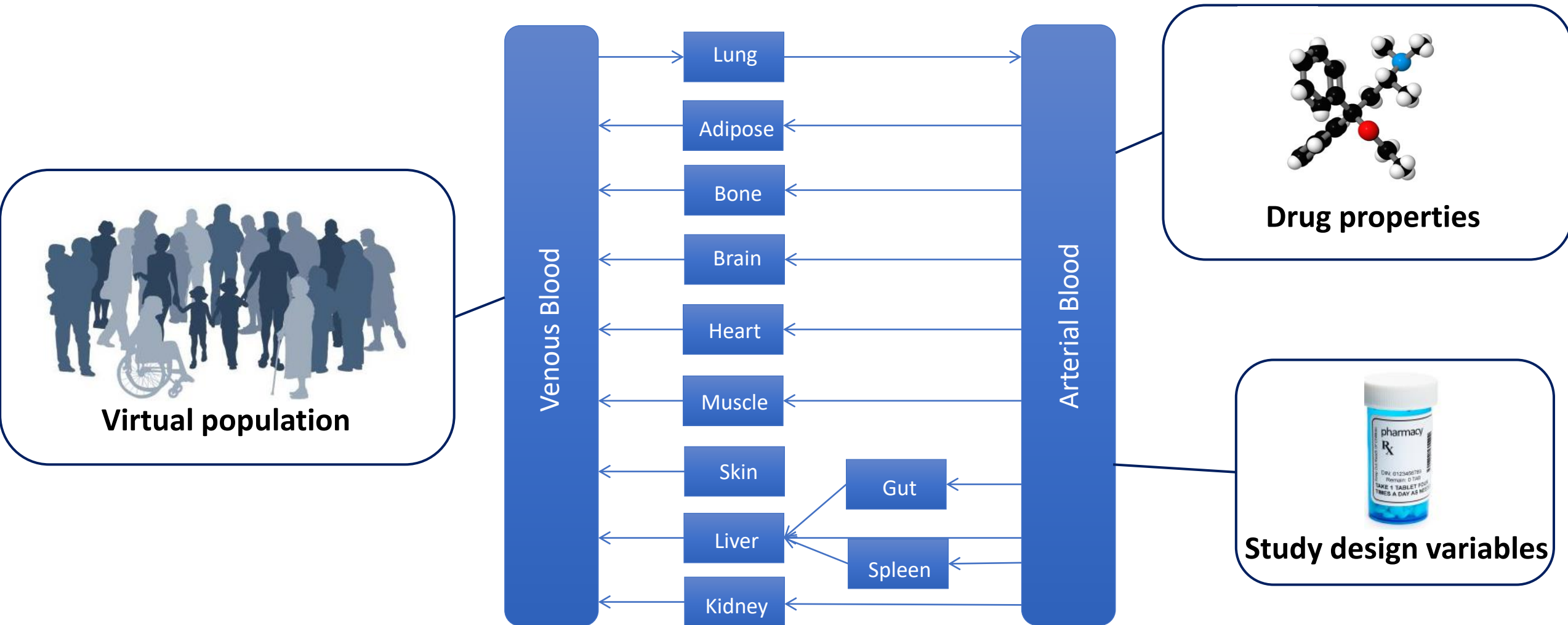
Pantoprazole Dose Optimization in Children with Obesity

- When compared to total body weight-based and lean body weight-based dosing, the FDA-approved weight-tiered dosing resulted in pantoprazole exposure more comparable to non-obese peers and adults

Table. Population pharmacokinetic model predicted pantoprazole exposure in children and adolescents with obesity compared to published reported values in non-obese peers and adults.

Dosing regimen	Obese						Non-obese		Adults [34]
	Children (aged 6–11 years) <i>n</i> = 18			Adolescents (aged 12–17 years) <i>n</i> = 19			Children (aged 6–11 years) <i>n</i> = 12 [34]	Adolescents (aged 12–16 years) <i>n</i> = 11 [33]	
	FDA-approved weight-tiered dosing	LBW-based dosing	TBW-based dosing	FDA-approved weight-tiered dosing	LBW-based dosing	TBW-based dosing	40 mg	FDA-approved weight-tiered dosing	FDA-approved dosing
Dose	20 mg (weight 15–39 kg) 40 mg (weight ≥ 40 kg)	1.2 mg/kg	1.0 mg/kg	20 mg (weight 15–39 kg) 40 mg (weight ≥ 40 kg)	1.2 mg/kg	1.0 mg/kg	40 mg	20 mg (weight 15–39 kg) 40 mg (weight ≥ 40 kg)	40 mg
<i>C</i> _{max} (µg/mL)	3.69 ± 1.08 (2.02–5.45)	4.47 ± 1.12 (2.34–6.59)	5.60 ± 1.08 (3.55–7.46)	2.58 ± 0.61 (1.70–3.41)	4.37 ± 0.76 (3.14–6.35)	4.98 ± 1.09 (3.39–6.75)	1.8	2.2 ± 1.4	2.5
AUC _{0–∞} (µg × h/mL)	5.94 ± 1.97 (3.00–8.89)	7.28 ± 2.56 (3.12–13.39)	9.15 ± 2.92 (4.39–15.13)	4.73 ± 1.93 (2.35–11.03)	7.95 ± 2.68 (4.70–16.55)	9.20 ± 3.89 (4.70–22.07)	6.9	4.3 ± 3.1	4.8 (1.4–13.3)

PBPK Modeling to Evaluate Obesity Effects



Development of a Virtual Population of Children with Obesity

ORIGINAL RESEARCH ARTICLE



Development and Evaluation of a Virtual Population of Children with Obesity for Physiologically Based Pharmacokinetic Modeling

Jacqueline G. Gerhart¹ · Fernando O. Carreño¹ · Andrea N. Edginton² · Jaydeep Sinha¹ · Eliana M. Perrin³ · Karan R. Kumar^{4,5} · Aruna Rikhi⁴ · Christoph P. Hornik^{4,5} · Vincent Harris¹ · Samit Ganguly^{1,6} · Michael Cohen-Wolkowicz^{4,5} · Daniel Gonzalez¹  on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee

Objectives:

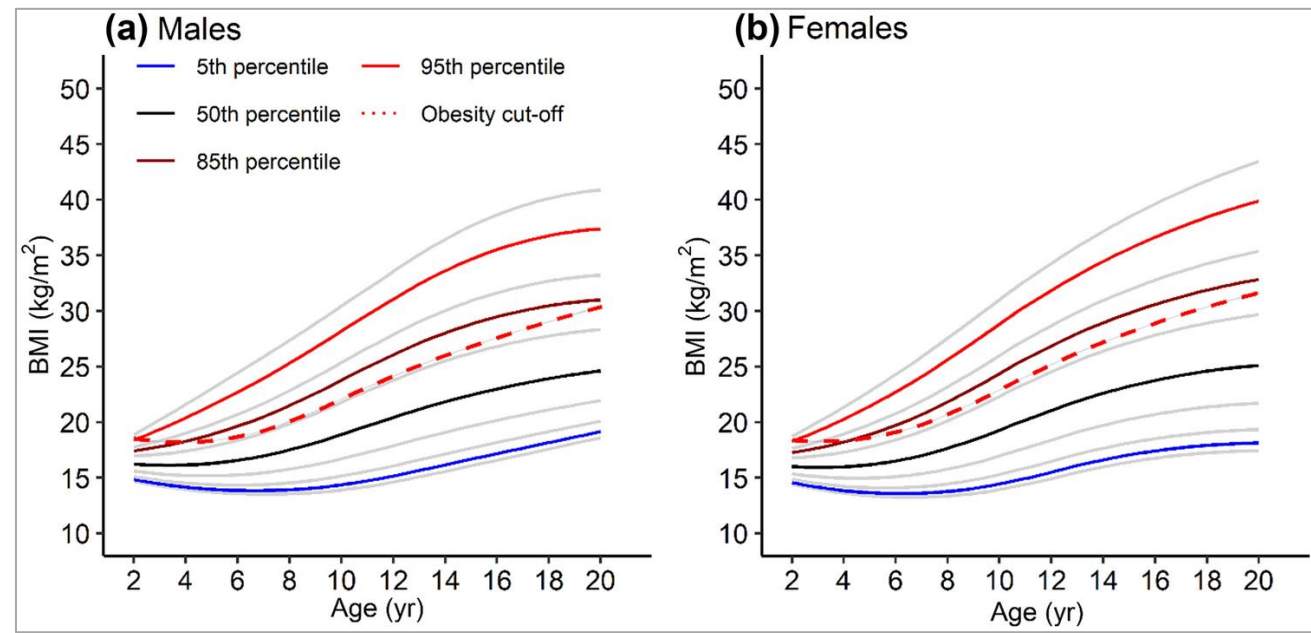
- To develop a virtual population of children with obesity to enable PBPK modeling¹
- To use the virtual population to evaluate the PK of various drugs, including clindamycin¹, trimethoprim/sulfamethoxazole¹, metformin², fentanyl³, methadone³, and enoxaparin⁴

Development of a Virtual Population of Children with Obesity

Data

- Growth curve generation:
 - Pooled NHANES data (n = 34,135)
 - Asian-, Black-, Mexican-, and White-American populations
- Growth curve evaluation:
 - Pediatric Trials Network Data Repository data (n = 76,258)
 - Asian-, Black-, Mexican-, and White-American populations

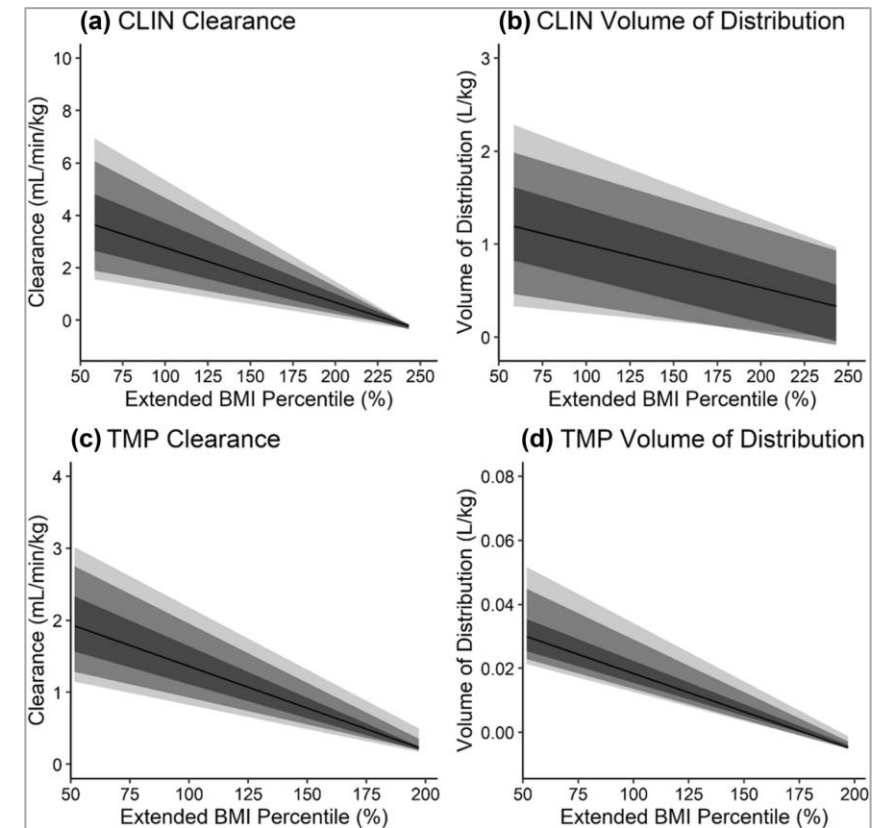
Figure. Updated growth curves based on NHANES pooled data for male and female groups. Key BMI percentiles: blue (5th percentile), black (50th percentile), dark red (85th percentile), and red (95th percentile). BMI cutoff for obesity as defined by the CDC is shown in the bold red dashed line.



PBPK Modeling of Clindamycin in Children with Obesity

- Decrease in weight normalized clearance and volume of distribution for clindamycin and trimethoprim with increasing extended BMI percentile
- The extended BMI percentile is the BMI percentile for a child's given age and sex divided by 95% (obese = extended BMI percentile $\geq 100\%$)
- Although absolute clearance is increased, it is not increased to the same degree as body weight with obesity

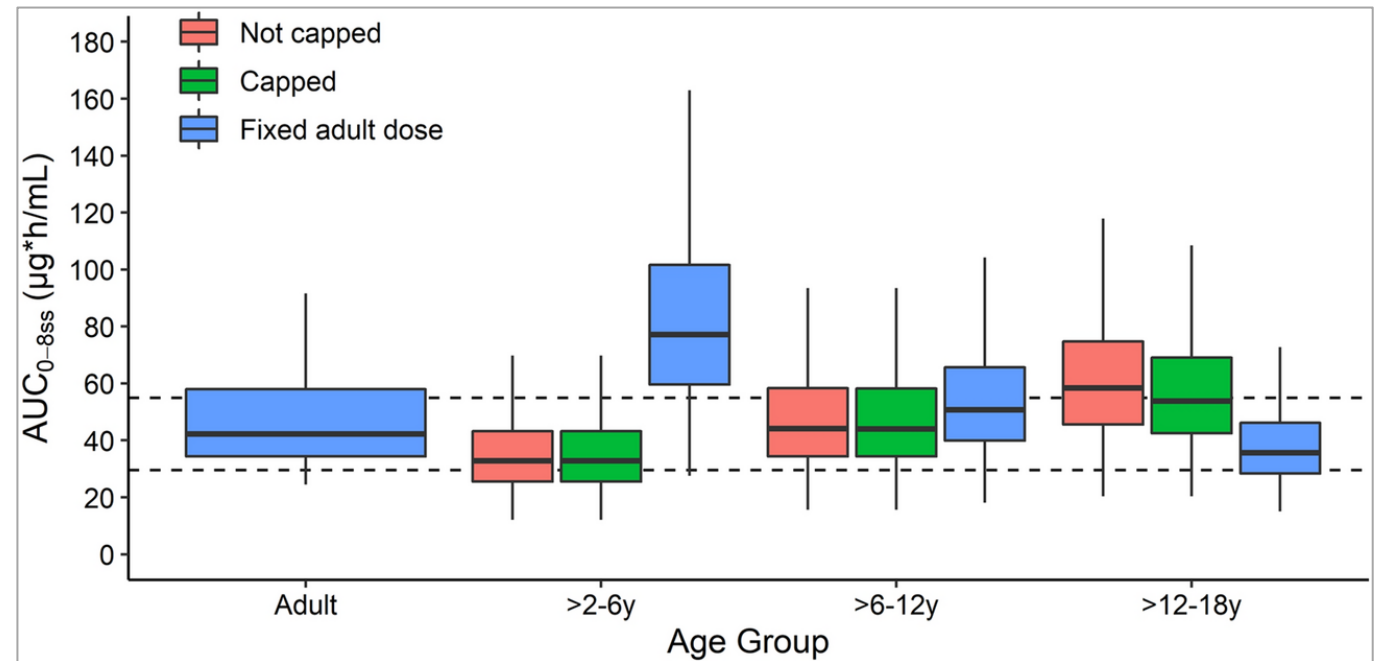
Figure. Clindamycin and trimethoprim weight normalized clearance and volume of distribution vs. extended BMI percentile.



Clindamycin PBPK Modeling in Children with Obesity Confirms PopPK-Guided Dosing

- PBPK modeling confirms the PopPK-guided dosing selection based on total body weight (12 mg/kg IV for children aged > 2–6 years and 10 mg/kg IV for children aged > 6–18 years)
- Dose capped (900 mg) vs. unrestricted dosing resulted in similar exposure, especially for children >2-6 years and >6-12 years

Figure. Boxplots of simulated clindamycin $AUC_{0-8,ss}$ in virtual healthy adults (reference) and virtual children with obesity following population simulations (n = 1000 per age group).



Adult dose: 600 mg IV; Adult capped dose: 900 mg; Dashed lines: $AUC_{0-8,ss}$ range that is within 30% of the adult median $AUC_{0-8,ss}$ value.

Metformin PBPK Modeling in Children with Obesity

Figure. Population simulation (n = 1000) of plasma concentration in children and adolescents with severe obesity following a 1000-mg dose of metformin. The solid line is the simulated median, the shaded region is the 90% prediction interval, and the open circles are observed data from 28 children with severe obesity.

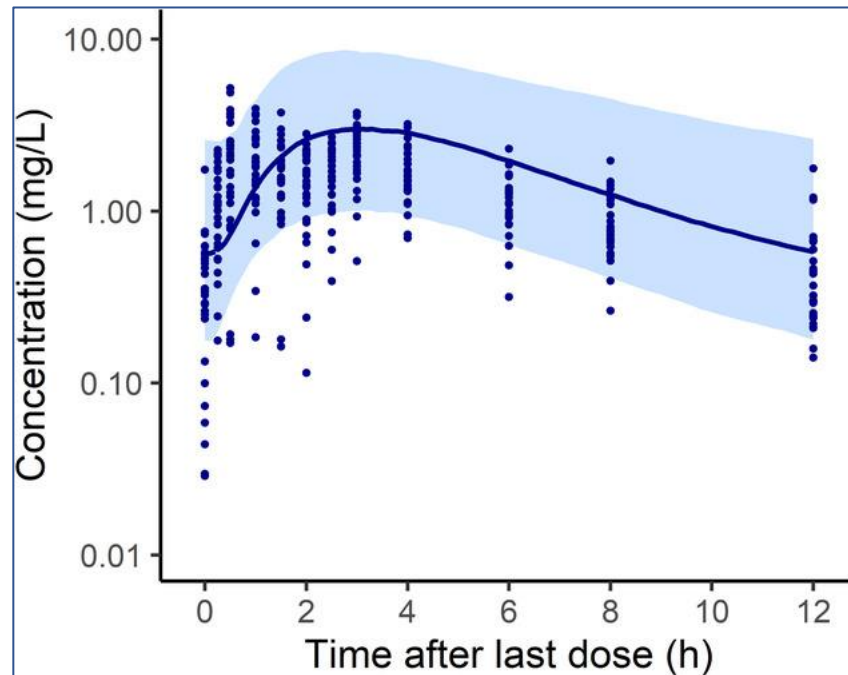
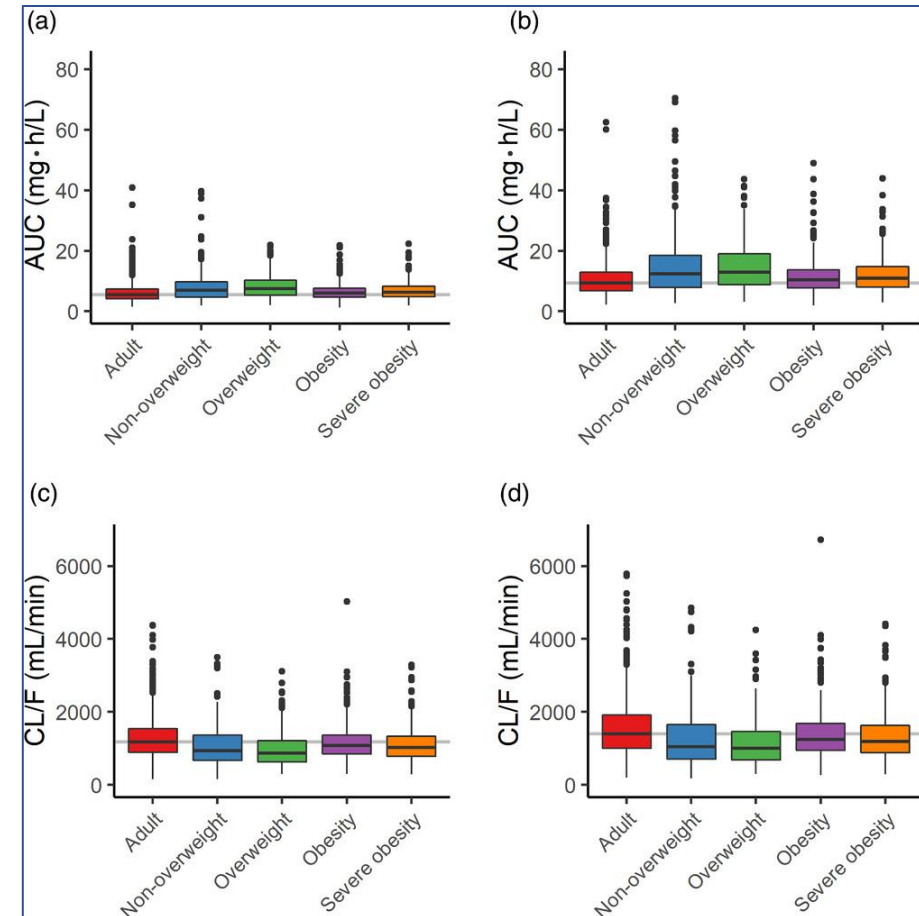
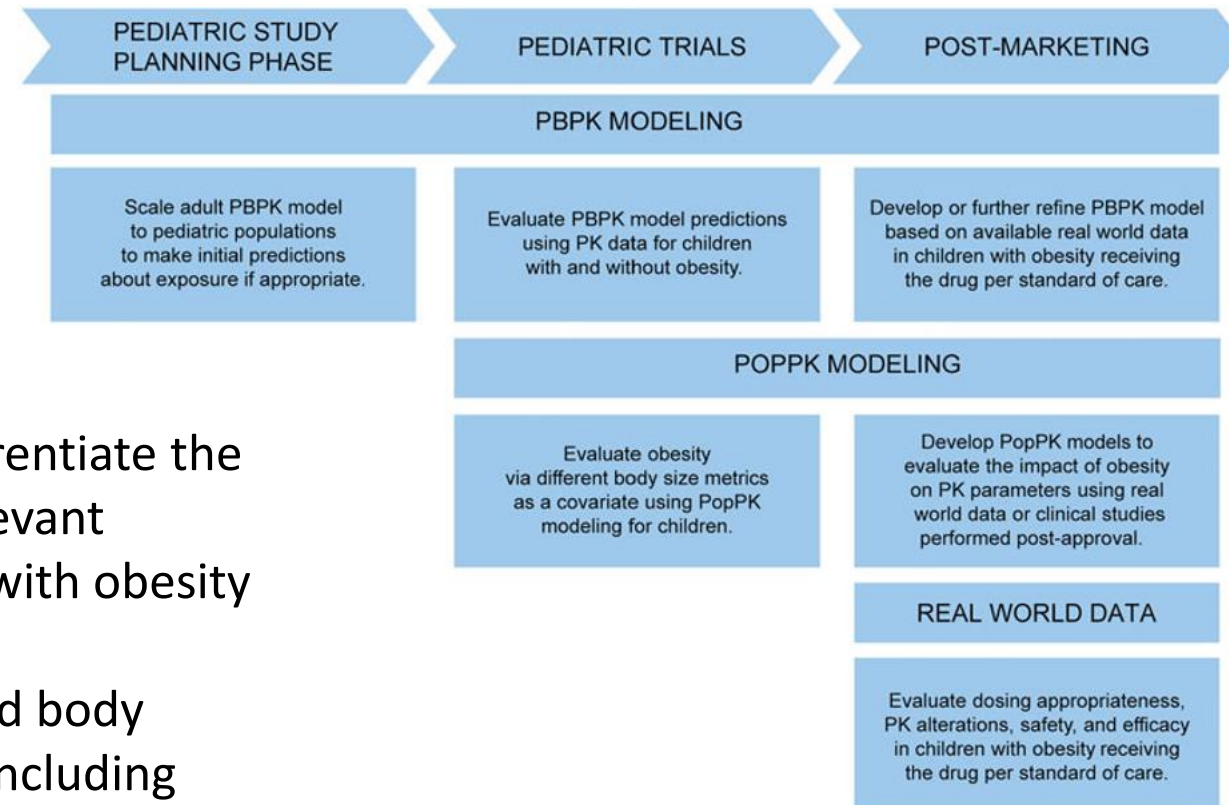


Figure. Simulated metformin plasma AUC (a, b) and CL/F (c, d) at steady state following a 500-mg (a, c) or 1000-mg (b, d) dose.



Conclusions

- Dosing recommendations for children with obesity are generally lacking
- Pediatric clinical pharmacology studies should include children with and without obesity to evaluate differences in pharmacokinetics/pharmacodynamics
- Population pharmacokinetic analyses can help to differentiate the effects of body size, age, organ function, and other relevant covariates and facilitate dose optimization in children with obesity
- PBPK models can account for changes in physiology and body composition, and be used to simulate drug exposure, including initial predictions during the pediatric study planning phase



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Questions

