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Individualization of drug clearance predictions and dose regimens in patients with obesity using pharmacometric approaches

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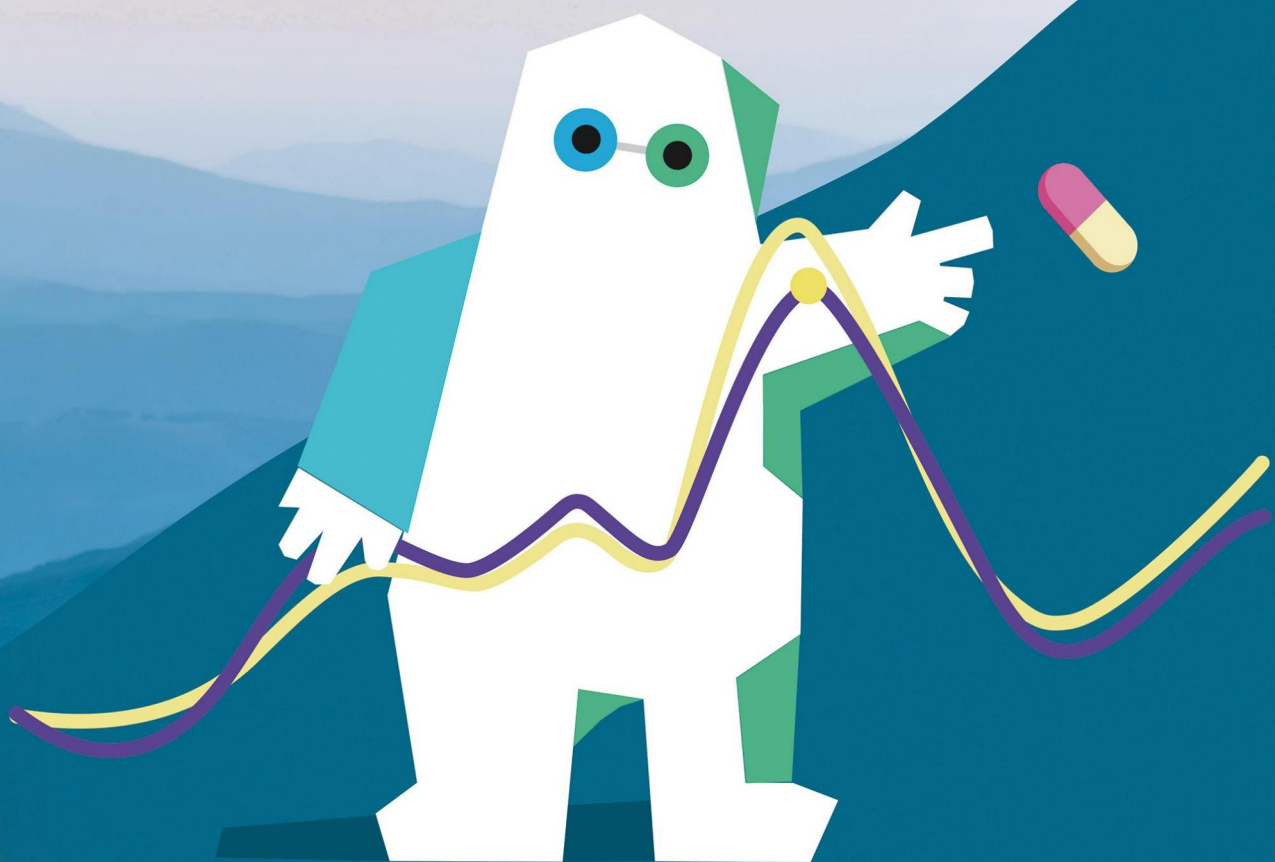
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INDIVIDUALIZATION OF DRUG CLEARANCE PREDICTIONS AND DOSE REGIMENS IN PATIENTS WITH OBESITY USING PHARMACOMETRIC APPROACHES



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TAN ZHANG

**INDIVIDUALIZATION OF DRUG
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Individualization of Drug Clearance Predictions and Dose Regimens in Patients with Obesity Using Pharmacometric Approaches

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I

Introduction and background

1

General introduction and scope



Overweight and obesity, characterized by an excess of body fat, are some of the leading risk factors for early death [1]. Body mass index (BMI) is a simple index for categorizing overweight and obesity, with different criteria for adults and children and adolescents [2]. In adults, BMI is calculated based on weight and height, whereas in adolescents, the classification is based on the BMI distribution categorized by age and sex in growth charts from the Centers for Disease Control and Prevention (CDC), as shown in **Table 1.1**. According to the World Health Organization (WHO), overweight and obesity affect more than 1.9 billion adults and 340 million children and adolescents worldwide [2]. As illustrated in **Figure 1.1**, the global prevalence of overweight and obesity has been increasing since 1975 and it is projected to increase further in the coming years. Due to comorbidities associated with obesity, patients with overweight and obesity may require more frequent drug treatment, for instance for infections, a range of cancers (e.g., colorectal, thyroid, ovarian, and gallbladder cancers), or surgery such as orthopedic and bariatric surgery [3].

Table 1.1 Bodyweight classification for adults and adolescents.

Bodyweight classification	Adults (> 19 years)	Adolescents (10–18 years)
	BMI (kg/m ²)	BMI percentile [#]
Underweight	< 18.5	< 5 th
Normal weight	18.5 ~ 24.9	5 th ~ 85 th
Overweight	25 ~ 29.9	85 th ~ 95 th
Obese	30.0 ~ 39.9	95 th ~ 99 th
Morbidly obese	≥ 40.0	≥ 99 th

BMI, body mass index.

[#] Adjusted for age and sex based on the growth charts from the Centers for Disease Control and Prevention (CDC).

1.1 Drug dosing challenges in patients with overweight and obesity

Overweight and obesity are associated with various physiological changes, such as increased cardiac output and organ flow, altered (hepatic) enzyme activity and changes in body composition [4]. These can significantly influence the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, potentially leading to suboptimal efficacy or increased toxicity. To date, the exact influence of these physiological changes on the PK parameters of drugs with various drug properties is not fully understood. As a result,

for many drugs, it is unknown how they should be dosed in adults with overweight and (morbid) obesity, with even fewer evidence-based dosing recommendations being available for adolescents with overweight and obesity [5]. This brings great challenges for clinicians and pharmacists who need to determine potential dosage adjustments for these populations.

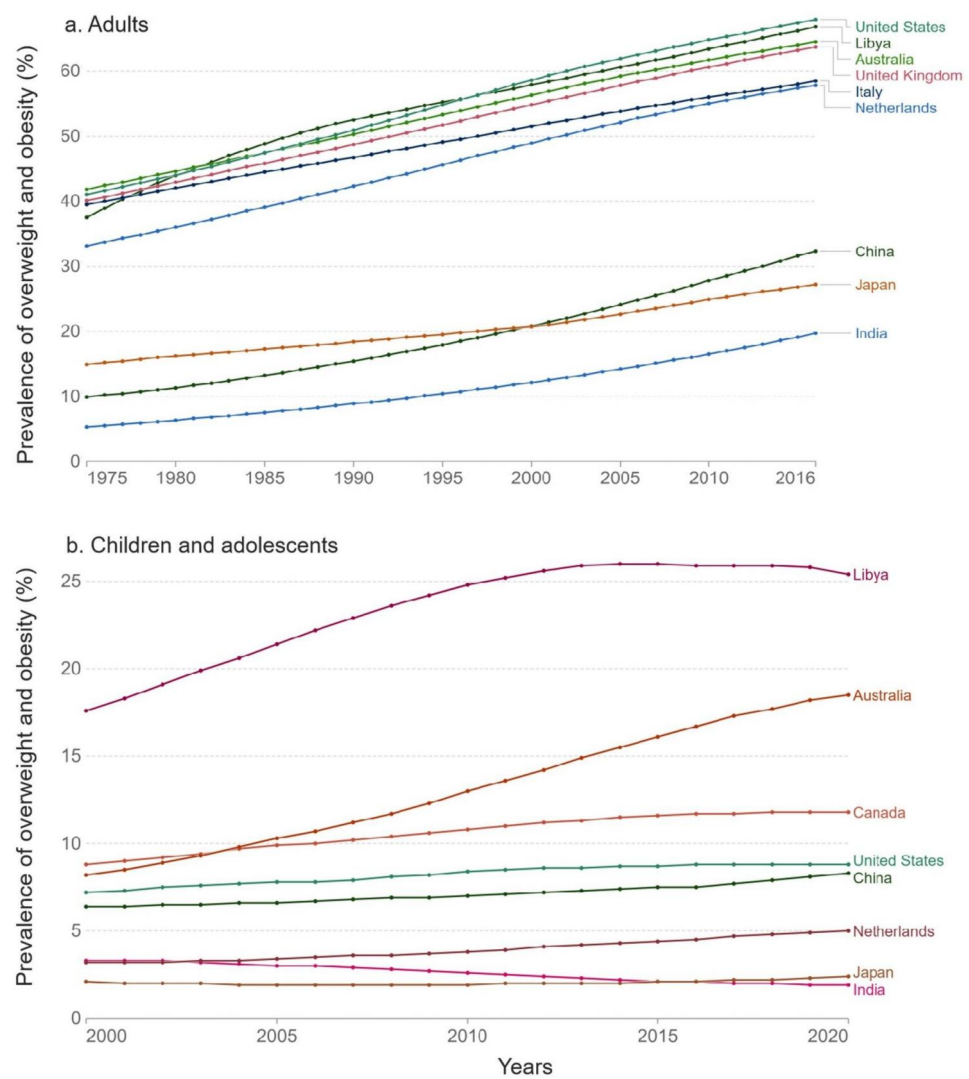


Figure 1.1 Prevalence of overweight and obesity for (a) adults and (b) children and adolescents around the world. Data are derived from the World Health Organization (WHO) Global Health Observatory [1].

Quantitative pharmacological modeling approaches are mathematical methodologies used to describe and predict the behavior of drugs within the body. They involve the mathematical equations to quantify drug absorption, distribution, metabolism, and excretion, and help with getting insights into the impact of drug- or disease-related variations on drug exposure [6]. These modeling approaches can be useful tools to investigate the impact of overweight and obesity on drug PK and to guide dosing in this population. Two common approaches are population pharmacokinetic (pop PK) modeling and physiologically-based pharmacokinetic (PBPK) modeling.

1.2 Population PK modeling in predicting clearance and guiding dosing in patients with obesity

When PK observations are available in patients with and without obesity, pop PK modeling is the preferred approach to analyze the PK characteristics of the population as well as inter-individual variability. This modeling approach allows for the identification of covariates that quantify correlations between individual deviations from typical model parameters and patient or treatment-related factors [7]. In the obese population, key covariates may include body size descriptors (e.g., total bodyweight, lean bodyweight, ideal bodyweight, standard bodyweight) or the severity of obesity. Additionally, factors such as sex, age, comorbidities, and renal function, particularly in subpopulations with varying renal functions, should be considered. The incorporation of these covariates may improve drug exposure at the individual level. These types of analyses are pivotal for developing individualized dosing guidelines, optimizing therapeutic outcomes, and minimizing adverse effects, particularly when uniform dosing is unsuitable due to significant inter-individual variability in drug PK relative to the therapeutic window.

1.3 PBPK modeling in predicting obese clearance and guiding dosing in patients with obesity

PBPK modeling is a powerful tool for predicting drug clearance for special populations like individuals with obesity by accounting for physiological differences be-

tween individuals with and without obesity. These differences, such as variations in organ size, blood flow, adipose tissue distribution, and metabolic enzymes or transporters, can impact drug absorption, distribution, metabolism, and elimination. With PBPK modeling, researchers and clinicians can gain insights into how drug PK varies in individuals with obesity for drugs with different properties, which can ultimately result in predictions of drug clearance in the absence of clinical data.

This approach can also be used to assess the accuracy of dosing methods under different scenarios by accounting for the patient characteristics and drug properties. In the absence of obesity-related clinical data, this can provide a yardstick for scaling drug clearance from normal-weight subjects to those with obesity. This in turn facilitates the development of personalized dosing guidelines for individuals with obesity to ensure optimal drug exposure and therapeutic outcomes.

1.4 Scope of this thesis

The overall aim of this project is to develop model-based methods to optimize drug dosing in patients with overweight and (morbid) obesity. To achieve this aim, this thesis is divided into four sections:

Section I

To anticipate how to adjust the dose of drugs in adults and adolescents with (morbid) obesity, several general assumptions regarding the changes in PK of drugs in the obese have emerged in the literature. Before delving into the development of model-based methods for optimizing drug dosing in the obese, a review is conducted in **Chapter 2** to examine available evidence regarding five commonly accepted assumptions to *a priori* predict the impact of obesity on drug PK.

Section II

This section comprises two chapters, both of which utilize a pop PK modeling approach to explore the intricate interplay of obesity with other variables that influence vancomycin PK. In **Chapter 3**, vancomycin PK in adolescents and adults with overweight and obesity is investigated, aiming to evaluate whether drug dosing information from obese adults can be directly extrapolated to obese adolescents. This chapter

pays special attention to the impact of age- and sex-related weight on vancomycin clearance, in order to distinguish between the effects of weight resulting from pubertal physical development and the effects of weight resulting from obesity on drug clearance. **Chapter 4** delves into quantifying vancomycin PK in a special subgroup—hospitalized patients with obesity and varying severity of renal insufficiency. Since the latest guideline recommends AUC-targeted vancomycin dosing for efficacy and safety, and considering the absence of specific guidelines for hospitalized patients with obesity and renal insufficiency, model-derived AUC-targeted dosing recommendations for this population are proposed.

Section III

Drug clearance in obese individuals varies widely across different drugs and among subjects with various severity of obesity. In **Section III**, the goal is to explore correlations between clearance and drug and subject characteristics in patients with overweight and obesity, and to identify scenarios where common weight-based dosing methods are systematically accurate. To achieve this, both **Chapter 5** and **Chapter 6** utilize a PBPK modeling approach to simulate clearance for a normal-weight subject and subjects with varying severity of obesity, for hypothetical drugs with different properties. **Chapter 5** focuses on drugs metabolized through hepatic metabolism, while **Chapter 6** focuses on drugs eliminated through glomerular filtration with various degrees of active renal secretion. Noteworthy is the special emphasis in **Chapter 6** on studying the impact of obesity on the contribution of glomerular filtration and active tubular secretion to total renal clearance.

Section IV

This section summarizes the key findings and conclusions of the investigations presented in this thesis. Furthermore, it outlines future perspectives concerning relevant topics related to model development and optimal dosing in the population with obesity. These topics emphasize: **1)** the added value of external validation for model improvement and implementation in the clinic, **2)** the impact of different intravenous infusion methods on PK parameter estimation, and **3)** appropriate dosing scaling methods for subjects with overweight or obesity based on the outcomes of **Chapter 5** and **6** to select appropriate methods for dose adjustments for the population with obesity.

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2

Drug pharmacokinetics in the obese population: challenging common assumptions on predictors of obesity-related parameter changes

This chapter is based on  Zhang T, et al. Drug pharmacokinetics in the obese population: challenging common assumptions on predictors of obesity-related parameter changes. *Expert Opin Drug Metab Toxicol.* 2022;18(10):657-674.

ABSTRACT

2

Introduction

Obesity is associated with many physiological changes. We review available evidence regarding five commonly accepted assumptions to *a priori* predict the impact of obesity on drug pharmacokinetics (PK).

Areas covered

The investigated assumptions are: **1)** Lean body weight is the preferred descriptor of clearance and dose adjustments; **2)** volume of distribution increases for lipophilic, but not for hydrophilic drugs; **3)** CYP-3A4 activity is suppressed and UGT activity is increased, implying decreased and increased dose requirements for substrates of these enzyme systems, respectively; **4)** glomerular filtration rate is enhanced, necessitating higher doses for drugs cleared through glomerular filtration; **5)** drug dosing information from obese adults can be extrapolated to obese adolescents.

Expert opinion

Available literature contradicts, or at least limits the generalizability, of all five assumptions. Clinical studies should focus on quantifying the impact of duration and severity of obesity on drug PK in adults and adolescents, and also include oral bioavailability and pharmacodynamics in these studies. Physiologically-based PK approaches can be used to predict PK changes for individual drugs, but can also be used to define in general terms based on patient characteristics and drug properties, when certain assumptions can or cannot be expected to be systematically accurate.

Article highlights

- It is not justified to *a priori* select lean body weight as a size descriptor for inter-individual variability in clearance in obese individuals, nor does any other size descriptor qualify for this. Total body weight in a non-linear function is mostly reported as the optimal descriptor to predict clearance.
- The impact of obesity on distribution volume varies widely and cannot be predicted based solely on lipophilicity. In general, there seems a (small) increase for hydrophilic drugs, while for lipophilic drugs, there is high inter-drug variability.
- Hepatic clearance is influenced not only by changes in activity or abundance of hepatic enzymes resulting from obesity-related changes but also by changes in plasma protein binding and hepatic blood flow, with the exact influence depending on drug extraction ratios.
- Despite a possible increase in glomerular filtration rate (GFR) in obese individuals, absolute renal clearance does not necessarily increase for all drugs that are mainly eliminated by GFR, because kidney function and transporter-mediated secretion and reabsorption may also be impacted by obesity.
- Findings on clearance and dose adjustments from obese adults cannot always be extrapolated to obese adolescents, possibly due to differences in the duration of obesity and time needed for physiological changes to manifest and impact PK parameters.

2.1 Introduction

2 Obesity is characterized by an abnormal or excessive fat accumulation that can impair health [1]. For adults, obesity is defined as a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ and morbid obesity as a BMI $\geq 40 \text{ kg/m}^2$ or a BMI $\geq 35 \text{ kg/m}^2$ with obesity-related comorbidity, while for adolescents, obesity and morbid obesity are, respectively, defined as a BMI corrected for age and sex $\geq 95^{\text{th}}$ and $\geq 99^{\text{th}}$ percentile based on the growth charts from the Centers for Disease Control and Prevention (CDC) [2] (**Supplementary Table S2.1**). Obesity is increasing worldwide in both adults and adolescents, with the prevalence being more than 20% in several countries such as the United States, Canada, Spain, and the United Kingdom [3].

Obesity is associated with increased risks of hypertension, dyslipidemia, metabolic syndrome, infections, chronic pain, a range of cancers (e.g., colorectal, thyroid, ovarian, and gallbladder cancers) and many other comorbidities [4–6]. These comorbidities usually require treatments with a variety of medications and/or surgery. However, for many drugs, dosing guidelines for (morbidly) obese patients are not specified [7, 8]. This is true for the adult population, but this situation is even worse for obese adolescents [9]. To anticipate on how to adjust the dose of drugs in (morbidly) obese adults and adolescents in the absence of data, several general assumptions regarding the changes in PK of drugs in the obese have emerged in literature:

1) Lean body weight (LBW), representing the mass of lean tissue, is the preferred descriptor of clearance (CL) and volume of distribution (V_d) and therefore of dose adjustments; 2) the V_d increases for lipophilic, but not for hydrophilic drugs; 3) cytochrome P450 (CYP)-3A4 activity is suppressed, and uridine diphosphate glucuronosyltransferase (UGT) enzyme activity is increased, implying decreased and increased dose requirements for drugs metabolized by these enzyme systems, respectively; 4) glomerular filtration rate (GFR) is enhanced necessitating higher doses for drugs cleared through glomerular filtration; 5) drug dosing information from obese adults can be extrapolated to obese adolescents.

With the emergence of a growing number of studies on the PK of drugs in the obese, we systematically evaluated these assumptions to provide an overview of the current evidence. This information can be used to increase our knowledge on how to adjust

dosages of drugs on which no PK studies are available.

2.2 Search strategy and selection criteria

2

2.2.1 Search strategy

As illustrated in **Figure 2.1**, literature search was performed in the PubMed database in November and December of 2021. The following terms were used in the search: ((obesity OR obese OR morbidly obese OR morbid obesity) AND (control OR normal OR healthy OR match OR non-obese OR lean)) AND (pharmacokinetics OR PK OR pharmacokinetic).

2.2.2 Inclusion/exclusion criteria

To allow for direct comparisons between obese and non-obese individuals, only clinical studies that investigated drug PK in both populations simultaneously were collected. Additionally, a study was excluded if it was **1)** a review, commentary, case report, or letter to the editor, **2)** an animal study, **3)** a study on drug pharmacodynamics (PD) only, **4)** a simulation-based study, **5)** a study not related to drugs, **6)** not an original research, **7)** not written in English, or **8)** incomplete or inaccessible. After the primary screening, 1673 studies were selected.

To select literature related to each assumption regarding drug PK in obesity, further screening was executed according to the following inclusion criteria:

For the assumption of LBW being the preferred CL or V_d scalar in obese individuals, studies were included if **1)** LBW was evaluated together with total body weight (TBW) and possible other size descriptors for its potential as a descriptor of inter-individual variability for PK parameters, or **2)** PK parameters were found to be unaltered or comparable in obese population compared to the non-obese population, and no dose adjustment was suggested for the obese population. For this assumption, a total of 44 articles were included.

For the assumption on the impact of lipophilicity on V_d , studies were included if they **1)** reported the value of V_d , and **2)** studied a drug for which the logP value was avail-

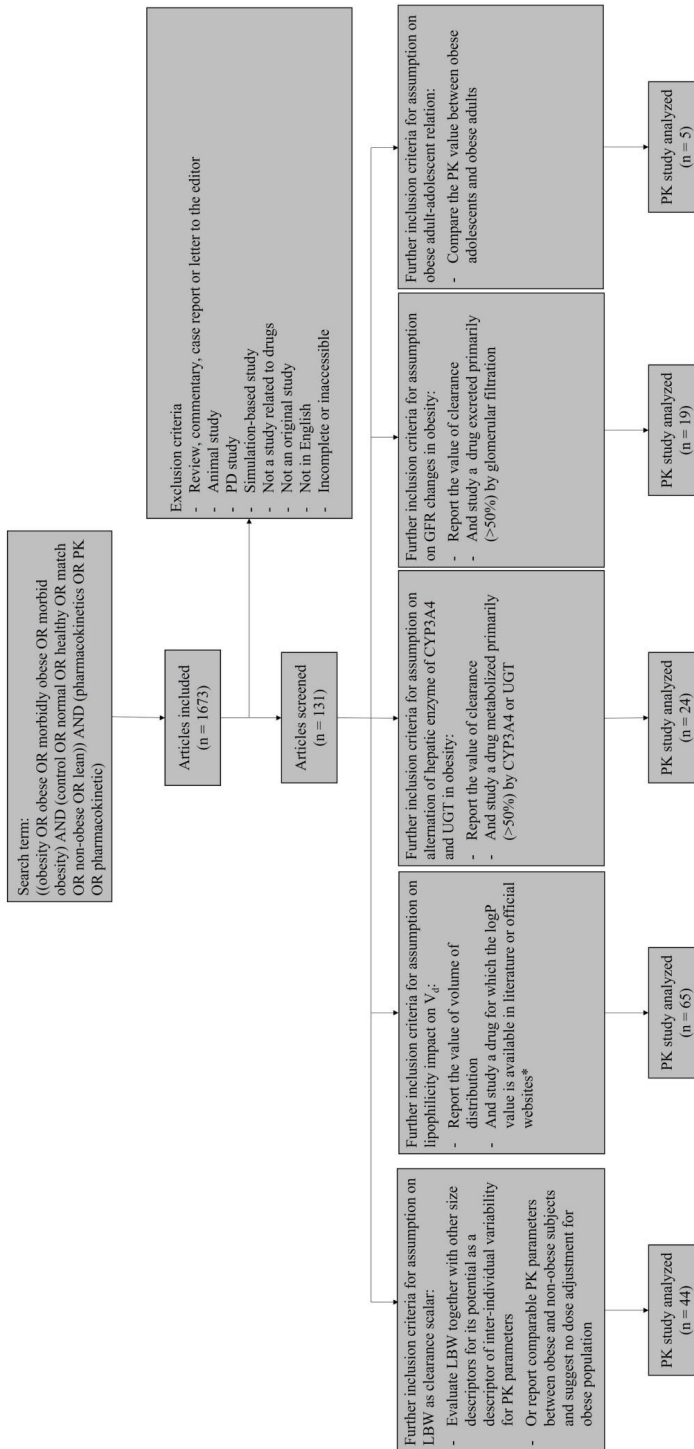


Figure 2.1 Flow diagram of the article selection process.

able in literature or official websites (<https://go.drugbank.com>, <https://pubchem.ncbi.nlm.nih.gov>, or <https://www.chemsrc.com>). A total of 65 articles were included.

For the assumption on the alteration of hepatic enzyme activity for CYP3A4 and UGT in obesity, studies were included if they **1)** reported the value of CL or apparent (oral) CL (CL/F), and **2)** studied a drug that metabolized primarily (e.g., > 50%) by CYP3A4 enzymes or UGT enzymes reported on the aforementioned official websites or in the literature. For this topic, a total of 24 articles were included.

For the assumption on GFR changes in obesity, studies were included if they **1)** reported the value of CL , and **2)** studied a drug that excreted primarily (e.g., > 50%) by glomerular filtration reported on the aforementioned official websites or in the literature. A total of 19 articles were available.

For the assumption on obese adult-adolescent relation, studies were included if they compared PK parameter values between obese adults and obese adolescents. For this assumption, five articles were included.

2.3 Evaluation of assumptions based on literature

2.3.1 LBW is the preferred size descriptor of CL and dose adjustment in the obese

Background on LBW as clearance scalar in the obese

The maintenance dose of a drug is dependent on CL and CL is therefore considered the most important parameter for drug dosing. Considering CL scalars, TBW is commonly used for inter-individual differences in CL in non-obese populations. However, as obese individuals have increased adipose tissue and a decreased lean/adipose tissue ratio, it was suggested that it is unlikely that CL proportionally increases with TBW, unless adipose tissue is assumed to have intrinsic extraction properties [10]. Therefore, fixed allometric scaling, meaning bodyweight-based scaling in an exponential equation with an exponent of 0.75, has for instance been proposed. This practice finds its basis in the observed trends in basal metabolic rate and drug metabolism between species and the assumption that these trends apply within species as well [11–15]. Additionally, various other body size and/or body composition descriptors have

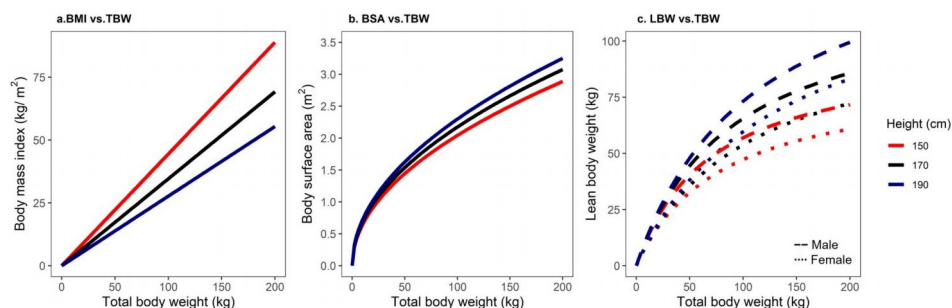


Figure 2.2 Body mass index (a) body surface area (b) and lean body weight (c) versus total body weight for individuals of both sexes with various heights.

been proposed to predict obesity-related differences in *CL*.

As illustrated by the equations that defined the different body size descriptors (in **Supplementary Table S2.1** and **Figure 2.2**), BMI, an international metric to classify obesity, has a linear relation with TBW for people of the same height (**Figure 2.2a**) and cannot differentiate adipose tissue from muscle mass or other tissue mass [14]. Body surface area (BSA) is widely used to dose chemotherapeutic agents [16] and its non-linear relation with TBW (**Figure 2.2b**) shows that with increasing TBW the absolute increase of *CL* and dose calculated by BSA is decreasing. Ideal body weight (IBW) is calculated based on sex and height, and as it is not based on TBW, it does not provide a measure for over- or underweight or body composition. To provide a rough measure of body composition, adjusted body weight (ABW) was proposed by taking the differences between TBW and IBW and using a “correction factor” ranging from 0.14 to 0.98 [17]. Predicted normal weight (PNWT) represents the sum of lean body mass and predicted “normal” fat mass, and was derived to describe the PK of drugs specifically [18].

LBW was initially derived to relate patient size to epidemiological trends in morbidity and mortality. It has since also been used to describe the altered body composition in obese individuals to predict PK changes. LBW represents the total bodyweight without the fat mass. Several methods have been devised to estimate LBW. The most common equation is derived from the study of James *et al.* in 1976 [19]. However, this equation was not designed for the obese population, which could lead to an inaccurate description of PK parameters for subjects with extremely high weight [10,

20]. Therefore, an alternate equation for LBW was developed by Janmahasatian *et al.* in 2005 based on a wide range of age, body weight, and BMI [21]. This equation has been proven to yield accurate predictions of LBW and has been increasingly used for LBW calculations [22]. As LBW takes not only TBW and height but also sex into account (**Figure 2.2c**), it should be noted that LBW is higher for males than females of the same TBW and height [23, 24]. Fat free mass (FFM) is another measure of body composition, that deviates from LBW in that it excludes the fat in cell membranes [25]. However, the fat in cell membranes contributes a mere 3~5% of fat to lean tissues [26], which makes FFM and LBW have similar values and therefore they are sometimes used in the same way [24].

As lean tissue is reported to be highly correlated with (drug) metabolism [15], and since adipose tissue is believed to not contribute to metabolism, some reviews suggest that LBW is the preferred descriptor of *CL* and dose adjustments [10, 12, 27, 28]. For example, Green *et al.* summarized in a review of 11 PK studies that no one size descriptor is most suitable for all drugs, but LBW had the highest percentage of successful *CL* predictions compared to other descriptors [10]. All studies included in this review used James' equation to calculate LBW. In another systematic review paper, Mcleay *et al.* concluded that LBW is the best predictor for *CL* and proposed that an exponential equation with LBW and an exponent of 2/3 may be suitable for describing an increase in *CL* with increasing body weight [12]. Based on these reviews, LBW is regarded as most suitable size-descriptor of *CL* for the *a priori* selection in obese individuals, and it is also widely tested as a covariate in PK studies.

Literature results on LBW as clearance scalar for the obese

A summary of the 44 publications on 37 studied drugs retrieved on this topic is provided in **Table 2.1**, and an overview of the number of studied drugs that evaluated LBW amongst other size predictors and covariates, and that did or did not identify size predictors for *CL*, V_d , and dose adjustment, is shown in **Figure 2.3a**. As shown in **Figure 2.3a**, of 37 studied drugs, size predictors for *CL*, V_d , and dose adjustment are identified in 15 (41%), 19 (51%) and 11 (30%) studies, respectively. An overview of size descriptors that are identified to be predictive for *CL* is further displayed in **Figure 2.3b**, showing that the descriptors identified to be best were TBW (11 drugs), LBW (five drugs), FFM (one drug) and BMI (one drug). It is noted that for one drug

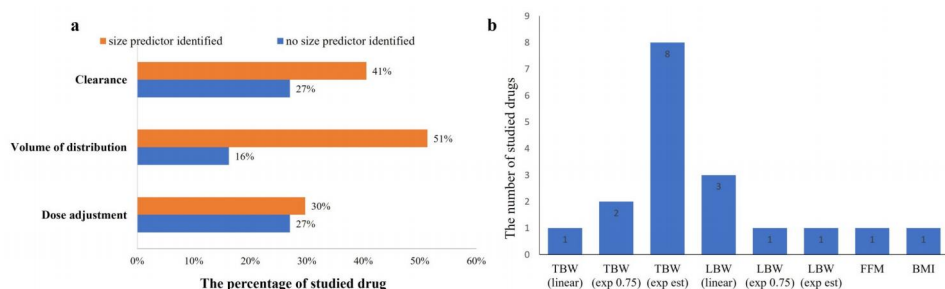


Figure 2.3 Overview of (a) the percentage of studied drugs that evaluated lean body weight amongst other size predictors and covariates, and identified or did not identify a size predictor for clearance, volume of distribution, or dose adjustment, and (b) the number of drugs that identified different size descriptors for clearance.

(e.g., propofol), different size descriptors have been found to predict *CL* in different studies. In **Figure 2.3b**, the information on the relationship (linear, exponential with estimated exponents, or exponential with an allometric scalar of 0.75) between *CL* and TBW or LBW is also provided.

Of the five drugs that found LBW to be the superior size descriptor for *CL*, two studies, one on enoxaparin and one on remifentanyl, found that *CL* linearly increased with LBW in obese patients [34, 35], while another study found the *CL* of paracetamol and all of its metabolites to increase with LBW in a non-linear manner [36]. Two studies found that, in addition to LBW, other covariates (i.e., liver blood flow in a study on dexmedetomidine, and age and serum creatinine in a study on metformin) further impact *CL*, indicating LBW alone was insufficient to predict *CL* for these drugs in these patients [37, 38]. In a second study on dexmedetomidine, FFM was found to be a covariate on *CL*, which is in line with the results of the aforementioned study, as FFM is very similar to LBW. It is worth noting that this study reported an average of 23% higher *CL* in males than in females in three groups of subjects with matched height and weight. Given that both FFM and LBW have different functions for the two sexes, they are specifically suitable for drugs that show sex-related differences in PK parameters. For enoxaparin, LBW was also found useful in the description of the sex-related difference in the *CL* [35].

Of 11 drugs that identified TBW as best predictor for *CL*, one (nadroparin [39]) found a linear relationship between *CL* and TBW; two (propofol [40] and vancomycin [41])

reported inclusion of an exponential relationship between *CL* and TBW with a fixed exponent of 0.75; eight (anidulafungin [42], carboplatin [43], ertapenem [44], gentamicin [45], micafungin [46], posaconazole [47], propofol [48], and vancomycin [49]) found an exponential relationship between *CL* and TBW with a varying exponent. BMI was found to be a predictor of *CL* in a study on alfentanil, but it should be noted that no male subjects were included in this study, so potential sex-related differences leading to the identification of LBW as the most optimal covariate, could not be assessed [50].

Besides size descriptors, renal function is also a commonly known covariate for drug *CL*. Traditionally, various equations are used to calculate variables to quantify renal dysfunction. All include TBW as a size descriptor and some may or may not be expressed normalized to BSA, a practice that may lead to artifacts in the calculation of renal dysfunction in the obese. Some authors have however selected alternative size descriptors in these equations for obese patients. As shown in **Table 2.1**, nine studies found the renal function to best predict *CL*, with the renal function being calculated using either TBW, LBW, or IBW in five, three and one study, respectively [22, 51–57]. However, of these studies, only a few formally evaluated and compared different size descriptors in the calculation of renal function, and the equations used to calculate renal function varied and composited other covariates such as age and sex in addition to size descriptors. It is therefore hard to extract from these findings what could be the added value of LBW as a size descriptor.

In addition to the studies that reported LBW as a covariate on *CL*, four studies (one on folic acid and three on propofol) recommended adjusting the dose for obese patients based on LBW, as dosing according to LBW provided superior systemic exposure compared to other size-based dosing strategies [58–60, 127]. However, for propofol, how to adjust the dose in obese individuals remains controversial, as two other studies found a non-linear relation between *CL* and TBW [40, 48], while a sixth study suggested that no dose adjustment was needed which may be due to the weight range in this study was small [61]. Besides LBW, BSA was suggested to be the most informative descriptor of drug dosing for eight anti-cancer drugs (i.e., docetaxel, doxorubicin, cisplatin, irinotecan, paclitaxel, carboplatin, topotecan and troxacitabine) [62]. TBW yielded an accurate prediction of PK and the required dose adjustment in one study

of daptomycin [63].

No significant influence of obesity was found on any PK parameters of 10 out of 37 drugs (27%) including meropenem [54, 64], omarigliptin [126], propofol [61], glimepiride [125], morphine [65], oseltamivir [30, 31, 55], tedizolid [66], telavancin [67], daptomycin [68] and ximelagatran [69], suggesting that dose adjustments are not required in obese patients. Studies on meropenem [54], omarigliptin [126], propofol [61], and ximelagatran [69] included obese individuals without morbidly obese individuals. However, other studies on meropenem [64], tedizolid [66], telavancin [67], and daptomycin [68] did include morbidly obese patients with more extreme body-weights, showing that (morbid) obesity does not have a clinically relevant effect on required dose adjustments as a result of comparable *CL* between patients with normal weight and with various degrees of obesity. For oseltamivir [55] systemic exposure of the active metabolite was largely unchanged and therefore dose adjustment would not be needed, even though the systemic exposure of the parent compound was decreased in morbidly obese subjects (data not shown). Similarly, for morphine, its metabolism was found to be not altered in morbidly obese patients, but the elimination of its pharmacologically active metabolites, and therefore metabolite exposure, was reduced [67].

In summary, in clinical PK studies where LBW was evaluated amongst other size descriptors in obese and non-obese individuals, we found that most studied drugs (11 out of 15) found TBW as the preferred descriptor for *CL*, while LBW was the most predictive descriptor for *CL* in only five out of 15 studied drugs. LBW/FFM was found to be useful in the description of the sex-related difference in the PK in two drugs. In 10 studies, no significant influence of size descriptors on PK was found. There is therefore no evidence for the *a priori* selection of LBW as a size descriptor for inter-individual variability in *CL* in the obese.

Table 2.1 Identified significant covariates, including most optimal size descriptors, for pharmacokinetic parameters and/or dose adjustment in studies of obese and non-obese individuals in which LBW was evaluated amongst other size descriptors and covariates. In case LBW was identified as the most optimal size descriptor, LBW is placed in bold.

Drug	Number of subjects (n)		Identified optimal size descriptor ^a			Dose adjustment	Remark	Ref
	Non-obese	(Morbidly) obese	CL	V _d				
Alfentanil	6	10	BMI	No size descriptor was identified	-	-	Only female subjects were included.	[50]
Anidulafungin	12	8	TBW ^{d(0.32)}	TBW	-	-	-	[37]
Carboplatin	357		TBW ^{d(0.50)} , sex, Scr, cystatin C, age	No size descriptor was identified	-	-	LBW ₁₉₇₆ was tested. 74% of subjects were female.	[38]
Carboplatin	64	14 ^b	-	-	BSA	BSA	BSA was calculated by PNWT	[60]
Cefazolin	7	9	Age	TBW	-	-	-	[123]
Ceftaroline	8	24	Renal function	TBW	-	-	Renal function was calculated with CG.	[47]
Cisplatin	165	23 ^b	-	-	BSA	BSA	-	[60]
Daptomycin	7	7	Renal function	TBW	-	-	LBW ₁₉₇₆ was tested. The renal function was calculated by the MDRD equation using IBW. Only female subjects were included.	[46]
Daptomycin	12	13	-	-	TBW	TBW	-	[61]
Daptomycin*	7	7	-	-	Not required	-	-	[68]
Dexmedetomidine	40		LBW ^{d(1)} , liver blood flow	LBW	-	-	LBW was measured by dual X-ray absorptiometry.	[32]
Dexmedetomidine	20	20	FFM, fat mass	FFM, intraoperative period	-	-	Sex was found to have an impact on PK.	[113]

To be continued

Docetaxel	92	21 ^b	-	-	BSA	BSA was calculated by LBW_{1976} . Sex was found to have an impact on PK	[60]
Doxorubicin	41	23 ^b	-	-	BSA	BSA was calculated by LBW_{1976} . Sex was found to have an impact on PK	[60]
Ertapenem	10	10	$TBW^{4(0.28)}$	BSA	-	-	[39]
Enoxaparin	32	64 ^b	$LBW^{4(1)}$	TBW	-	LBW_{1976} was tested. 26% of patients were female.	[30]
Folic acid	12	12 ^b	-	-	LBW	Only female subjects were included.	[58]
Glimepiride*	14	14	-	-	Not required	-	[64]
Gentamicin	1237	298	Renal function	LBW	-	Renal function was calculated by CKD-EPI	[22]
Gentamicin	8	20	$TBW^{4(0.73)}$	TBW	-	-	[40]
Gentamicin	542		Renal function, ICU status	TBW	-	Renal function was calculated by deindex CKD-EPI.	[49]
Irinotecan	102	25 ^b	-	-	BSA	LBW_{1976} was tested.	[60]
Linezolid	15	15 ^b	Arterial blood pressure	LBW	-	86.7% of patients were female.	[139]
Metformin	105		$LBW^{4(0.75)}$, age, Scr	LBW	-	-	[33]
Meropenem	11	29	Renal function	No size descriptor was identified	Not required if based solely on weight	Renal function was calculated by modified CG using IBW for non-obese and obese patients, and LBW for morbidly obese patients.	[50]
Meropenem*	15	15	-	-	Not required	-	[62]
Micafungin	8	16 ^b	$TBW^{4(0.74)}$	TBW	-	-	[41]
Morphine	20	20	-	-	Not required	-	[65]
Nadroparin	7	28	$TBW^{4(1)}$	LBW	-	-	[34]
Onarigiptin*	24	8 ^b	-	-	Not required	-	[63]

Troxacitabine	50	21 ^b	–	–	BSA	LBW ₁₉₇₆ was tested.	[60]
Vancomycin	8	20	TBW ^{d(0.54)}	TBW, age	–	–	[44]
Vancomycin	87	87 ^b	TBW ^{d(0.75)} , age, Scr	TBW	–	–	[36]
Ximelagatran*	12	12 ^b	–	–	Not required	–	[69]

CL, clearance; V_d , volume of distribution; TBW, total body weight; LBW, lean body weight calculated using the equation by James *et al.* in 1976 [143]; BSA, body surface area; FFM, fat-free mass; PNWT, predicted normal weight; Scr, serum creatinine; CKD-EPI, renal function calculated using the equation by the chronic kidney disease epidemiology collaboration; MIDRD, renal function calculated by modification of diet in renal disease; CG, renal function calculated by Cockcroft-Gault; Ref, reference.

– no predictors were explored in the non-compartment analysis or no remark.

^{a(i)} relationship between CL and TBW or LBW found to be linear ($i = 1$) or exponential with indicated exponent value (i).

^b no morbidly obese subjects were included.

^c the CYP2E1-mediated CL, sulphation CL, glucuronidation CL, and glucuronide elimination CL of paracetamol increased with LBW to the power of 0.67, 0.92, 1.33 and 0.89, respectively.

[#] LBW was calculated using the equation by Jannahasatian *et al.* in 2005 unless stated otherwise.

* studies did not evaluate the impact of LBW and other size descriptors on pharmacokinetics but compared PK of drugs in obese and non-obese.

2.3.2 V_d increases for lipophilic, but not for hydrophilic drugs

Background on the impact of lipophilicity on V_d

V_d is a PK parameter that represents the ratio of the amount of a drug and drug concentration. It drives peak concentrations, elimination half-life and time to the steady state [70]. Drug distribution in different tissues depends on the ability of drug molecules to cross biological membranes. This is dependent on several physicochemical properties (e.g., lipophilicity, molecular weight and degree of ionization), tissue perfusion and partitioning into the tissue, which relies on adiposity of the tissue as well as on binding to proteins and other constituents in blood and tissue. Disease states such as (morbid) obesity have been reported to induce low-grade inflammation which can impact capillary permeability and protein binding [71]. Obesity is associated with increased adipose and lean tissue volume, blood volume, blood flow, and cardiac output and with changed plasma constituents and decreased tissue perfusion, all of which may influence the V_d of a drug [70].

To study how V_d alters in obese patients, some early studies focused on its relation to the lipid solubility of drugs. In 1976, Gillis *et al.* [72] found that obesity has an impact on the distribution of lipophilic drugs of methohexital and thiopental in obese individuals. Abernethy *et al.* and Greenblatt *et al.* successively reported that the distribution volume of some lipophilic drugs such as midazolam and diazepam was increased in obese patients [73–76]. In the same period, Blouin *et al.* and Bauer *et al.* found that V_d only changed a little or remained unchanged in some hydrophilic drugs such as gentamicin and tobramycin [17, 77]. These early studies were all single-dose PK studies, and the V_d of the drug was calculated using the area method, commonly referred to as V_{area} , and sometimes parameterized as V_z or V_β in different studies. These results led to the intuitive hypothesis that drug lipophilicity is correlated with V_d in the obese, i.e., the V_d can be expected to increase for lipophilic, but not for hydrophilic drugs [78–81]. This assumption was deemed reasonable since obese individuals have increased adipose tissue into which lipophilic drugs are believed to more easily penetrate compared with hydrophilic drugs. However, Jain *et al.* [71] found that lipophilicity alone cannot predict the variability in V_d between drugs, because for some lipophilic drugs, the V_d (after normalization with TBW) in obese patients could be increased, unchanged or decreased compared to non-obese patients. Despite

this report, the assumption that lipophilicity is relevant for the impact of obesity on changes in V_d of a drug seems to prevail.

2

Literature results on the impact of lipophilicity on V_d

To evaluate the assumption on the impact of lipophilicity on V_d , we compared the V_d between obese and non-obese patients for drugs with different degrees of lipophilicity, quantified by the octanol/water partition coefficient ($\log P$). Drugs with a $\log P < 0.5$ have a higher affinity for the aqueous phase and are hydrophilic, whereas drugs with a $\log P \geq 0.5$ tend to dissolve better in lipids and are considered lipophilic.

The findings of the 65 studies that were reviewed for this topic are summarized in **Supplementary Table S2.2** and visualized as the ratio of V_d between obese and non-obese individuals *versus* drug lipophilicity in **Figure 2.4**. **Figure 2.4** shows that the V_d of several highly lipophilic drugs is indeed considerably higher in obese than non-obese individuals. However, this figure also shows that V_d is increased in obese individuals for most hydrophilic drugs, although not all findings reached statistical significance. Moreover, there are highly lipophilic drugs that have a ratio in volumes between obese and non-obese individuals comparable to the ratio of hydrophilic drugs or even lower. For the readers' interests, the same results are also presented by quantifying volumes per kilogram bodyweight, rather than absolute volume, in **Supplementary Table S2.2** and **Supplementary Figure S2.1**. This figure shows a similar pattern, in that the ratio in these volumes is in a similar range for most hydrophilic and lipophilic drugs, with only a few (highly) lipophilic drugs showing deviations toward an increased volume in obese patients of which even fewer findings reach statistical significance.

An explanation for the finding that not all lipophilic drugs show a (large) increase in volume in the obese is sought in the observation that some of these drugs show relatively high partitioning into other tissues that are not very different in volume between the obese and non-obese or in that they show relatively low partitioning into adipose tissue. Digoxin [82], procainamide [83], glyburide [84], prednisolone [128] and methylprednisolone [129] all show relatively low partitioning into adipose tissue. Instead, digoxin shows relatively high partitioning into skeletal muscle, while glyburide partitions into well-perfused tissues like heart, kidney, and liver. Plasma

protein binding may limit drug distribution into peripheral tissues, including adipose tissue [85], and since albumin expression is reportedly unaltered with obesity, this has been used as a potential explanation for the lack of difference in volume between obese and non-obese patients for the extensively bound drugs paclitaxel [62] and triazolam [86].

Cyclosporine [87] and propranolol [88], two highly lipophilic drugs, even showed to have a statistically significant lower distribution volume in the obese compared to non-obese individuals. For cyclosporine, the reason for this was suggested to be that cyclosporine is almost exclusively bound to lipoproteins and its distribution is primarily retained within the blood [87]. For propranolol, Cheymol *et al.* [88] attributed the reduced volume in morbidly obese to a less efficient diffusion into adipose tissue than into lean tissue due to decreased blood flow per unit weight of adipose tissue with obesity. Interestingly, in a later study, Cheymol *et al.* [89] found an unaltered V_d for the same drug in obese individuals compared with lean individuals, while Bowman *et al.* in a similar study design found a greatly increased V_d in obese individuals and hypothesize that propranolol was highly distributed into excess body weight [90]. Differences between findings in obesity and morbid obesity were also found for other drugs, including telavancin [67], daptomycin [51, 63, 68], and ceftaroline [52], which may be due to the greater physiological alteration in morbidly obese individuals compared to moderately obese individuals, not in the direction of the difference compared to non-obese individuals. Interestingly, for lidocaine [91] and paracetamol [92], sex was also found to have an impact on the V_d , with the V_d of males being higher than females. However, for paracetamol, other studies did not confirm this [36, 93].

A potential explanation for the general trend toward increased V_d in the obese for hydrophilic compounds is that patients with obesity have not only increased fat mass but also increased lean body mass and an enlarged blood volume [24]. Besides, even though adipose tissue contains predominately fat, it also contains approximately 40% of the amount of extracellular fluid to which drugs may distribute, compared to lean tissue [17, 94].

In summary, the impact of obesity on the V_d of a drug generally varies widely. Based on our literature review, it seems not justified to utilize one single factor such as lipophilicity to predict the direction and extent of changes in V_d . In general, there

seems a (small) increase in V_d for hydrophilic drugs, while for lipophilic drugs, there is high inter-drug variability. Besides lipophilicity itself, other drug properties, such as pKa and logD, affinity to adipose/non-adipose tissue and protein binding, and disease states such as (morbid) obesity, could also impact the V_d of a drug.

2.3.3 CYP3A-mediated clearance is reduced and UGT-mediated clearance is increased in the obese population

Background on the alteration of hepatic clearance of CYP3A and UGT substrates in obesity

Drug metabolism usually occurs in the liver and is classically recognized in two phases: in phase I, drugs are transformed into polar metabolites with CYP450 (predominantly CYP3A4) enzymes involved; in phase II, drugs are combined with endogenous substituent to form a more polar conjugate mainly under the help of UGT enzymes. Hepatic plasma CL is dependent on liver intrinsic clearance (CL_{int}) which is in its turn driven by enzyme activity and hepatic transporters, but also on hepatic blood flow (Q_h), unbound drug fraction in plasma (f_u), and to a small extent by blood-to-plasma ratio [24]. The hepatic extraction ratio of a drug, representing the efficiency of an organ to clear a drug from the circulating blood, is also of impact on hepatic plasma CL . For drugs with a low extraction ratio, the CL is mainly dependent on CL_{int} and f_u and changes in both these parameters may impact CL , while for drugs with a high extraction ratio, the CL is primarily dependent on Q_h and is less sensitive to changes in CL_{int} .

Pathophysiological changes, such as abnormal adipose deposition, including adipose infiltration in the liver, and low-grade inflammation have been shown to occur in obese patients [95, 96]. This could result in nonalcoholic fatty liver disease (NAFLD) ranging from simple liver steatosis to nonalcoholic steatohepatitis (NASH) with active hepatic inflammation [24, 97], which can alter the activity of metabolizing enzymes as well as liver blood flow and/or perfusion [98–100].

It has been suggested that the influence of obesity on drug metabolism may differ between metabolic pathways [97]. For CYP3A, suppressed enzyme activity related to obesity or NAFLD was reported in some animal studies and in *in vitro* studies with

human materials [101–103]. Moreover, decreased *CL* of CYP3A substrates was shown in obese patients and attributed to CYP3A suppression resulting from low-grade inflammation associated with obesity [97, 104, 105]. For UGT-mediated metabolism, increased *CL* of a number of UGT substrates was found in obese patients, which was attributed to an increased UGT enzyme capacity due to the increased liver size and the expression of UGT enzymes in visceral and subcutaneous adipose tissue [97, 106]. From these observations, the generalization was derived that *CL* of CYP3A substrates is reduced, while *CL* of UGT substrates is increased in the obese population, thereby also implying that dose adaptations may be required for drugs metabolized via these pathways [97, 104–106].

Literature results on the alteration of hepatic clearance of CYP3A and UGT substrates in obesity

To evaluate the general assumption regarding *CL* of CYP3A and UGT substrates in obesity, we compared the absolute *CL* between obese and non-obese subjects for drugs that are mainly (e.g., > 50%) metabolized by CYP3A4 or UGT enzymes. Summaries of 12 studies on 10 CYP3A4 substrates and 12 studies on eight UGT substrates are provided in **Tables 2.2** and **2.3**, respectively.

Table 2.2 shows that the absolute *CL* is significantly decreased in obese individuals for alfentanil [110], which supports the assumption that CYP3A *CL* is reduced in the obese. However, similar absolute *CL* values were found in obese individuals compared to non-obese individuals for alprazolam [86], cyclosporin [87], docetaxel [62], glyburide [84], and trazodone [75], five drugs that all have low (to intermediate) extraction ratio. Kvitne *et al.* [111] observed that patients with severe obesity and NAFLD indeed have a decreased hepatic CYP3A4 expression and activity. A potential explanation for similar absolute drug *CL* of these drugs in obese and non-obese subjects could be that in the obese patients in these studies the lower enzyme activity is compensated by a larger liver or liver flow.

An almost 50% higher systemic *CL* in obesity compared to lean controls was found for midazolam [111], a drug that is predominantly metabolized by CYP3A and has been used as a probe for *in vivo* CYP3A enzyme activity. Given that midazolam is a medium-to-high extraction ratio drug and its metabolism is mainly dependent on hepatic blood

Table 2.2 Cytochrome P450 (CYP) 3A-mediated absolute drug clearance in obese and non-obese subjects.

Drug	Subjects (n)		Parameter	Clearance (CL, L/h) [#]			Ref
	(Morbidly) Obese	Non-obese		CL _{obese}	CL _{non-obese}	Difference between obese versus non-obese	
Alfentanil	6	7	CL	10.74	19.26	↓	[110]
Alprazolam	12	12	CL	3.98	5.28	↔	[86]
Carbamazepine	17	13	CL/F	1.19	1.38	↔	[107]
Carbamazepine	6	6 ^a	CL/F	1.22	1.90	↓	[113]
Cyclosporin	10	35	CL	0.48	0.75	↔	[87]
Docetaxel	21	92	CL	40.0	36.80	↔	[62]
Glyburide	12	8	CL	3.26	3.10	↔	[84]
Midazolam	20	20	CL	28.32	31.80	↔	[76]
Midazolam	20	12	CL	21.54 ^b	21.54 ^b	↔	[112]
Midazolam	Mean BMI 44.5: 41		CL	23.00	17	↑	[108]
				27.00		↑	
	Mean BMI 42.0: 41		CL/F	102.00	194	↑	
Taranabant	385	187	CL/F	149.00		↑	
Taranabant	385	187	CL/F	22.60 ^b	33.12 ^b	↓	[112]
Trazodone	23	23	CL	8.76	8.16	↔	[75]
Triazolam	9	9	CL/F	20.40	31.87	↓	[86]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

[#] Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

^a The same patients after weight loss

^b Population pharmacokinetic study. The CL values for typical obese and non-obese individuals were given directly or calculated by changing the weight-related covariate values while keeping other covariates the same. The reported median value of the weight-related covariate of obese and non-obese patients was used for this calculation.

flow, the authors hypothesized that midazolam is only to a moderate extent sensitive to changes in enzyme activity, and that hepatic blood flow has a more significant role in determining the CL of midazolam. Brill *et al.* [112] and Greenblatt *et al.* [76] who found a similar systemic CL of midazolam in the obese compared to non-obese also hypothesized that the reduced CYP3A enzyme activity may be compensated for the increased liver blood flow or by the increased liver size [24, 112].

When apparent (oral) CL (CL/F) is studied, it should be remembered that bioavailability and systemic CL together determine CL/F . Kvitne *et al.* [111] and Brill *et al.* [112] both reported the CL/F of midazolam to be lower in morbidly obese patients compared to non-obese patients and an assessment of the bioavailability found that this was higher in obese compared to non-obese patients. Rather than reflecting differences in the systemic CL , the lower CL/F of midazolam in morbid obesity is therefore most likely explained by the increase in oral bioavailability, which may be the result

of increased paracellular absorption through the gut wall, and/or a decreased contact between drug and CYP3A enzymes in the gut wall due to increased splanchnic blood flow [70]. Similar arguments might also be used to explain the lower CL/F of carbamazepine [113], triazolam [86], and taranabant [114]. It is, however, uncertain whether the decreased CL/F can be entirely attributed to the effect of obesity on oral bioavailability based on the lack of information regarding systemic CL .

Table 2.3 Uridine diphosphate glucuronosyltransferase (UGT)-mediated absolute drug clearance in obese and non-obese subjects

Drug	Subjects (n)		Parameter	Clearance (CL , L/h) *			Ref
	(Morbidly) Obese	Non-obese		CL_{obese}	$CL_{non-obese}$	Difference between obese versus non-obese	
Dexmedetomidine	20	20	CL	$CL = (FEM/56.1)^{0.75} \times 1.09 \times EXP(-0.00548 \times FAT) \times 60$			[113]
Dexmedetomidine	8	8	CL	58.64	44.93	↑	[114]
Garenoxacin	196	384	CL/F	5.66 ^a	5.00 ^a	↑	[145]
Labetalol	9	9	CL	89.90	81.50	↔	[89]
Lorazepam	14	14	CL	6.12	3.78	↑	[146]
Morphine	20	20	CL	a slight decrease in the formation CL of M6G and a delay in the formation CL of M3G were found (both $p < 0.001$).			[65]
Oxazepam	11	11	CL	9.42	3.00	↑	[146]
Paracetamol	Male: 7	10	CL	29.04	19.38	↑	[92]
	Female: 14	11	CL	18.72	13.62	↑	
Paracetamol	20	8	CL	13.49 ^{ab}	9.67 ^{ab}	↑	[31]
Paracetamol	14	14	CL/F	38.70	21.50	↑	[93]
Propofol	17	17	CL	48.3 ^a	48.3 ^a	↔	[59]
Propofol	20	44	CL	211.01 ^a	145.51 ^a	↑	[43]
Propofol	51		CL	193.80 ^a	115.20 ^a	↑	[35]
Propofol			CL	600.00 ^a	246.6 ^a	↑	[56]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

* Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

^a The same patients after weight loss

^b Population pharmacokinetic study. The CL values for typical obese and non-obese individuals were given directly or calculated by changing the weight-related covariate values while keeping other covariates the same. The reported median value of the weight-related covariate of obese and non-obese patients was used for this calculation.

Table 2.3 shows that of eight UGT substrates, six were found to have significantly higher CL or CL/F in obese individuals, which could indeed be the result of an increase in UGT enzyme expression or activity in obese patients. Particularly for paracetamol, which is predominantly metabolized by UGT enzymes, the absolute CL (intravenous administration) of both paracetamol and its metabolites [36], and CL/F (oral administration) of paracetamol was found to be increased in obese patients compared to non-obese patients. However, for drugs with high extraction ratios such as mor-

phine [65], labetalol [89], and dexmedetomidine [124], total CL is less sensitive to alterations in enzyme expression or activity and CL is more dependent on hepatic blood flow [24]. For morphine, a drug predominantly metabolized by UGT2B7 to active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), a study showed that besides a slight decrease in the formation of M6G, the formation of M3G was similar between morbidly obese and non-obese subjects, although the formation appeared to be delayed [65]. According to these authors, the lack of increased formation of these glucuronides relates to altered hepatic and bile transporters related to obesity. For dexmedetomidine, a study that included subjects with no liver disease or abnormal laboratory data found increased CL in obese individuals compared to non-obese individuals and the authors contributed the increased CL to an increased hepatic blood flow [130]. In another study of dexmedetomidine, despite a slightly negative relation between fat mass and CL , the value of CL increased in obese patients compared to non-obese patients when taking the total body weight into account [124].

In summary, total CL in obese individuals was reported to be suppressed in one, unaltered in five, and increased in one CYP3A substrates, and CL/F in obese individuals was reported to be decreased in four CYP3A substrates. UGT-mediated total CL and CL/F are reported to be increased in six drugs and unaltered in two out of eight drugs in obese individuals. Hepatic plasma CL is not equal to CL_{int} and is dependent on drug extraction ratios, influenced not only by the changes in activity or abundance of hepatic enzymes resulting from obesity-related changes but also by changes in plasma protein binding and hepatic blood flow, and by hepatic drug transporters. For some drugs, the latter factors can partially or completely compensate for the obesity-related differences in enzyme activity, which may result in an unaltered total CL and no dose adaptation.

2.3.4 GFR is enhanced in obese patients necessitating higher doses for renal cleared drugs

Background on GFR changes in obesity

2 Renal *CL* represents the net excretion of a drug into the urine, by glomerular filtration and active tubular secretion, and by active tubular reabsorption that may cause the reuptake of excreted drugs from the pre-urine back into the blood, although some metabolism may also occur in the kidneys. Renal *CL* of unbound drug that is neither actively secreted nor reabsorbed by the tubules, is assumed to be equal to the GFR [115]. In the clinic, GFR is either measured (mGFR) involving exogenous (e.g., inulin, iothexol, and iothalamate) filtration markers [116], or estimated (eGFR) for which various functions are available [116] based on serum creatinine or urea and individual characteristics such as race, age, sex, or body weight [24]. Of these equations, Cockcroft-gault provides absolute eGFR values while the others provide BSA-normalized eGFR, with the validity of most of the equations not being confirmed in the obese. Equations specifically aimed at predicting creatinine *CL* in obese patients, such as the Salazar-Corcoran equation, are proposed, but have hitherto not yet been widely used [117]. Conflicting results on the influence of obesity on kidney function have been reported. Some studies showed that *CL* mediated by glomerular filtration was increased, possibly as a result of an enhancement in the number or efficiency of functional nephrons in obesity and/or an increase in renal blood flow as a consequence of the increased cardiac output [17, 77, 94, 118]. Additionally, a systematic review summarizing clinical studies that investigated drugs primarily excreted by the kidney concluded that obese individuals have enhanced renal *CL* [97]. From these observations, it is hypothesized that GFR is increased in obese patients, necessitating higher doses for renal cleared drugs in these patients.

Literature results on GFR changes in obesity

To evaluate the GFR in obesity, 19 studies that directly compared the *CL* between obese and non-obese subjects for 13 drugs that are mainly (e.g., >50%) eliminated through glomerular filtration are evaluated and provided in **Table 2.4**. In line with the assumption, reports on five drugs (i.e., amikacin [17], gentamicin [17, 45, 53], vancomycin [49, 77, 94], enoxaparin [119] and fosfomycin [120]), accounting for 38.5% of the included drugs, show significantly increased *CL* in obese individuals. In the sixth example on ceftaroline, *CL* was not significantly altered in obese patients compared

Table 2.4 Glomerular filtration-mediated drug clearance in obese and non-obese subjects.

Drug	Subjects (n)		Clearance (CL, L/h) [#]			Ref
	(Morbidly) Obese	Non-obese	CL _{obese}	CL _{non-obese}	Difference between obese versus non-obese	
Amikacin	8	8	9.40	5.90	↑	[17]
Carboplatin	14	64	6.48	5.88	↔	[62]
Ceftaroline	BMI 30–35: 8		13.20		↔	
	BMI 35–40: 8	8	14.20	12.00	↔	[52]
	BMI ≥ 40: 8		16.20		↑	
Cefazolin	8	7	22.26 ^a	22.26 ^a	↔	[123]
Cefazolin	15	15	5.14	4.63	↔	[122]
Dalteparin	10	10	1.30	1.11	↔	[132]
Daptomycin	BMI 30–40: 6	6	0.50	0.42	↔	[63]
	BMI ≥ 40: 6	6	0.50	0.37	↔	
Daptomycin	7	7	0.50	0.59	↔	[68]
Enoxaparin	21	21	0.99	0.74	↑	[119]
Fluconazole	10	11	0.95	0.95	↔	[121]
Fosfomycin	13	14	6.99	5.55	↑	[120]
Gentamicin	12	12	8.15	5.75	↑	[17]
Gentamicin	20	8	9.27 ^a	5.51 ^a	↑	[45]
Gentamicin	542		–	–	↑	[53]
Meropenem	BMI 30–40: 9		9.10		↔	
	BMI ≥ 40: 20	11	10.00	8.40	↔	[54]
Meropenem	15	15	12.50	11.10	↔	[64]
Tobramycin	10	10	9.73	6.08	↑	[17]
Tobramycin	20	8	6.33 ^a	6.33 ^a	↔	[57]
Vancomycin	6	4	11.25	4.85	↑	[77]
Vancomycin	20	8	8.26 ^a	5.70 ^a	↑	[49]
Vancomycin	24	24	11.82	4.62	↑	[94]

↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.

[#] Total clearance unless stated otherwise. Units not reported as L/h are converted to L/h. The value was reported as the mean value.

^a Population pharmacokinetic study. The CL values for typical obese and non-obese individuals were given directly or calculated by changing the weight-related covariate values while keeping other covariates the same. The reported median value of the weight-related covariate of obese and non-obese patients was used for this calculation.

BMI, body mass index; Ref, reference

with non-obese subjects, but *CL* was higher in morbidly obese subjects compared with non-obese and obese subjects [52]. Interestingly, for tobramycin, an aminoglycoside similar to gentamicin, findings in an early study showed *CL* to be increased in the obese, which is in line with findings for gentamicin [17]. A more recent study identified estimated GFR expressed as deindexed MDRD (i.e., not normalized based on BSA) as predictor for *CL* of tobramycin, which indirectly shows a relation with body weight [57]. The authors of the latter publication explained that gentamicin may be more dependent on organic cation transporter (OCT)2-mediated renal uptake than tobramycin, which leads to a more pronounced increase in *CL* in obese individuals for gentamicin compared to tobramycin.

In addition to the studies above reporting increased GFR-mediated drug *CL* in the obese, six other drugs that are predominantly eliminated by GFR, showed unaltered *CL* in obese subjects compared to non-obese subjects [54, 63, 64, 68, 121 – 123, 131, 132]. As obesity was not found to impact renal *CL* for these drugs, dose adjustments based on obesity alone seem unwarranted. *CL* of fluconazole [121], dalteparin [132], cefazolin [122], and daptomycin [63, 68] in obese individuals might be unaltered, because subjects in these studies all had a comparable renal function, as assessed based on eGFR. For one study of meropenem [54], the eGFR of morbidly obese patients was significantly higher than obese or non-obese patients, and eGFR was implemented as the only covariate to describe inter-individual differences in *CL*. Given that the eGFR is a composite parameter derived not only from body weight, this suggests that obesity may only indirectly impact *CL*. Besides, obesity is an important risk factor for the development of chronic kidney disease. It was suggested that with increasing duration of obesity, the renal function might decrease, which could compensate for the observed increase in GFR in obese individuals, leading to an unaltered or even decreased *CL* eventually [24].

In summary, we found that GFR-mediated *CL* is enhanced in six drugs and unaltered in six other drugs in obese individuals, indicating renal *CL* in obese individuals does not necessarily increase for all renally cleared drugs. Transporter-mediated renal uptake and long-term kidney disease might also influence *CL* in patients with obesity.

2.3.5 Drug dosing information from obese adults can be predictive for obese adolescents

Background of extrapolating dosing information from obese adults to obese adolescents

2

Similarly to adults, the prevalence of obesity in adolescents is quickly growing. However, PK and dosing information in this population are even more scarce due to the paucity of clinical trials involving obese adolescents [133]. This hampers the determination of the optimal dose of drugs that are prescribed to obese adolescents, which is especially important for a drug with a narrow therapeutic window and a high risk of toxicity [134].

In the absence of PK and dosing information in obese adolescents, some review articles have suggested that functions based on size descriptors used for the prediction of clearance or dose adjustments in obese adults, can be extrapolated to obese adolescents, implicitly assuming that maturation in adolescents is complete [134–137]. However, dosing recommendations for obese pediatrics are proposed based on studies in obese adults and have not been further investigated in an obese pediatric population yet.

Literature results on extrapolating dosing information from obese adults to obese adolescents

To investigate whether drug-dosing information from obese adults can be extrapolated to obese adolescents, we searched studies on comparisons of PK between obese adults and obese adolescents and summarized the results in **Table 2.5**. Five studies for three drugs met our inclusion criteria. Of these studies, only one study on busulfan showed comparable PK values in obese adults and adolescents with the same TBW, which was indicated by the obtained covariate relationship describing trends in inter-individual variability for the entire population being based on TBW only, without additional age descriptors [138, 139].

Studies on propofol and midazolam showed that in addition to TBW, other covariates are necessary to describe inter-individual variability in PK parameters, particularly *CL*. These additional covariates include either age or other descriptors that quan-

Table 2.5 Pharmacokinetic parameters in obese adolescents and obese adults.

Drugs	Age range (yrs)	Total body weight range (kg)	Subjects (n)		Final covariate relationships	PK parameters calculated for obese adults and adolescents of the same TBW	Ref
			Adolescents	Adults			
Propofol	9.0~79.0	37~184	34	60	$CL = 2.34 \times (TBW/70)^{0.77} \times F_{age}$ age $\leq$ 41 yrs: $F_{age} = 1 + 0.0103 \times (age - 41)$ age $>$ 41 yrs: $F_{age} = 1 - 0.00539 \times (age - 41)$ $V_c = 3.17$ L	$CL_{adolescents, TBW 70 \text{ kg}} < CL_{adults 19-79 \text{ yrs, TBW 70 kg}}$	[140]
					$V_c = 3.17$ L	$V_{c, adolescents} = V_{c, adults}$	
Propofol	2.0~88.0	12~100	270		$CL = 1.44 \times (TBW/70)^{0.75}$, if age $\leq$ 60 $CL = 1.44 \times (TBW/70)^{0.75} \times (age - 60) \times 0.045$, if age $>$ 60 $V_c = 9.3 \times (TBW/70)^{0.71} \times (age/30)^{-0.39} \times F$, (if bolus, F is 2.61 otherwise 1)	$CL_{adolescents, TBW 70 \text{ kg}} = CL_{adults 60 \text{ yrs, TBW 70 kg}}$ $CL_{adolescents, TBW 70 \text{ kg}} > CL_{adults 60 \text{ yrs, TBW 70 kg}}$	[141]
					$CL - 3.32 \times (TBW/15.3)^{-0.226}$ $V_c = 10.6 \times (TBW/15.3)^{0.89}$	$V_{c, adolescents, TBW 70 \text{ kg}} > V_{c, adults 19 \text{ yrs, TBW 70 kg}}$	
Busulfan	0.1~26 0.1~35.0	3.1~109 3.5~86	245 158		$CL_{obese adolescents} = 0.71 \times (TBW/104.7)^{1.2}$ $V_c = 0.45 \times (W_{T_{for age and length}}/70)^{0.75} + (0.007 \times W_{T_{excess}})$	$CL_{adolescents, TBW 15.3 \text{ kg}} = CL_{adults, TBW 15.3 \text{ kg}}$ $V_{c, adolescents, TBW 15.3 \text{ kg}} = V_{c, adults, TBW 15.3 \text{ kg}}$	[138] [139]
					$CL_{morbidly obese adults} = 0.44$ L/min	$CL_{adolescents, TBW 104.7 \text{ kg}} = CL_{adults, TBW 104.7 \text{ kg}}$ $V_{c, adolescents} = V_{c, adult}$ $V_c = 55.2$ L	[142]

PK, pharmacokinetics; CL, clearance; V_c , central volume of distribution; TBW, total body weight; $W_{T_{for age and length}}$, $W_{T_{excess}}$, excess body weight; Ref, reference; yrs, years.

tify the difference in the TBW of an individual and their appropriate developmental weight based on their age, length, and sex. As a result, the PK parameters in obese adults differ from those in obese adolescents of the same TBW, suggesting that for these drugs covariate functions or dosing guidelines based on size descriptors in obese adults cannot be directly extrapolated to obese adolescents. For propofol, *CL* was found to increase until the age of 41 and decrease thereafter, with *CL*, however, being lower in adolescents compared to the adults of the same TBW [140]. In another study of propofol, age was also found to impact the *CL* in obese patients, however only when it was higher than 60 years [141]. This would indicate that the bodyweight-based covariate relationship for *CL* obtained in young adults can be extrapolated to adolescents, yielding the same *CL* for individuals of the same TBW, but that the *CL* of the elderly is lower than that in adolescents of the same TBW. The authors of both publications seek the explanation of these findings in the fact that propofol is a drug with a high extraction ratio for which hepatic blood flow is the main rate-limiting factor for hepatic metabolism. In the elderly, hepatic blood flow decreases with age, it is hypothesized that in younger adults hepatic blood flow increases with the duration of obesity, with older obese adults generally being obese for a longer time than younger obese adults or obese adolescents [140].

For midazolam, the opposite was found in that *CL* was higher in obese adolescents than in morbidly obese adults. To distinguish between the influence of growth-related and obesity-related weight changes in *CL* in obese adolescents, the authors proposed a novel approach based on so-called “excess weight” which quantifies the difference in the TBW of an individual and their appropriate developmental weight based on their age, length, and sex. With this, it was found that the *CL* of midazolam in obese adolescents increases mainly with obesity-related weight changes, which may be due to the increased liver blood flow in obesity. However, in adults, this increase in *CL* is not apparent anymore, possibly due to prolonged and/or more extensive obesity-induced suppression of CYP3A activity [142].

In this context, studies on the PK of a drug in obese adolescents for which the results were compared to findings in obese adults from the literature, are worth mentioning. A study of metformin showed that the oral *CL* in obese adolescents is comparable to adults, indicating adult dosages of metformin could be extrapolated to obese adoles-

cents, particularly when pediatric dosages are ineffective [143]. Alternatively, the CL of fentanyl was found to be increased in obese adolescents compared to obese and non-obese adults, implying dose information of adults cannot simply be extrapolated to obese adolescents for this drug [144].

V_d values are comparable in obese adults and adolescents with the same TBW in studies shown in **Table 2.5**, with one study on propofol as an exception. This study found age as a descriptor in addition to TBW to describe trends in inter-individual variability [141]. The slightly decreased central V_d of propofol in elderly patients reported in this study could result from a reduction in the volume of highly perfused tissues relative to body mass or reduced perfusion of these tissues due to the lower cardiac output in the elderly [141]. However, the author also mentioned that this study only had few data around the peak concentration and the samples were mainly from bolus administration, which may lead to model misspecification.

In summary, the number of studies involving both obese adults and obese adolescents is very limited. Overall, very few studies found comparable PK between obese adults and obese adolescents, other studies found both higher and lower CL for adults and adolescents with the same TBW. This suggests that based on the currently available information it cannot be known *a priori* whether covariate relationships for obese adults can be extrapolated to obese adolescents. Ideally, studies performed with adolescents and adults simultaneously with a wide range of body weight in both groups are required.

2.4 Conclusion

To summarize, the available evidence that we found and reported in this review often challenges the common assumptions. It is not justified to *a priori* select LBW as a size descriptor for inter-individual variability in PK in the obese population, in fact, no body size descriptor always outperforms the others. When sex in addition to body weight is found to impact PK, LBW could be considered as a potential size descriptor for PK. Other size descriptors, such as TBW in a non-linear function, have shown on multiple occasions to be superior predictors for drug CL compared to LBW. The impact of obesity on the V_d of drugs varies widely and lipophilicity by itself seems

insufficient to predict the direction and extent of changes in V_d . Other properties, such as pKa and logD, affinity to adipose or non-adipose tissue, protein binding, and disease states, could also impact the V_d of a drug. For hepatic CL , it should be noted that plasma CL is not the same as intrinsic liver CL and that it is not only influenced by changes in activity or abundance of hepatic enzymes but also by changes in plasma protein binding and hepatic blood flow, depending on extraction ratio and transporters. This complicates between drug extrapolation of findings on CL or the translation from *in vitro* findings on enzyme activity to *in vivo* CL . Renal CL does also not necessarily increase for all renally cleared drugs in obese individuals. Although GFR may be increased, kidney disease and changes in transporter-mediated secretion and reabsorption, cause renal CL and required doses to not always be increased. Finally, information from obese adults on CL and dose adjustments cannot always be extrapolated to obese adolescents, possibly due to differences in duration of obesity and time needed for physiological changes to manifest as alterations in PK parameters.

2.5 Expert opinion

It remains challenging to *a priori* predict PK parameters or required dose adjustments for obese individuals. This is due to the many physiological changes that occur with obesity over different time-courses and the complex interaction between all these changes and the varying properties of drugs. Unfortunately, pharmaceutical companies are hesitant to include different dosing guidelines for special patient populations, particularly for obese patients. Our review of available literature however suggests that studies in the obese population should be performed to make accurate PK predictions and inform dosing in these patients. This may require regulatory authorities to stimulate the pharmaceutical industry to include the patients in their studies and to avoid convenient but overly generalized rules-of-thumb to pass without clinical scrutiny. To achieve this, dedicated clinical studies should be performed for all drugs of interest in obese adolescents and adults. In these studies, the duration and severity of obesity are important variables to investigate, as evidence suggests that the time-course and extent of pathophysiological alterations may impact drug PK, but insights into these mechanisms are currently insufficient. After evaluating the current evi-

dence, it can be concluded that obese adolescents cannot always be considered small obese adults. More well-designed clinical studies, including both adults and adolescents with a wide range of body weights, are needed to evaluate the PK changes in obese adolescents compared to adults and investigate possibilities for extrapolation of findings from obese adults to adolescents. Furthermore, studies on drug disposition after both oral and intravenous administration in obese and non-obese subjects are scarcely performed, which results in an inability to characterize the impact of obesity on oral bioavailability. Upon extravascular dosing, bioavailability is one of the most important drivers of required dose adjustments and should therefore be considered more seriously. Thirdly, PK changes associated with (extreme) weight loss upon various interventions in obese patients, are a trending topic, as it is not clear how and to what extent a history of obesity impacts drug PK. Therefore, obtaining information on PK changes in patients who are losing weight upon various interventions, is of relevance. Finally, PD studies were kept outside of the scope of this paper. This is in part because PD analyses rely on PK as input, but also because the number of PD studies in the obese population is very limited. It should, however, not be forgotten that both PK and PD drive drug effects, therefore studies on both are essential to determine optimal dosing. There is therefore a need for more PD studies in the obese population and for the validation of PD endpoints for the obese populations in situations where PD endpoints in “standard” adults do not suffice for this population.

Population modeling, also known as non-linear mixed effects modeling, is the preferred method to analyze the pharmacological data from clinical studies, because it can handle sparse and/or unbalanced data and because it will quantify both general trends as well as inter-individual variability in PK and/or PD. With this modeling approach, data from small-scale clinical studies could serve as a basis to inform a structural model, while this could be augmented with additional data from routine clinical practice, to increase the power to quantify variability and detect covariate relationships. In these analyses, it is important to apply a data-driven approach that does not include preconceived ideas, but that considers multiple size descriptors in combination with other patient and treatment characteristics in different linear and non-linear functions. The number of resources to cover all drugs and all obese subpopulations with this approach would, however, be unrealistically large.

To be able to better predict obesity-related alterations in PK and required dose adjustments, physiologically based PK (PBPK) principles could be applied, based on the physiological changes in obesity and drug properties. This, however, requires trained personnel and the retrieval of a large amount of quantitative and longitudinal information on both physiological changes and drug properties, some of which may not even be known. Instead of applying a full PBPK-approach to make predictions for individual drugs, PBPK models can also be used to systematically evaluate the accuracy of simplified approaches and define in general terms scenarios based on patient characteristics and drug properties for which certain assumptions or generalizations can or cannot be expected to be accurate. An approach for this has been developed by Calvier *et al.* [13, 15, 145] for the pediatric population and can be extended to other special patient populations, including the obese.

With the epidemic of obesity, the challenge of drug dosing in (morbidly) obese adults and adolescents keeps increasing. Nevertheless, we are only just beginning to understand the complexity of the influence of obesity on drug PK with many factors such as (patho)physiological changes, drug properties and longitudinal changes all interfering with each other. More research with novel approaches such as population modeling and PBPK modeling should be employed to further increase our understanding of drug PK in obesity.

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Supplementary Material

Table S2.1 Equations used to calculate different bodyweight descriptors.

Body size descriptor	Equation	Reference
TBW (kg)	–	
BMI (kg/m ²)	TBW/HT^2	[1]
BSA (m ²)	$\sqrt{TBW \times HT/3600}$	[2]
IBW (kg)	Male: $49.9 + 0.89 \times (HT - 152.4)$ Female: $45.5 + 0.89 \times (HT - 152.4)$	[3]
ABW (kg)	$IBW + F \times (TBW - IBW)$ <i>F</i> is drug specific correction factor (genrally 0.3-0.6)	[4]
PNWT (kg)	Male: $1.57 \times ABW - 0.0183 \times BMI \times ABW - 10.5$ Female: $1.75 \times ABW - 0.0242 \times BMI \times ABW - 12.6$	[5]
LBW ₁₉₇₆ (kg)	Male: $(1.10 \times TBW) - 0.0128 \times TBW \times BMI$ Female: $(1.07 \times TBW) - 0.0148 \times TBW \times BMI$	[6]
LBW ₂₀₀₅ (kg)	Male: $(9.27 \times 10^3 \times TBW)/(6.68 \times 10^3 + 216 \times BMI)$ Female: $(9.27 \times 10^3 \times TBW)/(8.78 \times 10^3 + 244 \times BMI)$	[7]
FFM (kg)	Male: $0.285 \times TBW + 12.1 \times HT^2$ Female: $0.287 \times TBW + 9.74 \times HT^2$	[8]

TBW, total body weight; BMI, body mass index; HT, height; BSA, body surface area; ABW, adjusted body weight; PNWT, predicted normal weight; LBW₁₉₇₆, lean body weight calculated using the James equation proposed in 1976; LBW₂₀₀₅, lean body weight calculated using the Janmahasatian equation proposed in 2005, FFM, fat free mass.

Table S2.2 Overview of included subjects and reported values of the volume of distribution (V_d) and weight-normalized volume of distribution between obese and non-obese subjects, from studies comparing both populations.

Drugs	logP	Subject (n)		Reported volume parameter (V, [L])			Weight normalized volume parameter (V_bw, [L/kg])				Ref
		Obese	Non-obese	Studied volume parameter	V_ob	V_nw	Difference in obese compared to nonobese individuals	V_bw_ob	V_bw_nw	Difference in obese compared to non-obese individuals	
Acyclovir	-1.76	7	7	V _d	31.80	25.90	↔	NA	NA	NA	[9]
Alprazolam	2.12	12	12	V _d	113.50	73.10	↑	1.06	1.16	↔	[10]
Amikacin	-7.40	8	8	V _d	26.81	18.61	↑	0.18	0.26	↓	[4]
Antipyrine	0.38	23	25	V _d	44.90	39.70	↔	0.46	0.63	↓	[11]
Atenolol	0.57	25	18	V _d	43.60	47.60	↔	0.40	0.70	↔	[12]
Atracurium	1.04	9	9	V _{ss}	8.60	8.50	↔	0.07	0.14	↓	[13]
Bisoprolol	2.20	8	8	V _d	182.00	135.00	↑	2.00	2.70	↓	[14]
Caffeine_1	-0.07	16	23	V _d	69.90	43.60	↑	0.65	0.69	↔	[15]
Caffeine_2	-0.07	20	14	V _d	48.30	40.10	↔	0.44	0.59	↓	[16]
Carbamazepine	2.77	17	13	V _d	98.40	60.70	↑	NA	NA	NA	[16]
Carboplatin	0.14	14	64	V _{ss}	17.50	15.50	↔	NA	NA	NA	[17]
Cefazolin	-0.40	14	15	V _{ss}	19.40	14.20	↑	NA	NA	NA	[18]
		BMI 30-35: 8		V _d	42.9		↔	0.42		↔	
Ceftaroline	-0.79	BMI 35-40: 8	8	V _d	45.3	36.4	↔	0.40	0.49	↔	[19]
		BMI ≥ 40: 5		V _d	56.9		↔	0.39		↔	
Cefoxitin	0.22	14	11	V _{ss}	18.00	12.00	↑	0.14	0.19	↓	[20]

To be continued

Cimetidine	0.40	6	6	V_{ss}	82.00	84.00	$\leftrightarrow$	NA	NA	NA	[21]
Ciprofloxacin_1	0.28	23	23	V_{ss}	144.26	150.71	$\leftrightarrow$	NA	NA	NA	[22]
Ciprofloxacin_2	0.28	17	22	V_{ss}	269.17	219.03	$\uparrow$	2.46	3.06	$\downarrow$	[23]
Cisplatin	-2.19	23	165	V_{ss}	58.90	50.20	$\uparrow$	NA	NA	NA	[17]
Cyclosporine	2.92	10	35	V_{ss}	230.00	295.00	$\downarrow$	2.55	4.54	$\downarrow$	[24]
Daptomycin_1	-4.07	BMI 30-40: 6 BMI $\geq$ 40: 6	6	V_{ss}	7.90	6.35	$\uparrow$	0.09	0.11	$\leftrightarrow$	[25]
Daptomycin_2	-4.07	7	7	V_d	10.68	6.74	$\uparrow$	0.08	0.10	$\downarrow$	[26]
Daptomycin_3	-4.07	7	7	V_{ss}	10.04	7.69	$\leftrightarrow$	0.09	0.13	$\downarrow$	[27]
Desmethyl/diazepam	2.79	12	12	V_d	9.44	8.46	$\leftrightarrow$	NA	NA	NA	[28]
Dexfenfluramine	3.30	10	10	V_{ss}	159.00	63.00	$\uparrow$	1.52	0.94	$\uparrow$	[29]
Dexmedetomidine	2.80	20	20	V_d	969.70	668.70	$\uparrow$	10.20	11.30	$\leftrightarrow$	[30]
Diazepam_1	2.82	17	17	V_d	310.36	163.75	$\uparrow$	2.48	2.38	$\leftrightarrow$	[31]
Diazepam_2	2.82	6	5	V_d	291.90	90.70	$\uparrow$	2.81	1.53	$\uparrow$	[32]
Digoxin	2.37	16	13	V_d	228.00	70.00	$\uparrow$	NA	NA	NA	[33]
Docetaxel	2.40	21	92	V_{ss}	981.00	937.00	$\leftrightarrow$	10.70	14.30	$\downarrow$	[17]
Doxorubicin	1.27	23	41	V_{ss}	978.00	531.00	$\uparrow$	NA	NA	NA	[17]
Enoxaparin	-1.70	21	21	V_{ss}	14.50	14.00	$\leftrightarrow$	NA	NA	NA	[34]
Ertapenem	0.30	20	20	V_d	5.77	4.37	$\uparrow$	0.06	0.07	$\downarrow$	[35]
Folic acid	-0.04	12	12	V_d	7.18	5.15	$\uparrow$	0.06	0.08	$\downarrow$	[36]
Fosfomycin	-1.60	13	14	V_{ss}	18.90	17.40	$\leftrightarrow$	NA	NA	NA	[37]
Gentamicin_1	-3.10	30	30	V_d	24.40	19.00	$\uparrow$	NA	NA	NA	[38]
Gentamicin_2	-3.10	6	6	V_d	13.30	10.00	$\uparrow$	0.15	0.19	$\downarrow$	[39]
Gentamicin_3	-3.10	12	12	V_d	19.20	13.36	$\uparrow$	0.19	0.24	$\downarrow$	[4]
Glyburide	3.75	12	8	V_d	23.31	17.01	$\uparrow$	0.17	0.25	$\downarrow$	[40]
					47.00	56.80	$\leftrightarrow$	NA	NA	NA	

Ibuprofen	3.97	11	11	V_d	14.90	10.80	↑	0.14	0.18	↓	[41]
Irinotecan	3.20	25	102	V_{ss}	130.00	122.00	↔	NA	NA	NA	[17]
Labetalol	1.73	9	9	V_{ss}	367.90	278.60	↑	3.80	4.80	↔	[42]
Levonorgestrel	3.80	BMI 30-40:11 BMI ≥ 40: 5	10	V_{ss}	404.70	162.20	↑	NA	NA	NA	[43]
Lidocaine_male	2.44	13	19	V_d	325.00	186.00	↑	2.67	2.71	↔	[44]
Lidocaine_female	2.44	11	12	V_d	264.00	209.00	↑	2.88	3.57	↔	[44]
Lithium	-0.54	10	10	V_{ss}	NA	NA	NA	0.42	0.66	↓	[45]
Lorazepam	2.39	14	14	V_d	131.00	77.00	↑	1.25	1.23	↔	[46]
Melagatran	-0.51	12	12	V_d/F	221.00	185.00	↔	1.98	2.53	↔	[47]
Meropenem	-0.60	29	11	V_{ss}	29.70	33.70	↔	0.31	0.47	↓	[48]
Methylprednisolone	1.53	6	6	V_{ss}	104.00	122.00	↔	0.90	1.50	↓	[49]
Metronidazole	-0.15	14	15	V_{ss}	73.90	51.80	↑	NA	NA	NA	[18]
Midazolam	3.76	20	20	V_d	311.00	114.00	↑	2.66	1.74	↔	[50]
Nebivolol	4.03	9	9	V_{ss}	898.00	673.00	↑	9.40	11.20	↔	[42]
Nitrazepam	2.25	14	14	V_d	290.00	137.00	↑	2.62	2.22	↔	[51]
Oseltamivir	1.00	10	10	V_d/F	2320.00	1670.00	↔	20.70	26.70	↔	[52]
Oxazepam	2.24	11	11	V_d	97.00	38.00	↑	0.84	0.62	↔	[46]
Paclitaxel	3.00	14	58	V_{ss}	6298.00	4295.00	↔	NA	NA	NA	[17]
Paracetamol_1_male	0.91	7	10	V_d	108.50	77.00	↑	0.81	1.09	↓	[53]
Paracetamol_1_female	0.91	14	11	V_d	61.40	51.60	↔	0.71	0.95	↓	[53]
Paracetamol_2	0.91	38	14	V_d	90.80	62.30	↑	0.81	0.96	↔	[54]
Piperacillin	0.50	16	11	V_d	32.50	24.50	↑	0.24	0.35	↓	[55]
Phenytoin	2.47	14	10	V_d	82.20	40.20	↑	0.68	0.61	↔	[56]

To be continued

Prednisolone	1.62	8	4	V_d	44.10	36.70	$\leftrightarrow$	0.35	0.50	$\downarrow$	[57]
Procainamide	0.88	7	7	V_{ss}	158.00	150.00	$\leftrightarrow$	1.64	2.22	$\downarrow$	[58]
Propranolol_1	3.48	6	6	V_d	339.00	198.00	$\uparrow$	2.6	3.0	$\downarrow$	[59]
Propranolol_2	3.48	12	12	V_d	208.90	318.60	$\downarrow$	1.90	4.80	$\downarrow$	[60]
Propranolol_3	3.48	9	9	V_d	226.80	180.00	$\leftrightarrow$	2.40	3.1	$\leftrightarrow$	[42]
Ranitidine	0.27	10	10	V_{ss}	83.30	79.50	$\leftrightarrow$	0.80	1.50	$\downarrow$	[61]
Salicylate	1.09	20	20	V_d	15.50	13.00	$\uparrow$	0.14	0.19	$\downarrow$	[62]
Sufentanil	3.95	8	8	V_d	547.00	346.00	$\uparrow$	5.82	4.82	$\leftrightarrow$	[63]
Tazobactam	-1.40	15	10	V_d	51.20	24.90	$\uparrow$	0.29	0.23	$\leftrightarrow$	[55]
Tedizolid	0.95	9	9	V_d	101.00	88.20	$\leftrightarrow$	NA	NA	NA	[64]
		BMI 30-35:8		V_{ss}	13.04		$\leftrightarrow$				
Telavancin	-6.20	BMI 35-40:8	8	V_{ss}	15.06	11.71	$\uparrow$	NA	NA	NA	[65]
		BMI ≥ 40 :8		V_{ss}	16.24		$\uparrow$				
Theophylline	-0.02	14	57	V_d	0.38	0.08	NA	NA	NA	NA	[66]
Thiopental	2.90	7	8	V_{ss}	NA	NA	NA	4.70	1.40	$\uparrow$	[67]
Tobramycin_1	-5.80	7	7	V_d	19.21	17.00	$\uparrow$	0.23	0.30	$\downarrow$	[39]
Tobramycin_2	-5.80	10	10	V_d	29.01	18.31	$\uparrow$	0.19	0.26	$\downarrow$	[4]
Topotecan	0.80	21	108	V_{ss}	28.60	30.00	$\leftrightarrow$	NA	NA	NA	[17]
Trazodone	2.68	23	23	V_d	162.00	67.00	$\uparrow$	1.40	1.00	$\uparrow$	[68]
Triazolam	2.42	9	9	V_d	116.70	115.50	$\leftrightarrow$	NA	NA	NA	[10]
Troxacitabine	-1.70	21	50	V_{ss}	124.00	115.00	$\leftrightarrow$	NA	NA	NA	[17]
Vancomycin_1	-3.10	6	4	V_{ss}	43.00	28.90	$\uparrow$	0.26	0.39	$\downarrow$	[69]
Vancomycin_2	-3.10	24	24	V_d	52.00	46.00	$\leftrightarrow$	0.32	0.68	$\downarrow$	[70]
Vancomycin_3	-3.10	704		V_d	51.60	44.40	$\uparrow$	0.56	0.64	$\downarrow$	[71]
Vecuronium	0.89	7	7	V_d	44.70	59.00	$\leftrightarrow$	0.47	0.99	$\downarrow$	[72]

Verapamil	3.79	12	11	V_{ss}	713.00	301.00	↑	NA	NA	NA	[73]
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↔ = no significant difference between obese and non-obese patients (p value ≥ 0.05); ↓ = statistically significantly lower value (p value < 0.05) in obese compared to non-obese patients; ↑ = statistically significantly higher value (p value < 0.05) in obese compared to non-obese patients.
 V_d , volume of distribution; V_{ss} , the volume of distribution at the steady-state; V_d/F , oral volume of distribution; V_{ob} , reported volume parameter for obese patients; V_{nw} , reported volume parameter for non-obese patients; V_{bw_ob} , weight normalized volume parameter for obese patients; V_{bw_nw} , weight normalized volume parameter for non-obese patients; NA, not available; Ref, references

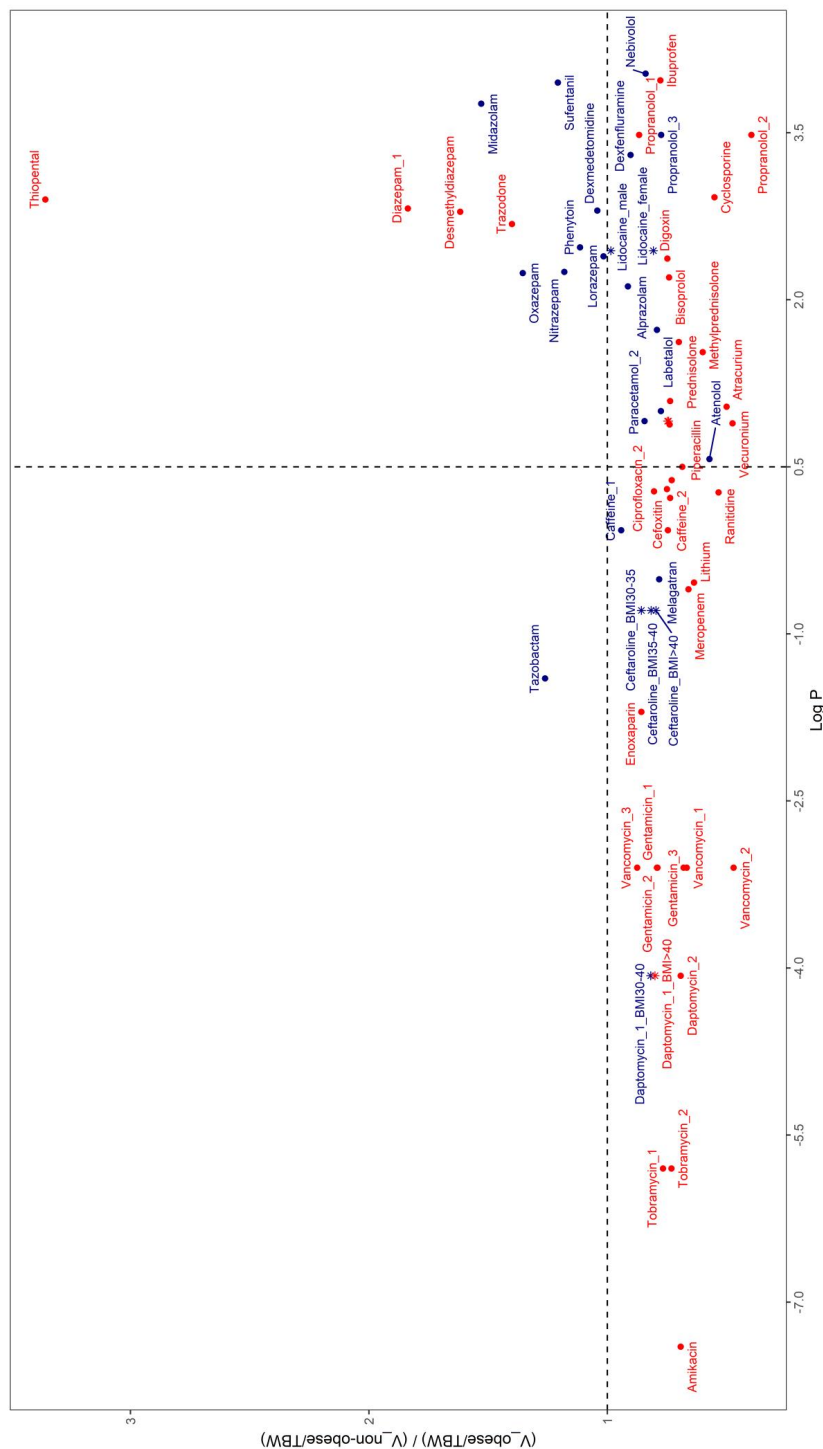


Figure S2.1 The relationship between the reported ratio of the volume of distribution (V_d) normalized with total body weight (TBW) between obese and non-obese subjects and drug lipophilicity expressed as logP. Statistically significant differences in V_d (p value < 0.05) are represented in red, while statistically non-significant differences in V_d are represented in blue (p value ≥ 0.05). Study details and references are shown in **Supplementary Table S2.2**. Different V_d ratios reported within one study are indicated with an asterisks. Different V_d ratios from different studies for one drug were marked as “drug name_study number”.

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II

Population pharmacokinetic
modeling to guide dosing in
obese adolescents and adults

3

Vancomycin clearance in obese adults is not predictive of clearance in obese adolescents

This chapter is based on  Zhang T, et al. Vancomycin clearance in obese adults is not predictive of clearance in obese adolescents. *Clin Pharmacokinet.* 2023;62(5):749-759.

ABSTRACT

Background and Objective

Contradictory pharmacokinetic (PK) results have been observed between obese adults and obese adolescents, with absolute clearance (CL) reported to be either unaltered, lower, or higher in obese adolescents compared to obese adults. This study investigates the PK of vancomycin in adolescents and adults who are overweight or obese.

Methods

Data from 125 overweight and obese adolescents (aged 10~18 years, weight 28.3~188 kg) and 81 overweight and obese adults (aged 29~88 years, weight 66.7~143 kg) were analyzed using population PK modelling. In addition to age, sex, renal function estimates, and regular weight descriptors, we evaluated standard weight (WT_{standard} , defined as weight for length, age, and sex in adolescents and weight for length in adults) and excess weight (WT_{excess} , defined as total body weight (TBW) minus WT_{standard}) as covariates in order to distinguish between weight resulting from length *versus* weight resulting from obesity.

Results

Analyzing adolescents and adults together, vancomycin CL was found to increase with TBW and decrease with increasing age ($p < 0.001$). A covariate analysis investigating adolescents and adults separately found that vancomycin CL increased with WT_{standard} in adolescents and adults, albeit with different functions, with adolescents having a higher CL per WT_{standard} than adults. Moreover, in this separate model, adolescent males had 21% higher CL than adolescent females of the same WT_{standard} , while in adults, CL decreased with increasing age ($p < 0.001$).

Conclusion

There are apparent differences in vancomycin CL in overweight and obese adults *versus* overweight and obese adolescents, implying that dosing of vancomycin cannot be directly extrapolated between these populations.

Key Points

- Vancomycin clearance (CL) in overweight and obese adolescents is on average higher than in overweight and obese adults, and vancomycin doses therefore cannot be directly scaled between these populations.
- In obese adolescents, males have higher vancomycin CL than females, while in obese adults, CL decreases with increasing age.
- Vancomycin CL is higher in our population of overweight and obese individuals compared to reported values in the non-obese, but within our population of overweight and obese individuals, vancomycin CL is stronger correlated with standard bodyweight compared to excess bodyweight.

3.1 Introduction

3 Overweight and obesity in adults are defined as a body mass index (BMI) ≥ 25 kg/m² and ≥ 30 kg/m², respectively, and in adolescents as a BMI corrected for age and sex $\geq 85^{\text{th}}$ percentile and $\geq 95^{\text{th}}$ percentile, respectively [1]. Obesity is associated with many physiological changes beyond increased adipose and lean tissue, such as increased cardiac output and blood flow, decreased tissue perfusion, and a permanent state of low-grade inflammation, all of which may influence the pharmacokinetics (PK) and, therefore, the required dosing regimen of drugs [2]. However, for many drugs there is limited information on how these changes translate into PK differences and dosage requirements in obese adults, and this information is even more scarce in obese adolescents, a population in which growth and maturation may still play a role [3, 4]. As the prevalence of overweight and obesity is increasing rapidly, clinicians are confronted with a growing number of dosing challenges [5, 6].

Extrapolation approaches to derive PK and dosing information for obese adolescents in the absence of actual data are sought. It has been suggested that maturation in adolescents is complete, leaving only size-related differences compared to adults, suggesting that PK values and dosing information from obese adults could be predictive for obese adolescents [7 – 10]. One study on busulfan, a hepatically cleared drug, found that clearance (*CL*) is influenced only by body weight, indicating *CL* in obese adults can be scaled to obese adolescents [11, 12]. However, contradictory PK results have been observed between obese adults and obese adolescents for other hepatically cleared drugs, with the absolute *CL* of propofol [13] being lower in obese adolescents and the absolute *CL* of midazolam being higher [14]. These studies found that in addition to body weight, covariates like age or growth- and obesity-related metrics are essential to describe inter-individual variability in PK parameters, indicating that PK values and dosing information in obese adults are likely not generalizable for obese adolescents for hepatically cleared drugs.

For renally cleared drugs, one study on metformin found comparable PK values between obese adolescents and obese adults, indicating that adult dosages of this drug could be used in obese adolescents [15]. However, for other renally cleared drugs such as vancomycin, a glycopeptide antibiotic commonly used in severe gram-positive infections, no study simultaneously analyzing drug PK in obese adolescents and obese

adults has been performed. Therefore, in our study we investigate the PK of vancomycin in adolescents and adults who are overweight or obese using population PK modelling.

3.2 Methods

3.2.1 Data and patients

Data on overweight and obese adolescents were taken from a previously published, retrospective PK dataset, including data on pediatric patients from 21 hospitals in Utah, USA, receiving vancomycin [16]. Selected subjects from this dataset were aged between 10 and 18 years and had a BMI corrected for age and sex that was higher than the 85th percentile of the Centers for Disease Control and Prevention (CDC) growth charts. Subjects with a reduced renal function, defined as estimated glomerular filtration rate (eGFR estimated using the equation of bedside Schwartz [17]) < 60 mL/min/1.73 m², were excluded. According to routine practice, subjects received a 15–20 mg/kg vancomycin dose two to four times a day per 60-minute infusion. Blood samples taken for therapeutic drug monitoring (TDM) were drawn within 30 min before dosing and/or 30 min after the end of infusion or opportunistically at random time points. The requirement of informed consent was waived by the Intermountain Healthcare and University of Utah Institutional Review Boards [16].

Data of overweight and obese adolescents were combined with the data of overweight and obese adults extracted from the St. Antonius Hospital's electronic health records in Nieuwegein, the Netherlands. Data were used from subjects with a BMI higher than 25 kg/m², were admitted to the general ward, received one or more vancomycin doses, had at least one vancomycin plasma concentration measurement, and had at least one body weight measurement between start and end of vancomycin treatment. Similar to adolescents, adults were omitted if they had a reduced renal function (eGFR estimated using the equation of chronic kidney disease epidemiology collaboration [CKD-EPI] < 60 mL/min/1.73 m² [18]). Vancomycin dosing was based on protocols for routine clinical practice and included a loading dose of 1000 mg or 1500 mg. Intermittent vancomycin infusions consisted of doses of 500–1500 mg twice or three times daily. Continuous infusion of vancomycin varied between 1000 mg/day and 3500 mg/day.

The Institutional Review Board (IRB) approved the study and waived the informed consent requirement.

3.2.2 Population pharmacokinetic analysis

To analyze the data, a non-linear mixed effect modelling analysis was performed using NONMEM 7.4 (Icon Development Solutions, Hanover, MD, USA) with Perl-speaks-NONMEM (4.9.0) and the Pirana interface (2.9.9) (Certara USA, Inc, Princeton, USA) [19, 20]. R 4.0.3 (Xpose4 package 4.7.1) and RStudio (2022.02.3) were used for data management and visualization. Using first-order conditional estimation, the population PK model was developed under the ADVAN3 TRANS4 subroutine.

Structural and stochastic model development

The 1-, 2-, and 3-compartment models with linear elimination were tested as structural models. Inter-individual variability was assumed to be log-normally distributed and tested on each model parameter. Additive, proportional, and combined error models were investigated for the unexplained residual variability. Nested models were compared and selected according to the objective function value (*OFV*, i.e., $2\log$ likelihood function). A decrease in *OFV* (ΔOFV) of more than 3.84, corresponding to $p < 0.05$ for one degree of freedom, was considered statistically significant.

Covariate model development

Covariates that were considered in the analysis included age, sex, length, BMI, total body weight (TBW), lean body weight (LBW, calculated according to the equation of Janmahasatian *et al.* [21], Peters *et al.* [22] and Foster *et al.* [23]), adjusted body weight (ABW), ideal body weight (IBW), serum creatinine concentration, and eGFR calculated by the equations of bedside Schwartz [17] (for adolescents only), chronic kidney disease epidemiology (CKD-EPI), Cockcroft-Gault (CG), and modification of diet in renal disease (MDRD). The values of eGFR estimates for adolescents were capped at 200 mL/min/1.73 m² during covariate analysis. The equations for calculating body weight descriptors and eGFR can be found in **Supplementary Table S3.1**. Additionally, standard weight and excess weight were defined to distinguish between weight resulting from the length and weight resulting from obesity [12]. For

adolescents, standard weight ($WT_{\text{standard_adol}}$) was calculated using the 50th percentile in BMI ($BMI_{50\text{th percentile}}$) for the subject's age and sex according to the CDC growth charts [1] and the length of the subject in meters (**Equation 3.1**). For adults, standard weight ($WT_{\text{standard_adu}}$) was calculated based on a BMI of 22 kg/m² and the subject's length in meters (**Equation 3.2**). Absolute and relative excess weight (WT_{excess}) were defined as the difference between the standard weight and TBW.

$$WT_{\text{standard_adol}} = BMI_{50\text{th percentile}} \times Length^2 \quad (3.1)$$

$$WT_{\text{standard_adu}} = 22 \times Length^2 \quad (3.2)$$

Continuous covariates were tested using **Equations 3.3** and **3.4** for linear and exponential relations, respectively, and binary covariates were tested using **Equation 3.5**:

$$P = TV_p \times (1 + \theta_x \times (COV - COV_{\text{median}})) \quad (3.3)$$

$$P = TV_p \times \left(\frac{COV}{COV_{\text{median}}} \right)^{\theta_y} \quad (3.4)$$

$$P = TV_p \times \theta_z^{COV} \quad (3.5)$$

where P is the parameter value, which is based on TV_p , which is the typical value or population estimate of the parameter, COV , which is the value of the covariate, COV_{median} , which is the median value of the covariate, θ_x , which is the slope parameter for linear covariate relationships, θ_y , which is the exponent for power functions, and θ_z , which is the proportional change of the parameter. In **Equation 3.5**, values of zero and one are used for COV to indicate the absence or presence of a binary covariate, respectively. Covariates of standard weight and excess weight were also tested using a so-called excess weight covariate model adapted from Van Rongen *et al.* [15] as defined in **Equation 3.6**:

$$P = TV_p \times \left(\frac{WT_{\text{standard}}}{WT_{\text{standard_median}}} \right)^{\theta_u} + (\theta_w \times WT_{\text{excess}}) \quad (3.6)$$

where θ_u is the scaling exponent for WT_{standard} , which was either fixed to 0.75 or estimated, and θ_w is the linear influence of WT_{excess} on the parameter value.

3 For covariate model selection, ΔOFV of more than 10.83 ($p < 0.001$) was considered statistically significant. Shark plots [24] were used to ascertain a sufficient number of individuals drove statistical significance. Additional assessments included visual inspection of basic goodness-of-fit plots, plots of conditional weighted residuals (CWRES) or individual *post hoc* parameter estimates *versus* individual covariate values, and plots displaying obtained covariate relationships. All plots were constructed with different stratifications that included sex, age- and weight-related covariates. Lastly, the plausibility and precision of parameter estimates were considered, where for the latter, values of the relative standard error of the estimates (RSE) of $< 50\%$ were considered acceptable.

The covariate analysis was conducted using data from adolescents and adults simultaneously. When visual inspection of the graphical output suggested different covariate relationships may be needed for the adolescents and adults, separate covariate analyses for adolescents and adults were also performed. This resulted in a final simultaneous model and a final separate model.

Validation of the final models

The final models were internally validated by a bootstrap resampling analysis using PsN [19], with 1000 replicates stratified on the two populations (adolescents and adults). A normalized prediction distribution error (NPDE) analysis based on 1000 simulated datasets using the NPDE package in R [25] was performed to assess the predictive performance of the final model. Also, for the NPDE, stratification based on population (adolescents and adults) was used.

3.3 Results

3.3.1 Data and patients

The PK analysis was based on 364 concentrations from 125 overweight and obese adolescents (aged 10~18 years, TBW 28.3~188 kg, BMI 20.2~60.0 kg/m²) [16], and 393 concentrations from 81 overweight and obese adults (age 29~88 years, TBW 66.7~143 kg, BMI 25.1~40.8 kg/m²). A summary of baseline demographic and clinical data characteristics is shown in **Table 3.1**.

3.3.2 Population pharmacokinetic analysis

Structural and stochastic model development

Regarding the structural and statistical structure of the base model, a two-compartment model with a proportional error model with inter-individual variability on CL and peripheral volume of distribution (V_p) best described all data from adults and adolescents. For this base model without covariates, box plots depicted in **Figure 3.1** show that absolute vancomycin CL in obese adolescents is, on average, higher than in obese adults ($p < 0.01$). This is even more clear when CL is normalized by total body weight (TBW) ($p < 0.001$). Additional plots from the base model in **Figure 3.2** suggest that the covariate relationships may not be the same for overweight and obese adolescents and overweight and obese adults with trends of WT_{standard} and sex for adolescents and age for adults.

Covariates in the simultaneous model for adolescents and adults

Although all GFR estimates and serum creatinine were statistically significantly correlated with CL , the magnitude of statistical significance of the covariate effects differed greatly, with ΔOFV ranging from -8.01 to -92.1 . This can be explained by the fact that the GFR estimates are composite measures, calculated by combining measured serum creatinine with other covariates, such as age, sex, body weight, race and/or height (see **Supplementary Table S3.1**). This could suggest that the impact of the GFR estimates is driven by the covariates used in their calculations, rather than by an actual impact of renal function. This was further supported by the finding that only

Table 3.1 Demographic and clinical data characteristics from the overweight and obese adult and overweight and obese adolescent patients included in this analysis

Parameters	Adolescents	Adults	Total
Number of individuals	125	81	206
Male/female (% male of total)	67/58 (53.6)	51/30 (63.0)	118/88 (57.3)
Age (years)	13 (10~18)	68 (29~88)	40 (10~88)
Overweight/obese (% obese of total)	56/69 (55.2)	49/32 (39.5)	105/101 (49.0)
Body size descriptors			
Height (m)	1.59 (1.13~1.96)	1.74 (1.50~1.95)	1.67 (1.13~1.96)
BMI (kg/m ²)	26.4 (20.2~60.0)	28.7 (25.1~40.8)	27.9 (20.2~60.0)
Total body weight (kg)	70.4 (28.3~188)	90.3 (66.7~143)	83.8 (28.3~188)
Lean body weight (kg)	44.7 (19.5~90.0)	61.3 (40.5~85.4)	52.8 (19.5~90.0)
Adjusted body weight (kg)	60.4 (18.3~119)	78.0 (57.1~106)	70.3 (18.3~119)
Ideal body weight (kg)	52.4 (11.6~89.5)	67.8 (43.3~88.6)	59.6 (11.6~89.5)
WT _{standard_adol/adu} (kg)	47.3 (21.3~81.6)	66.6 (49.5~83.7)	59.2 (21.3~83.7)
WT _{excess} (kg)	18.6 (5.20~124)	21.4 (8.26~65.8)	20.2 (5.20~124)
Percentage of WT _{excess} (%)	41.4 (18.2~200)	30.6 (14.1~85.5)	34.5 (14.1~200)
Estimated renal function			
Serum creatinine (μmol/L)	49.5 (18.6~95.5)	62.0 (24.0~107)	56.0 (18.6~107)
Bedside Schwartz (mL/min/1.73 m ²)	112 (60.5~264)	–	–
CKD-EPI (mL/min/1.73 m ²)	145 (83.3~231)	91.5(60.1~157)	120 (60.1~231)
Cockcroft-Gault (mL/min)	192 (66.4~463)	115 (61.6~378)	152 (61.6~463)
MDRD (mL/min/1.73 m ²)	168 (77.1~606)	108 (57.6~285)	126 (57.6~606)
Dose information			
Vancomycin dose (mg)	1000 (300~2500)	1250 (500~4000)	1000 (300~4000)
Vancomycin dose (mg/kg)	14.7 (2.66~26.8)	15.1 (3.50~46.1)	14.8 (2.66~46.1)
Number of samples	364	393	757
Number of samples per individual	2 (1~27)	4 (1~19)	2 (1~27)
Time after dose (h)	6.10 (1.32~34.6)	10.8 (1.03~44.6)	9.37 (1.03~44.6)

Data are shown as median (range) unless specified otherwise

BMI body mass index, CKD-EPI renal function estimate calculated by chronic kidney disease epidemiology collaboration, MDRD renal function estimate calculated by modification of diet in renal disease, WT_{standard_adol} standard body weight defined in adolescents as body weight for length and age and sex according to **Equation 3.1** and WT_{standard_adu} in adults as body weight for length according to **Equation 3.2**, WT_{excess} excess weight defined as standard body weight minus total body weight

Equations for body size descriptors and renal function estimates can be found in **Supplementary Table S3.1**

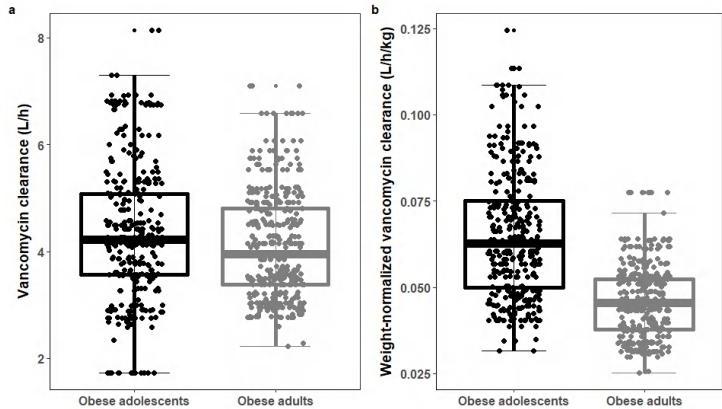


Figure 3.1 Individual *post hoc* parameter estimates were obtained from the base model for (a) absolute vancomycin clearance and (b) weight-normalized vancomycin clearance of overweight and obese adolescents (black) and overweight and obese adults (gray). Box plots are depicted based on both median and interquartile ranges of clearance. Dots represent each individual's *post hoc* estimate of clearance.

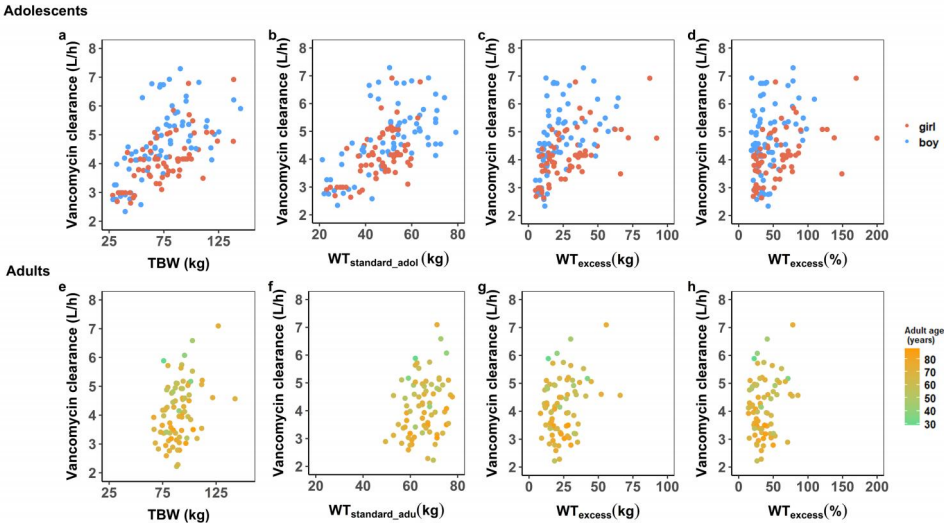


Figure 3.2 Individual *post hoc* parameter estimates obtained from the base model for absolute vancomycin clearance in (a-d) overweight and obese adolescents (e-h) and overweight and obese adults versus (a, e) total body weight (TBW), (b, f) standard weight (WT_{standard}), (c, g) excess body weight (WT_{excess}) and (d, h) relative excess body weight (%WT_{excess})

two individuals (0.97%) contributed to reaching statistical significance for the relation between serum creatinine and CL and by the plot of CWRES *versus* serum creatinine of the base model showing no trend (**Supplementary Figure S3.1**). Additionally, of the GFR estimates, only the inclusion of CG that uses TBW in its calculation, resulted in a higher ΔOFV than the drop obtained with TBW on its own (ΔOFV -92.1 and -57.6, respectively). Therefore, the covariate analysis was continued based on the covariates unrelated to renal function.

Total body weight, in a power function on CL , was the most significant covariate and included first. Age was subsequently found to have a negative linear correlation with CL . Moreover, the central volume of distribution (V_c) increased statistically significantly with TBW in an exponential relation. Although sex did not have a statistically significant impact on vancomycin PK, there was a trend for sex in the adolescent (**Supplementary Figure S3.2**).

The obtained covariate relationships for CL in the simultaneous model for adolescents and adults are visualized in **Figure 3.3a**. This figure shows that CL decreases with age in subjects with the same TBW, suggesting that even if obese adolescents have the same weight as obese adults, dose information for obese adults is not directly applicable to obese adolescents. The parameter values and bootstrap estimates for this final simultaneous model are summarized in **Table 3.2**.

Covariates in the separate models for adolescents and adults

Results regarding covariates related to renal function were similar to those found in the simultaneous model. Following the same reasoning, these covariates were excluded from the covariate analysis.

In overweight and obese adolescents, $WT_{\text{standard_adol}}$ in a power function was identified as the most predictive covariate based on the defined statistical criteria and visual assessments. The model incorporating $WT_{\text{standard_adol}}$ and WT_{excess} , shown in **Equation 3.6**, resulted in a comparable OFV and diagnostic plots as the model with only $WT_{\text{standard_adol}}$ as a covariate on CL , indicating that CL in adolescents is correlated with standard weight rather than excess weight. Sex was another covariate on CL in adolescents, with CL in males being 21% higher than in females of the same $WT_{\text{standard_adol}}$. The V_c was found to increase with $WT_{\text{standard_adol}}$ in a power function. After including

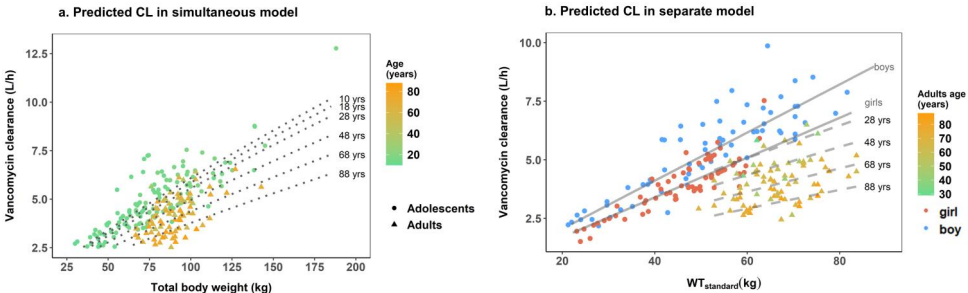


Figure 3.3 (a) Vancomycin clearance in the final simultaneous model, and (b) vancomycin clearance in the final separate models. Dotted lines represent the decreasing *CL* for adolescents and adults of 10, 18, 28, 48, 68 and 88 years; solid lines represent the obtained covariate relationship for adolescent males and females, while dashed lines represent the decreasing *CL* for adults of 28, 48, 68 and 88 years. Symbols represent individual clearance values

all the covariates in adolescents, the exponents in power functions of $WT_{\text{standard_adol}}$ on *CL* and V_c were 1.09 and 1.10, respectively. Since fixing these exponents to one increased the *OFV* by only 0.818 points, they were fixed to one to simplify the model to a linear function.

In overweight and obese adults, a negative linear relationship between age and *CL* was found ($p < 0.001$). Besides, TBW and $WT_{\text{standard_adu}}$ were found to be correlated with *CL* ($\Delta OFV = -13.0$ and -11.3 , respectively). Given the slight difference in *OFV* between these covariates, the $WT_{\text{standard_adu}}$ was selected to enable a comparison of the covariate relationship on *CL* between both populations. Similar to adolescents, incorporating WT_{excess} in addition to $WT_{\text{standard_adu}}$ did not lead to a significant *OFV* drop, indicating *CL* is mainly correlated with standard weight rather than excess weight in adults. No covariates were found for V_c in adults.

Figure 3.3b illustrates the influence of covariates on vancomycin *CL* in the separate populations of overweight and obese adolescents and adults. The obtained parameter values and bootstrap estimates for the final separate model are presented in **Table 3.2**.

Validation of the final models

For both the final simultaneous model and the final separate models, the RSE values of the obtained parameters are all below 40%, indicating that the models are well

Table 3.2 Population PK parameters and bootstrap medians of vancomycin in overweight and obese adolescents and adults for the final simultaneous model and the final separate model

Parameters	Final model (RSE%)	Bootstrap median for the final model [95% CI]
Simultaneous model		
Structural parameters		
$CL_{\text{adolescents and adults}} (L/h) = TVCL1 \times (TBW/60)^{\theta_1} \times [1 + \theta_2 \times (Age-40)]$		
TVCL1	3.39 (3)	3.36 (2.80~3.60)
θ_1	0.836 (8)	0.849 (0.638~1.029)
θ_2	-0.00570 (13)	-0.00559 (-0.00744 to -0.00410)
$Vc_{\text{adolescents and adults}} (L) = TVVc1 \times (TBW/60)^{\theta_3}$		
TVVc1	20.0 (4)	19.9 (16.4~22.9)
θ_3	0.775 (16)	0.768 (0.381~0.994)
$Q (L/h)$	2.27 (4)	2.27 (1.62~2.92)
$V_p (L)$	56.4 (10)	57.3 (33.5~105.4)
Inter-individual variability		
CL (%)	20.6 (9)	20.4 (15.8~23.9)
V_p (%)	94.8 (14)	94.2 (61.8~120)
Residual variability		
Proportional error	0.0383 (3)	0.0371 (0.0218~0.0514)
Separate model		
Structural parameters		
$CL_{\text{adolescents}} (L/h) = TVCL2 \times (WT_{\text{standard_adol}}/47) \times \theta_4^{\text{sex}}$		
$CL_{\text{adults}} (L/h) = TVCL2 \times [1 + \theta_5 \times (Age - 68)] \times (WT_{\text{standard_adu}}/67)^{\theta_6}$		
TVCL2	3.99 (3)	3.98 (3.74~4.22)
θ_4	1.21 (4)	1.20 (1.11~1.31)
θ_5	-0.00990 (32)	-0.0100 (-0.0143 to -0.00520)
θ_6	0.842 (39)	0.830 (0.430~1.23)
$Vc_{\text{adolescents}} (L) = TVVc2 \times (WT_{\text{standard_adol}}/47)$		
$Vc_{\text{adults}} (L) = TVVc2$		
TVVc2	22.7 (4)	22.7 (19.9~25.2)
$Q (L/h)$	2.43 (6)	2.43 (1.96~3.12)
$V_p (L)$	52.8(12)	53.0 (38.0~73.4)
Inter-individual variability		
CL (%)	19.9 (8)	19.5 (15.2~23.5)
V_p (%)	92.7 (12)	92.2 (65.0~115)
Residual variability		
Proportional error	0.0381 (3)	0.0370 (0.0260~0.0510)

CL clearance, Q inter-compartmental clearance, RSE relative standard error based on the covariance step in NON-MEM, TVCL1 and TVCL2 represent the value of typical clearance in simultaneous model and separate model respectively, TVVc1 and TVVc2 represent the value of typical central volume in simultaneous model and separate model respectively, V_c the volume of distribution of central compartment, V_p the volume of distribution of peripheral compartment, $WT_{\text{standard_adol}}$ standard body weight defined in adolescents as body weight for length and age and sex and $WT_{\text{standard_adu}}$ in adults as body weight for length

supported by the data. The bootstrap analyses confirm the robustness of parameter estimates, as the bootstrap medians deviate less than 10% from the original estimate and as the obtained estimates are all within the 95% confidence interval (CI) of the bootstrapped values. The goodness-of-fit plots stratified by age groups did not show model misspecifications across any subpopulations (**Supplementary Figure S3.3**). The NPDE analyses indicate that the models can accurately predict typical trends as well as the variability in the populations. Statistical tests and visual inspection of the results show that the final models have a good predictive performance for subpopulations of different ages (**Supplementary Figure S3.4**).

3.4 Discussion

This study investigates the PK of vancomycin in adolescents and adults who are overweight or obese. Our model indicates that the PK of vancomycin in overweight and obese adolescents differs from that in overweight and obese adults, with *CL* being generally higher in adolescents compared to adults.

Vancomycin is primarily eliminated via glomerular filtration. It has been suggested that GFR in normal-weight children is lower than in adults and increases from birth until it reaches adult levels [26]. However, our results in overweight and obese adolescents and adults show an opposite trend, with both absolute and relative *CL* being, on average, higher in adolescents compared to adults. It should be noted that the data from the adults in this study originate from a different country (Netherlands) than the data from the adolescents (USA), which could introduce confounding factors that drive the differences that we found. However, supporting evidence and explanations for these findings do exist in literature. A potential explanation is that the renal function in obese adolescents is generally better than in obese adults although all included subjects had a normal renal function (e.g., median CKD-EPI for adolescents and adults are 145.23 and 91.54 mL/min/1.73 m², respectively). In literature, GFR is reported to be increased in obese patients due to the number or efficiency of functional nephrons being enhanced and/or renal blood flow being increased as a consequence of the increased cardiac output [27–30]. Along with the increased GFR, *CL* of some renally cleared drugs such as gentamicin and tobramycin is increased in obese individuals [16, 31–33]. However, for other renally cleared drugs such as cefazolin and ciprofloxacin

3 [34–36], *CL* remains unchanged with obesity. Alternatively, long-term obesity is also highly associated with decreased renal function as the result of (chronic) kidney disease, compensating for an initial increase in GFR, eventually leading to an unaltered or even decreased *CL* of drugs. Therefore, we anticipate that adolescents, who have generally been overweight or obese for a shorter duration than adults, may have an obesity-induced higher GFR that is not yet impaired in comparison to overweight or obese adults. In a study on midazolam, a hepatically cleared drug, Van Rongen *et al.* reported that the duration of obesity might influence (patho)physiological changes related to obesity [14]. They found that *CL* of midazolam in obese adolescents increases mainly with obesity-related weight changes. However, in adults, this increase in *CL* was no longer apparent, possibly due to prolonged and/ or more extensive obesity-induced suppression of CYP3A activity. As the duration of obesity has a possible influence on drug PK, the PK parameter values in overweight and obese adults may differ from those in overweight and obese adolescents and cannot be extrapolated between the populations. The value of vancomycin *CL* in overweight and obese adolescents in our study (e.g., 6.03 L/h with TBW of 100 kg and age of 12 years) is higher than the value reported in the literature in normal-weight adolescents of the same age (e.g., 3.38 L/h with TBW of 40 kg and age of 12 years [16]), and also higher than the value reported in normal-weight adults (e.g., 2.55 L/h with TBW of 65 kg and age of 60 years [37]). The increased *CL* in obese adolescents compared to normal-weight adolescents or adults might be explained by the increased GFR in obesity [38]. This difference in *CL* indicates that, similar to overweight and obese adults, the PK data and dosing information from non-obese adolescents or adults cannot be extrapolated to overweight or obese adolescents.

The obtained simultaneous and separate models have comparable *OFV* values (2916 *versus* 2914), and both show that the PK values in obese adolescents differ from those in obese adults. Both models found that *CL* is influenced by sex in adolescents. Although this is not statistically significant in the simultaneous model, **Supplementary Figure S3.5** shows that population-predicted concentrations obtained from the simultaneous model tend to be higher for male adolescents and lower for female adolescents than the concentrations from the separate model. From this figure it can be concluded that the two models have different predictive performances for vancomycin PK in obese adolescents, with the separate model being able to predict PK

for both sexes in adolescents, whereas the simultaneous model shows bias. However, for adults, no difference between sexes is visible in **Figure S3.5** in either of the two models, indicating that these two models have comparable abilities to predict the PK in obese adults. Interestingly, in the separate models for adolescents and adults, in addition to WT_{standard} , which already includes a correction for sex (and age and length), sex was found to be an additional covariate on vancomycin CL in overweight and obese adolescents, with males having larger CL than females. This suggests that in these adolescents, besides sex-related differences in body weight, other factors that vary between sexes also impact CL . During puberty, whole kidney GFR and single nephron GFR have been reported to be higher in male rats, possibly due to higher renal plasma flow and lower vascular resistance caused by the anabolic effects of testosterone on proximal tubular cells in males [39, 40]. However, after puberty until the age of 50 years, overall sex differences in GFR are no longer evident [41, 42]. GFR changes can also account for age as an independent covariate on CL in adults, as it has been recognized that the GFR declines steadily with aging, beginning around 30~40 years, due to reductions in the glomerular capillary plasma flow rate, and the glomerular capillary ultra-filtration coefficient [43]. In addition, other age-associated changes, such as the decreased renal blood flow in concert with the structural change in diminished kidney mass, can also decrease kidney function and thereby influence the renal CL of drugs [44]. Interestingly, the CL values of the adolescents in this study seem to be more in line with what can be expected based on extrapolations from the adult population, taking into account the relationships with both standard weight and age, although the underlying mechanisms driving the relationship of age at both ends of the age-range may be different.

Despite all individuals having normal renal function values, GFR estimates were significantly correlated with CL . However, these were not implemented in the final models, as we suspected that this finding was driven by the covariates included in the calculations of eGFR rather than by actual renal function. Moreover, the equation of CG has been reported to have a low accuracy and high bias in estimating GFR in patients with obesity [45, 46] and other equations used to derive eGFR have not been validated for the obese population [46]. As this study aimed to compare the PK between two populations, we continued by testing the single covariate instead of implementing eGFR as a composite covariate that may mask covariates that are

driving the correlation. When testing GFR estimates again in the final simultaneous and final separate models, this did lead to statistically significant improvements in the model fits, but this was again driven by very few individuals. It was noted that this also leads to very different functions being estimated for the covariates that were already included in the models, further driving our suspicion that in obese patients with good renal function, the predictive value of GFR estimates to reflect kidney function is limited. Finally, the fact that serum creatinine concentration was only a significant covariate due to two individuals, confirmed the idea that the covariates in the GFR functions instead of the creatinine values itself drive the significance of the GFR functions. Future studies conducted in obese adolescents and adults with different renal functions are needed to extrapolate these models and quantify the impact of renal function on vancomycin *CL*.

When body weight impacts drug PK in obese individuals, it is essential to distinguish between weight resulting from the length and weight resulting from obesity [47]. Our study shows that in a population of overweight and obese individuals, vancomycin *CL* increases with TBW in adolescents and adults and that this increase is best correlated to standard weight rather than excess weight. Besides, this study also shows that the increase in vancomycin V_c with TBW in both populations is also mainly driven by standard weight, not excess weight, in overweight and obese adolescents. Finally, it should be noted that LBW, another covariate that can be used to describe the altered body composition and to predict the PK differences between sexes in obese individuals, was not superior to $WT_{\text{standard_adol/adu}}$ or the combination of $WT_{\text{standard_adol}}$ and sex ($\Delta OFV = -57.288$ [$p < 0.001$], -66.634 [$p < 0.001$], -78.416 [$p < 0.001$], respectively) in this study.

3.5 Conclusion

Vancomycin *CL* in overweight and obese adolescents is generally higher than in overweight and obese adults, with male adolescents having larger *CL* than female adolescents. Therefore, vancomycin *CL* in overweight and obese adults is not predictive of vancomycin *CL*, and as a result, vancomycin dose cannot be directly scaled from overweight and obese adults to overweight and obese adolescents.

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Supplementary Material

Table S3.1 Equations used to derive different body weight descriptors and estimates of renal function

Covariate	Equation	Reference
Body weight descriptors		
TBW (kg)	–	–
BMI (kg/m ²)	$TBW/Height^2$	–
IBW (kg)	Male: $50.0 + 2.3 \times (Height \times 0.3937 - 60)$ Female: $45.5 + 2.3 \times (Height \times 0.3937 - 60)$	[1]
ABW (kg)	$IBW + 0.4 \times (TBW - IBW)$	[2]
LBW (kg)	Male: $(9.27 \times 10^3 \times TBW)/(6.68 \times 10^3 + 216 \times BMI)$ Female: $(9.27 \times 10^3 \times TBW)/(8.78 \times 10^3 + 244 \times BMI)$	[3]
WT _{standard} (kg)	Adolescents: $BMI_{50th\text{ percentile}} \times Length^2$ Adults: $22 \times Length^2$	–
WT _{excess} (kg)	$TBW - WT_{\text{standard}}$	–
Estimates of renal function		
Bedside Schwartz (mL/min/1.73m ²)	Male: $0.5 \times Height/Scr$ (mg/dL) Female: $0.7 \times Height/Scr$ (mg/dL)	[4]
Indexed CKD-EPI (mL/min/1.73m ²)	Male & $Scr \leq 0.9$ (mg/dL): $141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age} \times F$	[5]
	Male & $Scr > 0.9$ (mg/dL): $141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age} \times F$	
	Female & $Scr \leq 0.7$ (mg/dL): $141 \times (Scr/0.7)^{-0.329} \times 0.993^{Age} \times F$	
	Female & $Scr > 0.7$ (mg/dL): $141 \times (Scr/0.7)^{-1.209} \times 0.993^{Age} \times F$	
F: if black people, F = 1.15, otherwise F = 1		
Cockcroft-Gault (mL/min)	Male: $(140 - Age) \times TBW/(0.815 \times Scr)$ Female: $(140 - Age) \times TBW/(0.815 \times Scr) \times 0.85$	[6]
Indexed MDRD (mL/min/1.73m ²)	Male: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times F$	[7]
	Female: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times 0.742 \times F$	
F: if black people, F = 1.212, otherwise F = 1		

TBW, total body weight; LBW, lean body weight; ABW, adjusted body weight; BMI, body mass index; WT_{standard}, standard weight; BMI_{50th percentile}, the 50th percentile in BMI for the subject's age and sex according to the CDC growth charts; WT_{excess}, excess weight; CKD-EPI, renal function calculated by chronic kidney disease epidemiology collaboration; MDRD, renal function calculated by modification of diet in renal disease; Scr, serum creatinine.

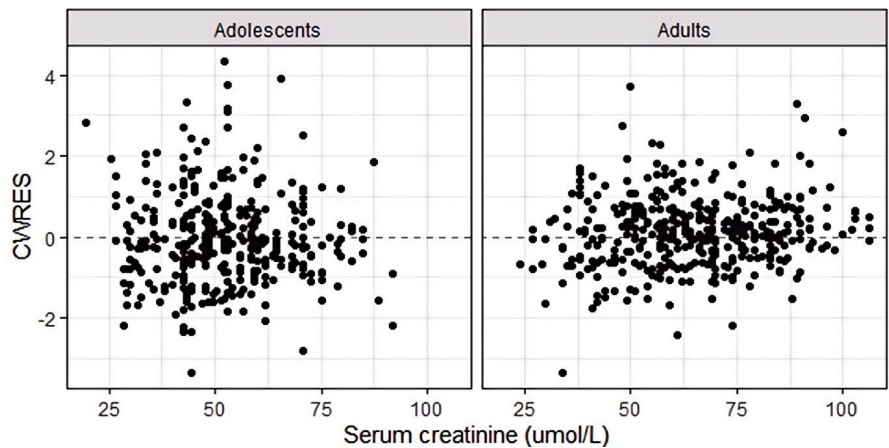


Figure S3.1 Conditional weighted residuals (CWRES) versus serum creatinine (umol/L) obtained from the base model in overweight and obese adolescents.

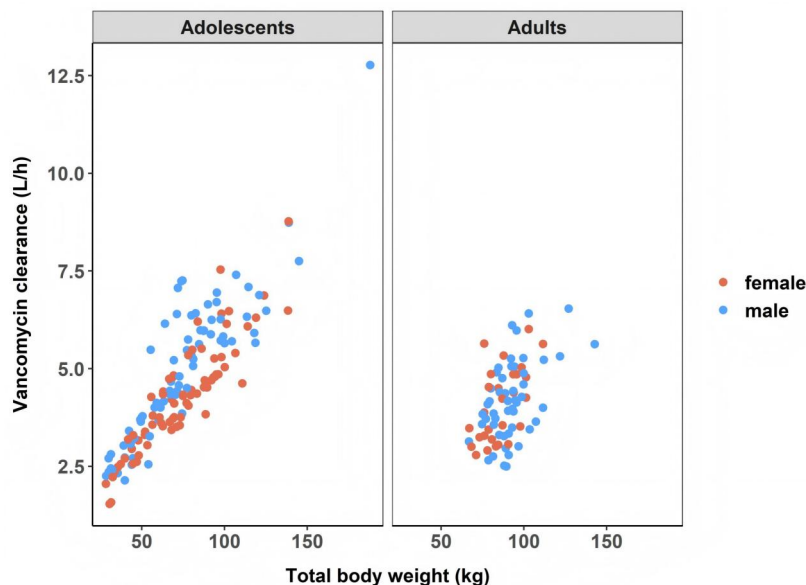


Figure S3.2 Individual *post hoc* parameter estimates of absolute vancomycin clearance obtained from the final simultaneous model versus total body weight in overweight and obese adolescents and overweight and obese adults

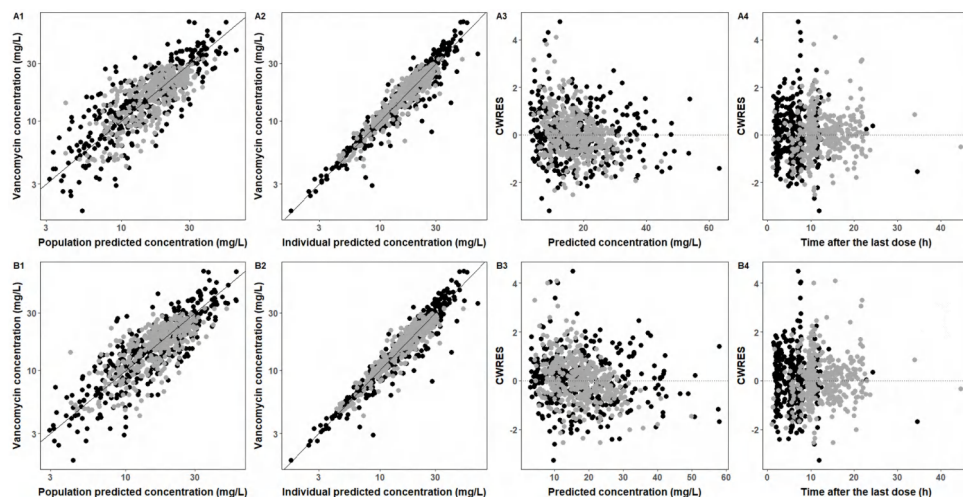


Figure S3.3 Goodness-of-fit plots of the (A1-4) final simultaneous model and (B1-4) final separate model for vancomycin in overweight and obese adolescents and adults. (1) Observed concentration versus population predicted concentration; (2) observed concentration versus individual predicted concentration; (3) conditional weighted residuals (CWRES) versus population predicted concentration; (4) CWRES versus time after the last dose. Black dots represent adolescents, and grey dots represent adults

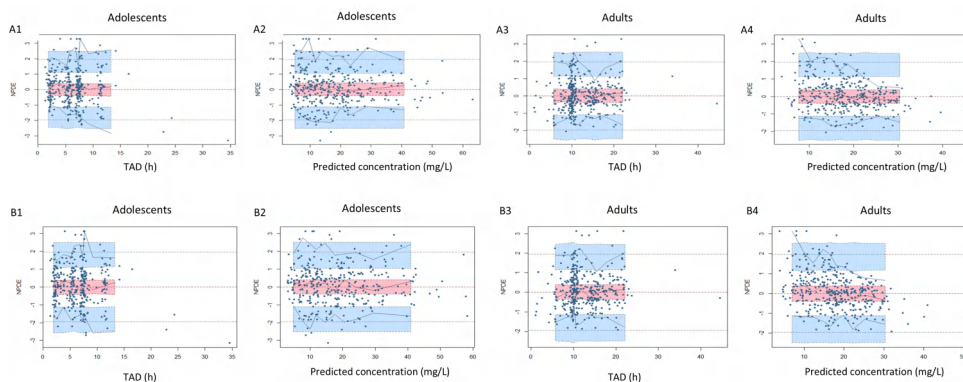


Figure S3.4 Scatterplots of the normalised prediction distribution error (NPDE) versus (A1, A3, B1, B3) time after dose (TAD) and (A2, A4, B2, B4) population predicted concentrations of the (A1-4) final simultaneous model and (B1-4) final separate model for vancomycin in overweight and obese adolescents and adults ($n = 1000$). Plots are stratified on adolescents and adults. The blue dots represent the NPDE of the observations. The dashed lines represent the 5th, 50th, and 95th percentiles NPDE of the observations. The color shaded areas represent the 95% confidence intervals around the simulated 5th, 50th, and 95th percentiles

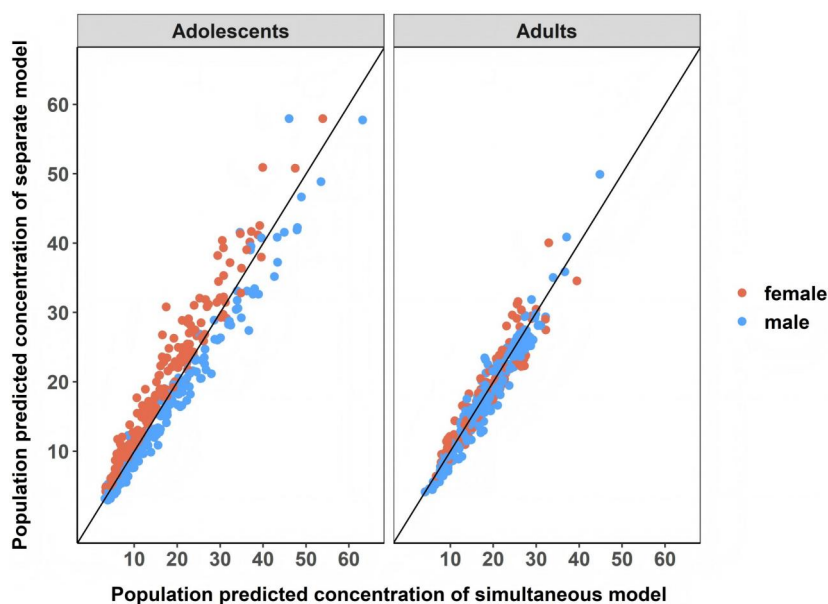


Figure S3.5 Population predicted concentrations obtained from the final simultaneous model *versus* the concentrations obtained from the final separate model

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4

How to dose vancomycin in overweight and obese patients with varying renal (dys)function in the novel era of AUC 400-600 mg·h/L-targeted dosing

This chapter is based on  Zhang T, et al. How to dose vancomycin in overweight and obese patients with varying renal (dys)function in the novel era of AUC 400-600 mg·h/L-targeted dosing. Clin Pharmacokinet. 2023 Nov 16.

ABSTRACT

Background and Objective

The latest vancomycin guideline recommends area under the curve (AUC)-targeted dosing and monitoring for efficacy and safety. However, guidelines for AUC-targeted starting dosing in patients with obesity and/or renal insufficiency are currently lacking. This study quantifies the pharmacokinetics (PK) of vancomycin in this population and provides AUC-targeted dosing recommendations.

Methods

Vancomycin concentrations ($n = 1188$) from therapeutic drug monitoring of 210 overweight and obese patients with varying degrees of renal (dys)function from the ward (74.8%) and intensive care unit (ICU, 25.2%) were pooled with published rich concentration-time data ($n = 207$) from 20 (morbidly) obese subjects undergoing bariatric surgery. A population model was developed using NONMEM 7.4. Stochastic simulations were performed to design dosing guidelines targeting an AUC_{24} between 400–600 mg·h/L.

Results

Vancomycin clearance (CL) was found to increase linearly with total bodyweight and with renal function (CKD-EPI) in a power relation. Additionally, CL proved 15.5% lower in ICU patients. Our model shows that, to reach the target AUC between 400 and 600 mg·h/L in the first 48 h, two loading doses are required for both continuous infusion and intermittent dosing regimens. Maintenance doses were found to require adjustment for total bodyweight, renal function, and ICU admission status. With this guideline, the median AUC_{24} is well within the target from the start of the treatment onwards.

Conclusions

To achieve safe and effective vancomycin exposure for maintenance doses in overweight and obese patients, renal function, total bodyweight, and ICU admission status should be taken into account.

4.1 Introduction

Obesity is a global epidemic, with a prevalence nearly tripling over the last five decades [1]. The World Health Organization (WHO) reported that approximately 39% of the global adult population are overweight [body mass index (BMI) ≥ 25 kg/m²] and about 13% are obese (BMI ≥ 30 kg/m²) [2]. Increasing numbers of patients with obesity with or without renal insufficiency are admitted to the hospital or develop renal insufficiency during hospital stay. These patients run the risk of getting severe bacterial infections for which antibiotic therapy is required.

Vancomycin is frequently used to treat severe infections caused by Gram-positive bacteria [e.g., *methicillin-resistant Staphylococcus aureus* (MRSA)]. For patients receiving vancomycin therapy, therapeutic drug monitoring (TDM) based on trough concentration was until recently commonly used as a surrogate target for the ratio of area under the curve over 24 h and minimal inhibitory concentration (AUC₂₄/MIC) [3]. However, the latest consensus guideline of vancomycin, published in 2020, recommends using the direct target of AUC₂₄ of 400~600 mg·h/L (assuming a MIC of 1 mg/L) to ensure clinical efficacy and minimize toxicity for various infections [4]. This revision is based on the evidence that the trough concentration is insufficient to predict AUC in at least 25% of cases, resulting in an overestimation of the required dose and a corresponding rise in vancomycin exposure for patients [5]. In addition, evidence also reveals that the AUC-targeted monitoring method is associated with significantly less vancomycin-induced acute kidney injury than a trough concentration-based approach. [6]

The new guideline also strongly recommends AUC-targeted dosing and monitoring in patients with obesity, renal insufficiency, or critical illness, since these conditions may significantly alter vancomycin clearance (*CL*) and increase the risk of nephrotoxicity if the dosage is not modified [4]. A recent prospective study of obese individuals weighing up to 235 kg and without renal insufficiency from our group quantified the increase of vancomycin *CL* with bodyweight, confirming reports of other studies showing vancomycin clearance increases with bodyweight [7 – 10]. However, this study did not consider overweight and obese individuals with renal dysfunction, who may have lower *CL* than those without renal dysfunction. To propose starting doses leading to target AUC and reduce the need for TDM-based dosage adjustments, quan-

tification of vancomycin pharmacokinetics (PK) in patients who are overweight or obese with varying levels of renal (dys)function is urgently needed.

This study uses population PK modeling to quantify the PK of vancomycin in a representative clinical population of overweight and (morbidly) obese patients with varying degrees of renal (dys)function. Using the developed model, AUC-targeted dosing recommendations are designed to obtain effective and safe vancomycin exposures from treatment initiation onward.

4 4.2 Patients and methods

4.2.1 Patients and data

Model building was based on the data from two datasets. The first dataset (patient dataset) contained retrospective PK data and patient characteristics extracted from electronic health records of St. Antonius Hospital in the Netherlands. Patients were included in this analysis when they 1) were overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$), 2) received vancomycin as a continuous infusion or intermittent dosing and had at least one vancomycin plasma concentration measurement within 168 h after the last dose, and 3) had regular serum creatinine measurements across vancomycin treatment. Patients could be admitted to the ward or ICU and were excluded if they received renal replacement therapy during vancomycin treatment. Vancomycin was administered according to protocols for routine clinical practice, including TDM-based initial dosage and dose adjustments. The second dataset (healthy obese dataset) was obtained from the AMIGO trial, a prospective PK study that has been published previously [7]. Data from 20 (morbidly) obese ($\text{BMI} \geq 35 \text{ kg/m}^2$) subjects undergoing bariatric surgery were included in the analysis. All individuals had normal renal function defined as an estimated glomerular filtration rate ($\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$). Subjects from this study were all dosed with 12.5 mg/kg vancomycin (maximum 2500 mg) by single intravenous infusion. Rich sampling was performed, yielding a median number of 11 samples per individual within 24 h after infusion.

In both datasets, vancomycin concentrations were measured with a validated and commercially available immune assay (VANC3) using Cobas platforms (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of quantification was 4 mg/L .

and the upper limit of quantification was 80 mg/L. The coefficient of variation was ≤ 4.4 .

4.2.2 Ethics

For the first TDM dataset that was obtained during routine clinical care in the hospital, the Institutional Review Board (IRB) approved the protocol and waived the requirement of informed consent. The second dataset was part of the AMIGO trial, which was approved by the local human research and ethics committee (registered in the Dutch Trial Registry [NTR6058]) and all participants provided informed consent. All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines in Good Clinical Practice.

4.2.3 Population pharmacokinetic analysis

A population PK analysis was performed using NONMEM 7.4 (ICON Development Solutions, Hanover, MD, USA). Pearl-speaks-NONMEM (PSN) 4.9.0 [11], Pirana 2.9.7 (Certara USA, Inc, Princeton, USA) [12], and R 4.0.3 (Xpose4 package 4.7.1) were used to organize, evaluate, and visualize data. ADVAN11 TRANS4 subroutine with the first-order conditional estimation method with interaction was used.

The structural model was selected from one-, two-, and three-compartment candidate models. Inter-individual variability on the parameters was assumed to follow a log-normal distribution and tested for statistical significance on each parameter. Inter-occasion variability (*IOV*) was investigated. Additive, proportional, and combined error models were tested to describe residual unexplained variability. For model selection, a drop in objective function value (*OFV*, -2 log-likelihood) of more than 3.84 was considered statistically significant ($p < 0.05$, assuming a χ^2 distribution).

Covariates that were considered in the analysis were age, sex, bodyweight-related descriptors (including total bodyweight [TBW], lean bodyweight [LBW], adjusted bodyweight [ABW], ideal bodyweight [IBW], and BMI), and renal function estimates (quantified using Cockcroft-Gault calculated with LBW [CG-LBW] or TBW [CG-TBW], modification of diet in renal disease [MDRD], or chronic kidney disease epidemiology collaboration [CKD-EPI]). MDRD and CKD-EPI de-indexed for body surface area

(BSA) were also tested. The equations for calculating bodyweight descriptors and renal function can be found in **Supplementary Table S4.1**. ICU admission status, indicating whether a patient was admitted to ICU, was also explored as a covariate. Potential covariates were implemented into the model separately using a linear function or a power function with an estimated exponent. A covariate relationship was considered statistically significant when *OFV* dropped more than 10.83 ($p < 0.001$). The model fits were assessed using goodness-of-fit (GOF) plots stratified for the BMI group (overweight [BMI 25~30 kg/m²] and obese [BMI > 30 kg/m²]), stratified for the estimated renal function group (CKD-EPI < 30, 30~50, 50~90, > 90 mL/min/1.73 m²) and ICU admission status. Plots of individual influence on change in *OFV* (also known as shark plots) in Xpose 4 were used to ascertain that statistical significance was driven by a sufficient number of individuals and it was checked that the inclusion of a covariate reduced the random inter-individual variability on a parameter [13]. In addition, covariate relationships were visually inspected in plots of eta value *versus* individual covariate value for time-independent covariates, conditional weighted residuals (CWRES) *versus* individual covariate value for time-dependent covariates, and individual *post hoc* parameter estimates *versus* covariate value overlain with lines representing the obtained covariate relationships, with the stratifications previously mentioned. Finally, relative standard errors of estimates (RSE) were considered to indicate adequate precision if they were below 50%.

4.2.4 Model evaluation

In addition to the diagnostic plots used during model development, the robustness of the parameter estimates of the final model was validated by a bootstrap resampling analysis using PsN [12], with 1000 replicates stratified on the two datasets.

The predictive performance of the final model was assessed and visualized by a normalized prediction distribution error (NPDE) analysis using the NPDE package in R [14]. The analysis was based on 1000 simulations of the dataset.

4.2.5 Model-based dose optimization

On the basis of the obtained covariate relationships in the final model and clinical feasibility, AUC-targeted dosing recommendations for continuous infusion and intermittent dosing regimen were developed, which were assessed in stochastic simulations using the final vancomycin PK model. For representative virtual individuals with assigned values of indexed CKD-EPI (20, 40, 60, 80, and 100 mL/min/1.73 m²), body-weight (80, 120, 160, and 200 kg), and ICU admission status (non-ICU *versus* ICU), 1000 simulations with inter-individual variability were performed. The target exposure for efficacy was defined as $AUC_{24}/MIC \geq 400$ mg·h/L. An AUC_{24}/MIC threshold of 600 mg·h/L was selected as the safety limit to minimize the probability of nephrotoxicity according to the literature [15–17]. Since the MIC was assumed to be 1 mg/L in this study, AUC_{24}/MIC is abbreviated as AUC_{24} for simplicity. Therefore, optimal dose regimens should achieve the target AUC_{24} from the first day of dosing onward. To explore the concentrations that are obtained upon these AUC_{24} 400~600 mg·h/L targeted dosing recommendations, concentration-time profiles for the different body-weight and renal function groups were also explored.

4.3 Results

4.3.1 Data

A total of 1188 concentrations were available from 210 overweight and obese hospitalized patients, which were analyzed in conjunction with 207 concentrations from 20 morbidly obese healthy subjects. Of the 1188 concentrations, 11 were peak and 416 were trough concentrations taken upon intermittent infusion, while 761 were random samples taken upon the continuous infusion. A summary of baseline demographics, clinical characteristics, and dosing information from the study groups is presented in **Table 4.1**.

4.3.2 Population pharmacokinetic analysis

A three-compartment model outperformed both one- and two-compartment models, exhibiting the best GOF plots. This model, which incorporated inter-individual vari-

Table 4.1 Baseline demographics, clinical characteristics, and dosing information from the overweight and obese patients and otherwise healthy obese subjects undergoing bariatric surgery included in the analysis

Parameters	Overweight and obese patients	Otherwise healthy obese subjects [7]	Total dataset
Number of individuals	210	20	230
Male/Female	133/77	7/13	140/90
Height (m)	1.73 (1.49~1.97)	1.74 (1.59~1.90)	1.72 (1.49~1.97)
Age (years)	72 (33~92)	39 (23~54)	70 (23~92)
ICU/non-ICU	53/157	0/20	53/177
TBW (kg)	90.1 (58.6~143.0)	141.2 (110.6~234.6)	91.8 (58.6~234.6)
LBW (kg)	60.8 (36.5~85.4)	65.1 (52.7~104.2)	61.0 (36.5~104.2)
ABW (kg)	76.1 (50.4~106.0)	98.3 (75.1~143.7)	77.0 (50.4~143.7)
BSA (m ²)	2.1 (1.6~2.7)	2.5 (2.1~3.3)	2.1 (1.6~3.3)
BMI (kg/m ²)	29.2 (25.0~53.4)	45.3 (40.8~65.7)	30.0 (25.0~65.7)
25~30 (no. of patients)	122	0	122
> 30 (no. of patients)	88	20	108
Serum creatinine (μmol/L)	84.0 (23.0~748.0)	72.0 (41.0~101.0)	84.0 (23.0~748.0)
No. of serum creatinine per individual	11.0 (1.00~91.0)	1	11.0 (1.00~91.0)
CKD-EPI (mL/min/1.73 m ²)	73.7(6.0~154.9)	100.3 (70.3~119.8)	74.5 (6.0~154.9)
< 30 (no. of patients)	15	0	15
30~60 (no. of patients)	60	0	60
60~90 (no. of patients)	87	6	93
90~130 (no. of patients)	46	14	60
> 130 (no. of patients)	2	0	2
De-indexed CKD-EPI (mL/min)	86.6 (6.5~209.5)	142.4 (95.5~221.8)	87.8 (6.5~221.8)
MDRD (mL/min/1.73 m ²)	71.5 (6.4~304.1)	88.0 (61.9~145.5)	72.6 (6.4~304.1)
De-indexed MDRD (mL/min)	85.8 (6.9~371.0)	128.7 (84.1~207.4)	86.6 (6.9~371.0)
CG-TBW (mL/min)	86.4 (9.6~420.6)	208.9 (143.4~432.1)	87.8 (9.6~432.1)
CG-LBW (mL/min)	56.3 (6.9~280.7)	107.0 (70.7~192.0)	57.2 (6.9~280.7)
Vancomycin dose (mg)	1250 (250~3500)	690 (1400~2500)	1250 (250~3500)
Vancomycin dose (mg/kg)	13.6 (2.4~36.6)	12.3 (10.7~13.6)	13.6 (2.4~36.6)
Treatment duration (h) ^a	134.2 (7.52~1407.8)	13.1 (4.5~22.2) ^b	112.8 (4.5~1407.8)
No. of concentrations	1188	207	1395
No. of concentrations per individual	4 (1~31)	11 (7~12)	5 (1~31)
Time after the last dose (h)	11.4 (0.02~44.6)	4.7 (0.5~22.2)	10.7 (0.02~44.6)

Data are shown as median (range) unless specified otherwise

TBW total bodyweight, LBW lean bodyweight, ABW adjusted bodyweight, BSA body surface area, BMI body mass index, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration, MDRD renal function calculated by modification of diet in renal disease, CG-TBW renal function calculated by Cockcroft-Gault with TBW, CG-LBW renal function calculated by CG calculated with LBW For the equations of bodyweight descriptors and renal function, see **Supplementary Table S4.1**

^a Time between the first dose and the last observation

^b Single dose infusion

ability on *CL* and central volume of distribution (*V*₁), best described the data.

In the covariate analysis, indexed CKD-EPI gave the largest reduction in *OFV* and was identified as the most predictive covariate on *CL*, with an estimated exponent in a power relationship of 0.658 ($p < 0.001$). TBW was identified as the second covariate on *CL*, as it was significantly correlated with vancomycin *CL* in a linear function ($p < 0.001$) and found to be superior to the other tested size descriptors. Furthermore, ICU admission status was also significantly correlated with vancomycin *CL* ($p < 0.001$), with *CL* in ICU patients being 15.5% lower than in non-ICU patients. For the volume of distribution of the peripheral compartments and the inter-compartmental clearances, a statistically significant correlation with TBW was found ($p < 0.001$). However, since for each parameter only three individuals (1.30%) were found to contribute to yielding statistical significance, we decided not to include TBW as a covariate on the peripheral compartments and intercompartmental clearances. No other covariates were found to have a statistically significant impact on vancomycin PK in our population. The PK parameters of vancomycin for the final model are presented in **Table 4.2**.

In the final model, *CL* was 3.36 L/h in a typical patient with a TBW of 100 kg and indexed CKD-EPI of 75 mL/min/1.73 m². For a patient admitted to the ICU, this value was 2.84 L/h. The influences of renal function (CKD-EPI), bodyweight (TBW), and ICU admission status on *CL* are illustrated in **Figure 4.1**.

4.3.3 Model evaluation

The GOF plots of the final model, stratified on renal function (CKD-EPI), bodyweight (TBW), and ICU admission status, are shown in **Supplementary Figure S4.1**. The figure shows that observed vancomycin concentrations are described without bias in all subpopulations, with the exception of the group with the worst kidney function (CKD-EPI < 30 mL/min/1.73 m²) in which a small trend towards under-prediction can be seen.

The bootstrap analysis (presented in **Table 4.2**) confirmed the robustness of the parameter estimates in the final model. Bootstrapped median values generally deviated less than 10% from the original estimate and all originally estimated values were within the 95% confidence interval (CI) of the bootstrapped values.

Table 4.2 Population pharmacokinetic parameter estimates of vancomycin for the final model for overweight and obese patients and otherwise healthy obese subjects, and results of bootstrap analysis

Parameters	Final model (RSE%)	Bootstrap median [95% CI]
$CL(L/h) = TVCL \times \left(\frac{CKDEPI}{75} \right)^{\theta_1} \times [1 + \theta_2 \times (TBW - 90)] \times F_{ICU}$		
$TVCL$	3.36 (2.60)	3.35 (3.17~3.56)
θ_1	0.658 (3.10)	0.657 (0.526~0.773)
θ_2	0.0106 (13.8)	0.0105 (0.00806~0.0129)
F_{ICU}^a	0.845 ^a (2.30)	0.841 (0.717~0.963) ^a
$V1$ (L)	16.7 (14.0)	16.8 (11.7~23.1)
$Q2$ (L/h)	16.1 (11.5)	16.0 (14.0~18.7)
$V2$ (L)	23.1 (3.60)	23.1 (19.7~25.8)
$Q3$ (L/h)	2.44 (8.00)	2.47 (1.90~3.91)
$V3$ (L)	83.0 (4.50)	83.2 (65.3~111.2)
Inter-individual variability (ω^2)		
CL	0.0730 (10.5)	0.0730 (0.0503~0.104)
$V1$	0.978 (29.1)	0.926 (0.428~1.48)
Residual unexplained variability		
PA data: additive error (mg/L)	9.32 (3.20)	9.26 (7.98~10.9)
HS data: proportional error (–)	0.00216 (41.2)	0.00231 (0.000278~0.00571)
HS data: additive error (mg/L)	1.10 (15.4)	0.783 (0.119~2.30)

CL clearance, $V1$ volume of distribution of central compartment, $V2$ volume of distribution of peripheral compartment 2, $V3$ volume of distribution of peripheral compartment 3, $Q2$ inter-compartmental clearance between $V1$ and $V2$, $Q3$ inter-compartmental clearance between $V1$ and $V3$, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation (indexed, mL/min/1.73 m²), TBW total bodyweight (kg), F_{ICU} scaling factor to be used for ICU patients, PA patients (ICU and non-ICU), HS obese but otherwise healthy subjects undergoing bariatric surgery, RSE relative standard error, CI confidence interval

^a The parameter is 1 in the case that the patient is not admitted to ICU

Visual inspection and statistical tests of the NPDE results based on 1000 simulation shows the final model have had a good predictive performance for subpopulations with different renal function, bodyweights, and ICU admission status (**Supplementary Figure S4.2**). The model is shown to accurately describe typical trends as well as the variability in the populations.

4.3.4 Model-based dose optimization

To achieve AUC_{24} exposure of 400~600 mg·h/L in overweight and obese patients with varying degrees of renal function, dosing guidelines for continuous infusion and intermittent dosing regimens were developed. The regimens for the ward patients are

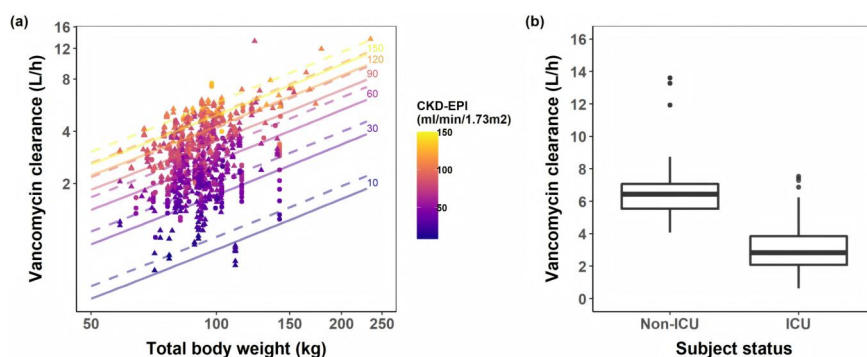
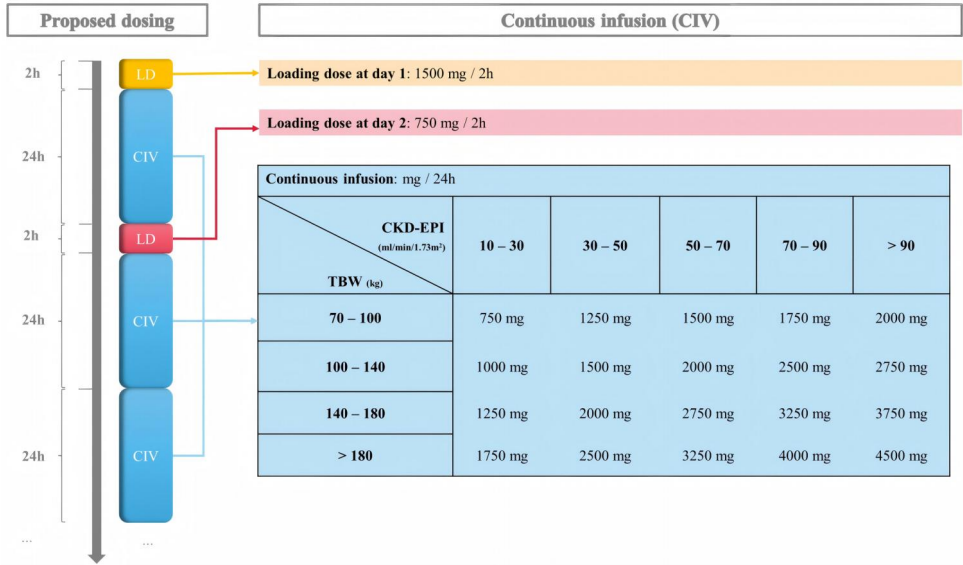


Figure 4.1 Illustration of covariate effects on vancomycin clearance (CL) in overweight and obese individuals with varying renal function. **(a)** Individually predicted CL values *versus* bodyweight (symbols) and population-predicted CL values *versus* bodyweight (lines) (log scale for both x - and y -axes). Non-ICU subjects are indicated by triangles and dashed lines and ICU patients by circles and solid lines. The color of symbols and lines vary with renal function expressed as CKD-EPI as indicated in the legend. **(b)** The distributions of individually predicted CL values are shown as a boxplot for non-ICU and ICU patients ($p < 0.001$). The boxplot shows the median and interquartile ranges. Whiskers represent values from interquartile to maximum or minimum; values beyond the minimum or maximum are drawn as circles. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation. Note: The y -axes are different in **(a)** and **(b)**

shown in **Figures 4.2** and **4.3**, while those for the ICU patients are shown in **Figures 4.4** and **4.5**. These tables present that for both schemes, higher doses are needed with increasing bodyweight and renal function, and in non-ICU patients compared with ICU patients.

To obtain the vancomycin therapeutic exposure immediately at the start of the treatment, two loading dose administrations for both continuous infusion and intermittent dosing regimens were required. For continuous infusion, a loading dose of 1500 mg is given as a 2-h infusion before starting the maintenance infusion on day 1, and another loading dose of 750 mg is given over 2 h on day 2, after which the maintenance infusion is continued. In patients on an intermittent dosing, two loading doses given as a 2-h infusion at 12-h intervals are proposed on the first day of treatment. From the second day onwards, maintenance doses can be given one or two times per day depending on the patient renal function, bodyweight, and ICU admission status. More details of these dosing regimens can be found in **Figures 4.2**, **4.3**, **4.4** and **4.5**.

The obtained daily AUC_{24} and concentration profiles in the first week of treatment for the defined representative virtual individuals with various combinations of the



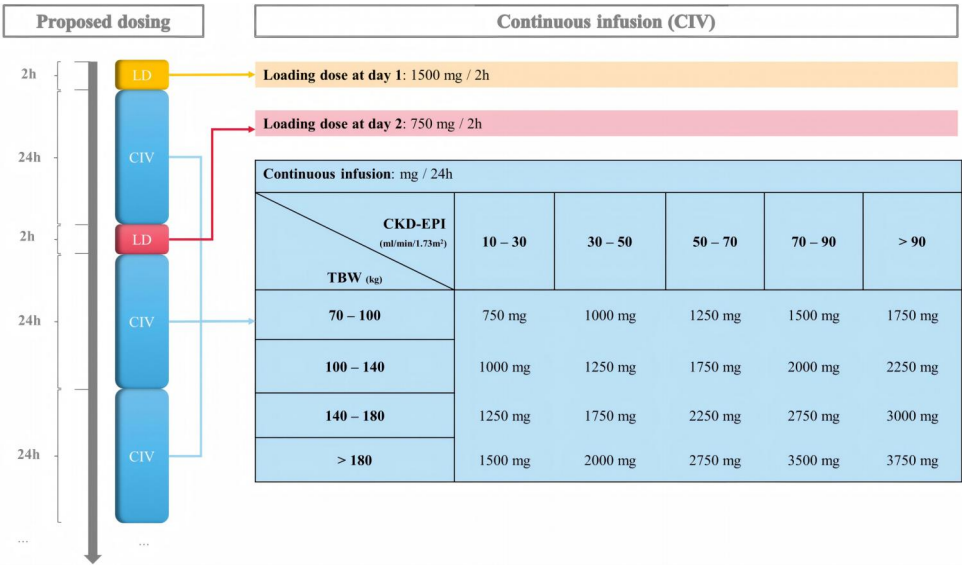


Figure 4.4 Dosing guideline for vancomycin in overweight and obese patients (**ICU patients**) with varying renal function receiving continuous infusion. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation

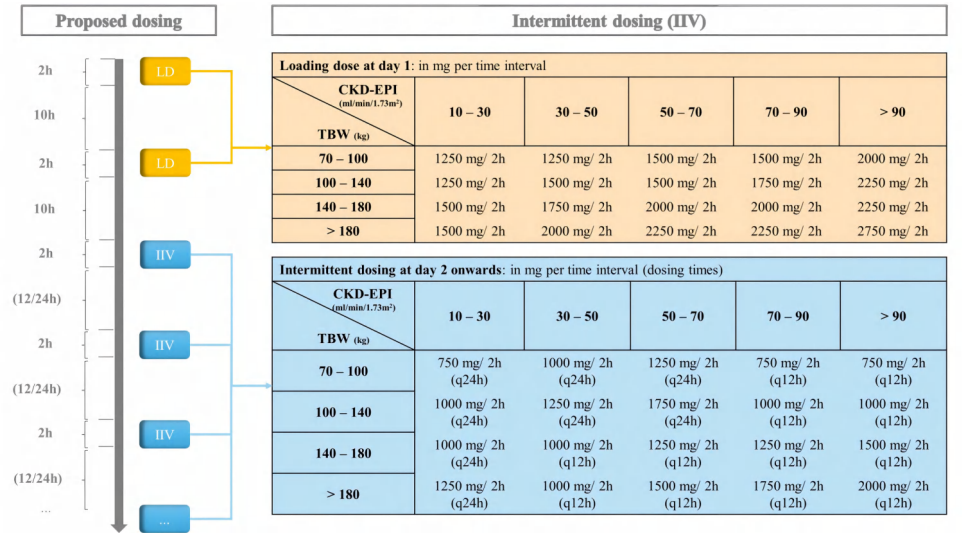


Figure 4.5 Dosing guideline for vancomycin in overweight and obese patients (**ICU patients**) with varying renal function receiving intermittent dosing regimen. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation, q24h once daily, q12h twice daily

bodyweight and renal function are illustrated in **Figures 4.6 and 4.7**, for the ward patients and ICU patients, respectively. These figures indicate that when our proposed guidelines for either continuous infusion or intermittent dosing are applied, the median AUC_{24} is within the target of 400~600 mg·h/L, regardless of renal function, bodyweight, and ICU admission status, even though for some ICU subgroups AUC may be slightly above 600 mg·h/L (**Figure 4.7**). However, even though the AUC_{24} generally reaches the target, the concentrations that are obtained across the entire patient population are highly variable and often lower than previously used target concentrations. More specifically, median (interquartile range) values of (trough) concentration for continuous infusion and intermittent dosing are 23.08 (19.54~27.29) mg/L and 16.89 (12.65~20.50) mg/L, respectively. These figures also show that time to steady-state concentrations in obese patients, particularly in those with renal dysfunction admitted to the ICU, exceeds 5 days.

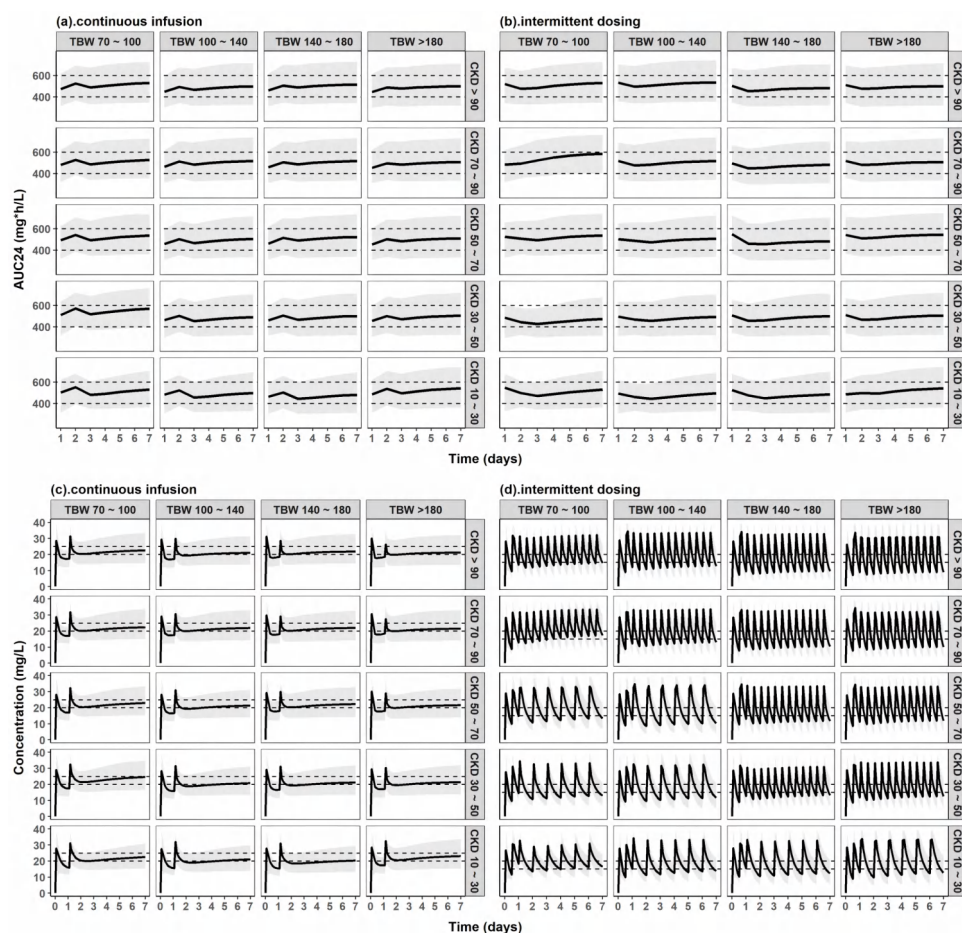


Figure 4.6 Vancomycin 24-h area under the curve values (AUC₂₄) (a, b) and concentrations (c, d) in the 7 days of treatment for representative virtual individuals from four bodyweight groups with renal functions estimates of 100, 80, 60, 40 and 20 mL/min/1.73 m² (**non-ICU patients**) receiving continuous infusion (a, c) and intermittent dosing regimen (b, d) on the basis of our proposed dosing guideline (see Figures 4.2, 4.3). Dashed lines in the plots of AUC₂₄ (a, b) represent the targeted efficacy and safety range, while in the plots of concentration (c, d) represent the defined concentrations corresponding to therapeutic range of the AUC₂₄ according to the literature (20~25 mg/L for continuous infusion and 15~20 mg/L for intermittent dosing regimens). The shaded areas represent the 95% prediction interval of the predicted AUC₂₄ or concentration. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation in (mL/min/1.73 m²), TBW total bodyweight in kg

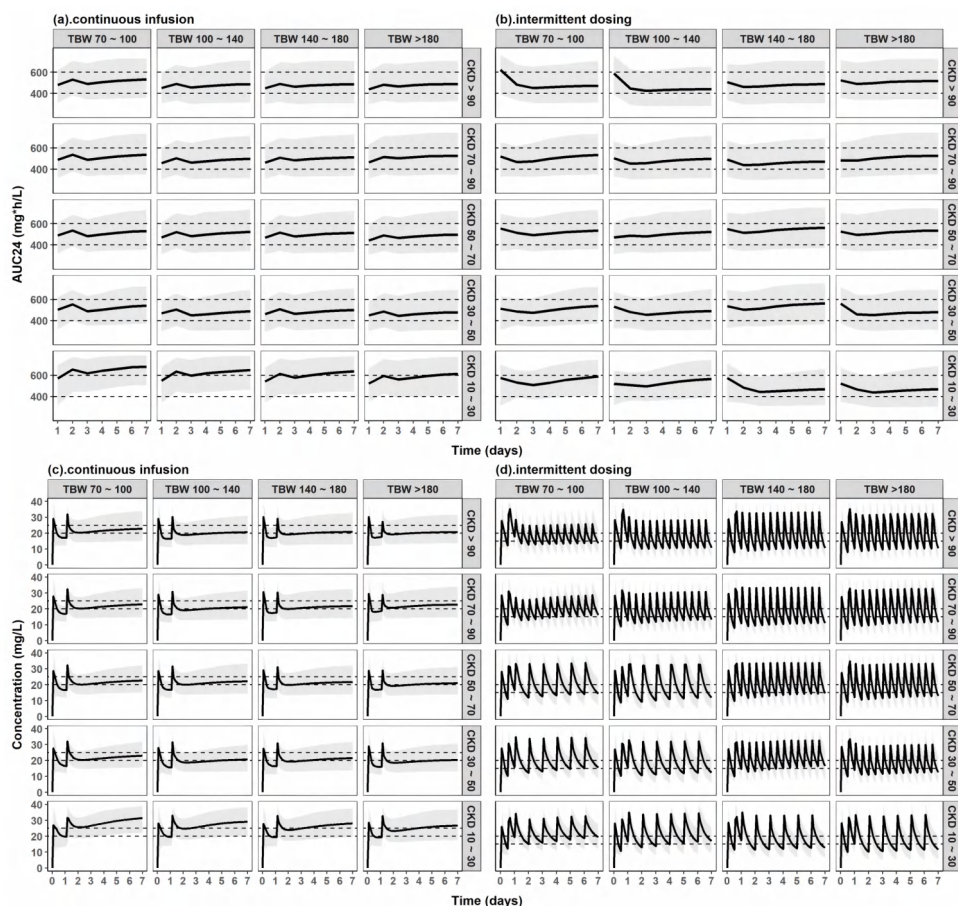


Figure 4.7 Vancomycin 24-h area under the curve values (AUC_{24}) (a, b) and concentrations (c, d) in the 7 days of treatment for representative virtual individuals from four bodyweight groups with renal functions estimates of 100, 80, 60, 40 and 20 mL/min/1.73 m² (ICU patients) receiving continuous infusion (a, c) and intermittent dosing regimen (b, d) on the basis of our proposed dosing guideline (see Figures 4.4, 4.5). Dashed lines in the plots of AUC_{24} (a, b) represent the targeted efficacy and safety range, while the plots of concentration (c, d) represent the defined concentrations corresponding to therapeutic range of the AUC_{24} according to the literature (20~25 mg/L for continuous infusion and 15~20 mg/L for intermittent dosing regimens). The shaded areas represent the 95% prediction interval of the predicted AUC_{24} or concentration. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation in (mL/min/1.73 m²), TBW total bodyweight in kg

4.4 Discussion

In this study, we quantified vancomycin PK in a large and representative clinical population, covering patients with varying degrees of overweight or obesity and renal function who were admitted to the hospital ward or ICU. Using the obtained insights, we proposed dosing guidelines for both continuous infusion and intermittent dosing regimens taking renal function, bodyweight, and ICU admission status into account. The proposed model-derived regimen is expected to yield better initial dosing and may reduce requirements for dose adjustment. Following our developed dosing guideline, daily AUC_{24}/MIC exposure is maintained between 400 and 600 mg h/L in patients with varying degrees of obesity and renal function who are admitted to the hospital ward or ICU. The AUC_{24}/MIC target of 400~600 mg·h/L was chosen to ensure clinical efficacy while enhancing patient safety, which is in line with the advice given by the recently released vancomycin consensus guideline [4, 18]. The vancomycin MIC is assumed to be 1 mg/L because the vancomycin MIC for serious infections (e.g., MRSA) is 1 mg/L at most institutions [19]. In cases of increased MIC values, the proposed doses should be increased proportionally, even though, in case the MIC is above 2 mg/L, an alternative agent would probably be preferable.

Achieving targeted AUC_{24} exposures within the initial 24~48 h of the vancomycin treatment course is recommended for early and appropriate therapy [19]. To achieve this, loading doses are necessary. Traditional vancomycin loading doses are administered in mg per kg as a 2-h infusion before the maintenance dose begins. However, on the basis of our model, we developed a dosing guideline for overweight and obese individuals with varying renal functions that involve two loading doses. For continuous infusion, a loading dose of 1500 mg is given as a 2-h infusion before starting the maintenance infusion on day 1, and another loading dose of 750 mg is given as a 2-h infusion on day 2, after which the maintenance infusion is continued. For intermittent dosing regimen, two loading doses are administered every 12 h on the first day to quickly achieve an effective and safe exposure. Even though this is a deviation from current clinical practice, these loading doses are necessary to achieve effective exposure early in the treatment.

Even though the AUC_{24} reaches the target range for most individuals with the proposed regimen, concentrations tend to fall below the commonly expected target ranges

4 with continuous infusion and intermittent dosing. This suggests that dose adjustment based on concentration at the early stages of treatment may result in concentration and AUC_{24} values outside the target window at later time points. Therefore, we recommended using AUC_{24} values, rather than solely relying on trough concentration values, to interpret TDM samples to guide dosing adjustments. AUC_{24} values can be accurately and reliably obtained by a Bayesian dose-optimization software program that embeds an appropriate reference population PK model. For overweight and obese patients, especially those with renal dysfunction admitted to ICU, particular attention should be paid as the time to steady-state might be prolonged to over a week, but with the appropriate software and models this will be taken into account properly [20].

Readily available and convenient biomarkers for renal function remain limited in overweight and obese patients, as most of the equations calculating renal function estimates are not confirmed in this population [21]. In fact, the equation of CG, which is commonly used, has been reported to have a low accuracy and high bias in estimating glomerular filtration rate in patients with obesity and should therefore be avoided [22, 23]. In our study, among the renal function estimates available in clinical practice, we found indexed CKD-EPI to be superior to CG and other renal function estimates, in correlation with vancomycin CL , which is in line with the vancomycin PK study of Kim *et al.* [24]. Moreover, our study confirmed that in overweight and obese populations, TBW is better correlated with CL than other bodyweight descriptors [8]. However, this is not always the case, as for cefazolin and ciprofloxacin, CL remains unchanged with different degrees of obesity [25, 26].

In addition to renal function and bodyweight, ICU admission status was identified as a significant independent covariate on CL , indicating differences between subjects from ICU and non-ICU. The age of ICU and non-ICU patients is comparable (median [range] values for ICU *versus* non-ICU: 70 [33–88] *versus* 71 [35–92] years). In addition, the eGFR range is similar between patients in the two settings (ICU 75 [20–155] *versus* non-ICU 74 [6–137] mL/min/1.73 m²). The potential reason for different CL in these two settings could be that rapidly varying disease states of ICU patients can lead to reduced kidney function and limited drug elimination [27], with serum creatinine being an inappropriate and/or late marker to indicate this [28]. Interestingly, Smit *et al.* also identified ICU status as an independent predictor for CL in a

comparable gentamicin PK study, reporting a 24.9% reduced *CL* in ICU patients [29]. These results contradict a seeming consensus from several studies indicating an augmented renal clearance ($\text{eGFR} > 130 \text{ mL/min/1.73 m}^2$) in critically ill patients [30–32]. This difference could be because compared with the other studies, our study included patients with more severe concomitant disease, but without trauma or burns. Future research investigating the underlying cause of the decreased *CL* in obese individuals with critical illnesses should be considered.

In this study, we included patients undergoing bariatric surgery receiving a single dose of vancomycin and patients treated with vancomycin for infections, resulting in a group covering a broad spectrum of bodyweight. However, patients with a bodyweight higher than 143 kg all had a good renal function. As a result, our dosing guidelines in this group are based on less evidence compared with the group below 143 kg. Moreover, as our dataset included only 15 patients (6.52%) with extremely poor renal function ($\text{CKD-EPI} < 30 \text{ mL/min/1.73 m}^2$), caution is warranted when employing the proposed dosing recommendation for this subgroup. In addition, the lack of covariates and the large inter-individual variability in volume may be due to the fact that we did not have enough peak samples to fully characterize volume and its covariates. However, for the AUC-targeted dose, *CL* is the primary parameter of interest, whereas volume is mainly related to the time to reach steady state. Because we had many (trough) samples both early after initiation of treatment and after several weeks of treatment, we are convinced that our model can be used for AUC-targeted dosing, which was the overall goal of our study, even though it may not accurately predict the peak concentration reached immediately after a 2-h infusion dose.

4.5 Conclusion

When dosing vancomycin in overweight and obese patients, renal function, bodyweight, and ICU admission status should be taken into account to get safe and effective vancomycin exposure. We propose a practical vancomycin dosing guideline for both continuous infusion and intermittent dosing regimens that can be used for this purpose.

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Supplementary Material

Table S4.1 Equations used for different bodyweight descriptors and renal function estimates.

Covariate	Equation	Reference
Body weight descriptors		
TBW (kg)	–	–
BMI (kg/m ²)	$TBW/Height^2$	–
BSA (m ²)	$\sqrt{TBW \times Height/3600}$	[1]
IBW (kg)	Male: $50.0 + 2.3 \times (Height \times 0.3937 - 60)$ Female: $45.5 + 2.3 \times (Height \times 0.3937 - 60)$	[2]
ABW (kg)	$IBW + 0.4 \times (TBW - IBW)$	[3]
LBW (kg)	Male: $(9.27 \times 10^3 \times TBW)/(6.68 \times 10^3 + 216 \times BMI)$ Female: $(9.27 \times 10^3 \times TBW)/(8.78 \times 10^3 + 244 \times BMI)$	[4]
Renal function estimates		
Indexed CKD-EPI (mL/min/1.73m ²)	Male & Scr ≤ 0.9 (mg/dL): $141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age} \times F$	[5]
	Male & Scr > 0.9 (mg/dL): $141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age} \times F$	
	Female & Scr ≤ 0.7 (mg/dL): $141 \times (Scr/0.7)^{-0.329} \times 0.993^{Age} \times F$	
	Female & Scr > 0.7 (mg/dL): $141 \times (Scr/0.7)^{-1.209} \times 0.993^{Age} \times F$	
	F: if black people, F = 1.15, otherwise F = 1	
De-indexed CKD-EPI (mL/min)	$CKD-EPI \times BSA/1.73$	
Indexed MDRD (mL/min/1.73m ²)	Male: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times F$	[6]
	Female: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times 0.742 \times F$	
	F: if black people, F = 1.212, otherwise F = 1	
De-indexed MDRD (mL/min)	$MDRD \times BSA/1.73$	
CG-TBW (mL/min)	Male: $(140 - Age) \times TBW/(0.815 \times Scr)$	[7]
	Female: $(140 - Age) \times TBW/(0.815 \times Scr) \times 0.85$	
CG-LBW (mL/min)	Male: $(140 - Age) \times LBW/(0.815 \times Scr)$	[8]
	Female: $(140 - Age) \times LBW/(0.815 \times Scr) \times 0.85$	

TBW, total bodyweight; LBW, lean bodyweight; ABW, adjusted bodyweight; BSA, body surface area; BMI, body mass index; CKD-EPI, renal function calculated by chronic kidney disease epidemiology collaboration; MDRD, renal function calculated by modification of diet in renal disease; CG-TBW, renal function calculated by Cockcroft-Gault with total bodyweight (conventional); CG-LBW, renal function calculated by CG calculated with lean bodyweight; Scr, serum creatinine.

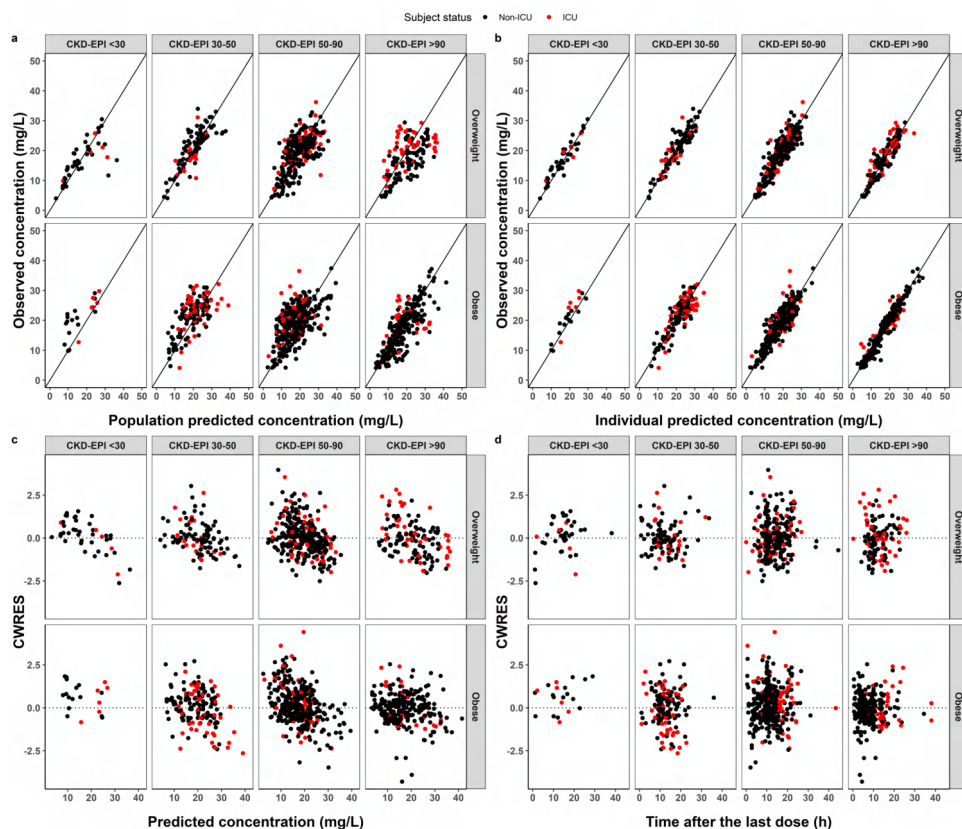


Figure S4.1 Goodness-of-fit plots of the final pharmacokinetic model for vancomycin in overweight and obese adults. (a) observed concentration *versus* population predicted concentration; (b) observed concentration *versus* individual predicted concentration; (c) conditional weighted residuals (CWRES) *versus* population predicted concentration; (d) CWRES *versus* time after the last dose. Black dots represent non-ICU patients, red dots represent ICU patients. Indexed CKD-EPI represents the estimated renal function calculated by chronic kidney disease epidemiology collaboration in mL/min/1.73m^2 .

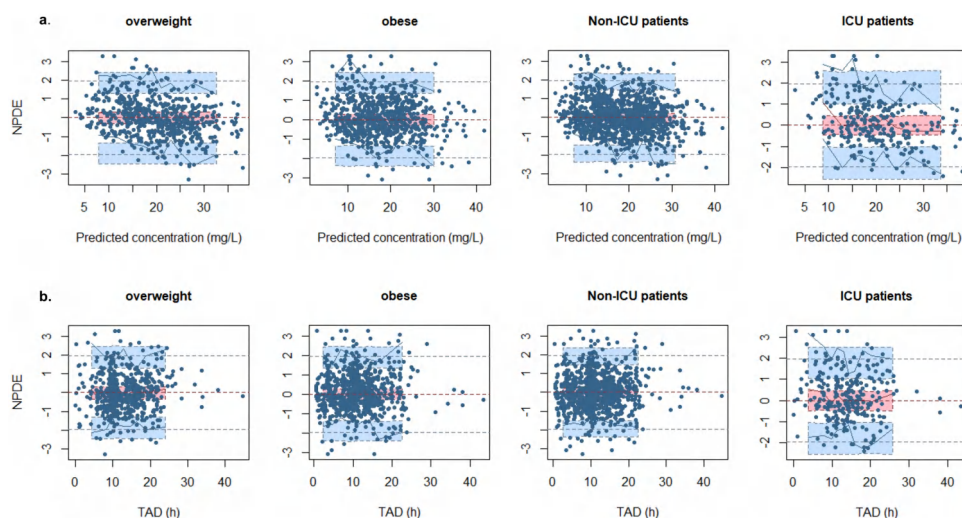


Figure S4.2 Normalized prediction distribution error (NPDE) versus **(a)** population predicted concentrations and **(b)** time after last dose (TAD) of the final model for vancomycin, based on 1000 simulations. Plots are stratified on bodyweight (overweight *versus* obese) and ICU-admission status (non-ICU *versus* ICU). The blue dots represent the NPDE of the observations. The dashed lines represent the theoretical 5th, 50th, and 95th percentiles of the NPDE. The color shaded areas represent the 95% confidence intervals around the simulated 5th, 50th, and 95th percentiles. The solid lines represent the 5th, 50th, and 95th percentiles of the observed NPDE values.

Supplementary References

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III

Physiologically-based
pharmacokinetic modeling to
understand obesity-related
change in clearance and guide
dosing in obese patients

5

Impact of obesity on hepatic drug clearance: what are the influential variables?

This chapter is based on  Zhang T, et al. *Impact of obesity on hepatic drug clearance: what are influential variables?* *The AAPS Journal* 2024; 26(3): 59.

ABSTRACT

Background

Drug clearance in obese subjects varies widely among different drugs and across subjects with different severity of obesity. This study investigates correlations between plasma clearance (CL_p) and drug- and patient-related characteristics in obese subjects, and evaluates the systematic accuracy of common weight-based dosing methods.

Methods

A physiologically-based pharmacokinetic (PBPK) modeling approach that uses recent information on obesity-related changes in physiology was used to simulate CL_p for a normal-weight subject (body mass index [BMI] = 20 kg/m²) and subjects with various severities of obesity (BMI 25–60 kg/m²) for hypothetical hepatically cleared drugs with a wide range of properties. Influential variables for CL_p change were investigated. For each drug and obese subject, the exponent that yields perfect allometric scaling of CL_p from normal-weight subjects was assessed.

Results and Conclusions

Among all variables, BMI and relative changes in enzyme activity resulting from obesity proved highly correlated with obesity-related CL_p changes. Drugs bound to α 1-acid glycoprotein (AAG) had lower CL_p changes compared to drugs bound to human serum albumin (HSA). Lower extraction ratios (ER) corresponded to higher CL_p changes compared to higher ER. The allometric exponent for perfect scaling ranged from –3.84 to 3.34 illustrating that none of the scaling methods performed well in all situations. While all three dosing methods are generally systematically accurate for drugs with unchanged or up to 50% increased enzyme activity in subjects with a BMI below 30 kg/m², in any of the other cases, information on the different drug properties and severity of obesity is required to select an appropriate dosing method for individuals with obesity.

5.1 Introduction

Overweight (body mass index [BMI] ≥ 25 kg/m²) and obesity (BMI > 30 kg/m²) are increasing worldwide. Clearance (CL) is the primary pharmacokinetic (PK) parameter driving exposure and required drug dosing. Literature suggests that the absolute CL of some drugs increases with obesity [1–4], while for other drugs CL does not change [5–7] or even decreases [8, 9], without single drug properties like elimination pathway being predictive for the nature of these changes [10]. Besides, studies on drugs such as propofol [11–14] or ceftaroline [15] show that the conclusions regarding changes in drug CL with obesity may vary depending on the severity of obesity in the studied subjects. This drug and patient-dependent variability in changes in CL makes it challenging for clinicians to determine the appropriate drug dosages for subjects with obesity. Due to the complex interplay between different variables, the impact of changes in patient-related variables may be different between different drugs, depending on their drug properties. Therefore, it is important to study which drug- and patient-related variables are influential in driving obesity-related changes in CL .

In practice, dosing methods in obese patients rely either on a flat dose strategy (same dose in obese as in normal-weight subjects) or a bodyweight-based scaling such as allometric scaling with an exponent of 0.75 ($AS_{0.75}$) or with an exponent of 1 (linear scaling) [10, 16]. The accuracy of these dosing methods in the obese population has however not been systematically assessed, particularly not taking different drug properties and severity of obesity into consideration.

Physiologically-based PK (PBPK) modeling is ideally suitable to investigate the impact of obesity-related physiological changes on PK parameters, including plasma CL (CL_p), for drugs with different properties. As such, this approach can also be used to assess the accuracy of scaling methods for drugs with different properties [17–19]. In the absence of obesity-related clinical PK data, this can provide a yardstick for scaling drug CL_p from normal-weight subjects to those with obesity. This in turn can inform required drug dosing adjustments for this population. Calvier *et al.* [17] developed a PBPK-based workflow written in R to systematically evaluate the accuracy of scaling approaches for pediatric CL_p , which can be extended to other special populations. This workflow can define scenarios in which specific dosing methods are or

are not accurate and/or the minimal information required to determine the accuracy of weight-based scaling methods.

In this study, we developed a PBPK-based workflow to study obesity-related changes in CL_p in subjects with varying severity of obesity for hypothetical drugs with a wide range of properties that undergo hepatic metabolism, as an extension to the pediatric PBPK-based workflow [17]. Within this workflow, the systematic accuracy of commonly used dosing methods is investigated to identify variables under which they yield systematically accurate CL_p values.

5.2 Materials and methods

5

A PBPK-based simulation workflow was developed analogous to the pediatric PBPK workflow published by Calvier *et al.* [17] using R (version 4.0.3) under R studio (version 1.1.43). This workflow consists of four steps as visualized in **Figure 5.1** and described below:

5.2.1 Step 1: CL_p for normal-weight and obese subjects

Drug-specific parameters

A total of 17,600 hypothetical drugs undergoing hepatic metabolism were generated using all possible combinations of the following drug-specific properties with realistic ranges defined for normal-weight individuals [18, 20–22]: **1)** the unbound drug fraction in plasma (f_u), which ranged from 1 to 100%, with eight equidistant intermediate values; **2)** the type of drug binding plasma protein, for which the drugs were assumed to exclusively bind to either human serum albumin (HSA) and α 1-acid glycoprotein (AAG); **3)** blood-to-plasma partition coefficient (K_p), which varied between 0.35 and 40 with 11 different values (i.e., 0.35, 0.8, 1, 2, 3, 4, 5, 10, 20, 30 and 40) [23, 24]; and **4)** the unbound intrinsic CL value for one microgram of liver microsomes (CL_{int_mic}), which reflects both enzyme affinity and abundance and which ranged from $0.56 \cdot 10^{-6}$ to $0.209 \cdot 10^{-3} \text{ mL} \cdot \text{min}^{-1} \cdot \mu\text{g}^{-1}$ microsomal protein with 100 equidistant intermediate values.

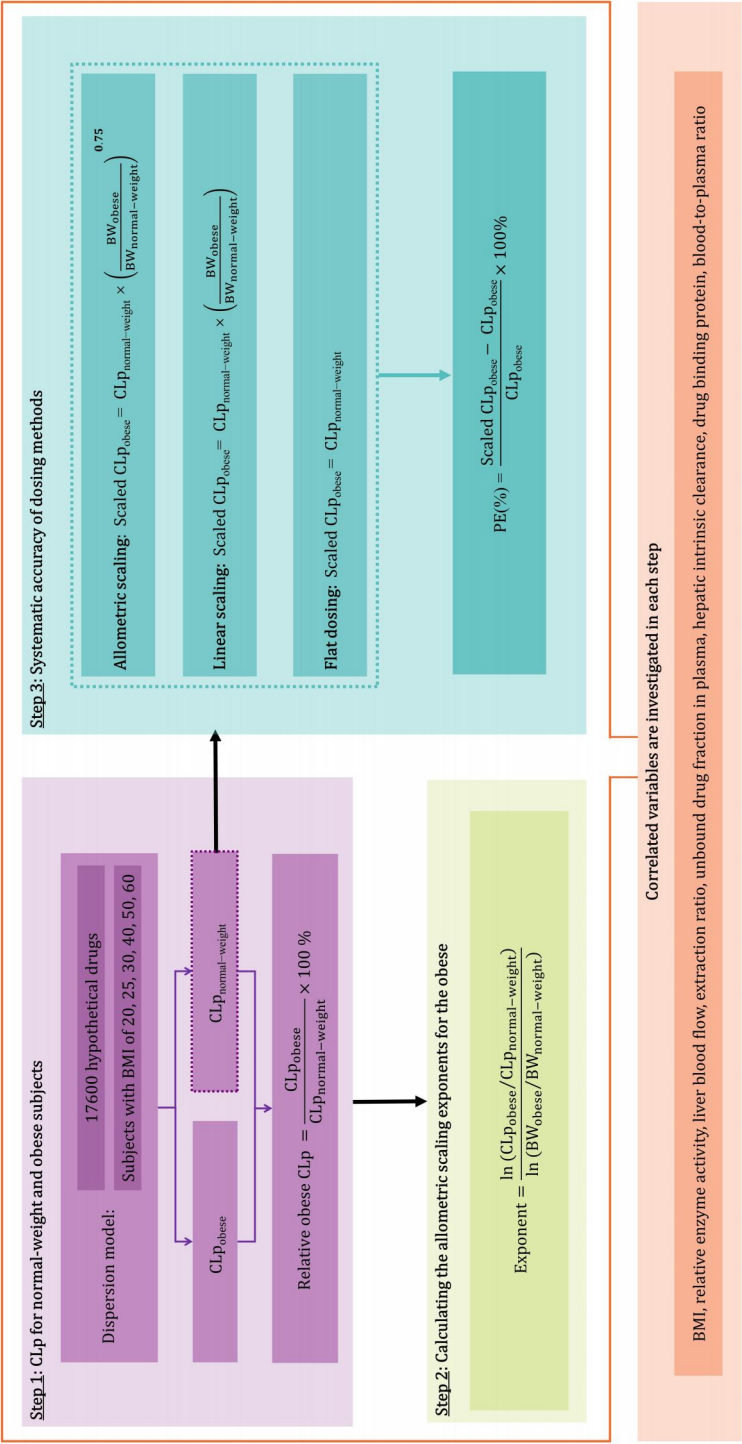


Figure 5.1 Schematic representation of the physiologically-based pharmacokinetic simulation workflow. CL_p , hepatic plasma clearance; BW, body weight; PE, prediction error

Subject-specific parameters

PBPK simulations were performed for a representative normal-weight subject with a BMI of 20 kg/m², as well as for five representative subjects with varying class of overweight or obesity, with BMIs of 25, 30, 40, 50, and 60 kg/m². The weight for these subjects was calculated based on their BMI and a typical height of 1.72 meters, which is the median height for adults in the National Health and Nutrition Examination Survey (NHANES) database [25]. This yields a bodyweight of 59.2 kg for the normal-weight subject and 74.0, 88.8, 118.3, 148.0, and 177.5 kg for the overweight and obese subjects, respectively.

Subject-specific parameters for each representative subject, including hepatic blood flow (Q_h), plasma concentrations for HSA and AAG, hematocrit, liver weight, and milligram protein per gram of liver (MPPGL) were calculated based on the equations reported by Berton *et al.* [26]. The demographic characteristics of the typical subjects implemented in the PBPK-based simulation workflow and their corresponding subject-specific parameter values are provided in **Supplementary Table S5.1**. Obesity-related change in fu , total hepatic intrinsic clearance (CL_{int}), and blood-to-plasma ratio ($B : P$) were calculated using **Equations 5.1–5.3**, respectively.

$$fu_{obese} = \frac{1}{1 + \frac{(1 - fu_{normal\ weight}) \times PP_{obese}}{fu_{normal\ weight} \times PP_{normal\ weight}}} \quad (5.1)$$

$$CL_{int} = CL_{int_mic} \times MPPGL \times Liver\ weight \times rEA \quad (5.2)$$

$$B : P = 1 + (Hematocrit \times (fu \times K_p - 1)) \quad (5.3)$$

In these equations, $fu_{normal\ weight}$, CL_{int_mic} and K_p were taken from the values for the hypothetical drugs for the normal-weight subject as defined above. PP is the concentration of plasma protein which was assumed to be either HSA or AAG. According to the equations reported by Berton *et al.* [26], PP and liver weight vary with BMI while hematocrit remains constant (**Supplementary Table S5.1**). In the absence of information on changes in K_p , this parameter was assumed to remain constant across

the BMI range. Consequently, the impact of obesity on $B : P$ is solely attributable to fu . As it is unknown how obesity impacts the CL_{int_mic} of the hepatic enzymes, scenarios with different relative enzyme activity (rEA in obesity) were investigated. For this, rEA values of 40%, 60%, 80%, 100%, 120%, 140%, 160%, and 180% of normal enzyme activity were selected, which is in line with reported changes in the obese on the basis of *in vitro* data [27]. Here, a rEA value of 100% indicates no change in enzyme activity compared to normal-weight subjects.

PBPK model

The dispersion model (**Equations 5.4–5.7**) was used to obtain PBPK-based CL_p values for all drugs and all subjects defined above. This model was selected as it has been reported to predict hepatic CL_p more accurately than the well-stirred model for highly cleared drugs, while both models lead to equivalent clearance predictions for other drugs [28].

$$CL_p = Q_h \times ER \times B : P \quad (5.4)$$

$$ER = 1 - \frac{4a}{(1+a)^2 e^{(a-1)/2D_N} - (1-a)^2 e^{(a+1)/2D_N}} \quad (5.5)$$

$$a = (1 + 4R_N \times D_N)^{1/2} \quad (5.6)$$

$$R_N = (fu/B : P) \times CL_{int}/Q_h \quad (5.7)$$

In these equations, CL_p is the total hepatic metabolic plasma clearance, Q_h is the hepatic blood flow, ER is the extraction ratio, $B : P$ is the blood-to-plasma ratio, fu is the unbound drug fraction in plasma, CL_{int} is the total hepatic intrinsic clearance, R_N is the efficiency number, and D_N is the axial dispersion number for which a value of 0.17 was used [29].

After the CL_p was generated for the representative subjects, relative CL_p in the obese was calculated according to **Equation 5.8**, reflecting obese CL_p as a percentage of

normal-weight CL_p . Correlations between the relative CL_p in the obese and drug or subject characteristics were investigated to identify the influential variables for predicting CL_p for subjects with obesity.

$$\text{Relative obese } CL_p = \frac{CL_{p_obese}}{CL_{p_normal \text{ weight}}} \times 100\% \quad (5.8)$$

5.2.2 Step 2: Calculating the allometric scaling exponents for the obese

For each drug and each obese subject, the allometric exponent that accurately scales CL_p from the normal-weight value, was calculated using **Equation 5.9** and the body-weights (BW) of the normal-weight subject and the obese subjects. Correlations between the exponent and drug or subject characteristics were visually inspected.

$$\text{Exponent} = \frac{\ln(CL_{p_obese}/CL_{p_normal \text{ weight}})}{\ln(BW_{obese}/BW_{normal \text{ weight}})} \quad (5.9)$$

5.2.3 Step 3: Systematic accuracy of dosing methods

Scale obese CL_p from normal-weight CL_p using different dosing methods

For each hypothetical drug, the normal-weight CL_p from step 1 was used to scale CL to obese subjects, using three commonly used bodyweight-based dosing methods (i.e., AS0.75, linear scaling and flat dosing). All three methods can be described using **Equation 5.10**:

$$\text{Scaled } CL_{p_obese} = CL_{p_normal \text{ weight}} \times \left(\frac{BW_{obese}}{BW_{normal \text{ weight}}} \right)^{\text{exponent}} \quad (5.10)$$

In **Equation 5.10**, the following three values were used for the exponent:

- 1) 0.75, this is also known as fixed allometric scaling and will be referred to as AS0.75,
- 2) 1, this is known as linear scaling, or
- 3) 0, this is known as flat dosing, which yields a constant CL_p value that does not

change with bodyweight.

Assess scaling accuracy

For each drug and each obese subject (defined by a unique combination of BMI and rEA), the accuracy of the three dosing methods was assessed. This was performed using the prediction error (PE) according to **Equation 5.11**, with scaled CL_{p_obese} corresponding to the CL_p scaled from normal-weight to obese using one of the three scaling methods, and CL_{p_obese} corresponding to the PBPK-based CL_p in obese subjects. Patterns in PE were assessed visually. Systematic scaling accuracy was defined as PE values of all hypothetical drugs being within $\pm 30\%$.

$$PE(\%) = \frac{\text{Scaled } CL_{p_obese} - CL_{p_obese}}{CL_{p_obese}} \times 100\% \quad (5.11)$$

5

5.3 Results

5.3.1 Variables correlating with changes in CL_p in obese subjects

The relative CL_p of all hypothetical drugs for the obese subjects with various BMI and rEA are shown in **Supplementary Table S5.2**. Its correlations with subject characteristics and drug properties are illustrated in **Figures 5.2** and **5.3**. These results demonstrate how subject characteristics and drug properties are correlated with obesity-related changes in CL_p .

Regarding subject characteristics, BMI is found to be strongly correlated with CL_p changes in obese subjects. **Table S5.2** indicates a significant increase in relative CL_p with increasing BMI values. For the situation where there is no change in enzyme activity (i.e., rEA is 100%), the relative CL_p in the obese varies from a value as low as 106% in overweight subjects with a BMI of 25 kg/m² to a maximum of 244% in morbidly obese subjects with a BMI of 60 kg/m². However, it is noteworthy that for overweight subjects with a BMI of 25 kg/m², the change in CL_p for all drugs was not more than 17%, suggesting a limited change in CL_p compared to the normal-weight subjects.

The correlations between relative CL_p in the obese and BMI are illustrated in **Figure**

5.2 and 5.3. **Figure 5.2** shows that as BMI increases, CL_{int} and hepatic blood flow all increase, albeit with varying magnitude, and that their correlations with obese relative CL_p become more pronounced. The rEA is an obesity-related physiological variable that is considerably correlated to changes in CL_p in obese subjects, as can be seen in **Supplementary Table S5.2** and **Figure 5.3**. When rEA varies from 40 to 180%, the relative CL_p in the obese increases approximately 4-, 2.5-, and 1.5-fold for drugs with low, intermediate, and high ER, respectively. It should be noted that relative CL_p decreases only when enzyme activity decreases.

In terms of drug properties, **Figure 5.2** provides insights into the correlation between relative CL_p in the obese with fu , in the absence of changes in enzyme activity. As fu and ER of drugs may change with obesity, in the description of drug properties these parameter values will refer to the values defined for each drug in the normal-weight subject. The patterns of the correlation between relative CL_p in the obese and fu differ between HSA- and AAG-bound drugs. For HSA, with fu of a drug increasing in normal-weight subjects, the relative CL_p in the obese is decreasing, especially when BMI is higher than 40 kg/m². For AAG this is the other way around. In addition to that, the differences between HSA- and AAG-bound drugs become more pronounced as BMI increases. Besides, the relative CL_p in the obese in HSA-bound drugs is generally higher than that of AAG-bound drugs. Moreover, as depicted in **Figure 5.2**, when CL_{int} increases, the relative CL_p in the obese only slightly changes for AAG-bound drugs. In contrast, an evident decline is observed in HSA-bound drugs, particularly among morbidly obese subjects.

The degree of hepatic ER of a drug in normal-weight subjects also shows a strong correlation with CL_p changes in obese subjects. As shown in **Supplementary Table S5.2**, a narrower range in relative CL_p in the obese is found for drugs with high ER compared to drugs with low ER (range of 62.6~215 versus 42.5~458), indicating that when ER is high, the relative CL_p is less variable and less dependent on obesity.

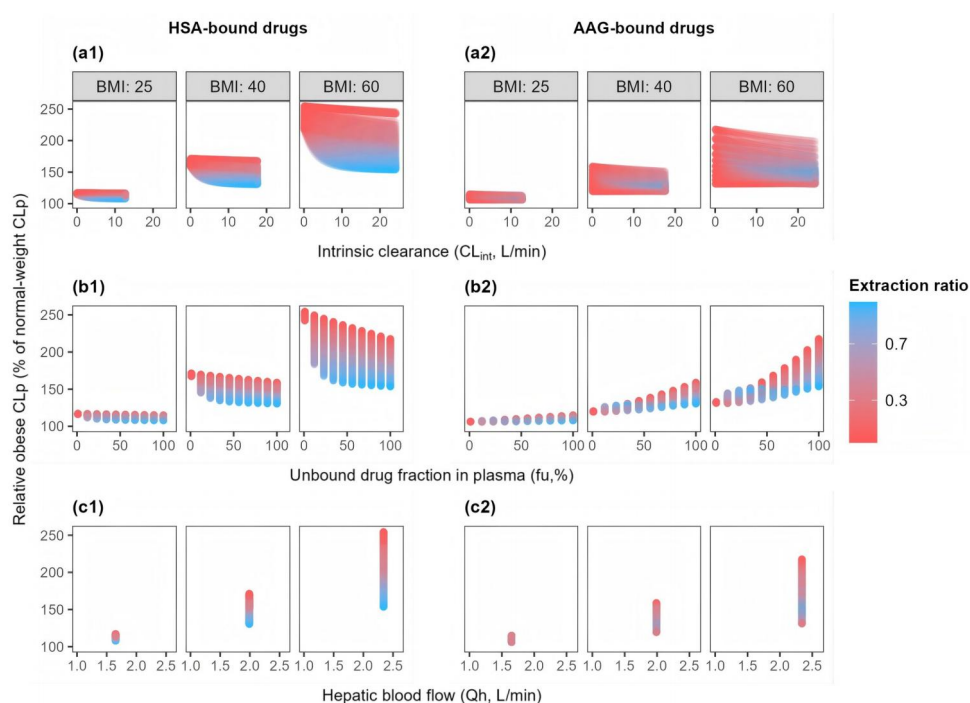


Figure 5.2 Correlation between the relative plasma clearance (CL_p) of subjects with body mass index (BMI) of 25, 40 and 60 kg/m² and (a1-a2) intrinsic clearance, (b1-b2) unbound drug fraction in plasma (f_u), and (c1-c2) hepatic blood flow for drugs bound to human serum albumin (HSA, left panel) and α 1-acid glycoprotein (AAG, right panel). Colors represent different extraction ratios. Note that the values of f_u and extraction ratio represent the values defined for the normal-weight subject. Some colors are overlapping

Moreover, as shown in **Figures 5.2** and **5.3**, the correlation between ER and relative CL_p is found to be more pronounced in subjects with higher BMI, especially in drugs with low to intermediate ER. Finally, these figures indicate that the correlation between ER and CL_p is highly dependent on the type of drug binding plasma protein. For HSA-bound drugs, relative CL_p in the obese is generally lower for drugs with high ER than for drugs with low ER, but this is not evident in AAG-bound drugs.

5.3.2 Scaling exponents for the obese

The allometric exponents for all hypothetical drugs are presented in **Supplementary Table S5.3** and are illustrated in **Figure 5.4**, categorized by BMI, rEA and drug properties. The correlations between the exponent and various drug properties or subject

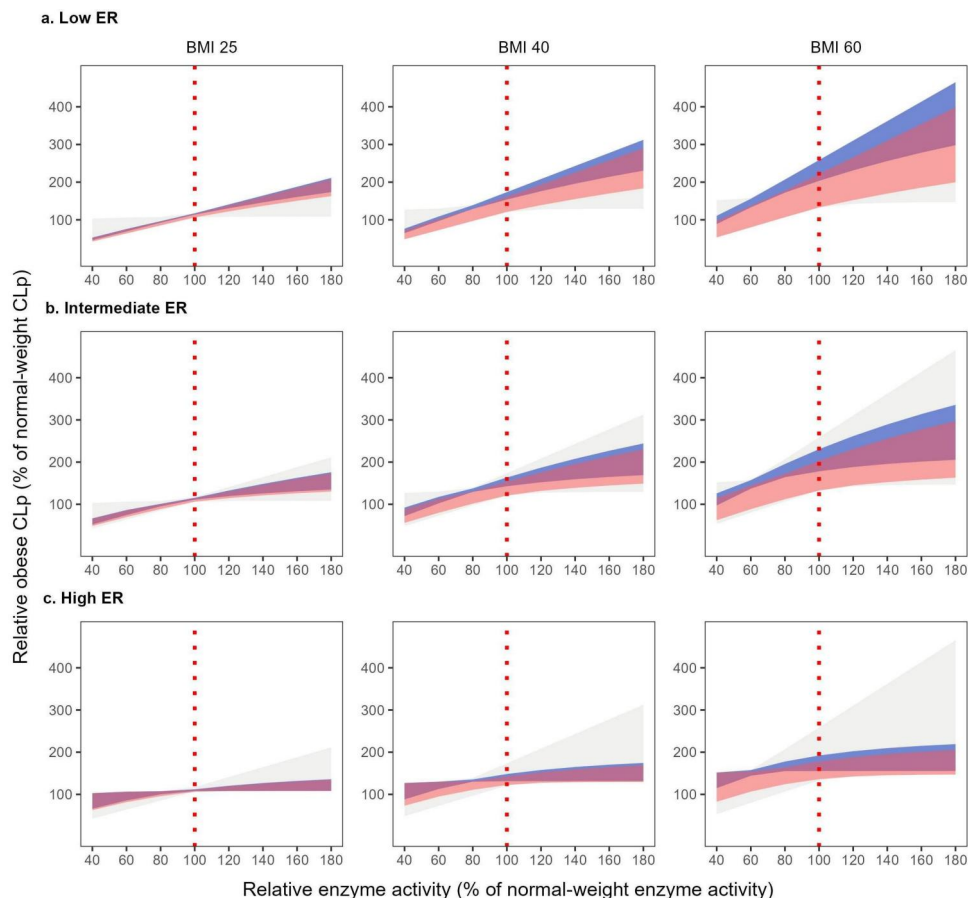


Figure 5.3 Correlation between the relative plasma clearance (CL_p) of subjects with body mass index (BMI) of 25, 40 and 60 kg/m^2 and representative relative enzyme activity for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER, and (c) high ER. Blue and pink areas represent drugs that bind to human serum albumin (HSA) or α 1-acid glycoprotein (AAG), respectively. The purple area represents drugs not binding to plasma proteins. The grey area represents all hypothetical drugs, allowing comparisons between the three plots of the same BMI. The red dotted line represents the scenario of no change in enzyme activity. Note that the values of the ER represent the values defined for the normal-weight subject

characteristics align with the correlations observed with the relative CL_p in the obese. According to **Supplementary Table S5.3**, the exponent that yields perfect scaling of obese CL_p values, ranges from -3.84 to 3.34 and is impacted strongly by rEA. In the absence of changes in rEA, the exponent ranges from 0.244 to 0.851 and decreases when the enzyme activity of a drug decreases in normal-weight subjects. Furthermore, as shown in **Figure 5.4**, drugs binding to AAG generally have a lower exponent compared to drugs binding to HSA, and drugs with higher ER generally have a smaller exponent compared to those with a lower ER.

5.3.3 Systematic accuracy of dosing methods

The accuracy of the predicted CL_p values in the obese obtained using the three different dosing methods (i.e., AS0.75, linear scaling, and flat dosing) was assessed using PE values and is provided in **Supplementary Table S5.4**. **Figures S5.1–S5.3** shows the accuracy of the three dosing methods, respectively AS0.75, linear scaling and flat dosing, and illustrate that none of the three methods can be universally applied.

Of the three investigated dosing methods, all of them are generally systematically accurate for subjects with overweight or obesity with a BMI below 30 kg/m^2 , with unchanged or up to 50% increased enzyme activity (**Figures S5.1–S5.3**). In any of the other cases, information on the drug binding plasma protein, ER, f_u , and relative change of enzyme activity is required to select an appropriate dosing method for the obese. Specifically, as shown in **Figure S5.3**, if the drugs bound to AAG have high ER, flat dosing performs generally accurately, regardless of the class of obesity. For drugs with low to intermediate ER, AS0.75 or linear scaling are more accurate, especially when there is a large (i.e., more than 60%) increase in enzyme activity for drugs binding to HSA (**Figures S5.1–S5.2**). When enzyme activity is reduced, flat dosing tends to be more accurate, especially for drugs binding to AAG.

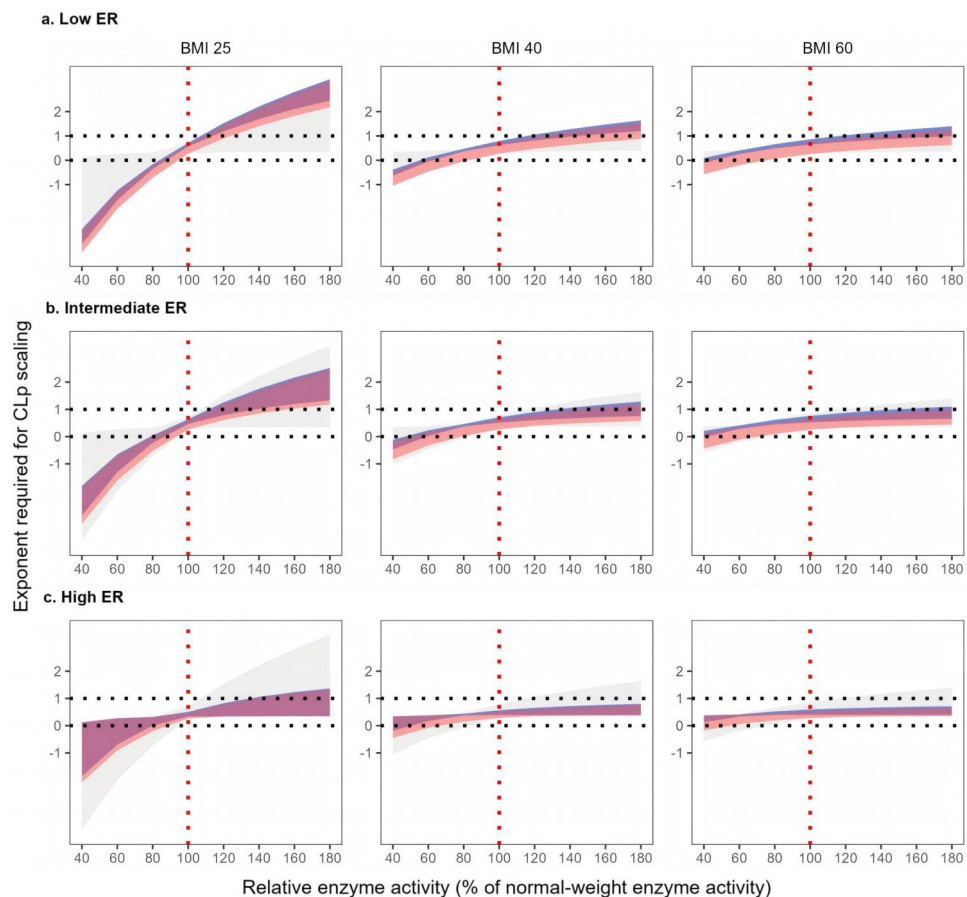


Figure 5.4 Correlation between the exponent in the allometric equation (see **Equation 5.9**) yielding perfect plasma clearance (CL_p) scaling and representative relative enzyme activity for subjects with body mass index (BMI) of 25, 40 and 60 kg/m² for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER and (c) high ER. Blue and pink areas represent drugs that are bound to human serum albumin (HSA) or α 1-acid glycoprotein (AAG), respectively. The purple area represents drugs not binding to plasma proteins. The grey area represents all hypothetical drugs, allowing comparisons between the three plots of the same BMI. The red dotted line represents no change in enzyme activity. Black dotted lines represent 0 and 1, the extreme values of the tested exponent values. Note that the values of the ER represent the values defined for the normal-weight subject

5.4 Discussion

This study utilizes a PBPK-based framework that was written in R and uses the most recent literature on physiological changes related to obesity to predict drug CL_p in subjects with different class of overweight and obesity, considering a diverse set of hypothetical drugs that undergo hepatic metabolism. This approach yields quantitative insights into the correlation between drug properties and subject characteristics on changes in CL_p in obesity. Furthermore, this study evaluates the systematic accuracy of commonly used weight-based dosing methods and identifies scenarios where these methods may or may not yield systematically accurate predictions.

This study investigates the physiological mechanisms driving pharmacological changes in CL_p in obese subjects, offering a basis for the interpretation of reported literature findings. For instance, El-Baraky *et al.* found unaltered CL_p of propofol in the obese [11] while others reported increased CL_p [12–14]. These seemingly contradictory findings can be explained by our results shown in **Figure 5.2c1**, indicating that changes in CL_p for propofol, an HSA-bound drug with high ER, are significant only in morbidly obese subjects with a BMI higher than 40 kg/m², a population that was not included in the study of El-Baraky *et al.* The result can be explained by the fact that for drugs with a high ER, CL_p is less sensitive to alterations in enzyme activity and is more limited by hepatic blood flow [10]. Hepatic blood flow changes as a function of the severity of obesity, as quantified by BMI. Significant alterations in hepatic blood flow become evident only when there are substantial changes in BMI, resulting in notable differences in CL_p .

Besides, increased CL_p of paracetamol has been reported in obese subjects [4]. This can be attributed to changes in CYP2E1, the major enzyme involved in paracetamol metabolism, which is reported to be increased in obese individuals, resulting in increased CL_p . Conversely, literature reported a decrease in CL_p in obese subjects for clozapine [8, 9], likely due to the reduced activity of CYP3A4, the principal enzyme responsible for clozapine metabolism, leading to a decrease in CL_p . It should be noted, however, that the existing literature contains limited information on quantitative change of enzyme activity in the obese population. Therefore, we defined relative changes in obesity-induced enzyme activity compared to normal enzyme activity. The range of these relative changes was selected so that it can encompass potential scenar-

ios of decreased enzyme activity (e.g., CYP3A4) as well as increased enzyme activity (e.g., CYP2E1) in overweight and (morbidly) obese subjects [27]. The generic nature of the applied functions for the relative change in enzyme activity can also be used to assess the impact of changes in enzyme activity driven by other factors, for instance polymorphisms or drug-drug interactions. When quantitative data regarding obesity-induced alterations in specific enzyme activities become available, our results can be used to predict corresponding changes in CL_p for drugs with different properties and in subjects with different severity of obesity.

Drug properties, such as fu , drug-binding protein, and ER, also correlate with obese CL_p . For fu , we found that with fu of the normal weight subject increasing, the change in CL_p decreases for HSA-bound drugs, but increases for AAG-bound drugs. This may seem counterintuitive, since with decreased HSA concentration and increased AAG concentration in the chronic inflammatory state caused by obesity [20, 22, 26], the fu increases for HSA-bound drugs and decreases for AAG-bound drugs in obese subjects compared to normal-weight subjects. However, **Supplementary Figure S5.4** shows that as fu in normal-weight subjects increases, the relative change in fu between obese and normal-weight subjects for AAG-bound drugs increases, while it decreases for HSA-bound drugs. Consequently, this leads to less CL_p change for HSA-bound drugs and a more pronounced CL_p change for AAG-bound drugs. Regarding ER, it is known that CL_p in drugs with low ER is dependent on multiple variables, such as fu and CL_{int} . The narrower range of CL_p changes with increasing ER may result from intricate interplay of multiple variables in drugs with a low ER causing more substantial variability in CL_p change compared to drugs with a high ER, which are influenced mainly by hepatic blood flow. Intriguingly, the correlation between hepatic ER and CL_p is notably seen in HSA-bound drugs, with the relative CL_p in the obese lower for drugs with high ER compared to low ER. This is likely due to increased fu in obese subjects as HSA concentration decreases, causing alterations in ER for HSA-bound drugs. Specifically, a low ER in normal-weight subjects increases to an intermediate (or high) ER in the obese, while a high ER in normal-weight subject remains high in the obese, resulting in limited changes in CL_p for drugs with a high ER. Conversely, for AAG-bound drugs, the decrease in fu with obesity partially counteracts the effects of other variables that contribute to the increase in CL_p , resulting in a reduced CL_p change between drugs with high and low ER.

BMI and rEA contributes to considerable variability in the changes of CL_p in the obese population. This variability leads to a wide range of exponent values yielding perfect scaling. However, in most scenarios, the exponent that yields perfect scaling remains within the range of zero to one. Of three investigated dosing methods, all of them are generally systematically accurate for subjects with overweight or obesity with a BMI below 30 kg/m², with unchanged or up to 50% increased enzyme activity. In any of the other cases, information on the drug binding plasma protein, ER, f_u , and relative change of enzyme activity is required to select an appropriate dosing method for the obese, as no single scaling method is universally accurate when dealing with the complex interplay of different drug properties and obesity severity. The figures provided in this paper can guide more detailed assessments of the accuracy of scaling methods in specific scenarios.

Through this PBPK approach, we identify the theoretical boundaries of allometric exponents when scaling CL_p to the obese and the PE for commonly used scaling methods. The following assumptions are important for the interpretation of our findings and could be further expanded on in future research. Firstly, the assumption made in this work is that hepatic metabolism is the sole elimination pathway of the hypothetical drugs. In this work, this does allow for a “clean” assessment of the impact of changes in parameters relevant to this clearance route. However, in real life, CL_p may be impacted by multiple clearance routes, including renal or biliary excretion, which have not been included in the framework. Moreover, as the impact of obesity on the expression and activity of transporters involved in hepatic CL_p remains unavailable, we assumed no transporter involvement in the hepatic clearance. The current framework could be extended to include this information once this information becomes available. Information on potential obesity-related changes in MPPGL is also not yet available, we therefore assumed this to remain unchanged [26]. According to **Equation 5.2**, a specific percentage of changes in MPPGL would impact the CL_p in the same way as the same percentage of changes in rEA. The presented work can therefore still be used to assess the potential impact of obesity-related changes in MPPGL. Besides, it has been suggested that dynamic free fraction leads to a greater free fraction for drugs and allows for better predictions of CL_{int} in human compared to *in vitro* $CL_{int,mic}$ [30]. Once the data becomes available for obese subjects, utilizing dynamic free fraction would likely yield superior results. Moreover, this study generated a

total of 17,600 hypothetical drugs to capture all possible combinations of the drug properties with realistic ranges. This enables us to explore a wide combination of drug properties, offering systematic insights into the relevance and optimal ranges of these properties. It is important to note, however, that K_p values are typically lower than one. Finally, the height of all representative subjects was assumed to be 1.72 meters when deriving their bodyweight from BMI. This value was selected as it is the average height from the NHANE database [25]. We also tested a height of 1.85 meters and presented these results in the **Supplementary Figure S5.5–S5.6**. These results indicate that the assumption made on subject height barely impacts our conclusion.

5.5 Conclusion

In subjects with obesity, the exponent of an allometric covariate function for CL_p , has a wide range of values depending on BMI, enzyme activity, and drug properties (i.e., f_u , drug binding plasma protein, and ER). AS0.75, linear scaling and flat dosing methods are generally systematically accurate for subjects with overweight or obesity with a BMI below 30 kg/m², with unchanged or up to 50% increased enzyme activity. In any of the other cases, information on the different drug properties and the severity of obesity is required to select an appropriate dosing method for the obese.

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Supplementary Material

Table S5.1 Demographic characteristics of the typical subjects included in the PBPK-based simulation workflow and their corresponding subject-specific parameter values

Demographic values						
	non-obese			obese		
Body mass index (kg/m ²)	20	25	30	40	50	60
Body weight (kg)	59.2	74.0	88.8	118	148	178
Height (m)	1.72	1.72	1.72	1.72	1.72	1.72
Subject-specific parameters						
Cardiac output (L/min) [#]	5.86	6.29	6.81	7.59	8.31	8.96
Hepatic blood flow (L/min) [#]	1.53	1.65	1.78	1.99	2.17	2.34
HSA (g/L) [#]	44.4	43.6	42.8	41.2	40.0	38.0
AAG (g/L) [#]	0.72	0.78	0.84	0.96	1.08	1.20
Hematocrit [#]	0.43	0.43	0.43	0.43	0.43	0.43
Liver weight (kg) [#]	1.54	1.77	1.99	2.45	2.90	3.36
MPPGL (mg protein/g liver) [†]	34.4	34.4	34.4	34.4	34.4	34.4

[#] Derived from Berton *et al.*¹.
^{*} Average value of both sexes.
[†] Changes with obesity unknown, assumed to remain constant, changes in MPPGL would result in proportional changes in relative enzyme activity (rEA).
HSA, plasma concentration for human serum albumin; AAG, plasma concentration for α 1-acid glycoprotein; MPPGL, milligram microsomal protein per gram of liver.

Table S5.2 Relative CL_p values of the investigated hypothetical drugs in subjects with different body mass index (BMI) and at different relative enzyme activity (rEA)

BMI (kg/m ²)	Relative enzyme activity (%)	Drug property					
		Low extraction ratio		Intermediate extraction ratio		High extraction ratio	
		HSA bound	AAG bound	HSA bound	AAG bound	HSA bound	AAG bound
25	40	48.6[46~52.8]	46.1[42.5~52]	57.8[52~66.5]	55.4[48.6~65.8]	77.4[65.8~103]	75.6[62.6~103]
	60	71.7[69~75.6]	68[63.7~74.4]	79.5[74.4~86.4]	76.4[69.6~85.4]	93.5[85.5~106]	91.6[81.5~106]
	80	94.2[92~96.3]	88.6[84.9~94.8]	97.8[94.8~101]	94.1[88.7~100]	103[100~108]	102[95.6~108]
	100	115[113~117]	108[106~115]	113[111~115]	108[106~113]	110[108~112]	108[106~111]
	120	136[130~140]	127[122~138]	126[119~132]	121[114~130]	114[108~120]	112[108~119]
	140	157[146~164]	147[137~161]	137[126~148]	132[121~146]	117[108~127]	115[108~126]
	160	176[160~187]	165[150~184]	147[131~162]	142[126~160]	119[108~132]	117[108~131]
30	180	196[173~211]	183[163~207]	155[135~176]	150[130~173]	121[108~136]	119[108~135]
	40	55.3[51.7~60.1]	49.5[44.4~58.2]	65[58.2~74.7]	59.9[51~73.1]	85.7[73.1~111]	81.9[66.2~111]
	60	81.6[77.6~85.8]	72.5[66.6~83.2]	89.2[83.2~96.5]	82.6[73~94.4]	103[94.4~115]	99[86.1~115]
	80	107[103~109]	94.2[88.7~106]	109[106~112]	101[92.9~110]	113[110~116]	110[101~116]
	100	131[126~134]	115[111~129]	126[122~130]	116[111~126]	120[116~124]	116[112~122]
	120	154[145~161]	135[128~155]	140[131~149]	129[121~145]	124[117~133]	120[116~131]
	140	177[162~188]	155[143~181]	152[137~167]	141[128~162]	127[117~140]	123[116~137]
30	160	199[178~214]	175[157~207]	163[143~183]	151[133~178]	130[117~145]	126[116~143]
	180	220[192~241]	195[170~232]	171[147~197]	160[137~192]	131[117~149]	127[117~147]

40	40	69.8[63.7~75.6]	55.2[47.9~71]	80.1[71~91.3]	68.3[55.4~87.2]	101[87.2~126]	93.4[72.4~126]
	60	103[95.5~107]	80.6[71.8~101]	109[101~116]	93[79~111]	120[111~129]	112[93.9~129]
	80	134[127~137]	105[95.7~128]	132[128~136]	112[100~129]	131[129~134]	123[110~130]
	100	163[152~171]	127[120~159]	151[141~162]	129[119~152]	138[130~147]	129[121~141]
	120	191[174~206]	149[137~191]	167[151~185]	143[131~174]	142[130~156]	133[127~151]
	140	219[194~240]	171[153~223]	181[158~206]	156[138~194]	145[131~163]	136[128~158]
	160	246[212~274]	191[168~254]	192[163~224]	167[143~212]	147[131~169]	139[129~163]
	180	272[228~308]	213[181~286]	202[168~241]	177[148~228]	148[131~173]	140[129~168]
	40	84.8[75.3~91.7]	59.6[50.4~83.2]	94.9[83.3~108]	74.8[58.6~100]	116[100~138]	103[77.2~138]
	60	125[113~130]	86.7[75.6~118]	128[118~135]	101[83.4~127]	136[127~141]	123[99.8~141]
50	80	161[149~169]	113[101~151]	154[146~163]	122[106~149]	146[142~155]	134[116~146]
	100	195[176~211]	137[126~188]	175[159~193]	139[126~176]	153[142~168]	140[128~159]
	120	229[201~253]	161[144~226]	193[169~220]	154[137~201]	158[142~178]	144[134~169]
	140	262[223~295]	183[161~263]	207[176~244]	168[145~223]	160[142~185]	147[136~176]
	160	293[243~337]	205[176~301]	219[182~266]	179[151~243]	162[142~191]	149[137~181]
	180	324[261~380]	226[190~339]	229[186~285]	189[156~261]	163[142~195]	151[138~186]
	40	101[87.3~109]	63.4[52.6~95.6]	110[95.6~124]	80.3[61.3~113]	131[113~150]	113[81.5~150]
	60	147[131~154]	92.4[78.9~135]	148[135~155]	108[87.2~142]	152[142~155]	133[105~152]
	80	190[170~204]	120[105~175]	176[162~193]	130[110~170]	161[153~175]	144[122~162]
	100	230[200~244]	145[131~218]	199[176~227]	149[131~200]	168[153~189]	150[134~176]
60							

To be continued

120	268[228~305]	170[150~262]	218[186~258]	164[143~228]	172[153~199]	154[141~186]
140	306[252~356]	194[167~305]	233[193~285]	178[151~252]	175[154~207]	156[144~193]
160	343[274~407]	217[183~349]	246[199~309]	191[157~274]	177[154~212]	159[145~199]
180	378[294~458]	238[197~392]	257[203~331]	201[161~294]	178[154~216]	160[145~203]

Data are shown as median [range] and are expressed as percentage of normal-weight values.

Low, intermediate, and high extraction ratios (ER) are defined as $ER \leq 0.3$, $0.3-0.7$, and >0.7 . HSA: drugs that bind to human serum albumin to different extents (including $fu=1$). AAG: drugs that bind to $\alpha 1$ -acid glycoprotein to different extents (including $fu=1$).

Table S5.3 Allometric exponent required for accurate scaling of the hypothetical drugs for the investigated body mass index categorized by drug property

BMI enzyme (kg/m ³)	Relative enzyme activity (%)	Drug property					
		Low extraction ratio			Intermediate extraction ratio		
		HSA bound	AAG bound	HSA bound	AAG bound	HSA bound	AAG bound
25	40	-3.23[-3.48~-2.86]	-3.47[-3.84~-2.93]	-2.45[-2.93~-1.83]	-2.65[-3.24~-1.88]	-1.15[-1.87~-0.125]	-1.26[-2.10~-0.125]
	60	-1.49[-1.66~-1.26]	-1.73[-2.02~-1.32]	-1.03[-1.32~-0.657]	-1.21[-1.63~-0.705]	-0.303[-0.704~-0.277]	-0.394[-0.916~-0.277]
	80	-0.27[-0.376~-0.171]	-0.540[-0.731~-0.239]	-0.101[-0.239~-0.0440]	-0.272[-0.539~-0.00147]	0.153[-0.00115~-0.325]	0.0733[-0.203~-0.325]
	100	0.645[0.563~0.704]	0.348[0.265~0.624]	0.549[0.464~0.630]	0.358[0.258~0.563]	0.422[0.342~0.506]	0.337[0.266~0.464]
	120	1.39[1.19~1.52]	1.08[0.894~1.44]	1.04[0.79~1.25]	0.857[0.607~1.19]	0.595[0.350~0.829]	0.517[0.345~0.789]
	140	2.01[1.69~2.21]	1.72[1.40~2.13]	1.42[1.03~1.76]	1.25[0.852~1.69]	0.710[0.353~1.06]	0.638[0.350~1.03]
	160	2.54[2.11~2.81]	2.25[1.82~2.73]	1.72[1.21~2.17]	1.56[1.04~2.11]	0.789[0.354~1.24]	0.721[0.353~1.20]
	180	3.01[2.46~3.34]	2.72[2.18~3.26]	1.96[1.34~2.52]	1.81[1.18~2.46]	0.843[0.355~1.38]	0.780[0.354~1.34]
30	40	-1.46[-1.63~-1.26]	-1.73[-2.00~-1.33]	-1.06[-1.33~-0.718]	-1.26[-1.66~-0.774]	-0.382[-0.774~-0.268]	-0.493[-1.02~-0.268]
	60	-0.502[-0.627~-0.378]	-0.792[-1.00~-0.454]	-0.281[-0.454~-0.088]	-0.473[-0.777~-0.141]	0.0705[-0.141~-0.344]	-0.0243[-0.368~-0.344]
	80	0.171[0.0821~0.214]	-0.147[-0.295~-0.139]	0.222[0.139~0.287]	0.0238[-0.181~-0.237]	0.312[0.237~0.368]	0.230[0.0223~0.368]
	100	0.661[0.576~0.722]	0.343[0.256~0.632]	0.568[0.485~0.651]	0.363[0.256~0.576]	0.450[0.377~0.532]	0.363[0.278~0.485]
	120	1.07[0.917~1.17]	0.740[0.604~1.08]	0.832[0.659~0.99]	0.633[0.465~0.917]	0.540[0.380~0.702]	0.451[0.363~0.658]
	140	1.41[1.19~1.55]	1.08[0.882~1.46]	1.04[0.784~1.26]	0.848[0.599~1.19]	0.599[0.381~0.825]	0.519[0.374~0.784]
	160	1.70[1.42~1.88]	1.38[1.11~1.79]	1.20[0.878~1.49]	1.02[0.7~1.42]	0.639[0.382~0.917]	0.564[0.376~0.877]
	180	1.95[1.61~2.17]	1.64[1.31~2.08]	1.33[0.949~1.68]	1.16[0.778~1.61]	0.667[0.383~0.987]	0.595[0.377~0.949]
40	40	-0.52[-0.652~-0.404]	-0.858[-1.06~-0.495]	-0.321[-0.495~-0.132]	-0.550[-0.854~-0.199]	0.0209[-0.198~-0.332]	-0.0983[-0.466~-0.332]
	60	0.0418[-0.0669~0.104]	-0.312[-0.479~-0.0135]	0.124[0.0136~0.219]	-0.105[-0.341~-0.157]	0.266[0.157~0.369]	0.165[-0.0911~-0.369]
	80	0.422[0.348~0.455]	0.0668[-0.0635~0.355]	0.405[0.355~0.444]	0.170[0.00484~0.365]	0.389[0.366~0.424]	0.299[0.133~0.379]
	100	0.704[0.605~0.778]	0.347[0.259~0.670]	0.596[0.501~0.693]	0.368[0.256~0.605]	0.462[0.383~0.555]	0.367[0.278~0.501]
	120	0.937[0.799~1.04]	0.580[0.458~0.934]	0.743[0.594~0.886]	0.519[0.386~0.799]	0.508[0.384~0.645]	0.410[0.342~0.594]
	140	1.13[0.955~1.26]	0.771[0.618~1.16]	0.855[0.661~1.04]	0.643[0.462~0.955]	0.537[0.385~0.709]	0.446[0.358~0.661]
	160	1.30[1.08~1.46]	0.936[0.750~1.35]	0.942[0.710~1.17]	0.741[0.519~1.08]	0.556[0.385~0.756]	0.472[0.362~0.710]
							<i>To be continued</i>

180	1.45[1.19-1.63]	1.09[0.861-1.52]	1.01[0.747-1.27]	0.821[0.563-1.19]	0.569[0.385-0.792]	0.488[0.364-0.747]
40	-0.180[-0.309--0.0948]	-0.566[-0.749--0.200]	-0.0571[-0.200-0.0791]	-0.317[-0.584-0.00275]	0.163[0.00304-0.353]	0.0353[-0.282-0.353]
60	0.239[0.134-0.284]	-0.156[-0.306-0.180]	0.272[0.180-0.332]	0.0115[-0.198-0.261]	0.337[0.261-0.378]	0.226[-0.00167-0.376]
80	0.52[0.434-0.571]	0.133[0.00841-0.448]	0.471[0.411-0.537]	0.219[0.0607-0.434]	0.416[0.383-0.477]	0.317[0.166-0.411]
50	100	0.73[0.619-0.815]	0.340[0.251-0.691]	0.610[0.507-0.721]	0.363[0.248-0.619]	0.467[0.385-0.568]
120	0.903[0.762-1.01]	0.517[0.400-0.890]	0.716[0.572-0.862]	0.475[0.347-0.762]	0.497[0.385-0.630]	0.395[0.323-0.571]
140	1.05[0.877-1.18]	0.658[0.519-1.06]	0.796[0.618-0.975]	0.566[0.406-0.876]	0.516[0.386-0.673]	0.418[0.340-0.617]
160	1.18[0.97-1.33]	0.781[0.617-1.20]	0.857[0.651-1.07]	0.639[0.451-0.970]	0.528[0.386-0.704]	0.436[0.346-0.651]
180	1.28[1.05-1.46]	0.892[0.699-1.33]	0.907[0.676-1.14]	0.698[0.484-1.05]	0.536[0.386-0.727]	0.448[0.350-0.676]
40	0.0109[-0.124-0.0784]	-0.415[-0.585--0.0409]	0.0898[-0.0408-0.197]	-0.200[-0.445-0.112]	0.243[0.112-0.368]	0.109[-0.186-0.368]
60	0.353[0.245-0.390]	-0.0724[-0.216-0.273]	0.356[0.273-0.399]	0.0688[-0.125-0.320]	0.378[0.32-0.402]	0.258[0.0456-0.384]
80	0.584[0.481-0.648]	0.166[0.0458-0.507]	0.512[0.438-0.597]	0.242[0.0896-0.481]	0.435[0.388-0.511]	0.329[0.184-0.438]
60	100	0.757[0.633-0.851]	0.338[0.246-0.710]	0.625[0.514-0.747]	0.360[0.244-0.633]	0.473[0.390-0.582]
120	0.898[0.749-1.02]	0.485[0.37-0.876]	0.709[0.564-0.862]	0.453[0.326-0.749]	0.495[0.390-0.629]	0.391[0.311-0.564]
140	1.02[0.842-1.16]	0.601[0.468-1.02]	0.772[0.599-0.953]	0.526[0.373-0.842]	0.509[0.390-0.661]	0.407[0.330-0.599]
160	1.12[0.918-1.28]	0.704[0.548-1.14]	0.820[0.625-1.03]	0.588[0.408-0.918]	0.518[0.390-0.684]	0.420[0.337-0.625]
180	1.21[0.981-1.39]	0.791[0.616-1.24]	0.859[0.644-1.09]	0.636[0.435-0.981]	0.523[0.390-0.701]	0.430[0.340-0.643]

Data are shown as median [range]

Low, intermediate, and high extraction ratios (ER) are defined as $ER \leq 0.3$, $0.3-0.7$, and >0.7 . HSA: drugs that bind to human serum albumin to different extents (including $f_u=1$). AAG: drugs that bind to $\alpha 1$ -acid glycoprotein to different extents (including $f_u=1$). BMI: body mass index.

Table S5.4 Range of prediction errors (PE) between CL_p values and CL_p values scaled from normal-weight to overweight and obese patients with different body mass index, stratified by drug properties and by relative enzyme activity in the obese. Results are shown for **a**) allometric scaling (using an exponent of 0.75), **b**) linear scaling (using an exponent of 1), or **c**) flat dosing (using an exponent of 0). The colors indicate the PE category, with green representing PE ranges within $\pm 30\%$, orange representing PE ranges within $\pm 50\%$, and red representing PE higher than 50% or lower than 50%

(a) Allometric scaling using a fixed exponent of 0.75

BMI (kg/m ²)	Relative enzyme activity (%)	Drug property					
		Low extraction ratio		Intermediate extraction ratio		High extraction ratio	
		HSA bound	AAG bound	HSA bound	AAG bound	HSA bound	AAG bound
25	40	[124~157]	[127~178]	[77.6~127]	[79.6~143]	[15.0~79.6]	[15.0~89.0]
	60	[56.5~71.4]	[58.8~85.6]	[36.9~58.8]	[38.4~70.0]	[11.1~38.3]	[11.1~45.0]
	80	[22.8~28.6]	[24.7~39.2]	[17.1~24.7]	[18.3~33.3]	[9.96~18.2]	[9.96~23.7]
	100	[1.02~4.25]	[2.86~11.4]	[2.70~6.59]	[4.25~11.6]	[5.59~9.53]	[6.60~11.4]
	120	[-15.8~-9.32]	[-14.3~-3.17]	[-10.6~-0.885]	[-9.32~3.25]	[-1.74~9.35]	[-0.874~-9.45]
	140	[-27.8~-19.0]	[-26.5~-13.5]	[-20.1~-6.00]	[-19.0~-2.25]	[-6.77~9.27]	[-5.99~9.33]
	160	[-36.9~-26.2]	[-35.7~-21.3]	[-27.2~-9.66]	[-26.2~-6.21]	[-10.4~9.23]	[-9.64~9.27]
	180	[-43.9~-31.8]	[-42.8~-27.3]	[-32.7~-12.4]	[-31.7~-9.14]	[-13.0~9.21]	[-12.3~9.24]
30	40	[126~162]	[133~205]	[81.3~133]	[85.5~166]	[21.6~85.5]	[21.6~105.]
	60	[58.0~74.8]	[62.9~104]	[40.5~62.9]	[43.5~85.7]	[17.9~43.5]	[17.9~57.4]
	80	[24.3~31.1]	[28.1~52.7]	[20.7~28.1]	[23.1~45.8]	[16.7~23.1]	[16.8~34.3]
	100	[1.15~7.29]	[4.90~22.2]	[4.10~11.3]	[7.29~22.2]	[9.23~16.3]	[11.3~21.1]

To be continued

120	[-15.7~-6.54]	[-12.6~-6.08]	[-9.26~-3.77]	[-6.53~-12.2]	[1.97~16.2]	[3.79~17.0]
140	[-27.7~-16.4]	[-25.0~-5.21]	[-18.8~-1.38]	[-16.4~6.30]	[-2.99~16.1]	[-1.36~16.5]
160	[-36.8~-23.7]	[-34.4~-13.6]	[-25.9~-5.06]	[-23.7~2.04]	[-6.53~16.1]	[-5.03~16.4]
180	[-43.8~-29.4]	[-41.7~-20.2]	[-31.3~-7.77]	[-29.4~-1.11]	[-9.15~16.1]	[-7.74~16.3]
40	[120~164]	[137~251]	[84.1~137]	[92.8~204]	[33.5~92.8]	[33.5~132]
60	[56.4~76.0]	[66.5~134]	[44.4~66.5]	[50.8~113]	[30.2~50.8]	[30.2~79.0]
80	[22.6~32.1]	[31.5~75.6]	[23.6~31.5]	[30.5~67.5]	[25.3~30.5]	[29.3~53.3]
100	[-1.89~-10.5]	[5.66~40.5]	[3.99~18.8]	[10.5~40.8]	[14.4~28.9]	[18.8~38.6]
120	[-18.2~-3.36]	[-11.9~-22.4]	[-8.99~-11.4]	[-3.35~28.6]	[7.52~28.8]	[11.4~32.6]
140	[-29.9~-13.2]	[-24.5~-9.57]	[-18.2~-6.37]	[-13.2~22.0]	[2.87~28.8]	[6.39~31.2]
160	[-38.7~-20.6]	[-33.9~0.00853]	[-25.1~-2.81]	[-20.6~17.3]	[-0.418~28.7]	[2.84~30.8]
180	[-45.5~-26.3]	[-41.3~-7.38]	[-30.4~0.207]	[-26.2~13.8]	[-2.83~28.7]	[0.242~30.6]
40	[117~164]	[139~294]	[84.8~139]	[98.2~239]	[43.8~98.2]	[43.8~157]
60	[53.2~75.9]	[68.6~163]	[46.7~68.5]	[56.5~138]	[40.6~56.5]	[40.8~99.0]
80	[17.8~33.6]	[31.9~97.2]	[21.6~36.4]	[33.6~88.0]	[28.5~40.0]	[36.4~70.7]
100	[-5.77~-12.7]	[5.55~57.9]	[2.73~25.0]	[12.7~58.3]	[18.1~39.7]	[25.0~55.0]
120	[-21.5~-11.2]	[-12.0~-37.8]	[-9.76~-17.7]	[-1.11~44.6]	[11.6~39.6]	[17.8~47.9]
140	[-32.7~-10.9]	[-24.6~-23.6]	[-18.6~12.9]	[-10.9~37.0]	[7.31~39.6]	[12.9~45.6]
160	[-41.1~-18.3]	[-34.0~-13.0]	[-25.2~-9.45]	[-18.2~31.5]	[4.28~39.6]	[9.49~44.7]
180	[-47.6~-23.9]	[-41.3~-4.78]	[-30.3~-6.97]	[-23.9~27.6]	[2.09~39.6]	[7.01~44.2]
40	[109~161]	[138~333]	[83.4~138]	[101.~271]	[52.1~101]	[52.1~180]

60	[48.4~74.0]	[68.9~189]	[47.1~68.9]	[60.4~161]	[46.6~60.4]	[49.4~117]
80	[11.9~34.4]	[30.6~117]	[18.3~40.8]	[34.4~107]	[29.9~48.7]	[40.8~86.2]
100	[-10.5~13.7]	[4.46~73.9]	[0.323~29.6]	[13.7~74.3]	[20.3~48.5]	[29.7~69.7]
120	[-25.4~0.0629]	[-12.9~51.8]	[-11.6~22.6]	[0.0767~59.3]	[14.2~48.5]	[22.7~61.9]
140	[-36.0~-9.63]	[-25.4~36.3]	[-20.0~18.0]	[-9.61~51.3]	[10.2~48.4]	[18.0~58.6]
160	[-44.0~-16.8]	[-34.7~24.8]	[-26.3~14.7]	[-16.8~45.5]	[7.48~48.4]	[14.8~57.3]
180	[-50.2~-22.4]	[-41.9~15.9]	[-31.1~12.4]	[-22.4~41.3]	[5.51~48.4]	[12.4~56.8]

(b) Linear scaling

BMI (kg/m ²)	Relative enzyme activity (%)	Drug property					
		Low extraction ratio		Intermediate extraction ratio		High extraction ratio	
		HSA bound	AAG bound	HSA bound	AAG bound	HSA bound	AAG bound
25	40	[137~172]	[140~194]	[87.8~140]	[89.9~157]	[21.6~89.9]	[21.6~99.8]
	60	[65.4~81.2]	[68.0~96.2]	[44.7~67.9]	[46.3~79.7]	[17.5~46.3]	[17.5~53.3]
	80	[29.9~35.9]	[31.8~47.2]	[23.8~31.8]	[25.0~41.0]	[16.3~25.0]	[16.3~30.8]
	100	[6.82~10.2]	[8.76~17.8]	[8.59~12.7]	[10.2~18.0]	[11.6~15.8]	[12.7~17.8]
	120	[-11.0~-4.12]	[-9.35~-2.39]	[-5.51~-4.80]	[-4.11~9.18]	[3.90~15.6]	[4.81~15.7]
	140	[-23.7~-14.3]	[-22.3~-8.58]	[-15.5~-0.610]	[-14.3~3.35]	[-1.42~15.5]	[-0.592~15.6]
30	160	[-33.2~-21.9]	[-32.0~-16.8]	[-23.0~-4.48]	[-21.9~-0.824]	[-5.22~15.5]	[-4.46~15.5]
	180	[-40.6~-27.8]	[-39.5~-23.1]	[-28.8~-7.34]	[-27.8~-3.92]	[-8.03~15.5]	[-7.32~15.5]
	40	[150~190]	[158~238]	[101~158]	[105~194]	[34.6~105]	[34.6~127]
	60	[74.9~93.4]	[80.3~125]	[55.5~80.3]	[58.9~106]	[30.4~58.8]	[30.4~74.2]
	80	[37.5~45.1]	[41.8~69.0]	[33.5~41.8]	[36.3~61.4]	[29.2~36.3]	[29.2~48.6]
	100	[11.9~18.7]	[16.1~35.2]	[15.2~23.2]	[18.7~35.2]	[20.9~28.8]	[23.2~34.0]
30	120	[-6.71~3.43]	[-3.24~17.4]	[0.417~14.8]	[3.44~24.2]	[12.8~28.6]	[14.9~29.5]
	140	[-20.0~-7.45]	[-17.1~4.90]	[-10.1~9.14]	[-7.44~17.6]	[7.36~28.5]	[9.16~28.9]
	160	[-30.0~-15.6]	[-27.4~4.43]	[-17.9~5.07]	[-15.6~12.9]	[3.44~28.5]	[5.10~28.8]
	180	[-37.8~-21.8]	[-35.5~-11.7]	[-24.0~2.07]	[-21.8~9.44]	[0.546~28.4]	[2.10~28.7]

40	40	[164~214]	[182~318]	[119~181]	[129~261]	[58.8~129]	[58.8~176]
	60	[86.0~109]	[98.0~178]	[71.7~98.0]	[79.3~153]	[54.8~79.3]	[54.8~113]
	80	[45.8~57.0]	[56.3~109]	[46.9~56.3]	[55.2~99.2]	[49.0~55.2]	[53.7~82.2]
	100	[16.6~31.4]	[25.6~67.1]	[23.6~41.3]	[31.4~67.4]	[36.0~53.3]	[41.3~64.8]
	120	[-2.79~14.9]	[4.71~45.5]	[8.20~32.4]	[14.9~52.9]	[27.8~53.2]	[32.5~57.7]
	140	[-16.7~3.17]	[-10.2~30.3]	[-2.76~26.5]	[3.18~45.1]	[22.3~53.1]	[26.5~56.0]
	160	[-27.1~-5.58]	[-21.4~18.9]	[-10.9~22.2]	[-5.56~39.5]	[18.4~53.1]	[22.3~55.5]
	180	[-35.2~-12.3]	[-30.2~10.1]	[-17.2~19.1]	[-12.3~35.3]	[15.5~53.1]	[19.2~55.3]
50	40	[172~232]	[200~396]	[132~200]	[149~327]	[80.8~149]	[80.8~223]
	60	[92.6~121]	[112~231]	[84.4~112]	[96.7~200]	[76.8~96.7]	[77.0~150]
	80	[48.1~68.0]	[65.8~148]	[52.9~71.5]	[68.0~136]	[61.5~76.0]	[71.5~115]
	100	[18.5~41.7]	[32.7~98.6]	[29.2~57.1]	[41.7~99.0]	[48.5~75.7]	[57.1~94.9]
	120	[-1.27~24.3]	[10.6~73.3]	[13.5~48.0]	[24.3~81.9]	[40.4~75.6]	[48.0~85.9]
	140	[-15.4~12.0]	[-5.18~55.4]	[2.31~41.9]	[12.0~72.2]	[34.9~75.5]	[41.9~83.1]
	160	[-25.9~2.76]	[-17.0~42.0]	[-5.98~37.6]	[2.78~65.4]	[31.1~75.5]	[37.7~82.0]
	180	[-34.2~-4.33]	[-26.2~31.7]	[-12.4~34.5]	[-4.31~60.4]	[28.4~75.5]	[34.5~81.3]
60	40	[175~243]	[214~470]	[141~214]	[165~389]	[100~165]	[100~268]
	60	[95.3~129]	[122~280]	[93.5~122]	[111~244]	[92.9~111]	[96.6~185]
	80	[47.3~76.8]	[71.8~185]	[55.7~85.3]	[76.8~172]	[71.0~95.7]	[85.3~145]
	100	[17.8~49.7]	[37.5~129]	[32.0~70.6]	[49.7~129]	[58.3~95.4]	[70.6~123]

To be continued

120	[-1.82~31.7]	[14.6~99.8]	[16.4~61.4]	[31.7~110]	[50.3~95.3]	[61.4~113]
140	[-15.8~18.9]	[-1.77~79.4]	[5.27~55.2]	[18.9~99.0]	[45.1~95.3]	[55.3~109]
160	[-26.4~9.44]	[-14.0~64.2]	[-2.98~51.0]	[9.46~91.5]	[41.4~95.3]	[51.0~107]
180	[-34.5~2.13]	[-23.6~52.5]	[-9.33~47.9]	[2.16~85.9]	[38.8~95.3]	[47.9~106]

(c) Flat dosing

BMI (kg/m ²)	Relative enzyme activity (%)	Drug property					
		Low extraction ratio		Intermediate extraction ratio		High extraction ratio	
		HSA bound	AAG bound	HSA bound	AAG bound	HSA bound	AAG bound
25	40	[89.4~117]	[92.3~135]	[50.3~92.3]	[52.0~106]	[-2.75~51.9]	[-2.75~59.9]
	60	[32.3~45.0]	[34.4~57.0]	[15.8~34.4]	[17.0~43.8]	[-5.99~17.0]	[-5.99~22.7]
	80	[3.89~8.75]	[5.47~17.7]	[-0.976~5.47]	[0.0327~12.8]	[-6.99~0.0256]	[-6.99~4.63]
	100	[-14.5~-11.8]	[-13.0~-5.75]	[-13.1~-9.83]	[-11.8~-5.60]	[-10.7~-7.35]	[-9.83~-5.77]
	120	[-28.8~-23.3]	[-27.5~-18.1]	[-24.4~-16.2]	[-23.3~-12.7]	[-16.9~-7.50]	[-16.1~-7.41]
	140	[-39.0~-31.5]	[-37.8~-26.9]	[-32.4~-20.5]	[-31.5~-17.3]	[-21.1~-7.57]	[-20.5~-7.52]
	160	[-46.6~-37.6]	[-45.6~-33.4]	[-38.4~-23.6]	[-37.5~-20.7]	[-24.2~-7.60]	[-23.6~-7.57]
	180	[-52.5~-42.3]	[-51.6~-38.5]	[-43.0~-25.9]	[-42.3~-23.1]	[-26.4~-7.62]	[-25.9~-7.59]
30	40	[66.5~93.4]	[71.7~125]	[33.8~71.7]	[36.9~96.0]	[-10.3~36.8]	[-10.3~51.0]
	60	[16.6~28.9]	[20.2~50.2]	[3.65~20.2]	[5.90~37.0]	[-13.0~5.88]	[-13.0~16.1]
	80	[-8.32~-3.27]	[-5.48~12.7]	[-11.0~-5.48]	[-9.15~7.60]	[-13.9~-9.15]	[-13.9~-0.902]
	100	[-25.4~-20.8]	[-22.6~-9.84]	[-23.2~-17.9]	[-20.8~-9.88]	[-19.4~-14.2]	[-17.9~-10.7]
	120	[-37.8~-31.0]	[-35.5~-21.7]	[-33.1~-23.4]	[-31.0~-17.2]	[-24.8~-14.3]	[-23.4~-13.7]
	140	[-46.7~-38.3]	[-44.7~-30.1]	[-40.1~-27.2]	[-38.3~-21.6]	[-28.4~-14.3]	[-27.2~-14.1]
	160	[-53.4~-43.7]	[-51.6~-36.3]	[-45.3~-30.0]	[-43.7~-24.7]	[-31.0~-14.4]	[-29.9~-14.1]
	180	[-58.5~-47.9]	[-57.0~-41.1]	[-49.3~-32.0]	[-47.9~-27.0]	[-33.0~-14.4]	[-31.9~-14.2]

To be continued

40	40	[32.2~57.1]	[40.9~109]	[9.54~40.9]	[14.7~80.6]	[20.5~14.7]	[20.5~38.0]
	60	[-6.95~4.74]	[-0.931~39.3]	[-14.1~-0.937]	[-10.3~26.6]	[-22.5~-10.3]	[-22.5~6.51]
	80	[-27.0~-21.4]	[-21.8~4.50]	[-26.5~-21.8]	[-22.4~-0.334]	[-25.4~-22.4]	[-23.1~-8.81]
	100	[-41.6~-34.2]	[-37.1~-16.4]	[-38.1~-29.3]	[-34.2~-16.2]	[-31.9~-23.3]	[-29.3~-17.5]
	120	[-51.4~-42.5]	[-47.6~-27.2]	[-45.9~-33.7]	[-42.5~-23.5]	[-36.0~-23.4]	[-33.7~-21.1]
	140	[-58.3~-48.4]	[-55.1~-34.8]	[-51.3~-36.7]	[-48.4~-27.4]	[-38.8~-23.4]	[-36.7~-21.9]
	160	[-63.5~-52.7]	[-60.7~-40.5]	[-55.4~-38.8]	[-52.7~-30.2]	[-40.8~-23.4]	[-38.8~-22.2]
	180	[-67.6~-56.1]	[-65.1~-44.9]	[-58.6~-40.4]	[-56.1~-32.3]	[-42.2~-23.4]	[-40.4~-22.3]
50	40	[9.07~32.7]	[20.1~98.5]	[-6.98~20.1]	[-0.252~70.7]	[-27.6~-0.278]	[-27.6~29.5]
	60	[-22.9~-11.5]	[-15.2~32.3]	[-26.2~-15.2]	[-21.2~19.9]	[-29.2~-21.3]	[-29.1~-0.153]
	80	[-40.7~-32.8]	[-33.6~-0.767]	[-38.8~-31.3]	[-32.8~-5.41]	[-35.4~-29.6]	[-31.3~-14.1]
	100	[-52.6~-43.3]	[-46.9~-20.5]	[-48.3~-37.1]	[-43.3~-20.3]	[-40.6~-29.7]	[-37.1~-22.0]
	120	[-60.5~-50.2]	[-55.7~-30.7]	[-54.6~-40.8]	[-50.2~-27.2]	[-43.8~-29.7]	[-40.7~-25.6]
	140	[-66.1~-55.2]	[-62.0~-37.8]	[-59.0~-43.2]	[-55.2~-31.1]	[-46.0~-29.8]	[-43.2~-26.7]
	160	[-70.4~-58.9]	[-66.8~-43.1]	[-62.4~-44.9]	[-58.9~-33.8]	[-47.5~-29.8]	[-44.9~-27.2]
	180	[-73.6~-61.7]	[-70.5~-47.3]	[-64.9~-46.2]	[-61.7~-35.8]	[-48.6~-29.8]	[-46.1~-27.4]
60	40	[-8.25~-14.5]	[4.59~90.2]	[-19.5~4.58]	[-11.6~63.0]	[-33.3~-11.6]	[-33.3~22.7]
	60	[-34.9~-23.6]	[-25.9~26.8]	[-35.5~-25.9]	[-29.6~14.7]	[-35.7~-29.6]	[-34.4~-4.89]
	80	[-50.9~-41.0]	[-42.7~-4.90]	[-48.1~-38.2]	[-41.0~-9.37]	[-43.0~-34.7]	[-38.2~-18.3]
	100	[-60.7~-50.1]	[-54.2~-23.7]	[-56.0~-43.1]	[-50.1~-23.5]	[-47.2~-34.8]	[-43.1~-25.5]
	120	[-67.3~-56.1]	[-61.8~-33.4]	[-61.2~-46.2]	[-56.1~-30.1]	[-49.9~-34.8]	[-46.2~-29.0]

140	[-71.9~-60.3]	[-67.2~-40.2]	[-64.9~-48.2]	[-60.3~-33.6]	[-51.6~-34.9]	[-48.2~-30.4]
160	[-75.4~-63.5]	[-71.3~-45.2]	[-67.6~-49.7]	[-63.5~-36.1]	[-52.8~-34.9]	[-49.6~-30.9]
180	[-78.2~-65.9]	[-74.5~-49.1]	[-69.8~-50.7]	[-65.9~-38.0]	[-53.7~-34.9]	[-50.7~-31.2]

Data are shown as median and are expressed as percentage of non-obese values
Low, intermediate, and high extraction ratios (ER) are defined as $ER \leq 0.3$, $0.3-0.7$, and >0.7 . HSA: drugs that bind to human serum albumin to different extents (including $f_u=1$). AAC: drugs that bind to $\alpha 1$ -acid glycoprotein to different extents (including $f_u=1$). BMI, body mass index.

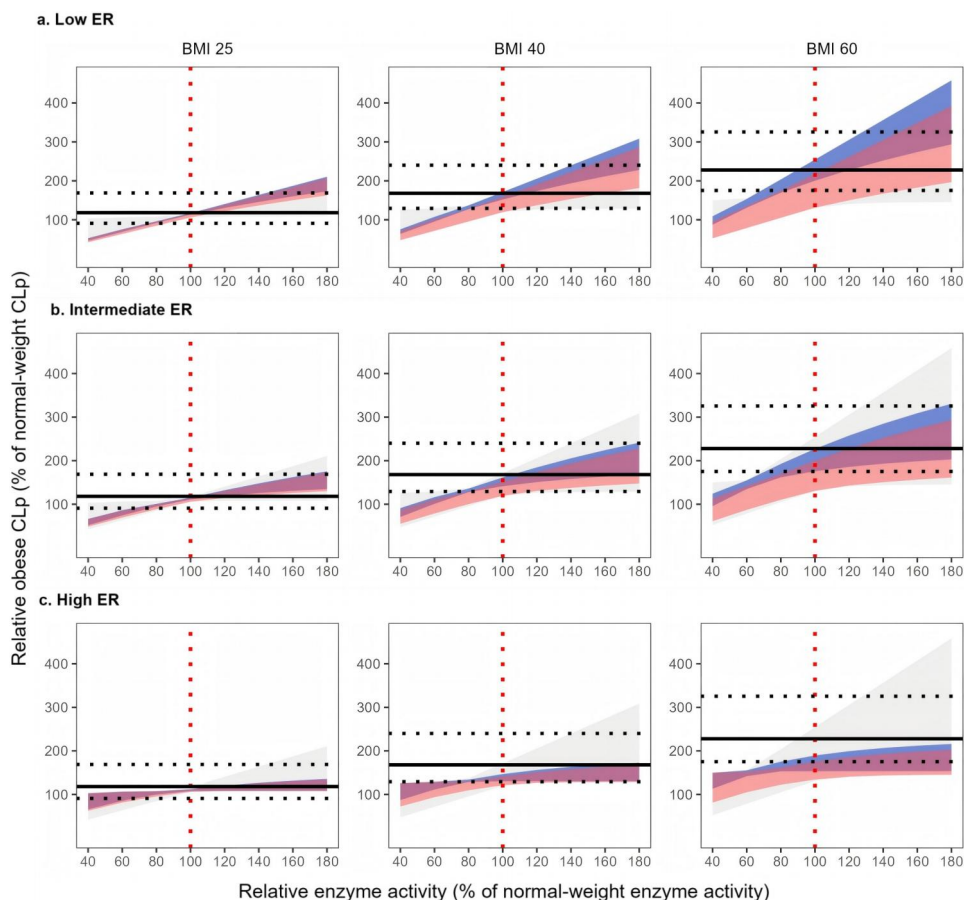


Figure S5.1 Accuracy of plasma clearance (CL_p) scaling obtained using bodyweight-based allometric scaling with an exponent of 0.75 for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER, and (c) high ER for representative relative enzyme activity for subjects with body mass index (BMI) of 25, 40 and 60 kg/m². Scaling is systematically accurate when the colored shaded areas completely fall between the black dotted lines. Blue and pink areas represent drugs that bind to human serum albumin (HSA) or α 1-acid glycoprotein (AAG). The purple area represents drugs not binding to plasma proteins. The black solid line represents the scaled CL_p for the bodyweight associated with the indicated BMI and the black dotted lines represent a range of $\pm 30\%$ prediction error of the scaled value. The red dotted line represents no change in enzyme activity. Note that the values of the extraction ratio represent the values defined for the normal-weight patient.

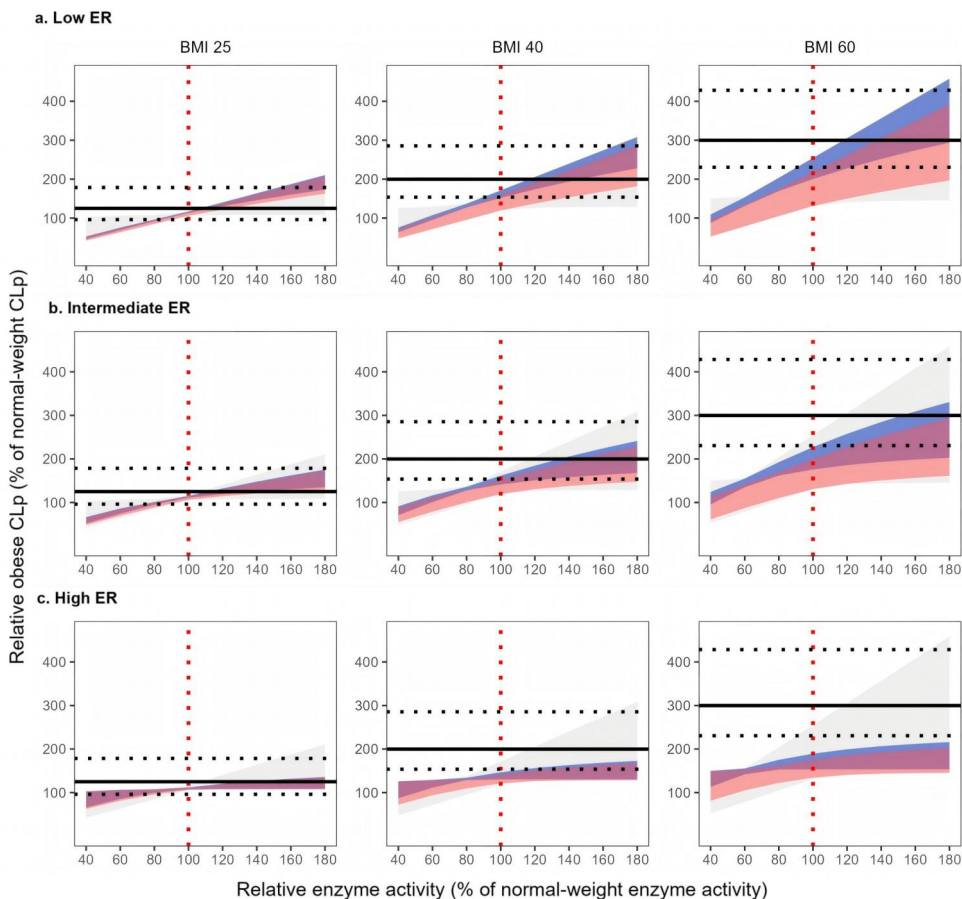


Figure S5.2 Accuracy of plasma clearance (CL_p) scaling obtained using bodyweight-based linear scaling with an exponent of 1 for all hypothetical drugs with **(a)** low extraction ratio (ER), **(b)** intermediate ER, and **(c)** high ER for respective relative enzyme activity for subjects with body mass index (BMI) of 25, 40 and 60 kg/m². Scaling is systematically accurate when the colored shaded areas completely fall between the black dotted lines. Blue and pink areas represent drugs that bind to human serum albumin (HSA) or α 1-acid glycoprotein (AAG). The purple area represents drugs not binding to plasma proteins. The black solid line represents the scaled CL_p for the bodyweight associated with the indicated BMI and the black dotted lines represent a range of $\pm 30\%$ prediction error of the scaled value. The red dotted line represents no change in enzyme activity. Note that the values of the extraction ratio represent the values defined for the normal-weight patient.

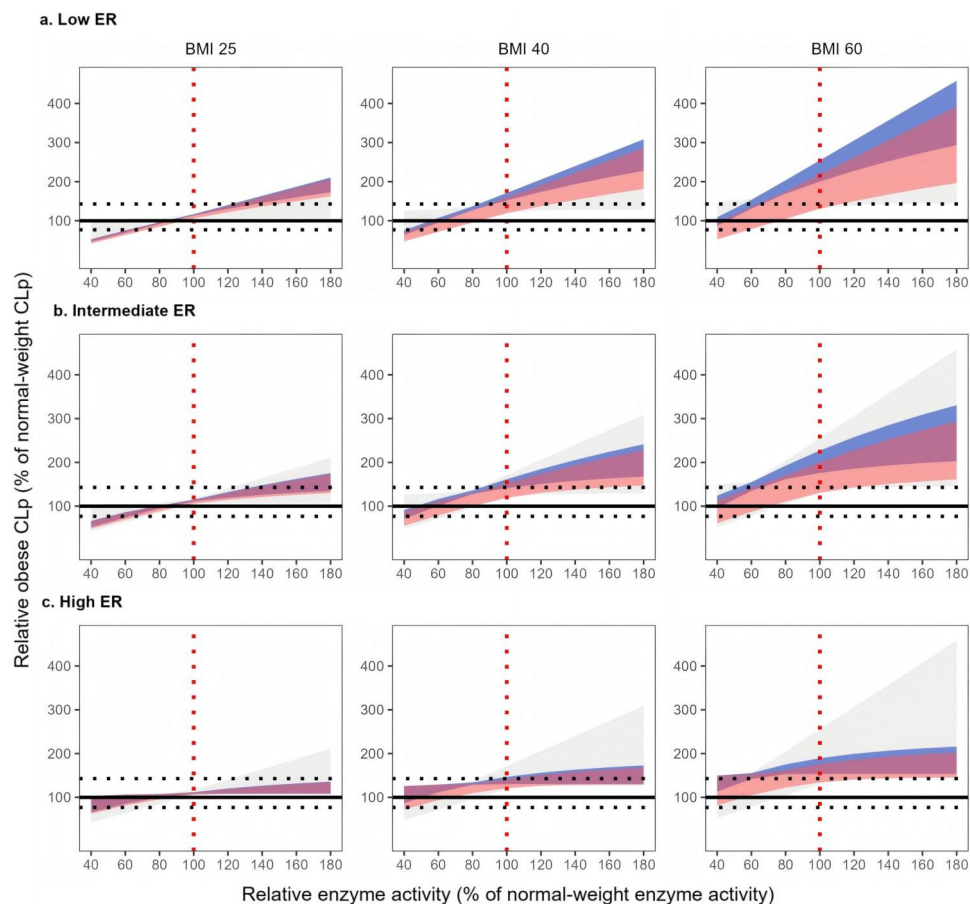


Figure S5.3 Accuracy of plasma clearance (CL_p) scaling obtained using flat dosing (with an exponent of 0) for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER, and (c) high ER for respective relative enzyme activity for subjects with body mass index (BMI) of 25, 40 and 60 kg/m². Scaling is systematically accurate when the colored shaded areas completely fall between the black dotted lines. Blue and pink areas represent drugs that bind to human serum albumin (HSA) or α 1-acid glycoprotein (AAG). The purple area represents drugs not binding to plasma proteins. The black solid line represents the scaled CL_p for the bodyweight associated with the indicated BMI and the black dotted lines represent a range of $\pm 30\%$ prediction error of the scaled value. The red dotted line represents no change in enzyme activity. Note that the values of the extraction ratio represent the values defined for the normal-weight patient.

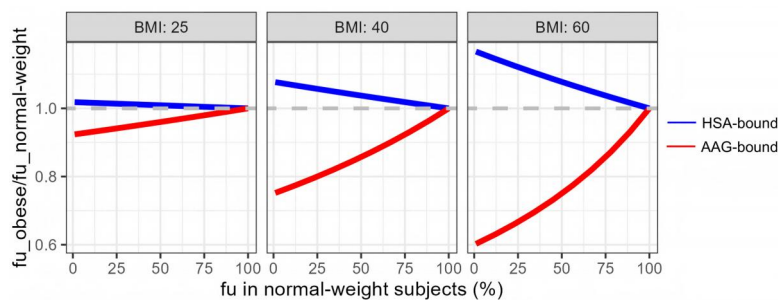


Figure S5.4 The correlation between the relative change in f_u (f_u in obese subjects/ f_u in normal-weight subjects) and f_u in normal-weight subjects. Blue and red lines represent drugs that are bound to human serum albumin (HSA) or α 1-acid glycoprotein (AAG), respectively.

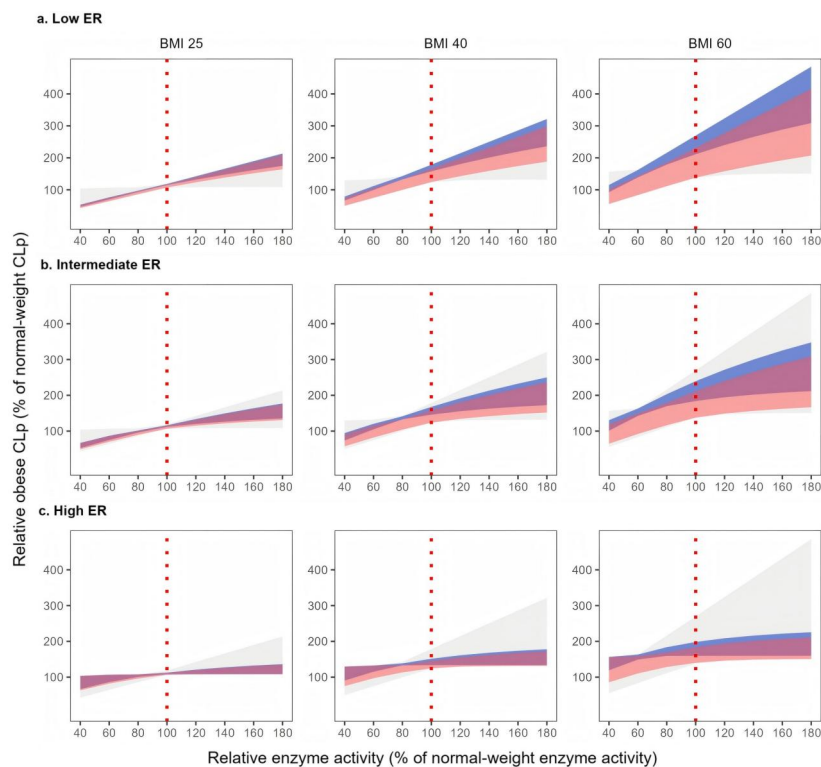


Figure S5.5 The correlation between the relative plasma clearance (CL_p) for subjects with body mass index (BMI) of 25, 40 and 60 kg/m^2 with a height of 1.85 meters and representative relative enzyme activity for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER, and (c) high ER. Blue and pink areas represent drugs that bind to human serum albumin (HSA) or α 1-acid glycoprotein (AAG), respectively. The purple area represents drugs not binding to plasma proteins. The grey area represents all hypothetical drugs, allowing comparisons between the three plots of the same BMI. The red dotted line represents the scenario of no change in enzyme activity.

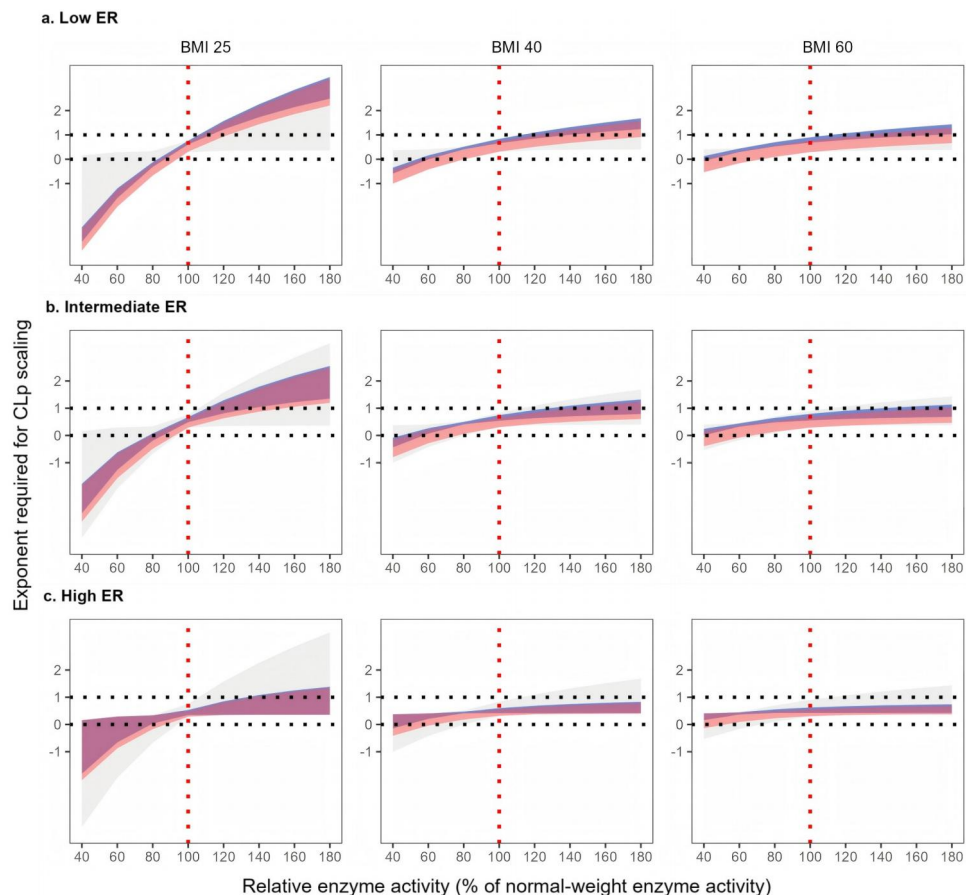


Figure S5.6 The correlation between the exponent in the allometric equation yielding perfect CL_p scaling for subjects with body mass index (BMI) of 25, 40 and 60 kg/m^2 with a height of 1.85 meters and representative relative enzyme activity for all hypothetical drugs with (a) low extraction ratio (ER), (b) intermediate ER and (c) high ER. Blue and pink areas represent drugs that are bound to human serum albumin (HSA) or α 1-acid glycoprotein (AAG), respectively. The purple area represents drugs not binding to plasma proteins. The grey area represents all hypothetical drugs, allowing comparisons between the three plots of the same BMI. The red dotted line represents no change in enzyme activity. Black dotted lines represent 0 and 1, the extreme values of the tested exponent values.

6

Influential variables affecting scaling from non-obese patients to obese patients for drugs eliminated through the kidney

This chapter is based on  Zhang T, et al. *The Impact of Drug Properties and Severity of Obesity on Renal Drug Clearance Through Glomerular Filtration and Active Tubular Secretion: A Systematic Analysis Using PBPK Modeling.* *Pharm Res.* 2025 Jul;42(7):1079-1088.

ABSTRACT

Objective

The influence of obesity on renal drug clearance (CL_r) remains difficult to predict. This study quantifies obesity-related alterations in CL_r for drugs eliminated via glomerular filtration (GF/CL_{GF}) and active tubular secretion (ATS/CL_{ATS}) and assesses the systematic accuracy of dosing based on allometric scaling with an exponent of 0.75 or flat dosing (exponent of 0).

Methods

A physiologically-based pharmacokinetic (PBPK) approach was used to simulate CL_{GF} and CL_{ATS} for 11,520 hypothetical drugs in typical subjects with body mass index (BMI) between 20 and 60 kg/m². Correlations between changes in CL_{GF} and CL_{ATS} and subject or drug properties were investigated. Moreover, for each drug, CL_r values scaled to individuals with obesity from CL_r values in normal-weight individuals were compared to PBPK predictions of CL_r . Systematic scaling accuracy was defined as the prediction error being less than $\pm 30\%$ for all drugs.

Results

CL_r through GF and ATS increased with BMI, albeit to different extents, depending on drug properties. When BMI was below 30 kg/m² and transporter activity remained unchanged, the CL_r between subjects of normal weight and with overweight or obesity differed less than 30% and both scaling methods were systematically accurate. For individuals with higher BMI, drug properties need to be taken into account when defining scenarios of systematic scaling accuracy.

Conclusion

In individuals with a BMI above 30 kg/m², neither 0.75 allometric scaling nor no scaling (flat dosing) is systematically accurate for renally cleared drugs. Strategies are provided to define systematic scaling accuracy *a priori*, based on subject and drug properties.

6.1 Introduction

Renal drug clearance (CL_r) is influenced by various processes including, amongst others, glomerular filtration (GF) and active tubular secretion (ATS). Obesity is a growing global health concern, but its influence on CL_r pathways has not been quantified in relation to different drug properties. Obesity can, for instance, lead to a higher glomerular filtration rate, but from clinical studies, it appears that this does not consistently result in a corresponding rise in CL_r , with studies showing enhanced CL_r for some drugs in obese individuals, and unaltered CL_r for others [1, 2]. This could stem from alterations in ATS counteracting the impact of GF alterations. Although obesity is thought to influence subject-related parameters such as transporter activity and, in turn, affect substance elimination via ATS [1, 3], information on specific obesity-induced changes in transporter activity is scarce, due to limited studies on this topic. As a result, the impact of obesity on ATS remains unclear. This knowledge gap makes it challenging to understand and predict obesity-related changes in the underlying mechanism of obesity influencing CL_r .

Meanwhile, simple clearance scaling methods that provide a convenient way to predict changes in CL_r in individuals with obesity without extensive data collection, are sought after. This is because changes in CL can often be directly translated into required changes of the maintenance dose. When dosing patients with obesity, two strategies are most commonly used: flat dosing, in which the same dose is administered to individuals with both normal weight and obesity, or a bodyweight-based exponential scaling strategy with an exponent of 0.75 (AS0.75). So far, the accuracy of these scaling methods for renally cleared drugs in the obese population has not been systematically evaluated.

In order to predict the obesity-induced changes in pharmacokinetics (PK) and the necessary dose adjustments, physiologically based PK (PBPK) principles can be used. With PBPK, CL changes can be derived for drugs with various drug properties from obesity-related physiological changes. However, applying a full PBPK model to make predictions for each drug requires a substantial amount of quantitative information on drug properties, some of which may be still unknown. Instead, a PBPK simulation workflow as developed previously by Calvier *et al.* [4–6] for the pediatric population, can be used to generate CL values for drugs of different properties upon which a

systematic evaluation of the accuracy of scaling methods can be performed. Such a method enables the definition of scenarios that lead to accurate weight-based scaling based on subject characteristics and drug properties. This allows for the definition of the minimal information required to select accurate clearance scaling methods.

This study quantifies obesity-related alterations in CL_r for drugs eliminated via GF and ATS across the entire drug-parameter space. Additionally, it explores the impact of potential obesity-induced changes in ATS on the total CL_r for these drugs, considering hypothetical relative changes in transporter activity (rTA) with obesity. Finally, in order to provide *a priori* guidance on selecting the most appropriate scaling method for subjects with overweight or obesity, scenarios are defined where commonly used scaling methods, like allometric scaling with an exponent of 0.75 or flat dosing (exponent of 0), lead to systematically accurate scaled CL_r values.

6.2 Methods

6.2.1 Renal clearance simulation for normal-weight and obese subjects

A PBPK-based simulation workflow was used to perform simulations in R (version 4.0.3) under R studio (version 1.1.43). Six BMI categories were investigated using typical subjects. Typical subjects incorporated in this simulation include a normal-weight subject (BMI 20 kg/m²), an overweight subject (BMI 25 kg/m²), and four (morbidly) obese subjects with BMI of 30, 40, 50, and 60 kg/m². The corresponding bodyweight of these subjects was calculated based on a typical height of 1.72 meters, which is the median height value for adults in the NHANES database [7], yielding weights of 59.2, 74.0, 88.8, 118.3, 148.0, and 177.5 kg, respectively.

The subject-specific parameters involved in the CL_r simulation included renal blood flow (Q_r), kidney weight, plasma concentrations of human serum albumin (HSA) or α 1-acid glycoprotein (AAG), hematocrit, glomerular filtration rate (GFR), and the number of proximal tubule cells per gram kidney (PTCPGK). The value of PTCPGK was 99.4, obtained from SimCYP Simulator[®] (version 22) and in the absence of information suggesting otherwise, this was assumed to remain unaltered with BMI. The

values of the other parameters were calculated based on the equations reported by Berton *et al.* [8]. The equations and the corresponding values of subject-specific parameters for each typical subject are provided in the supplementary materials, and the obesity-induced changes in subject-specific parameters relative to normal-weight subjects are illustrated in **Figure 6.1**.

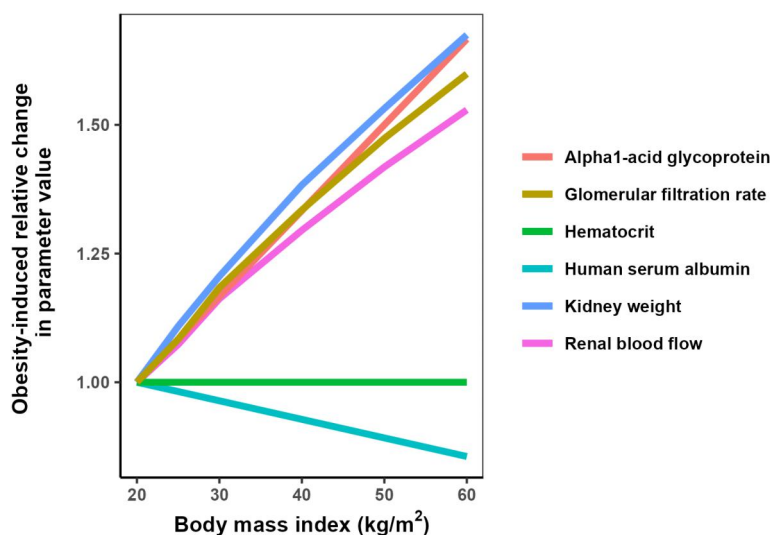


Figure 6.1 Obesity-induced changes in system-specific parameters relative to normal-weight subjects (based on Berton *et al.* [8])

To explore obesity-induced changes in CL_r across the entire drug-parameter space, 11,520 hypothetical drugs undergoing CL_r were generated. These hypothetical drugs were characterized by three drug-specific parameters. For each parameter, multiple values were selected within a realistic range of values:

- 1) unbound drug fraction in plasma in normal-weight subjects ($f_{u_{\text{normal weight}}}$) with values of 5%, 25%, 50%, 75%, 95%, and 100%. Drugs were assumed to exclusively bind to either human serum albumin (HSA) or α 1-acid glycoprotein (AAG);
- 2) blood-to-plasma partition coefficient (K_p) with values of 0.35, 1, 2, 3, 4, 5, 10, 20, 30, and 40 to indicate different degrees of drug diffusion into red blood cells [9, 10];
- 3) intrinsic active transporter-mediated secretion clearance ($CL_{\text{int_ATS}}$) with values from 2 to 500 $\mu\text{l}\cdot\text{min}^{-1}\text{mg protein}^{-1}$ with 32 different equidistant values, to reflect the drug affinity to the tubular secretion transporters together with the abundances

of the transporters.

As obesity-induced alterations in the activity of renal transporters remain largely unknown, obesity-induced changes in transporter activity are studied as hypothetical percentages of transporter activity compared to normal-weight individuals, referred to as relative transporter activity (rTA). For each BMI category, percentage changes between 20% and 250% were studied (i.e., 20%, 50%, 100%, 150%, 200%, 250%), with an rTA value of 100% indicating no change in transporter activity in individuals with obesity compared to normal-weight individuals. This range was derived from existing literature on changes in kidney transporter activity in obese or diabetic mice [11–13]. Although it is unlikely that large changes in rTA occur at relatively low degrees of overweight or obesity, it is unknown what ranges are relevant for each BMI category and therefore the entire rTA range was tested for each BMI category.

Parameters that are both drug-specific and subject-specific, including fu , blood-to-plasma ratio ($B : P$), and the total intrinsic secretion clearance (CL_{int_sec}), were calculated based on the subject- and drug-specific parameters as described in the supplementary materials. The fu in subjects with obesity was calculated based on $fu_{normal\ weight}$ and the plasma concentrations of the drug binding plasma proteins, being either HSA or AAG, and was negatively correlated with the plasma concentration of the drug binding protein [14, 15]. The affinity of drugs to these plasma proteins was assumed to remain constant with varying BMI. $B : P$ was calculated based on hematocrit, fu , and K_p , where hematocrit was influenced only by sex according to Berton *et al.* [8], and K_p was assumed to be constant across the BMI range. CL_{int_sec} was calculated as the product of CL_{int_ATS} , kidney weight, PTCPGK, and rTA.

With these parameters, CL_r was predicted using the PBPK models shown in **Equations 6.1–6.3**. The total CL_r was assumed to be the sum of the clearance through GF and ATS as outlined in **Equation 6.1**. The calculations for CL_r through GF and ATS are defined by **Equations 6.2 and 6.3**, respectively.

$$CL_r = CL_{GF} + CL_{ATS} \quad (6.1)$$

$$CL_{GF} = fu \times GFR \quad (6.2)$$

$$CL_{ATS} = \frac{(Q_r - GFR) \times fu \times CL_{int_sec}}{Q_r + fu \times \frac{CL_{int_sec}}{B:P}} \quad (6.3)$$

6.2.2 Obesity-related changes in renal clearance

With the PBPK model, CL_r was predicted for all 11,520 hypothetical drugs in all six BMI categories. Relative CL_r in subjects with overweight or obesity, compared to normal-weight individuals, was calculated. The correlation among relative CL_r with subject properties and drug properties was investigated graphically. Besides, the contribution of GF and ATS to CL_r was determined according to **Equations 6.4** and **6.5** respectively.

$$\text{Contribution of GF(\%)} = \frac{CL_{GF}}{CL_r} \times 100\% \quad (6.4)$$

$$\text{Contribution of ATS(\%)} = \frac{CL_{ATS}}{CL_r} \times 100\% \quad (6.5)$$

6.2.3 Systematic accuracy of CL_r scaling methods

For each hypothetical drug, CL_r was scaled from normal-weight subjects to overweight and obese subjects according to **Equation 6.6**. Values for the exponent of 0 and 0.75 were used to represent CL_r scaling that is associated with flat dosing and AS0.75-based dosing, respectively.

$$\text{Scaled } CL_{r_obese} = CL_{r_normal\ weight} \times \left(\frac{BW_{obese}}{BW_{normal\ weight}} \right)^{exponent} \quad (6.6)$$

The prediction error (PE) of the scaled CL_r and the PBPK-derived CL_r value was calculated according to **Equation 6.7**:

$$PE(\%) = \frac{\text{Scaled } CL_{r_obese} - \text{PBPK } CL_{r_obese}}{\text{PBPK } CL_{r_obese}} \times 100\% \quad (6.7)$$

A PE value within $\pm 30\%$ was regarded as accurate scaling. Systematic accuracy was defined as all hypothetical drugs within a defined category being scaled accurately.

Finally, the allometric exponent required to achieve the fully accurate scaling of CL_r for each drug and each BMI category was calculated according to **Equation 6.8**.

$$Exponent = \frac{\ln(CL_{obese}/CL_{normal\ weight})}{\ln(BW_{obese}/BW_{normal\ weight})} \quad (6.8)$$

6.3 Results

6.3.1 Obesity-related changes in renal clearance

Figure 6.2 illustrates how CL_{GF} , CL_{ATS} , and total CL_r differ between typical subjects with normal weight, overweight, and (morbid) obesity with varying rTA, for 27 representative drugs that bind to HSA, and that have different CL_{int_ATS} and $fu_{normal\ weight}$ values. Results obtained for drugs that bind to AAG are shown in **Supplementary Figure S6.1**. The values of CL_{GF} and CL_{ATS} for these hypothetical drugs can be found in **Supplementary Table S6.2** and **Table S6.3**.

From these figures and tables, it can be seen that both CL_{GF} and CL_{ATS} increase with BMI, albeit to different extents depending on drug properties. For drugs binding to HSA, CL_{GF} and CL_{ATS} consistently increase with increasing BMI, regardless of whether fu is low or high. In contrast, for drugs binding to AAG, CL_{GF} and CL_{ATS} largely increase with BMI only when fu is intermediate or high ($fu_{normal\ weight} \geq 50\%$). When fu is low (e.g., $fu_{normal\ weight} = 5\%$), CL_{GF} remains stable while CL_{ATS} only slightly increases with BMI. The observed differences are attributed to the decrease in HSA and the increase in AAG concentrations with rising BMI, as can be seen from **Figure 6.1**. This leads to an increase in fu for HSA and a decrease in fu for AAG. Consequently, for drugs binding to HSA, CL_{GF} , which depends on GFR and fu , rises with increasing BMI due to the combined effects of elevated GFR and increasing fu . In contrast, for AAG, the reduced fu counteracts the GFR increase, resulting in a relatively stable CL_{GF} with obesity. The influence of obesity-related changes in fu on CL_{ATS} is similar to its impact on CL_{GF} , causing CL_{ATS} to increase with obesity for drug binding to HSA, while it has a decreasing influence on CL_{ATS} for drug binding

to AAG.

In addition to $f u$, obesity-related changes in CL_{ATS} result from the interplay of other factors, including CL_{int_ATS} , K_p , rTA , kidney weight, renal blood flow, and GFR. As shown in **Figure 6.1**, kidney weight, renal blood flow, and GFR all increase with rising BMI, partially explaining why obesity-induced changes in CL_{ATS} can potentially be more pronounced than that changes in CL_{GF} . **Figure 6.2** and **Figure S6.1** show that rTA can either amplify or dampen the impact of obesity-induced changes in the other variables that impact CL_{ATS} , depending on the direction of change in rTA . It should be noted with these figures that rTA is unlikely to remain constant with BMI. It is more likely that differences in rTA become more extreme as BMI increases. Finally, these figures also show that as CL_{int_ATS} and $f u_{normal\ weight}$ increase, the range of CL_{ATS} resulting from varying K_p values also expands, ultimately leading to a wider range in CL_r .

Figure 6.2 and **Supplementary Figure S6.1** also illustrate the relative contribution of CL_{GF} and CL_{ATS} to total CL_r , providing insights into whether changes in total CL_r are predominantly driven by GF or ATS. In these figures, a line closer to the total CL line indicates a higher contribution from either GF or ATS to the overall renal clearance. These figures demonstrate that GF contributes significantly to total CL_r only when CL_{int_ATS} is low or rTA is considerably reduced.

The relative CL_r in the obese compared to CL_r in normal-weight individuals is illustrated in **Figure 6.3**. This figure shows that when BMI is below 30 kg/m² and transporter activity (rTA) remains unchanged, the CL_r in obese subjects compared to normal-weight subjects exhibited a change generally confined within $\pm 30\%$, regardless of drug properties. In this case, the impact of obesity on CL_r is considered negligible and flat dosing would be appropriate. Besides, this figure also indicates that for drugs with high protein binding (i.e., $f u_{normal\ weight} = 5\%$), when the drug is highly bound to AAG, the change in relative CL_r remains fairly stable across BMI values ranging from 25 to 60 kg/m². Similarly, only small changes are identified for drugs with low protein binding ($f u_{normal\ weight} = 95\%$) with high CL_{int_ATS} (500 $\mu\text{l}\cdot\text{min}^{-1}\cdot\text{mg protein}^{-1}$), binding to either HSA or AAG. Also for these drugs, flat dosing would be appropriate.

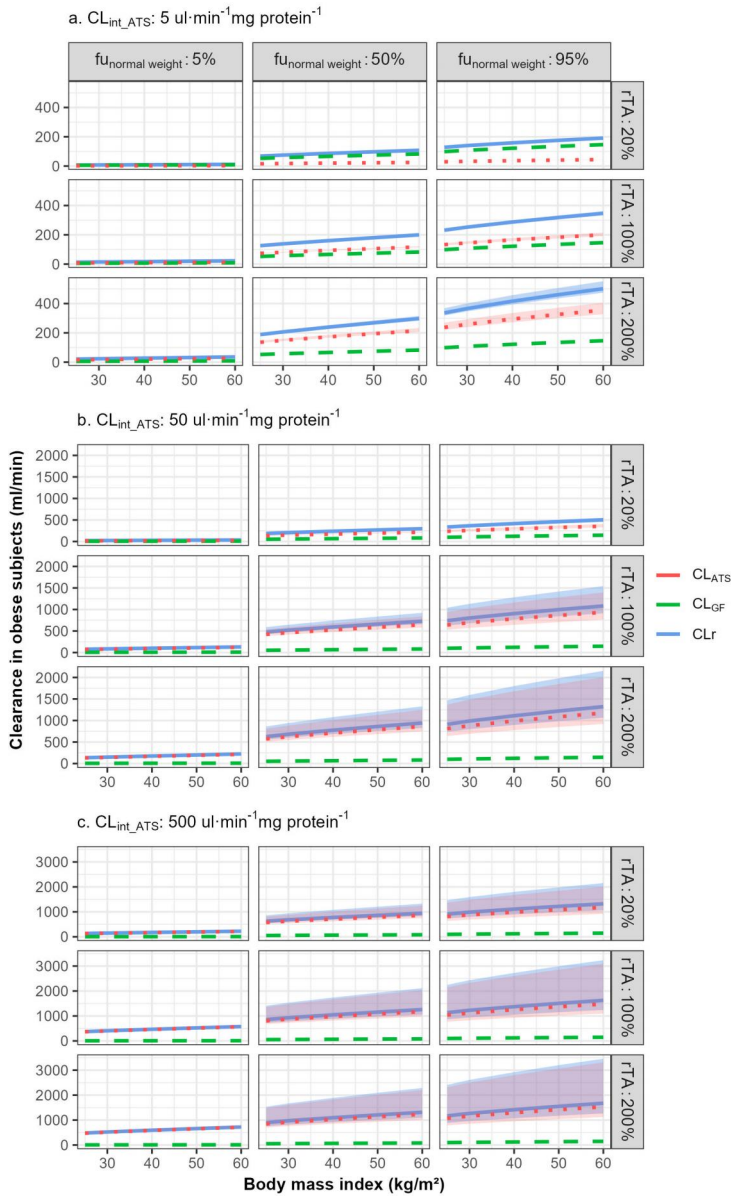


Figure 6.2 Total renal clearance (CL_r , blue solid line) and the clearance through glomerular filtration (CL_{GF} , green dashed line) and active tubular secretion (CL_{ATS} , red dotted line) for typical overweight and obese subjects with varying BMI with low, normal, or high relative transporter activity (rTA) for hypothetical drugs that bind to human serum albumin (HSA). These drugs have low, intermediate, or high unbound fractions in normal-weight individuals ($f_{u\text{normal weight}}$) and low, intermediate, or high transporter-mediated intrinsic clearance values (CL_{int_ATS}). Blue and red shaded areas represent the range of CL_r and CL_{ATS} , respectively, which results from differences in K_p (0.35, 1 or 4) impacting CL_{ATS} . Note that the overlapped area is shaded as purple and that the scale of the y-axis varies between panels.

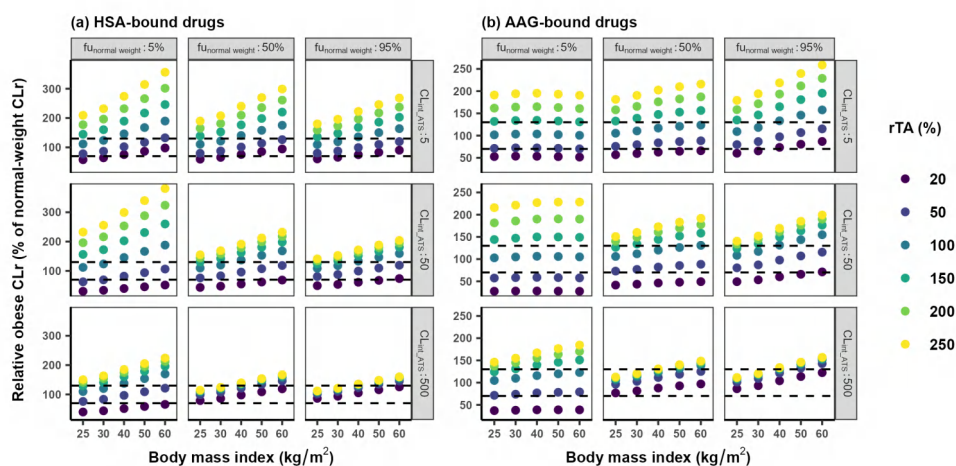


Figure 6.3 Relative total renal clearance (% of CL_r for normal weight subjects) for typical overweight and obese subjects with body mass index (BMI) between 25 and 60 kg/m^2 with different relative transporter activity (rTA) for hypothetical drugs that bind to (a) human serum albumin (HSA) or (b) $\alpha 1$ -acid glycoprotein (AAG). These drugs have low, intermediate, or high unbound fractions in normal-weight individuals ($f_{u,normal\ weight}$), low, intermediate or high transporter-mediated intrinsic clearance values (CL_{int_ATS}), and a K_p value of 1. Note that the scale of the y-axis differs between (a) and (b). The dashed black lines represent the threshold of change in CL_r within $\pm 30\%$ (i.e., 70% to 130%).

6.3.2 Systematic accuracy of CL_r scaling methods

The PE values of CL_r values scaled to obese individuals with an allometric equation with an exponent of 0 (assumed in flat dosing) and 0.75 are presented in **Figure 6.4**. These plots indicate that in general, both AS0.75 and flat dosing are systematically accurate only for subjects with a BMI below 30 kg/m^2 , provided their transporter activity remains unchanged. At BMI >30 kg/m^2 or when transporter activity changes, changes in CL_r become too variable to apply generalizable scaling rules, and systematic scaling accuracy can only be defined for specific scenarios taking subject and/or drug properties into account. For instance, AS0.75 is generally accurate for all investigated BMIs in scenarios in which CL_{int_ATS} is at or below 50 $\mu\text{L}\cdot\text{min}^{-1}\cdot\text{mg protein}^{-1}$ and transporter activity increases by up to 150% for drugs binding to HSA or up to 250% for drugs binding to AAG. In scenarios in which transporter activity is reduced to 50%, flat dosing becomes the only accurate scaling method, especially in subjects with a BMI over 30 kg/m^2 for drugs binding to HSA. For drugs binding to AAG, flat

dosing is accurate as long as there is no change in transporter activity, irrespective of BMI or drug properties. Additionally, flat dosing remains accurate when $f u_{\text{normal_weight}}$ exceeds 50% and $CL_{\text{int_ATS}}$ reaches $500 \mu\text{l}\cdot\text{min}^{-1}\text{mg protein}^{-1}$, regardless of BMI, transporter activity changes, and drug-binding proteins. In all other scenarios, neither scaling method achieves systematically accurate scaling, meaning that it cannot be determined whether a scaling method is accurate based on BMI, $f u$, and $CL_{\text{int_ATS}}$ alone and that PBPK-based approaches are required to ascertain accurate scaling.

To further increase our understanding of patterns in scaling accuracy, we also investigated for the various drugs and scenarios, which allometric exponent would be required to achieve fully accurate scaling of CL_r . **Supplementary Table S6.4** and **Figure S6.2** show that the range of allometric exponents required for perfect scaling falls within -6.26 to 4.17, with the range decreasing as BMI increases. Notably, there is a strong correlation between the exponent and rTA. When rTA is 100%, the exponent remains relatively stable across the BMI range between 0.33 and 0.59 for drugs binding to HSA and between 0.0053 and 0.43 for drugs binding to AAG. The exponent tends to decrease with decreasing transporter activity and increase with increasing transporter activity.

6.4 Discussion

In this study, a systematic analysis using a PBPK-based approach was used to quantify obesity-related changes in CL_r , across a large number of hypothetical drugs eliminated via GF and various degrees of ATS. How drug and subject characteristics correlate with these changes was studied and the impact of obesity-induced changes in ATS on the total CL_r for these drugs under various scenarios of change with obesity was explored. Moreover, this study also assessed the systematic accuracy of two commonly used weight-based scaling methods in predicting CL_r .

This study delves into the physiological mechanisms underlying alterations in CL_r among obese individuals, thereby providing a foundation for interpreting findings reported in literature. Studies of daptomycin [16, 17] and cefazolin [18–20], for instance, reported an unaltered CL_r in subjects with varying degrees of obesity compared to normal-weight subjects, suggesting that a flat dose or a weight-independent fixed

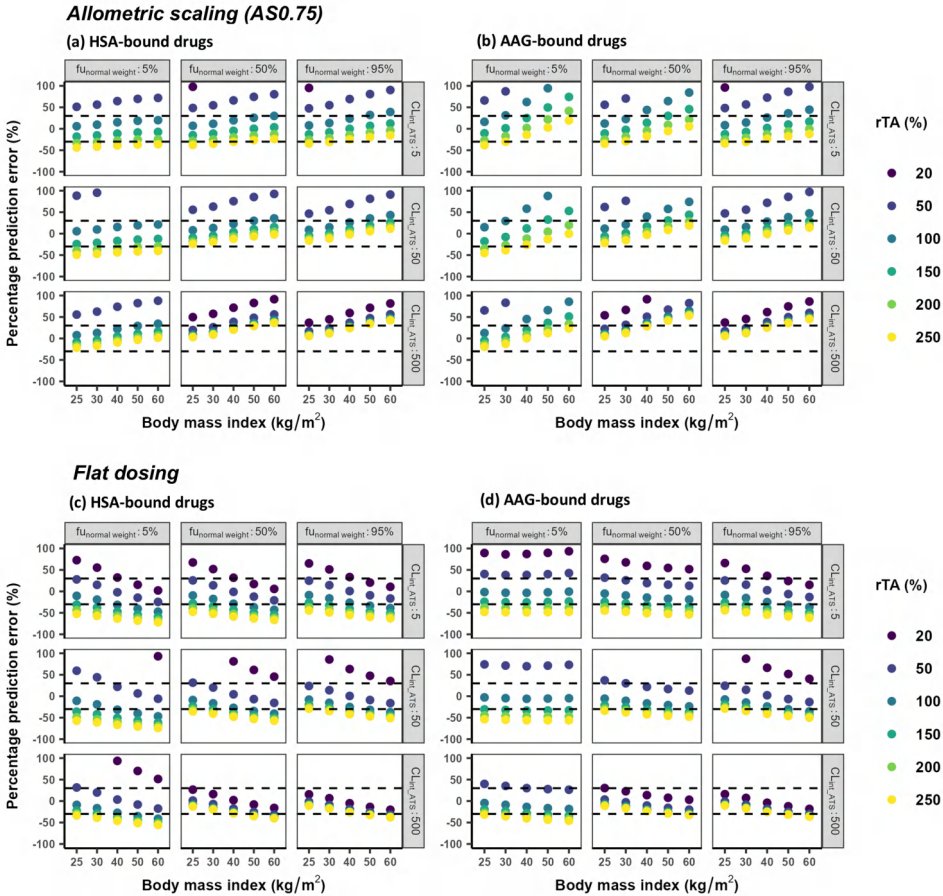


Figure 6.4 Percentage prediction error (PE) between renal clearance (CL_r) values scaled using allometric scaling with an exponent of 0.75 (AS0.75, upper panel) or flat dosing with an exponent of 0 (bottom panel) and CL_r obtained using the PBPK model for typical subjects with body mass index (BMI) between 25 and 60 kg/m² and different relative transporter activity (rTA) for hypothetical drugs that bind to (a,c) human serum albumin (HSA) and (b,d) α 1-acid glycoprotein (AAG). These drugs have low, intermediate, or high unbound fractions in normal-weight individuals ($f_{u,normal\ weight}$), low, intermediate or high transporter-mediated intrinsic clearance values ($CL_{int,ATS}$), and a K_p value of 1. The black dotted lines represent the threshold of reasonably acceptable CL_r prediction of $\pm 30\%$. Note that only changes in the range of $\pm 100\%$ are shown.

dose is appropriate when aiming for similar plasma concentrations. Daptomycin and cefazolin, both exhibit high plasma protein binding ($f u_{\text{normal weight}} < 20\%$), primarily undergo GF with very limited involvement of ATS [21–23]. Therefore, these findings can be explained by our results shown in **Figure 6.2** and **Supplementary Table S6.2**, indicating limited changes of CL_r for drugs eliminated through GF with a low $f u$ value, irrespective of the degree of obesity.

For drugs for which both GF and ATS contribute considerably to CL_r , the patterns in the changes in CL_r are more complex and the impact of transporter activity needs to be considered as well. For instance, a study of meropenem reported that the CL_r in obese subjects was not significantly different from that of normal-weight subjects [24]. Meropenem is barely bound to serum proteins and is a substrate of organic anion transporter (OAT) 1 and 3 [25]. The findings from this study suggest that for a drug with low protein binding, an increase in CL_r would be expected unless rTA is low. Therefore, the unchanged CL_r of meropenem could potentially be attributed to a reduction in OAT activity in subjects with obesity. Conversely, in the case of drugs such as metformin [26], gentamicin [27, 28] and vancomycin [2, 29, 30], which exhibit lower serum protein binding, their increased CL_r is likely due to the increased activity of organic cation transporter (OCT) 2 involved in their ATS [13, 31].

In subjects with overweight or obesity, both CL_{GF} and CL_{ATS} were found to increase with BMI, though the extent varied considerably depending on drug properties. In addition to BMI, the change in CL_{GF} primarily depended on the changes in $f u$, while changes in CL_{ATS} were influenced by multiple parameters, including $CL_{\text{int_ATS}}$, rTA, K_p , $f u_{\text{normal weight}}$, kidney weight, renal blood flow, and GFR. Notably, in this study, the transporter activity in individuals with overweight and obesity was evaluated relative to normal-weight subjects. When transporter activity decreased due to obesity (i.e., rTA below 100%), the absolute value of CL_{ATS} or CL_r may still increase with increasing BMI, but could still remain lower than those in normal-weight subject.

This study also evaluated the systematic accuracy of two commonly used scaling methods in predicting CL_r for obese individuals. When scaling is systematically accurate, the PE of all scaled CL_r values is less than $\pm 30\%$. The absence of systematic accuracy does not mean that scaling is inaccurate for all drugs, it merely indicates that it cannot be known *a priori* whether CL_r scaling for a drug will be accurate with-

out taking additional information into account. We found that when subjects had a BMI below 30 kg/m² and unaltered transporter activity, both AS0.75 and flat dosing methods were systematically accurate for any drugs. Under any other circumstance, details regarding the drug elimination pathway (i.e., degree of ATS), $f_{u_{\text{normal weight}}}$, $CL_{\text{int_ATS}}$, rTA, and/or the degree of obesity are required to be known for the *a priori* selection of an appropriate scaling method with the help of **Figure 6.4**. In cases when systematic accuracy is not achieved, PBPK-based approaches are essential for accurate CL_r predictions in individuals with obesity. For instance, our results show that when transporter activity decreases below 50%, neither scaling method could achieve systematically accurate scaling. This is because, as illustrated in **Supplementary Figure S6.2**, the exponent required for accurate scaling becomes negative in this scenario. PBPK modeling is the only appropriate method for predicting obesity-related CL_r changes in such cases.

The use of a PBPK approach enabled us to predict drug clearance by considering various drug properties, subject characteristics, and different degrees of obesity, in the absence of clinical data on individual drugs. Previously, we applied this approach to hepatically cleared drugs in obesity [32] and for hepatically and renally cleared drugs in the pediatric population [4–6]. Using this approach, rather than studying a limited number of existing drugs, we generated a total of 11,520 hypothetical drugs to cover the entire parameter space with realistic ranges for each parameter. Similar to the previous studies, we cannot exclude that uncommon or unrealistic combination of drug properties could have been generated, but similar to the previous study our findings will likely cover all currently existing drugs as well as small molecule drugs that are still to be developed in the future. As mentioned before, for rTA unrealistic combinations of subject properties were likely generated, for instance, when BMI is 25 kg/m², a 250% obesity-related increase in rTA is unlikely, but as it is unknown what ranges in rTA are realistic for the different BMI categories, our results cover a wide range of possible scenarios. In this respect, it is also worth mentioning that the overweight and obese subjects included in this PBPK study were defined based on BMI. The reason for this is that the only available literature reporting subject-specific parameters for overweight and obese subjects is based on BMI rather than bodyweight. If future studies demonstrate better correlation for some of the parameters with bodyweight or other descriptors, this can be easily adapted in the current workflow. Moreover,

this PBPK model incorporates GF and ATS, while intentionally excluding reabsorption and renal metabolism as renal elimination routes, to reduce the complexity of the findings. Nonetheless, exploring the impact of reabsorption, along with its dependence on physiological factors like ionization and pH, or renal metabolism could be investigated using similar approaches in future analyses. Finally, we defined the range of relative changes in obesity-induced transporter activity (rTA) according to the existing literature involving obese mice [30]. This is due to the fact that there is limited quantitative data on the change in transporter activity in obese humans. Upon the availability of quantitative data regarding obesity-induced changes in specific transporter activities, our findings can serve as a valuable tool for predicting corresponding alterations in CL_r .

6.5 Conclusion

In this study, we found that obesity-induced changes in fu , CL_{int_ATS} , and rTA primarily drive the obesity-related changes in CL_r . How fu changes with BMI depends on the plasma protein the drug binds to. For drugs binding to HSA, CL_r consistently increases with BMI regardless of fu changes, whereas for drugs binding to AAG, CL_r remains relatively stable as the direction of the change in fu negates the impact of increased CL driven by other variables. Based on the obesity-related changes in CL_r that were quantified with PBPK modeling, we could conclude that no single clearance scaling method can be systematically accurate for drugs cleared through GF and various degrees of ATS when BMI is higher than 30 kg/m² or when transporter activity is impacted by obesity. In these cases, the results of this study could inform the selection of appropriate scaling methods for subsets of drugs, based on fu , CL_{int_ATS} , drug binding protein, and rTA. In all other cases, PBPK modeling is the only method that can ascertain accurate scaling *a priori*.

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Supplementary Material

1. Equations and the corresponding values of subject-specific parameters for the typical individuals implemented in the PBPK-based simulation workflow

Table S6.1 Equations and the corresponding values

System-specific parameters	Equations from Berton <i>et al.</i> [1]	Demographic values									
		non-obese					obese				
Body mass index (BMI, kg/m ²)	–	20	25	30	40	50	60				
Height (HT, cm)	–	172	172	172	172	172	172				
Body weight (BW, kg)	$BMI \times (HT/100)^2$	59.2	74	88.8	118	148	178				
Fat mass (FM, kg)	$[(30.86 - 3.09 \times Sex - 0.13 \times HT + 0.14 \times BW) - BMI] \times (HT/100)^2$	14.1	22.7	31.4	48.8	66.1	83.4				
Blood weight (kg)	$2.58 + 0.057 \times BW - 0.061 \times (FM/BW)$	5.94	6.78	7.62	9.30	11	12.7				
Cardiac output (CO, L/min)	$Heart\ rate \times (43.13 + 12.96 \times Blood\ weight) \times (0.65 - 0.0018 \times BMI)/1000$	5.86	6.29	6.81	7.59	8.31	8.96				
Kidney blood flow (Qr, L/min)	$(20.57 - 1.76 \times Sex) \times CO/100$	1.15	1.24	1.34	1.49	1.64	1.76				
Human serum albumin (HSA, g/L)	$47.58 - 0.16 \times BMI$	44.4	43.6	42.8	41.2	40.0	38.0				
α 1-acid glycoprotein (AAG, g/L)	$0.48 + 0.012 \times BMI$	0.72	0.78	0.84	0.96	1.08	1.20				
Hematocrit	$0.45 - 0.04 \times Sex$	0.43	0.43	0.43	0.43	0.43	0.43				
Kidney weight (kg)	$-0.11 - 0.048 \times Sex + 0.003 \times Age + 0.18 \times Body\ surface\ area$	0.31	0.35	0.38	0.44	0.48	0.53				
Glomerular filtration rate (GFR, mL/min)	$13.02 - 0.51 \times Age + 0.93 \times (FM/BW) + 93.56 \times Qr/1000$	95.7	104	113	128	141	153				

Note: when calculating values that depend on sex, the average value for both sexes was used. Age was set as 50 years when required for parameter calculations.

2. Equations to calculate the drug- and system-specific parameters for the typical individuals implemented in the PBPK-based simulation workflow

$$f u_{\text{obese}} = \frac{1}{1 + \frac{(1 - f u_{\text{normal weight}}) \times PP_{\text{obese}}}{f u_{\text{normal weight}} \times PP_{\text{normal weight}}}} \quad (\text{S6.1})$$

$$CL_{\text{int_sec}} = CL_{\text{int_ATS}} \times PTCPGK \times K_{\text{ideney weight}} \times rTA \quad (\text{S6.2})$$

$$B : P = 1 + (\text{Hematocrit} \times (f u \times K_p - 1)) \quad (\text{S6.3})$$

In these equations, values for $f u_{\text{normal weight}}$, $CL_{\text{int_ATS}}$, and K_p are taken from normal-weight subjects as defined in the main text. PP is the concentration of plasma protein, which was assumed to be either human serum albumin (HSA) or $\alpha 1$ -acid glycoprotein (AAG). The number of proximal tubule cells per gram kidney (PTCPGK) was assumed to be 99.4, according to the SimCYP Simulator[®] (version 22) and is assumed to remain unaltered across varying BMI. Obesity-induced changes in transporter activity are integrated as fractions relative to transporter-mediated active clearance in normal-weight individuals (rTA).

Table S6.2 Clearance through glomerular filtration for the investigated body mass index (BMI) for hypothetical drugs categorized per drug binding protein with low to high unbound drug fraction in normal weight subjects ($f u_{\text{normal weight}}$)

	BMI (kg/m ²)	Clearance through glomerular filtration for drugs with varying $f u_{\text{normal weight}}$		
		5%	50%	95%
HSA-bound drugs	25	5.27	52.31	98.58
	30	5.87	57.69	107.83
	40	6.86	66.25	121.77
	50	7.86	74.55	134.71
	60	8.87	82.46	146.42
AAG-bound drugs	25	4.8	49.77	98.09
	30	4.89	52.29	106.75
	40	4.85	54.74	119.34
	50	4.78	56.41	130.71
	60	4.68	57.38	140.68

Table S6.3 Clearance through active tubular secretion for the investigated body mass index (BMI) for hypothetical drugs categorized per drug binding protein with low to high unbound drug fraction in normal-weight subjects ($f_{u_{\text{normal weight}}}$) and transporter-mediated intrinsic clearance values ($CL_{\text{int_ATS}}$). These drugs have K_p values of 0.35, 1, and 4. Note that obesity-induced changes in transporter activity are not considered in this table, and that total clearance is the sum of clearance through both active tubular secretion and glomerular filtration.

BMI (kg/m²)		Clearance through active tubular secretion for drugs with varying $f_{u_{\text{normal weight}}}$				
$CL_{\text{int_ATS}}$ ($\mu\text{l}\cdot\text{min}^{-1}\cdot\text{mg protein}^{-1}$)		5%		50%		95%
25	5	5	8 [7.99, 8.05]	76.67 [72.28, 79.58]	143.16 [127.34, 149.94]	
	50	50	73.06 [71.97, 77.05]	549.8 [382.95, 744.97]	971.74 [527.03, 1400.99]	
	500	500	391.35 [362.02, 541.51]	1438.67 [671.63, 4545.7]	2313.58 [768.11, 8457.57]	
30	5	5	8.84 [8.83, 8.9]	84.06 [79.17, 87.28]	155.68 [138.4, 163.09]	
	50	50	80.66 [79.41, 85.17]	601.45 [417.22, 816.73]	1055.18 [571.27, 1523.38]	
	500	500	428.46 [395.55, 596.64]	1567.53 [728.08, 4974.21]	2506.29 [831.28, 9180.75]	
HSA-bound drugs	5	5	10.5 [10.48, 10.57]	97.96 [91.99, 101.85]	178.42 [158.1, 187.16]	
	50	50	95.24 [93.64, 100.97]	694.1 [475.47, 951.24]	1198.53 [642.9, 1744.9]	
	500	500	493.26 [453.09, 698.63]	1776.96 [815.39, 5730.58]	2806.61 [927.24, 10404.15]	
50	5	5	12.06 [12.03, 12.14]	110.37 [103.43, 114.84]	197.67 [174.9, 207.47]	
	50	50	108.92 [106.95, 115.85]	778.09 [528.12, 1071.71]	1322.93 [706.67, 1932.72]	
	500	500	553.64 [506.14, 795.56]	1973.79 [896.04, 6426.37]	3080.1 [1015.4, 11474.47]	
60	5	5	13.69 [13.66, 13.79]	122.82 [114.83, 127.9]	216.2 [190.97, 227.08]	
	50	50	123.1 [120.69, 131.42]	860.79 [578.44, 1192.44]	1440.52 [765.71, 2113.41]	

	500	613 [557.49, 894.86]	2161.01 [970.12, 7110.4]	3330.65 [1095.38, 12481.3]
	5	7.29 [7.28, 7.33]	73 [69.06, 75.71]	142.44 [126.78, 149.19]
25	50	67.04 [66.19, 70.3]	526.12 [372.73, 708.88]	967.26 [525.75, 1393.93]
	500	371.19 [346.59, 499.33]	1389.8 [665.27, 4330.43]	2304.24 [767.18, 8415.52]
	5	7.39 [7.38, 7.42]	76.32 [72.37, 79.11]	154.13 [137.18, 161.45]
30	50	68.22 [67.45, 71.26]	551.58 [395.52, 740.64]	1045.47 [568.52, 1508.11]
	500	386.41 [363.07, 509.69]	1464.8 [714.63, 4521.12]	2486.14 [829.26, 9089.84]
AAG-	5	7.45 [7.44, 7.48]	81.2 [77.26, 84.16]	174.9 [155.35, 183.43]
bound	50	69.24 [68.6, 71.92]	587.03 [428.78, 786.67]	1176.7 [636.8, 1710.19]
drugs	500	405.22 [384.39, 518.46]	1559.57 [786.76, 4761.07]	2761.9 [922.79, 10199.82]
	5	7.37 [7.36, 7.39]	83.93 [80.15, 86.92]	191.88 [170.37, 201.32]
50	50	68.85 [68.34, 71.17]	609.53 [453.96, 812.12]	1287.1 [696.7, 1875.53]
	500	416.78 [398.41, 518.92]	1633.57 [850.77, 4903.67]	3007.09 [1008.14, 11139.21]
	5	7.27 [7.27, 7.3]	86.02 [82.41, 89.03]	207.83 [184.44, 218.18]
60	50	68.32 [67.88, 70.34]	627.07 [475.02, 831.39]	1388.94 [751.46, 2030.7]
	500	425.24 [408.95, 517.82]	1692.53 [907.27, 5003.7]	3226.26 [1085.02, 11999.04]

HSA, human serum albumin, AAG, α 1-acid glycoprotein

Table S6.4 Allometric exponent required for accurate scaling for the investigated body mass index (BMI) for hypothetical drugs categorized per drug binding protein with low to high unbound drug fraction in normal-weight subjects ($f_{u_{\text{normal weight}}}$) and transporter-mediated intrinsic clearance values ($CL_{\text{int_ATS}}$). Note that obesity-induced changes in transporter activity are not considered in this table.

BMI (kg/m²)		CL _{int,ATS} (µl·min ⁻¹ ·mg protein ⁻¹)	Clearance through active tubular secretion for drugs with varying <i>f_u</i> _{normal weight}		
			5%	50%	95%
25		5	0.49 [0.49~0.49]	0.45 [0.45~0.46]	0.42 [0.41~0.42]
		50	0.51 [0.51~0.52]	0.44 [0.40~0.48]	0.41 [0.37~0.45]
		500	0.43 [0.42~0.48]	0.37 [0.34~0.44]	0.34 [0.33~0.40]
30		5	0.53 [0.52~0.53]	0.48 [0.48~0.49]	0.44 [0.44~0.45]
		50	0.53 [0.52~0.54]	0.47 [0.44~0.49]	0.43 [0.40~0.45]
		500	0.46 [0.45~0.50]	0.42 [0.39~0.46]	0.39 [0.38~0.42]
40		5	0.55 [0.55~0.55]	0.49 [0.49~0.50]	0.45 [0.44~0.45]
		50	0.55 [0.54~0.56]	0.48 [0.45~0.51]	0.43 [0.41~0.46]
		500	0.47 [0.46~0.52]	0.42 [0.39~0.47]	0.39 [0.38~0.43]
50		5	0.56 [0.56~0.56]	0.50 [0.50~0.51]	0.45 [0.44~0.45]
		50	0.56 [0.56~0.57]	0.49 [0.45~0.51]	0.44 [0.41~0.46]
		500	0.48 [0.47~0.54]	0.44 [0.40~0.48]	0.40 [0.39~0.43]
60		5	0.58 [0.58~0.58]	0.52 [0.51~0.52]	0.45 [0.45~0.46]
		50	0.58 [0.57~0.59]	0.50 [0.46~0.53]	0.44 [0.42~0.46]
		500	0.50 [0.48~0.55]	0.45 [0.41~0.50]	0.40 [0.39~0.44]

25	5	0.07 [0.07~0.07]	0.23 [0.23~0.24]	0.39 [0.38~0.40]
	50	0.12 [0.11~0.13]	0.25 [0.25~0.27]	0.39 [0.35~0.42]
	500	0.19 [0.11~0.22]	0.22 [0.20~0.28]	0.32 [0.32~0.38]
30	5	0.08 [0.08~0.08]	0.24 [0.24~0.25]	0.42 [0.41~0.42]
	50	0.11 [0.09~0.12]	0.25 [0.25~0.29]	0.41 [0.39~0.43]
	500	0.20 [0.11~0.23]	0.25 [0.22~0.33]	0.37 [0.36~0.40]
AAG-bound drugs	5	0.05 [0.05~0.05]	0.22 [0.22~0.23]	0.42 [0.41~0.42]
	50	0.08 [0.07~0.09]	0.24 [0.23~0.28]	0.41 [0.39~0.43]
	500	0.19 [0.09~0.22]	0.23 [0.20~0.33]	0.37 [0.36~0.40]
50	5	0.02 [0.02~0.02]	0.20 [0.20~0.21]	0.42 [0.41~0.42]
	50	0.06 [0.04~0.06]	0.22 [0.21~0.27]	0.41 [0.39~0.43]
	500	0.17 [0.07~0.20]	0.23 [0.19~0.33]	0.37 [0.37~0.40]
60	5	0.00 [0.0053~0.01]	0.19 [0.19~0.20]	0.42 [0.41~0.42]
	50	0.04 [0.02~0.05]	0.21 [0.20~0.27]	0.41 [0.40~0.43]
	500	0.16 [0.06~0.19]	0.22 [0.17~0.33]	0.38 [0.37~0.40]

HSA, human serum albumin, AAG, α 1-acid glycoprotein

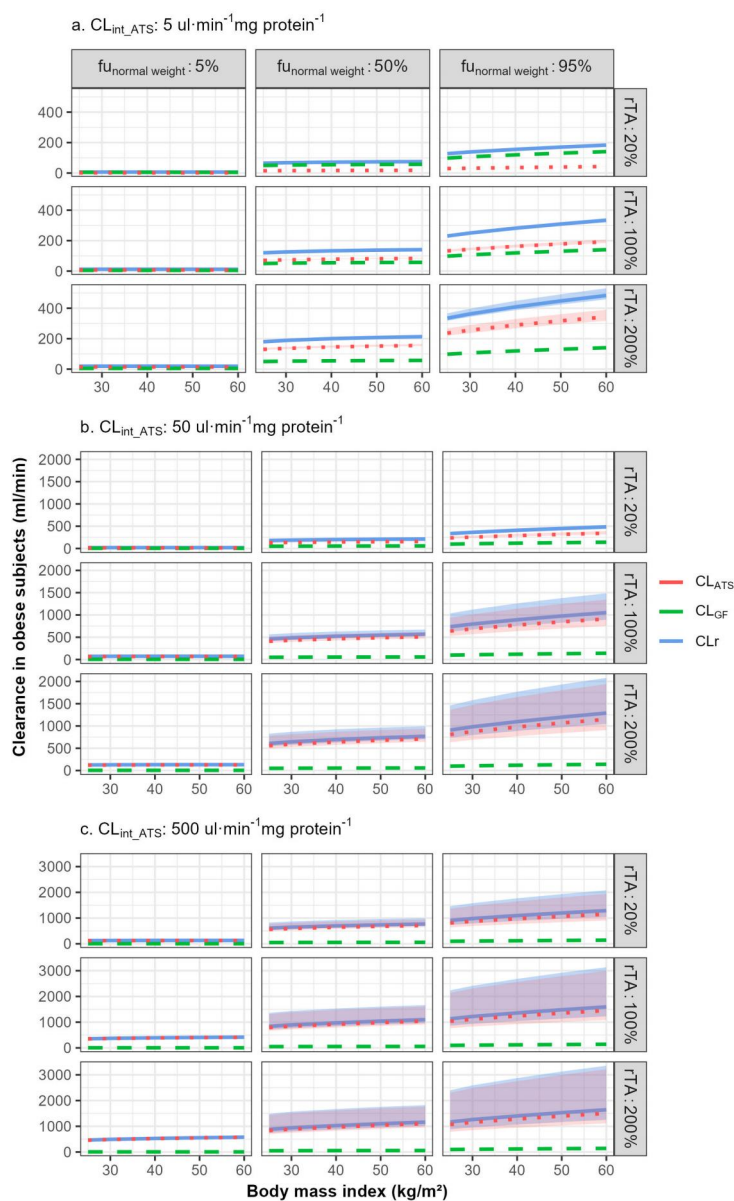


Figure S6.1 Total renal clearance (CL_r , blue solid line) and the clearance through glomerular filtration (CL_{GF} , green dashed line) and active tubular secretion (CL_{ATS} , red dotted line) for typical overweight and obese subjects with varying BMI with low, normal and high relative transporter activity (rTA) for hypothetical drugs that bind to α -1 acid glycoprotein (AAG). These drugs have low, intermediate, or high unbound fractions in normal-weight individuals ($f_{u\text{normal weight}}$) and low, intermediate, or high transporter-mediated intrinsic clearance values (CL_{int_ATS}). Blue and red shaded areas represent the value range of CL_r and CL_{ATS} , respectively, which results from differences in K_p (0.35, 1 or 4) impacting CL_{ATS} . Note that the overlapped area is shaded as purple and that the scale of the y-axis varies among panels.

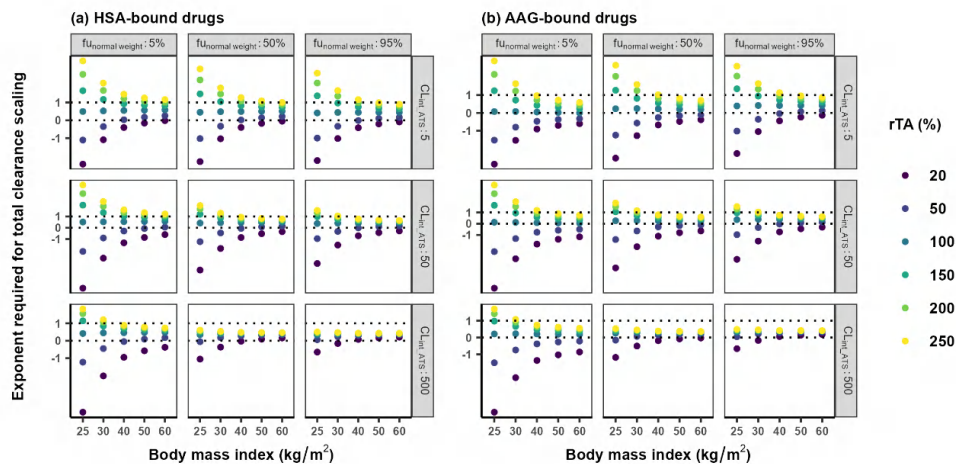


Figure S6.2 Exponent required for total clearance scaling for typical overweight and obese subjects with body mass index (BMI) between 25 and 60 kg/m² with low, intermediate, or high relative transporter activity (rTA) for hypothetical drugs that bind to (a) human serum albumin (HSA) and (b) α 1-acid glycoprotein (AAG). These drugs have low, intermediate, or high unbound fractions in normal-weight individuals ($f u_{\text{normal weight}}$), low, intermediate, or high transporter-mediated intrinsic clearance values (CL_{ATS}), and a K_p value of 1.

Supplementary References

1. Berton M, Bettonte S, Stader F, Battegay M, Marzolini C. Repository Describing the Anatomical, Physiological, and Biological Changes in an Obese Population to Inform Physiologically Based Pharmacokinetic Models. Clin Pharmacokinet. 2022;61(9):1251-1270. doi:10.1007/s40262-022-01132-3

IV

Summary, perspectives and
conclusion

7

Summary, perspectives and conclusion



7.1 Summary

This thesis focuses on predicting drug clearance and individualizing dose regimens in individuals with overweight and obesity. To accomplish this, two modeling approaches were used: population pharmacokinetic (popPK) modeling and physiologically based pharmacokinetic (PBPK) modeling. Through popPK modeling, we aimed to quantify the impact of obesity on vancomycin pharmacokinetics in overweight and obese adolescents and adults, as well as in patients with various degrees of renal (dys)function. In addition to that, optimal drug dosing guidelines for patients with overweight or obesity with or without renal dysfunction were developed. Through PBPK modeling, we aimed to study alterations in CL associated with obesity for drugs metabolized by the liver or eliminated via glomerular filtration and active tubular secretion, considering drug properties, subject characteristics, and severity of obesity. To achieve these objectives, several studies were conducted, and the results of these studies are summarized below.

Section I

In **Chapter 2**, we reviewed the available evidence regarding five commonly accepted assumptions that *a priori* predict the impact of obesity on drug PK. We found that available literature contradicts, or at least limits the generalizability, of all five assumptions: **1)** it is not justified to *a priori* select lean body weight as a size descriptor for inter-individual variability in clearance in obese individuals, nor does any other size descriptor qualify for this. Total body weight in a non-linear function is mostly reported as the optimal descriptor to describe the variability in clearance; **2)** The impact of obesity on distribution volume varies widely and cannot be predicted based solely on lipophilicity. In general, there seems a (small) increase in distribution volume for hydrophilic drugs, while for lipophilic drugs there is a high inter-drug variability with potentially very large changes; **3)** Hepatic clearance is influenced not only by changes in activity or abundance of hepatic enzymes resulting from obesity-related changes, but also by changes in plasma protein binding and hepatic blood flow, with the net influence depending on drug extraction ratio; **4)** Despite a possible increase in glomerular filtration rate (GFR) in obese individuals, absolute renal clearance does not necessarily increase for all drugs that are mainly eliminated through the kidneys, because transporter-mediated secretion and reabsorption may also be impacted by

obesity; 5) Findings on clearance and dose adjustments from obese adults cannot always be directly extrapolated to obese adolescents, possibly due to differences in the duration of obesity and time needed for physiological changes to manifest and impact PK parameters.

Section II

In Section II, the popPK modeling approach was used to explore the influence of obesity in relation to other variables that influence vancomycin PK. In **Chapter 3**, the PK of vancomycin in adolescents and adults with overweight or obesity was investigated. By analyzing adolescents and adults together, vancomycin *CL* was found to increase with total bodyweight (TBW) and decrease with increasing age. A covariate analysis investigating adolescents and adults separately found that vancomycin *CL* increased with standard weight (defined as weight for length, age, and sex in adolescents and weight for length in adults) albeit with different functions for adolescents and adults, and with adolescents having a higher *CL* per standard weight than adults. Moreover, in this separate covariate model, adolescent males had 21% higher *CL* than adolescent females of the same standard weight, while in adults, *CL* decreased with increasing age. These results suggest that there are apparent differences in vancomycin *CL* in overweight and obese adults *versus* overweight and obese adolescents, implying that dosing of vancomycin cannot be directly extrapolated between these populations.

In **Chapter 4**, a popPK model was developed to quantify the PK of vancomycin in patients with overweight or obesity and various degrees of renal (dys)function. Vancomycin *CL* was found to increase linearly with TBW and with renal function (CKD-EPI) in a power relation. Additionally, *CL* proved to be 15.5% reduced in ICU patients. Based on this model, AUC-targeted dosing recommendations for this population were proposed. To reach a target AUC_{24} between 400 and 600 mg·h/L in the first 48 hours, two loading doses in the first 48 hours of treatment are required for both continuous infusion and intermittent dosing regimens. Maintenance doses were found to require adjustment for TBW, renal function, and ICU admission status. With this guideline, the median AUC_{24} is well within the target from the start of the treatment onwards, potentially reducing the need for dose adjustments upon TDM.

Section III

In **Chapter 5**, a PBPK approach was used to investigate correlations between plasma clearance (CL_p) and drug and subject characteristics in subjects with overweight or obesity, for drugs metabolized through hepatic metabolism. We found that body mass index (BMI) and relative obesity-induced changes in enzyme activity are highly correlated with obesity-related CL_p changes. Drugs binding to α 1-acid glycoprotein (AAG) have smaller CL_p changes compared to drugs binding to human serum albumin (HSA). Lower extraction ratios (ER) in normal-weight individuals correspond to larger CL_p changes compared to drug with a higher ER in normal-weight individuals. The allometric exponent for perfect CL scaling ranged from -3.84 to 3.34, illustrating that no single scaling method (i.e., linear scaling, 0.75 allometric scaling or no scaling) will perform well in all situations. Instead, different drug properties and the severity of obesity need to be considered for accurate scaling.

Chapter 6 continues the exploration initiated in **Chapter 5**, employing a similar PBPK workflow focusing on drugs that undergo elimination through glomerular filtration (GF) and active renal secretion (ATS). This chapter paid particular attention to exploring the impact of obesity-induced changes in ATS on total CL_r under various scenarios of change with obesity. We found that CL_r through GF and ATS increased with BMI, albeit to different extents, depending on drug properties. When BMI was below 30 kg/m² and transporter activity remained unchanged, the CL_r between subjects of normal weight and with obesity differed less than 30% and both scaling methods were systematically accurate. For individuals with higher BMI, drug properties need to be taken into account when defining scenarios of systematic scaling accuracy.

7.2 Perspectives

Using the models and methods developed in this thesis, future perspectives related to model development and optimal dosing in the obese population were further investigated. These considerations center around three key topics:

- 1) The added value of external validation for model improvement and implementation in the clinic;
- 2) The impact of different intravenous infusion methods on PK parameter estimation;
- 3) Appropriate dosing scaling methods for subjects with overweight or obesity.

7.2.1 The added value of external validation for model improvement and implementation

Background

In **Chapter 4**, a popPK model for vancomycin in patients with overweight or obesity with varying degrees of renal (dys)function, admitted to the general ward or ICU was successfully developed [1]. This model was confirmed to be robust and to have a good predictive performance for the studied population in the internal validation. With this model, AUC-targeted dosing recommendations were designed to obtain effective and safe vancomycin exposures from treatment initiation onward. However, whether the developed model and dosing recommendations are directly applicable to diverse clinical settings, such as other institutions or hospitals, may be subject to debate.

External evaluation is considered to be the most rigorous form of evaluating a model [2]. It can assess the predictive performance and robustness of a model, by testing its performance on data from diverse sources, time periods, or experimental/clinical conditions. This helps to ensure the model's ability to accurately predict across various contexts and helps reveal the model's potential biases and limitations. After establishing a model's performance, the external data can also be combined with the existing dataset in a model update, in which parameter values are re-estimated, likely with improved accuracy due to the inclusion of additional data. Together these procedures may facilitate model improvement and enhance the overall reliability of the model and facilitate implementation in the clinic.

Here, an external validation of the published popPK model for vancomycin from **Chapter 4** was conducted using external data. This validation aimed to evaluate the model's predictive performance and robustness, ensuring its applicability to new datasets that involve patients with overweight or obesity and varying renal (dys)function admitted to the ward or ICU. As the validation procedure was also performed in cardiac ICU patients, which were not included in the original dataset, this was investigated as an additional covariate in the model update.

Methods

External model validation

The external validation study of the model from **Chapter 4** was conducted using two retrospective PK datasets that were previously reported by Thomson *et al.* [3]. The first external dataset consisted of 49 patients with overweight or obesity from a general ward, while the second external dataset consisted of 32 patients with overweight or obesity of which 20 were from a cardiac ICU and 12 were from a general ward. The 81 patients exhibited a wide range of bodyweight (TBW ranging from 53.1 to 215.8 kg) and renal function (eGFR estimated using the CKD-EPI equation ranging from 9.6 to 139.7 mL/min/1.73 m²). According to the routine TDM files, all patients were treated with intravenous vancomycin and had at least one vancomycin concentration measurement during the treatment [3]. More information about the patient demographics, clinical characteristics, and dosing information for the external data are detailed in **Table 7.1**.

The external evaluation was performed using NONMEM 7.3 (ICON Development Solutions, United States) with Perl-speaks-NONMEM (4.9.0) and the Pirana interface (2.9.9) (Certara USA, Inc, Princeton, USA). The output was displayed using R studio (version 4.2.3, <http://www.r-project.org>). The external validation was executed by performing a Bayesian re-estimation (MAXEVAL = 0) with the final model described in **Chapter 4** [1]. In this model, renal function, quantified by CKD-EPI, was correlated with *CL* with an exponent of 0.658 in a power relationship, while TBW was correlated with *CL* in a linear manner. ICU-admission status was reduced vancomycin *CL* by 15.5% compared to patients with non-ICU admission. More details are available in **Chapter 4**.

The model's ability to describe typical trends in the external data was assessed by visual inspection of GOF diagnostic plots and plots of eta-distributions. Besides, the predictive capability of the model was externally assessed using NPDE with 1000 simulations executed in NONMEM. The bias and precision of the model were evaluated using the prediction error (PE) and root mean square error (RMSE), which were calculated by **Equations S6.1** and **S6.2**, respectively:

$$PE(\%) = \frac{C_{\text{pred}} - C_{\text{obs}}}{C_{\text{obs}}} \times 100 \quad (\text{S6.1})$$

Table 7.1 Baseline demographics, clinical characteristics, and dosing information of the patients with overweight or obesity from the internal dataset [1] (**Chapter 4**), external dataset [3] and total dataset for the pharmacokinetics of vancomycin

Parameters	Internal [1]	External [3]			Total dataset
		External 1	External 2	Total External	
Number of individuals	230	49	32	81	311
Male/Female	140/90	18/31	13/19	31/50	171/140
Non-ICU/ICU/Cardiac ICU	177/53/0	49/0/0	12/0/20	61/0/20	238/53/20
Age (years)	70 (23–92)	59 (28–94)	55 (18–80)	57 (18–94)	69 (18–94)
Height (m)	1.72 (1.49–1.97)	1.72 (1.30–2.03)	1.64 (1.42–1.88)	1.69 (1.30–2.03)	1.72 (1.30–2.03)
TBW (kg)	91.8 (58.6–234.6)	112.7 (53.1–215.8)	94.0 (70.0–127.0)	100.0 (53.1–215.8)	92.2 (53.1–234.6)
LBW (kg)	61.0 (36.5–104.2)	60.7 (29.9–84.5)	53.3 (45.8–63.4)	57.7 (29.9–84.5)	60.4 (29.9–104.2)
ABW (kg)	77.0 (50.4–143.7)	82.8 (36.4–133.0)	71.0 (52.4–92.0)	77.7 (36.4–133.0)	77.0 (36.4–143.7)
BSA (m ²)	2.1 (1.6–3.3)	2.3 (1.4–3.4)	2.0 (1.7–2.5)	2.2 (1.4–3.4)	2.1 (1.4–3.4)
BMI (kg/m ²)	30.0 (25.0–65.7)	37.9 (30.2–66.4)	33.8 (28.6–40.9)	33.8 (28.6–66.4)	30.8 (25.0–66.4)
Overweight (BMI 25–30)	122	0	0	0	122
Obese (BMI >30)	108	49	32	81	189
Serum creatinine (μmol/L)	84.0 (23.0–748.0)	68.1 (45.1–571.1)	86.0 (50.0–303.0)	73.4 (45.1–571.1)	82.0 (23.0–748.0)
CKD-EPI (mL/min/1.73m ²)	74.5 (6.0–154.9)	88.4 (9.6–139.7)	71.1 (14.1–118.8)	82.8 (9.6–139.7)	75.8 (6.0–154.9)
< 30	15	5	3	8	23
30–60	60	11	10	21	81
60–90	93	13	14	27	120
> 90	62	20	5	25	87
De-indexed CKD-EPI (mL/min)	87.8 (6.5–221.8)	117.3 (13.3–212.4)	86.2 (16.5–145.6)	104.1 (13.3–212.4)	89.1 (6.5–221.8)
MDRD (mL/min/1.73m ²)	72.6 (6.4–304.1)	80.6 (9.4–170.2)	65.1 (13.8–148.0)	75.4 (9.4–170.2)	73.1 (6.4–304.1)
De-indexed MDRD (mL/min)	86.6 (6.9–371.0)	106.6 (13.1–258.8)	79.2 (16.1–153.5)	97.6 (13.1–258.8)	87.6 (6.9–371.0)
CG-TBW (mL/min)	87.8 (9.6–432.1)	142.0 (19.4–384.8)	98.6 (27.2–204.0)	125.0 (19.4–384.8)	90.4 (9.6–432.1)
CG-LBW (mL/min)	57.2 (6.9–280.7)	78.0 (12.9–216.0)	61.0 (13.7–122.0)	70.0 (12.9–216.0)	58.3 (6.9–280.7)
Vancomycin dose (mg)	1250 (250–3500)	1500 (250–3500)	1000 (500–2000)	1000 (250–3500)	1250 (250–3500)
Vancomycin dose (mg/kg)	13.6 (2.4–36.6)	11.4 (4.7–16.2)	11.4 (7.1–15.7)	11.4 (4.7–16.2)	14.0 (2.4–36.6)
No. of samples	1395	159	132	291	1686
No. of samples per individual	5 (1–31)	3 (1–7)	3 (1–16)	3 (1–16)	4 (1–31)
Treatment duration (h)	228.2 (12.7–1522.0)	119.6 (9.0–243.83)	108.0 (22.0–708.1)	115.7 (9.0–708.1)	181.0 (9.0–1522.0)
Time after dose (h)	10.7 (0.02–44.6)	11.1 (0.17–43.5)	10.5 (1.98–39.8)	11.0 (0.17–43.5)	10.8 (0.02–44.6)

All values are reported as median (range) or as total number of individuals or samples.

$$RMSE = \sqrt{\frac{1}{n} \times \sum_{i=1}^n PE^2} \quad (S6.2)$$

where C_{pred} is the concentration predicted using the published final model and parameter, C_{obs} is the concentration observed in the external evaluation dataset, and n is the total number of concentrations. The model was regarded to be satisfactory and clinically acceptable when both the mean value of PE (MPE) and median absolute values of PE (MAPE) were equal or less than 30% [4, 5].

The external dataset included data from cardiac-ICU patients, which were not present in the original dataset used to develop the published model (**Table 7.1**). Model per-

formance in these patients can therefore be regarded as an extrapolation, as these patients primarily experience cardiac-related conditions and tend to be limitedly debilitated and younger compared to general-ICU patients. Therefore, an additional stratification was performed on the output of the external validation, with the addition of cardiac-ICU to the already present categories of general-ICU and ward patients. Results of this analysis were used to determine whether the model update only comprised a re-estimation of model parameters or whether it should also comprise the potential inclusion of additional covariate relationships.

Model update

After the external model validation, the external dataset was combined with the internal data, for the model update. The combined data included a total of 311 patients with 1686 concentration measurements. Further details about this combined dataset can be found in **Table 7.1**. As the model validation procedures showed that the developed model could not be extrapolated to cardiac-ICU patients, the model update comprised more than a mere re-estimation of model parameters but also included an assessment of additional covariate relationships for the new population, thereby expanding the application of the developed model.

In the model update, the original structure and covariate functions for renal function and TBW of the existing model were retained as published [1]. In addition, a new ICU admission status, namely cardiac-ICU, was tested, expanding the ICU admission statuses to non-ICU, general-ICU, and cardiac-ICU. The updated ICU admission status was tested as a covariate in the covariate analysis for PK parameters in the existing model. The new covariate relationship was considered statistically significant when *OFV* dropped more than 10.83 points ($p < 0.001$). The model fits were assessed using GOF plots stratified for the different sources of the data. Moreover, the covariate relationships were visually inspected by plots of eta value *versus* individual covariate value for time-independent covariates, conditional weighted residuals (CWRES) *versus* individual covariate value for time-dependent covariates, and individual *post hoc* parameter estimates *versus* covariate value. Finally, relative standard errors of estimates (RSE) were considered to indicate adequate precision of the estimate if they were below 50%.

Findings

External model validation

Figure 7.1 displays the GOF plots derived from external validation. It shows that the predictive performance of the published model in Chapter 4 [1] is generally good for both external datasets, with the exception of over-predictions observed in cardiac-ICU patients from the second external dataset, which should be considered an extrapolation. This trend was also evident in the NPDE results based on 1000 simulations. The MPE and MAPE values for the entire external dataset were 11% and 26%, respectively, both falling at or below 30%, suggesting that the bias in model-predicted concentrations based on the external datasets was clinically acceptable. The RMSE was relatively low at 39%, indicating a reasonably good precision in the model’s predictions.

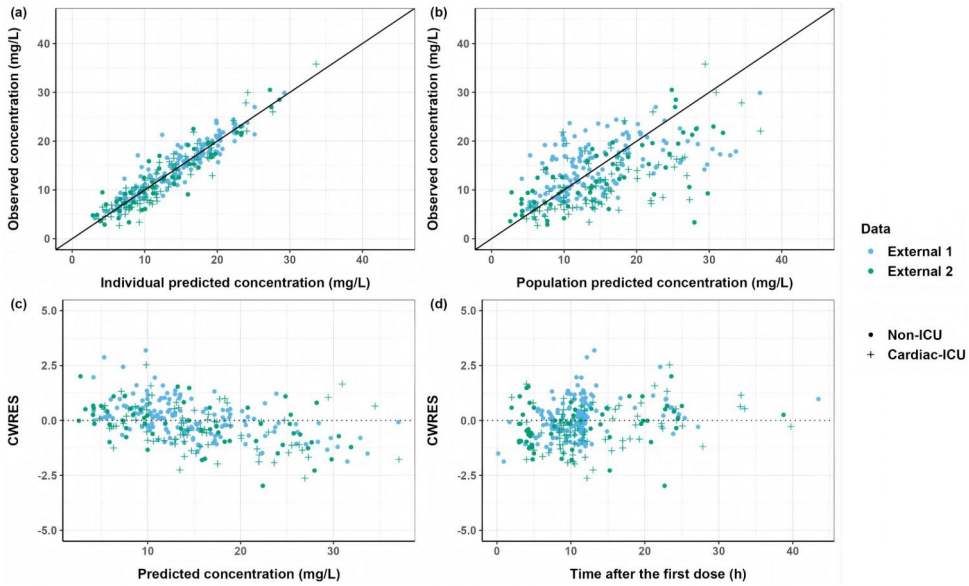


Figure 7.1 Goodness-of-fit plots of the final model (from Chapter 4) for external validation, based on a Bayesian re-estimation using the two external datasets of patients with overweight or obesity with varying renal function admitted to the ward, general-ICU, or cardiac-ICU (Table 7.1). (a) Observed vancomycin concentration versus individual predicted concentration; (b) Observed vancomycin concentration versus population predicted concentration; (c) Conditional weighted residuals (CWRES) versus population predicted concentration; (d) CWRES versus time after dose.

Model update

The results of external validation highlight significant differences between patients in

cardiac-ICU and those in general-ICU, indicating our published model cannot be directly extrapolated to cardiac ICU patients. Therefore, a further update of the existing model to ensure its application for patients in the cardiac-ICU was conducted using the combined dataset from both internal and external sources. The PK parameters of vancomycin for the updated final model are presented in (Table 7.2).

Table 7.2 Population pharmacokinetic parameter estimates of vancomycin for the final model based on both internal and external dataset

Parameter	Final model (RSE %)
$CL(L/h) = TVCL \times \left(\frac{CKD-EPI}{75}\right)^{\theta_1} \times (1 + \theta_2 \times (TBW - 90)) \times F_{ICU}$	
TVCL	3.38 (2.50)
θ_1	0.644 (2.80)
θ_2	0.0104 (13.4)
$F_{ICU_general}$	0.851 (2.30)
$F_{ICU_cardiac}$	1.26 (7.00)
V1 (L)	17.8 (12.9)
Q2 (L/h)	15.3 (9.00)
V2 (L)	23.4 (3.70)
Q3 (L/h)	2.46 (8.00)
V3 (L)	75.3 (4.20)
Inter-individual variability (ω^2)	
CL	0.0878 (8.5)
V1	1.08 (20.9)
Residual variability	
PA data: Additive error (mg/L)	8.98 (2.90)
HS data: Proportional error (-)	0.00255 (34.9)
HS data: Additive error (mg/L)	1.01 (16.0)

CL, clearance; V1, volume of distribution of central compartment; V2, volume of distribution of peripheral compartment 2; V3, volume of distribution of peripheral compartment 3; Q2, inter-compartmental clearance between V1 and V2; Q3, inter-compartmental clearance between V1 and V3; CKD-EPI, renal function calculated by chronic kidney disease epidemiology collaboration equation; TBW, total body weight; F_{ICU} , scaling factor of general-ICU or cardiac-ICU patient versus non-ICU patients; PA, patients from ward, general- and cardiac-ICU; HS, non-obese and obese but otherwise healthy subjects; RSE, relative standard error; CI, confidence interval

Figure 7.2 illustrates that clearance in cardiac-ICU patients is higher than that in both general-ICU patients and non-ICU patients. Even though the difference between non-ICU and general-ICU is well-described for the internal data by the published model, the difference in CL between patients in the cardiac-ICU required additional characterization. The updated ICU admission status, including non-ICU, general-ICU, and cardiac ICU, was identified as a covariate significantly correlating with CL ($p < 0.001$,

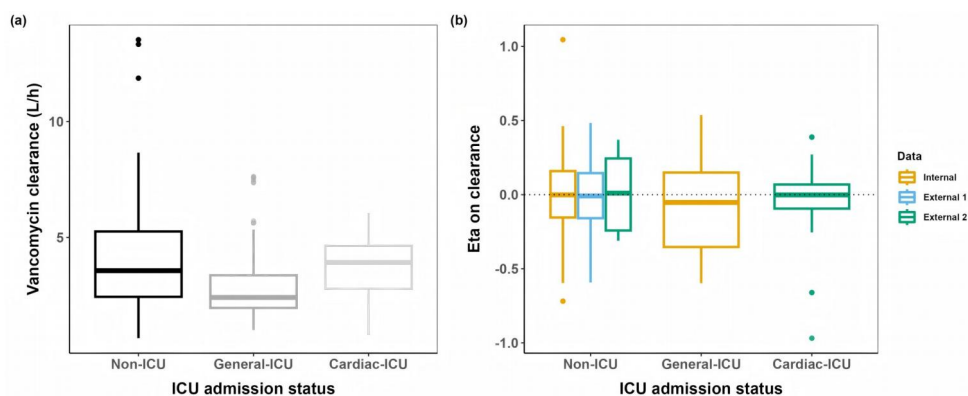


Figure 7.2 Illustration of differences in vancomycin CL with ICU admission status, i.e., non-ICU, general-ICU, and cardiac-ICU, on vancomycin clearance in patients with overweight or obesity based on the updated final model. **(a)** Individually predicted CL values versus ICU admission status. **(b)** Eta value of clearance versus ICU admission status. The boxplot shows the median and interquartile ranges. Whiskers represent values from interquartile to maximum or minimum; outliers are drawn as circles.

RSE 7.0%), revealing a 26.0% higher CL in cardiac ICU patients than non-ICU patients and a 40.9% higher CL than ICU patients. This can potentially be attributed to the younger age of cardiac-ICU patients compared to patients from the ward or general-ICU (53 versus 70 years) with potentially increased cardiac output and enhanced blood flow due to cardiac-related surgeries, increased kidney perfusion and consequently, higher clearance of renally eliminated medications [6, 7]. No other covariates were found to statistically significant improve the vancomycin PK model in this population.

The GOF plots of the final updated model are shown in **Figure 7.3**. This figure shows that observed vancomycin concentrations are described without bias in all populations across both internal and external datasets.

In conclusion, based on external datasets from different sources, the predictive performance of the published model in **Chapter 4** was found to be generally good with clinically acceptable bias. The external validation procedure also revealed the potential limitations of the original model in predicting concentrations for cardiac-ICU patients, necessitating a model update to this new population to expand its application to this population. The updated model indicated that, in addition to TBW and renal function, the updated ICU admission status (i.e., non-ICU, general-ICU, and cardiac ICU) needs to be taken into account for CL prediction for overweight and obese patients across all

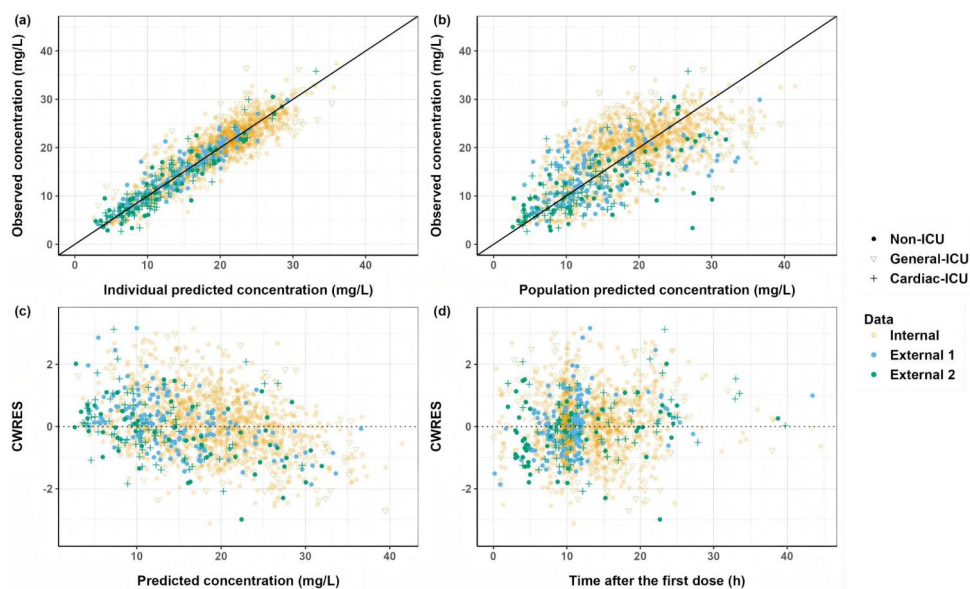


Figure 7.3 Goodness-of-fit plots of the final updated model in patients with overweight or obesity with varying renal function admitted to the ward, general-ICU, or cardiac-ICU. **(a)** Observed vancomycin concentration *versus* individual predicted concentration; **(b)** Observed vancomycin concentration *versus* population predicted concentration; **(c)** CWRES *versus* population predicted concentration; **(d)** CWRES *versus* time after dose.

three admission status. A 26.0% higher CL in cardiac-ICU patients compared to non-ICU patients and a 40.9% higher CL compared to general-ICU patients were found, suggesting that higher doses may be required for cardiac-ICU patients compared to non-ICU/general-ICU patients.

7.2.2 The impact of different intravenous infusion methods on PK parameter estimation

Background

The demand for clinical data on obese individuals is increasing. These data can come from different sources, including clinical trials, routine practice, and historical studies. Irrespective of the data source, ensuring that the collected data is as informative as possible is of great importance. To reduce patient burden and resources, data from routine practice is often used. For different antibiotics, including vancomycin,

continuous infusion (CIV) is increasingly utilized, because it achieves comparable exposure with anticipated reduced adverse effects compared to intermittent dosing regimens [8–11]. An important question is whether the data collected in patients treated with such a continuous infusion regimen are sufficiently informative for obtaining accurate PK parameter values. Besides, comprehensive comparisons of the results obtained upon continuous infusion with single-dose infusion (SIV) in terms of their impact on drug PK estimation are notably absent in the literature. This is of relevance in case the developed models are used to develop dosing guidelines to be used in clinical practice where both infusion methods may be applied.

Stochastic simulation and re-estimation (SSE) is a statistical technique that generates simulated data based on pre-defined model and model parameter values (including variability) and then re-estimates parameter values in model structures based on a subset of the simulated data. As the original model structure and parameter values are known, the identifiability of model structures and/or accuracy and precision of parameter estimates under different study designs can be assessed. As such, SSE can also be used to enable a comparison of the influence of different infusion methods on drug PK parameter estimation. Under this topic, SSE is used to explore the impact of infusion methods, in combination with other design factors such as the number of subjects and the number of observations per subject, on the estimation of primary PK model parameters from data obtained in a homogeneous population.

Methods

The SSE approach applied in this research included the following four steps:

Step 1. Population pharmacokinetic model selection:

A two-compartment PK model was used for the simulations. To allow for a clean assessment of the accuracy and precision of structural model parameters, covariates were not included. To ascertain the use of realistic and relevant parameter values, parameter values were selected from the base model developed in **Chapter 4**. In this model, the values for CL , Q , V_1 , and V_2 were 4.21 L/h, 3.55 L/h, 33.8 L, and 82.8 L, respectively.

Step 2. Simulation:

Concentration-time profiles were simulated using the selected pop PK model, considering two different dosing methods: SIV with a 1000 mg dose over 2 hours and CIV with a daily dose of 1500 mg. To mimic study conditions, different levels of residual unexplained variability (RUV) were introduced (i.e., sigma variance of 0.1 and 0.3) in a proportional error model. This resulted in four base sets of data: **1)** SIV + RUV of 0.1, **2)** SIV + RUV of 0.3, **3)** CIV + RUV of 0.1, and **4)** CIV + RUV of 0.3. Inter-individual variability (IIV) of 0.1 was incorporated for CL , $V1$ and $V2$. For all base sets, drug concentrations were simulated at 1, 3, 5, 8, 11, 16, 18, 23, 28, 33, 38, and 48 hours following the end of infusion (for SIV) or the initiation of the infusion (for CIV). Each base set involved simulations for 10,000 individuals.

Each base set was thereafter reformatted to subsets with a varying number of subjects (n_{sub}), for which values of 8, 25, 50, or 150 were used, and the number of observations per subject (n_{obs}), for which values of 3, 7, or 12 were used. Consequently, a total of 48 data subsets representing different study designs were created, as indicated in **Figure 7.4**. To ascertain that differences in outcomes between study designs were not driven by the inclusion of individuals with different IIV values, the subsets with fewer individuals were selected from the previous subset with more individuals, so that all individuals in the subsets with fewer individuals were included in all subsets with more subjects. The 48 subsets were selected from the four base sets according to this procedure, ten different times. The observations were selected to be at times that covered both the distribution and the elimination phase, as well as the point around which equilibration between the central and peripheral compartment was reached, in the SIV profiles. In the concentration-time profile of a typical individual receiving SIV, this equilibrium was reached at 11 hours post-infusion. Therefore, for 3, 7, and 12 observations, the designated observation times were 1, 11, and 48 hours; 1, 3, 8, 11, 18, 33, 48 hours; and 1, 3, 5, 8, 11, 16, 18, 23, 28, 33, 38, and 48 hours after the end of the infusion (for SIV) or the initiation of the infusion (for CIV), respectively.

Step 3. Parameter re-estimation:

The re-estimation process used the same model structure utilized for the simulation step. The PK parameters were re-estimated based on different simulated datasets representing studies with different designs as mentioned above, using first-order conditional estimations in NONMEM 7.4 (ICON Development Solutions, Hanover, MD,

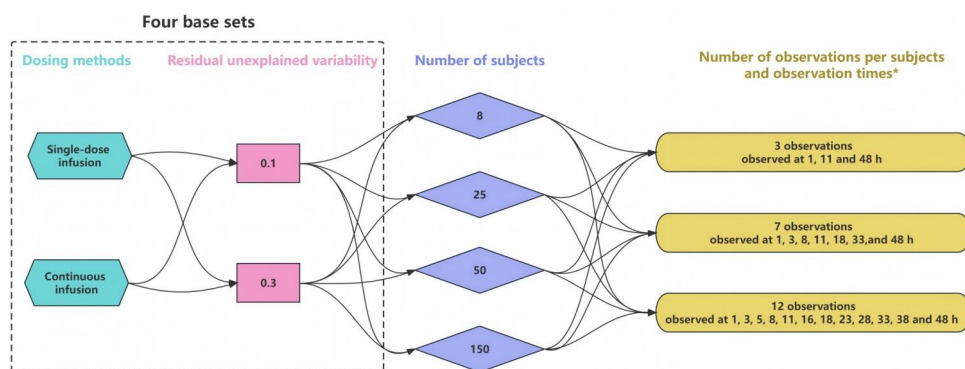


Figure 7.4 Simulation scenarios for concentration-time profiles considering varying the infusion method (single-dose infusion [SIV] versus continuous infusion [CIV]), residual unexplained variability (RUV, sigma variance of 0.1 versus 0.3), number of subjects, and number of observations per subject. *The observation time for SIV is defined as hours after the end of the infusion, whereas for CIV, it is defined as hours after the initiation of the infusion.

USA). Pearl-speaks-NONMEM (PSN) 4.9.0, Pirana 2.9.7 (Certara USA, Inc, Princeton, USA), and R 4.0.3 were used for preprocessing and visualization of the modeling results.

The capability to generate successful re-estimations was deemed an important factor indicating the potential success of a study design. In this study, unsuccessful re-estimation was defined as runs with **1)** unsuccessful minimization in NONMEM, and/or **2)** biologically implausible parameter estimates, defined as being 10-fold higher or lower than the parameter values from the simulation model. Assuming that PK information for a drug in a clinical study is generally available, for instance, from pre-clinical extrapolation, early phase studies, or studies in different populations, both situations would be recognizable during model development. Models that failed in re-estimation were therefore excluded from the accuracy and precision assessment.

Step 4. Quantification of accuracy and precision:

For each of the 48 subsets of data in each of the 10 samples, the accuracy and precision of the obtained PK parameter estimates were evaluated using relative Root Mean Square Error (rRMSE) and relative Bias (rBias), calculated using **Equations S6.3** and **S6.4**, respectively.

$$rRMSE = \sqrt{\frac{1}{N} \times \sum \frac{(P_E - P_T)^2}{P_T^2}} \times 100\% \quad (S6.3)$$

$$rBias = \frac{1}{N} \times \sum \frac{P_E - P_T}{P_T} \times 100\% \quad (S6.4)$$

The true parameter value (P_T) refers to the value used in the simulations, while the re-estimated parameter value (P_E) was obtained in the estimation based on the simulated subsets. N represents the number of successful re-estimations for a given study design. Acceptable accuracy and precision criteria were set at an rRMSE lower than 20% and an absolute rBias lower than 10%, respectively.

Findings

Through the four steps outlined above, the impact of SIV and CIV infusions on PK parameter estimation was explored. It was found that the estimations of structural PK parameter values based on a subset representing designs with SIV were more accurate and precise compared to CIV. Specifically, **Figure 7.5** highlights that data obtained with SIV achieves overall more precise estimations for CL , Q , and $V2$, with $V1$ being the only exception for which SIV and CIV show similar precision. This may be due to PK profiles after SIV offering a clearer distinction between distribution and elimination phases than CIV. **Figure 7.6** shows that it is particularly difficult to achieve accurate $V2$ estimation with data obtained upon CIV dosing. Only 4.2% of cases fell within the rBias targeted range of $\pm 10\%$ across all scenarios. However, for SIV, the estimation bias fell within the rBias targeted range in all scenarios, with only the exception when there were 3 observations per individual.

In addition to dosing methods, findings from **Figure 7.5** and **Figure 7.6** reveal that PK estimation is also influenced by RUV, the number of observations, and the number of subjects. An increase in RUV from a variance of 0.1 to 0.3 led to a notable decrease in precision and accuracy in parameter estimation for both infusion methods. Interestingly, the precision and accuracy in parameter estimation for SIV with an RUV of 0.3 was even better than CIV with an RUV of 0.1 in most scenarios. Besides, an increase in the number of observations significantly improved precision and accuracy for SIV,

particularly with observations rising from 3 to 7 resulting in substantial enhancement in the accuracy of estimating V_1 , Q , and V_2 . However, further increases to 12 observations showed limited additional benefit. Notably, such a correlation between observation numbers and precision and accuracy of parameter estimates was not observed for CIV. Moreover, as the number of subjects increased, rRMSE and rBias values gradually approached zero. For CIV, a substantial improvement in parameter estimation was observed with an increase in subject number to 150. However, the rBias values for CL and V_1 in SIV showed insensitivity to the increase in subject number, likely because the values are very low for 8 individuals already.

Besides, it was found that parameter estimations based on subsets of data with SIV have a higher probability of successful estimation compared to CIV (95.2% *versus* 61.4%). **Figures 7.5** and **7.6** show that compared to SIV, successful model re-estimation for CIV required more subjects and more observations. Specifically, when the subject number was below 150 or when there were only 3 observations per subject, NONMEM struggled to achieve successful minimization or yield biologically plausible parameter values for CIV compared to SIV.

In conclusion, the use of SSE revealed superior accuracy and precision in estimating PK parameters and a higher probability of successful estimation with SIV in comparison to CIV. This finding implies that when deciding on a study design or defining what data to collect retrospectively (either from historic studies or from clinical practice), opting for SIV is preferable over CIV. Given that intermittent dosing regimens involve repeated single bolus infusions throughout the treatment, the results could further imply that when other clinical considerations permit, an intermittent dosing regimen is more favorable in terms of study design compared to CIV. If only data upon CIV dosing are available or feasible, it should be kept in mind that generally a larger number of individuals and/or a larger number of samples per individual should be obtained to achieve acceptable accuracy and precision.

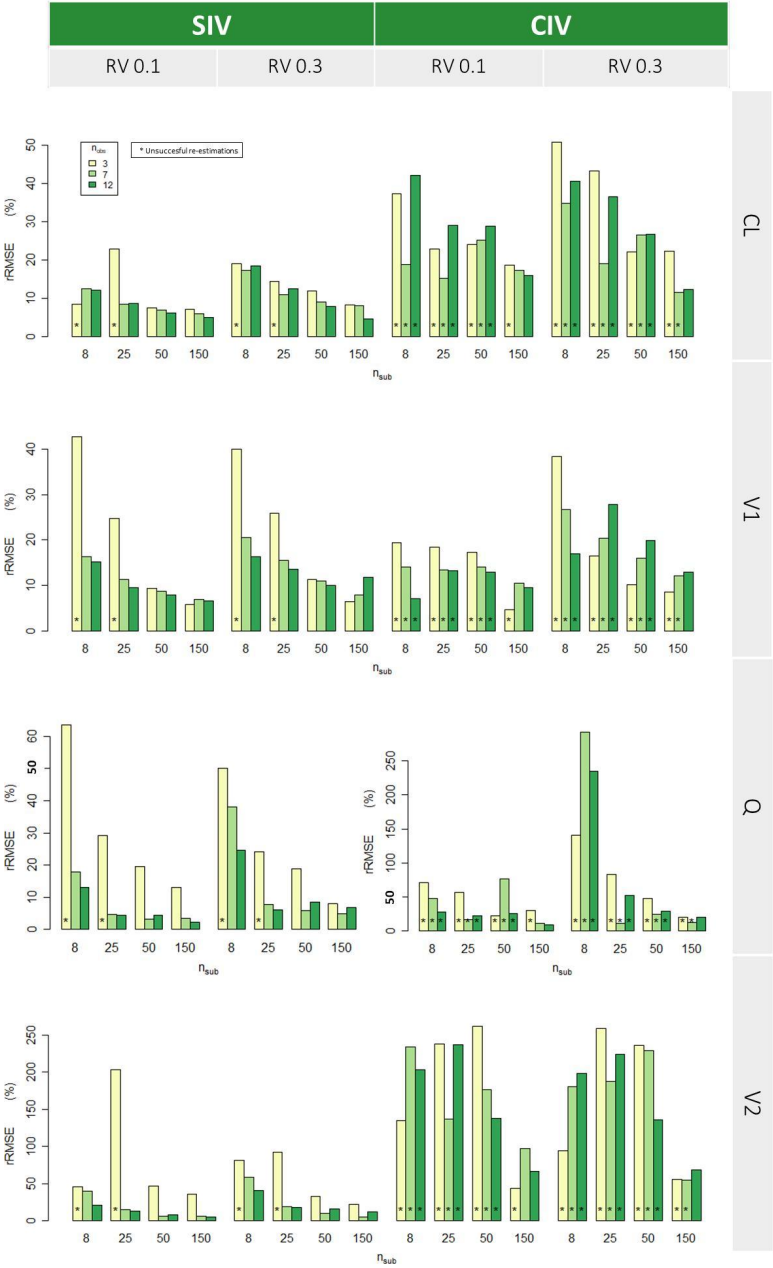


Figure 7.5 Relative root mean square error (rRMSE) of structural pharmacokinetic parameters obtained in the re-estimation of simulated data under different design scenarios. SIV: single dose infusion; CIV: continuous infusion; RUV: residual unexplained variability expressed as variance; n_{sub} : number of subjects; n_{obs} : number of observations per subject. * means some models failed in the re-estimation process and were subsequently excluded from the accuracy and precision assessment.

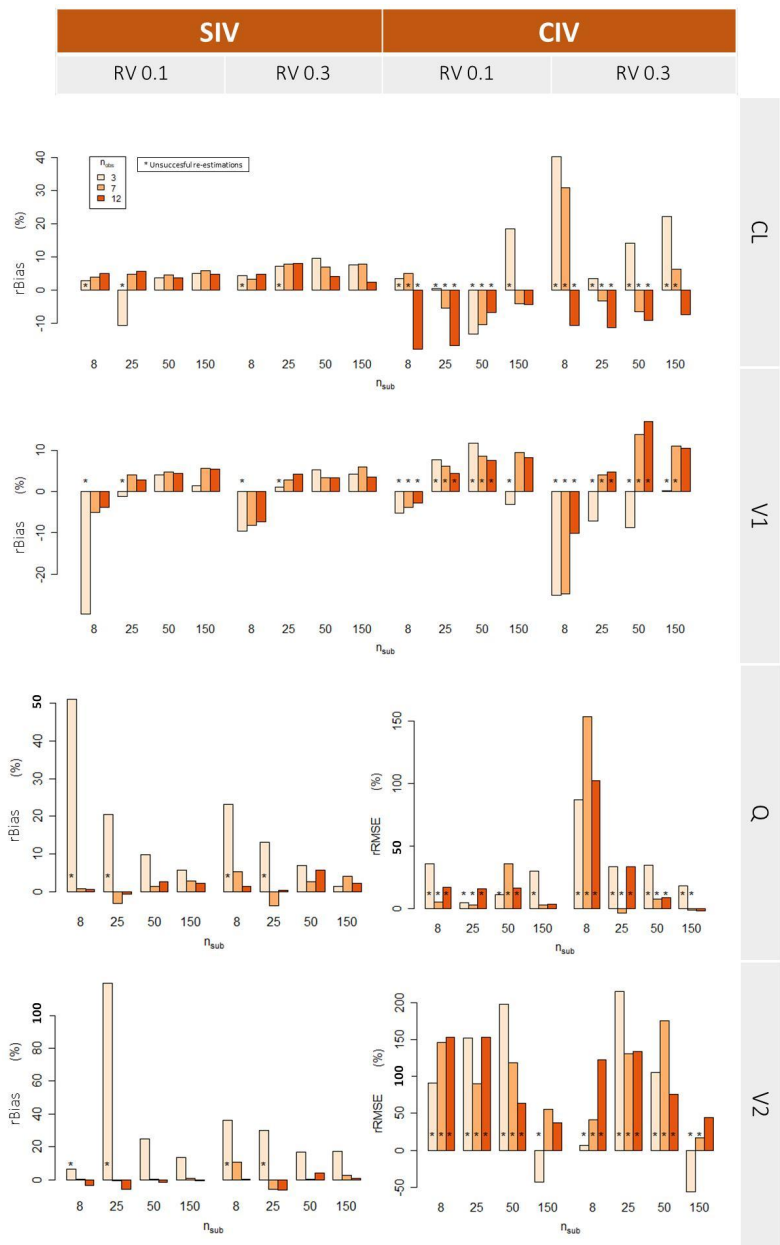


Figure 7.6 Relative Bias (rBias) of structural pharmacokinetic parameters obtained in the re-estimation of simulated data under different design scenarios. SIV: single dose infusion; CIV: continuous infusion; RUV: residual unexplained variability expressed as variance; n_{sub} : number of subjects; n_{obs} : number of observations per subject. * means some models failed in the re-estimation process and were subsequently excluded from the accuracy and precision assessment.

7.2.3 Appropriate dosing scaling methods for subjects with overweight or obesity

Background

Accurate scaling of clearance from subjects with normal weight to those with overweight or obesity is important for optimizing and expediting dose tailoring in subjects with overweight or obesity for drugs that have not been studied in this population. PBPK are recognized as the most accurate scaling method in the absence of clinical data, however their application demands specialized expertise and data from elaborate *in vitro* or *in vivo* experiments [12, 13]. Consequently, there is a need for simpler, yet accurate, dose scaling methods for subjects with overweight or obesity.

In current clinical practice, dosing in subjects with overweight or obesity relies either on a flat dose strategy (same absolute dose in the obese as in the normal-weight individuals) or bodyweight-based scaling such as allometric scaling with an exponent of 0.75 (AS0.75) or with an exponent of 1 (linear scaling). **Chapters 5 and 6 in Section III** present the application of a PBPK-based workflow to define scenarios in which these commonly used dosing methods exhibit systematic accuracy in subjects with overweight or obesity with varying BMI. In these chapters, systematic accuracy was assessed by studying 11520~17600 hypothetical drugs with various combinations of drug properties in realistic ranges, including the route of elimination, type of binding plasma protein, affinity to the plasma protein, blood-to-plasma partition coefficient, and unbound intrinsic clearance. A prediction error (PE) between scaled and PBPK-predicted clearance for subjects with overweight or obesity within $\pm 30\%$ is regarded as an acceptable prediction of *CL*. When a dosing method is not systematically reasonably accurate, it is still possible that scaling is accurate for some drugs with a particular subset of properties, but it will not be accurate for all drugs and it cannot be known *a priori* which will be the case for a specific drug.

Methods

To provide *a priori* guidance on selecting the appropriate dosing methods for subjects with overweight or obesity, the results of **Chapter 5** and **Chapter 6** are summarized in a set of decision tables for dose scaling selection (**Tables 7.4–7.6**). Notably, the dose

scaling method, considered systematically accurate with a PE value within $\pm 30\%$ and reasonably accurate within $\pm 50\%$, is included in these tables to offer further insights in the level of systematic accuracy. These tables provide clinical pharmacologists a tool to choose dose scaling methods requiring the minimum, yet sufficient, amount of information for deriving accurate dosing based on drug properties and characteristics of subjects with overweight or obesity. Both chapters utilized a similar PBPK simulation workflow [14], of which details are provided in the respective chapters. Notably, **Chapter 5** focuses on hepatically metabolized drugs, while **Chapter 6** focuses on drugs eliminated through the kidney by glomerular filtration with various degree of active tubular secretion. The original figures and tables forming the basis for the decision tables can be found in **Chapters 5** and **6**. Although **Chapter 6** did not evaluate the systematic accuracy of linear scaling, it is a commonly used scaling method in clinical settings. Therefore, it was examined using the same workflow as other scaling methods in **Chapter 6** and was included in the decision table.

Changes in obesity-induced hepatic enzyme or renal transporter activity compared to normal hepatic enzyme or renal transporter activity were defined as a range of relative changes for each BMI, rather than as enzyme or transporter-specific values that change with BMI. This is because existing literature contains limited information on how enzyme or transporter activities change in the obese population. The range of the relative changes was selected so that it encompasses potential scenarios of decreased enzyme or transporter activity as well as increased enzyme or transporter activity in subjects with overweight or (morbid) obesity [15].

It should also be noted that values of ER and f_u for drugs may vary with BMI. To avoid confusion, in the scaling tables they are defined for subjects with normal weight as this value does not require knowledge on how CL or ER change with obesity.

Findings

Table 7.3 shows that for drugs that are metabolized by the liver, the required information to select the appropriate dosing method for subjects with overweight or obesity with varying BMI includes:

- drug-binding plasma protein (i.e., exclusive binding to human serum albumin [HSA] or $\alpha 1$ -acid glycoprotein [AAG]),

- extraction ratio ($ER_{\text{normal weight}}$) of the drug in normal-weight subjects (i.e., low [< 0.3], intermediate [0.3 – 0.7], or high [> 0.7]), and
- obesity-induced changes in $CL_{\text{int_mic}}$, expressed as relative enzyme activity percentages of normal enzyme activity in subjects with overweight or obesity compared to those with normal weight.

Table 7.4 indicates that for drugs primarily eliminated through glomerular filtration in subjects with overweight or obesity with varying BMI, selecting the appropriate dosing method requires information on:

- drug-binding plasma proteins (i.e., exclusive binding to HSA or AAG),
- unbound drug fraction in plasma in normal-weight subjects ($fu_{\text{normal weight}}$).

In the case of drug elimination largely through both glomerular filtration and active tubular secretion (**Table 7.5**), it is essential to also consider the obesity-induced relative transporter activity, expressed as percentages of normal transporter activity in subjects with overweight or obesity compared to those with normal-weight.

As can be seen from **Tables 7.3 – 7.5**, in general, all of the three dosing methods are systematically reasonably accurate for subjects with overweight or obesity with a BMI below 30 kg/m^2 , with unchanged enzyme/transporter activity. In any of the other cases, information on the drug elimination route, type of binding plasma protein, $ER_{\text{normal weight}}$, $fu_{\text{normal weight}}$, and/or relative change of enzyme/transporter activity is required to select an appropriate dosing method for the obese. To summarize:

- For drugs undergoing hepatic metabolism, if the drugs have high $ER_{\text{normal weight}}$, flat dosing performs generally accurately, regardless of obese subject characteristics (see **Table 7.3**).
- For drugs undergoing hepatic metabolism with low to intermediate $ER_{\text{normal weight}}$, AS0.75 or linear scaling is most accurate, especially when there is a large (i.e., more than 60%) increase in enzyme activity for drugs binding to HSA.
- For drugs mainly eliminated by glomerular filtration, AS0.75 and flat dosing yield accurate dose scaling for subjects with overweight or obesity with varying BMI, except for those with a BMI higher than 40 kg/m^2 and drugs with low to intermediate $fu_{\text{normal weight}}$ that bind to AAG, for which systematically (reasonably) accurate dosing cannot be achieved by AS0.75 (see **Table 7.4**).

Table 7.3 Decision table for dose scaling method selection in subjects with overweight or obesity for drugs undergoing hepatic metabolism. The selection of dose scaling methods requires information on BMI and relative enzyme activity of subjects for drugs binding to either human serum albumin (HSA) or α 1-acid glycoprotein (AAG) with low, intermediate, or high extraction ratios in normal-weight subjects (ER_{normal weight}).

Low extraction ratio					
Relative enzyme activity	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
40%	FlatDose				
60%	FlatDose				
80%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
100%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
120%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
140%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
160%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
180%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
Intermediate extraction ratio					
Relative enzyme activity	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
40%	FlatDose				
60%	FlatDose				
80%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
100%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
120%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
140%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
160%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
180%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
High extraction ratio					
Relative enzyme activity	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
40%	FlatDose				
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
60%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
80%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
100%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
120%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
140%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
160%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
180%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose
	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW

Drugs binding to HSA

To be continued on the next page.

Drugs binding to AAG												
Relative enzyme activity	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60	Relative enzyme activity	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60	Relative enzyme activity
40%						40%						40%
60%						60%						60%
80%	AS0.75 LinearBW		FlatDose	FlatDose	FlatDose	80%	FlatDose	FlatDose	FlatDose	FlatDose	FlatDose	80%
100%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	100%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	100%
120%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	120%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	120%
140%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	140%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	140%
160%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	160%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	160%
180%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	180%	AS0.75 LinearBW	FlatDose	FlatDose	FlatDose	FlatDose	180%

Bold font indicates a systematically accurate dose scaling method (PE within $\pm 30\%$) and normal font indicates systematically (reasonably) accurate dose scaling options (PE within $\pm 50\%$). Relative enzyme activity is expressed as percentages of enzyme activity in normal-weight subjects, with a value of 100% indicating no change in enzyme activity in subjects with overweight or obesity compared to those with normal weight. Note that the values of the extraction ratio represent the values defined for the normal-weight subject. When none of the dosing methods can lead to accurate dosing, PK-based clearance predictions are required to scale drug clearance and drug dosing in subjects with overweight or obesity.

BMI, body mass index, kg/m^2 ; AS0.75, bodyweight-based allometric scaling with an exponent of 0.75; LinearBW, bodyweight-based linear scaling with an exponent of 1; FlatDose, flat dosing that can yield the same dose in the obese as in the normal-weight.

- For drugs eliminated by glomerular filtration and active tubular secretion, AS0.75 is an accurate dose scaling method for drugs binding to HSA or for drugs binding to AAG with $fu_{\text{normal weight}}$ above 75%, in subjects with varying BMI and increased transporter activity. When transported activity is reduced to 50%, flat dosing is the only accurate dose scaling method for all drugs (see **Table 7.5**).
- In case none of these methods lead to accurate dosing, PBPK-based clearance predictions are required to scale drug clearance.

Interestingly, a comparison of **Tables 7.4** and **7.5** reveals that, findings on the accuracy of dose scaling methods are highly similar for elimination through glomerular filtration alone and elimination through a combination of glomerular filtration and active tubular secretion when transporter activity is unchanged in subjects with overweight or obesity. This suggests that, in cases in which transporter activity remains unchanged, the impact of the active tubular secretion on CL can be ignored when selecting dose scaling methods.

In summary, decision tables for selecting dose scaling methods based on BMI, drug elimination pathways, drug binding plasma proteins, $ER_{\text{normal weight}}$, $fu_{\text{normal weight}}$, and obesity-induced enzyme/transporter activity in subjects with overweight and obesity are summarized. These decision tables indicate the minimal amount of information that is required for accurate dose scaling and can be used to *a priori* select the appropriate dosing method for subjects with overweight or obesity, thereby reducing the need for full PBPK-based clearance predictions.

Table 7.4 Decision table for dosing method selection in subjects with overweight or obesity for drugs eliminated through glomerular filtration. The selection of dose scaling methods requires information on the BMI of subjects for drugs binding to either human serum albumin (HSA) or α 1-acid glycoprotein (AAG) with different unbound drug fractions in normal-weight subjects ($f u_{\text{normal weight}}$).

Drugs binding to HSA	fu < 25%				fu 25% - 75%				fu > 75%			
	BMI 25	BMI 30	BMI 40	BMI 60	BMI 25	BMI 30	BMI 40	BMI 60	BMI 25	BMI 30	BMI 40	BMI 60
	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose

Drugs binding to AAG	fu < 25%				fu 25% - 75%				fu > 75%			
	BMI 25	BMI 30	BMI 40	BMI 60	BMI 25	BMI 30	BMI 40	BMI 60	BMI 25	BMI 30	BMI 40	BMI 60
	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose

Bold font indicates a systematically accurate dose scaling method (PE within $\pm 30\%$) and normal font indicates systematically (reasonably) accurate dose scaling options (PE within $\pm 50\%$). When none of the dosing methods can lead to accurate dosing, PBPK-based clearance predictions are required to scale drug clearance and drug dosing in subjects with overweight or obesity.

BMI, body mass index, kg/m^2 ; AS0.75, bodyweight-based allometric scaling with an exponent of 0.75; LinearBW, bodyweight-based linear scaling with an exponent of 1; FlatDose, flat dosing that can yield the same dose in the obese as in the normal-weight.

Table 7.5 Decision table for dosing method selection in subjects with overweight or obesity for drugs eliminated through glomerular filtration and active tubular secretion. The selection of dose scaling methods requires information on BMI and relative transporter activity of subjects for drugs binding to either human serum albumin (HSA) or α 1-acid glycoprotein (AAG) with different unbound drug fractions in normal-weight subjects ($f_{u,normal\ weight}$).

Drugs binding to HSA					
Relative transporter activity	fu < 25%				
	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
20%					
50%					
100%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
150%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
200%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
250%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
Relative transporter activity	fu 25% - 75%				
	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
20%					
50%					
100%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
150%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
200%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
250%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
Relative transporter activity	fu > 75%				
	BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
20%					
50%					
100%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
150%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
200%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose
250%	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 LinearBW FlatDose	AS0.75 FlatDose	AS0.75 FlatDose

To be continued on the next page.

Drugs binding to AaG													
Relative transporter activity		BMI 25	BMI 30	BMI 40	BMI 50	BMI 60	Relative transporter activity		BMI 25	BMI 30	BMI 40	BMI 50	BMI 60
20%							20%						
50%							50%						
100%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	100%	100%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW			LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
150%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	150%	150%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW			LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
200%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	200%	200%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW			LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
250%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75	250%	250%	AS0.75	AS0.75	AS0.75	AS0.75	AS0.75
	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW			LinearBW	LinearBW	LinearBW	LinearBW	LinearBW

Bold font indicates a systematically accurate dose scaling method (PE within $\pm 30\%$) and normal font indicates systematically (reasonably) accurate dose scaling options (PE within $\pm 50\%$). Relative transporter activity is expressed as percentages of transporter activity in normal-weight subjects, with a value of 100% indicating no change in transporter activity in subjects with overweight or obesity compared to those with normal-weight. When none of the dosing methods can lead to accurate dosing, PBPK-based clearance predictions are required to scale drug clearance and drug dosing in subjects with overweight or obesity.

BMI, body mass index, kg/m²; AS0.75, bodyweight-based allometric scaling with an exponent of 0.75; LinearBW, bodyweight-based linear scaling with an exponent of 1; FlatDose, flat dosing that can yield the same dose in the obese as in the normal-weight.

7.3 Conclusions

It remains challenging to *a priori* predict PK parameters or required dose adjustments for individuals with overweight or obesity. This difficulty arises from the diverse physiological changes that occur with obesity over different time courses and the complex interaction between all these changes and the varying properties of drugs. Throughout this thesis, we used different modeling approaches to explore the prediction of drug clearance and the individualization of dose regimens in individuals with overweight or obesity. When clinical data was available, pop PK modeling was used to quantify the impact of obesity on vancomycin pharmacology, and develop guidelines for optimal vancomycin dosing in the obese when it was required. Vancomycin *CL* was found to be apparently different between obese adults and obese adolescents, implying that dosing of vancomycin cannot be directly extrapolated between these populations. When dosing vancomycin in overweight and obese patients with different renal functions, renal function, bodyweight, and (general/cardiac-) ICU admission status should be taken into account to get safe and effective vancomycin exposure. The PBPK modeling was used to study alterations in clearance associated with obesity for drugs metabolized by the liver or eliminated via glomerular filtration and active tubular secretion, and identify the systematic accuracy of common weight-based scaling methods. This approach is useful when PK data is limitedly available or unavailable. For drugs metabolized through the liver or eliminated through the kidney in individuals with overweight or obesity, the exponent of an allometric covariate function for *CL* exhibited a wide range of values depending on BMI, relative enzyme/-transporter activity, and drug properties (i.e., $f_{u_{\text{normal weight}}}$, $ER_{\text{normal weight}}$, and drug binding plasma protein). No single scaling method was systematically accurate, and different drug properties and the severity of obesity need to be considered when selecting dose scaling methods for which we provide guidance in our dosing tables.

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8

Nederlandse samenvatting



Dit proefschrift richt zich op het voorspellen van medicijnklaring en het individualiseren van doseringsschema's bij mensen met overgewicht en obesitas. Om dit te bereiken werden twee modelbenaderingen gebruikt: populatiefarmacokinetische (popPK) modellering en fysiologisch gebaseerde farmacokinetische (PBPK) modellering. Door middel van popPK-modellering wilden we de invloed van obesitas op de farmacokinetiek van vancomycine kwantificeren bij adolescenten en volwassenen met overgewicht en obesitas, evenals bij patiënten met verschillende gradaties van nier(dis)functie. Daarnaast werden richtlijnen voor optimale medicijndosering ontwikkeld voor patiënten met overgewicht of obesitas met of zonder nierfunctiestoornis. Door middel van PBPK-modellering wilden we veranderingen in CL bestuderen die geassocieerd zijn met obesitas voor geneesmiddelen die gemetaboliseerd worden door de lever of geëlimineerd worden via glomerulaire filtratie en actieve tubulaire secretie, rekening houdend met de eigenschappen van het geneesmiddel, de kenmerken van de proefpersoon en de ernst van obesitas. Om deze doelstellingen te bereiken werden verschillende onderzoeken uitgevoerd, waarvan de resultaten hieronder worden samengevat.

Sectie I

In **Hoofdstuk 2** hebben we het beschikbare bewijsmateriaal beoordeeld met betrekking tot vijf algemeen geaccepteerde veronderstellingen die *a priori* de invloed van obesitas op PK van geneesmiddelen voorspellen. We ontdekten dat de beschikbare literatuur alle vijf aannames tegensprekt, of op zijn minst de generaliseerbaarheid ervan beperkt: **1)** het is niet gerechtvaardigd om *a priori* mager lichaamsgewicht te selecteren als maatdescriptor voor inter-individuele variabiliteit in klaring bij zwaarlijvige personen, noch komt een andere maatdescriptor hiervoor in aanmerking. Het totale lichaamsgewicht in een niet-lineaire functie wordt meestal gerapporteerd als de optimale descriptor om de variabiliteit in klaring te beschrijven; **2)** De invloed van obesitas op het distributievolume varieert sterk en kan niet alleen op basis van lipofiliteit worden voorspeld. In het algemeen lijkt er sprake te zijn van een (kleine) toename van het distributievolume voor hydrofiele geneesmiddelen, terwijl er voor lipofiele geneesmiddelen sprake is van een grote interdrugsvariabiliteit met potentieel zeer grote veranderingen; **3)** De leverklaring wordt niet alleen beïnvloed door

veranderingen in activiteit of overvloed van leverenzymen als gevolg van obesitas-gerelateerde veranderingen, maar ook door veranderingen in plasma-eiwitbinding en leverbloedstroom, waarbij de netto invloed afhankelijk is van de geneesmiddelextractieratio; 4) Ondanks een mogelijke toename van de glomerulaire filtratiesnelheid (GFR) bij zwaarlijvige personen, neemt de absolute renale klaring niet noodzakelijk toe voor alle geneesmiddelen die voornamelijk via de nieren worden geëlimineerd, omdat secretie en reabsorptie via transportermediairs ook kunnen worden beïnvloed door obesitas; 5) Bevindingen over klaring en dosisaanpassingen van volwassenen met obesitas kunnen niet altijd direct geëxtrapoleerd worden naar adolescenten met obesitas, mogelijk door verschillen in de duur van de obesitas en de tijd die nodig is voor fysiologische veranderingen om zich te manifesteren en PK-parameters te beïnvloeden.

Sectie II

In **Sectie II** werd de popPK modelbenadering gebruikt om de invloed van obesitas in relatie tot andere variabelen die vancomycine PK beïnvloeden te onderzoeken. In **Hoofdstuk 3** werd de PK van vancomycine bij adolescenten en volwassenen met overgewicht of obesitas onderzocht. Door adolescenten en volwassenen samen te analyseren, werd gevonden dat vancomycine *CL* toeneemt met het totale lichaamsgewicht (TBW) en afneemt met toenemende leeftijd. Een covariate analyse die adolescenten en volwassenen apart onderzocht vond dat vancomycine *CL* toenam met standaard gewicht (gedefinieerd als gewicht voor lengte, leeftijd en geslacht bij adolescenten en gewicht voor lengte bij volwassenen), zij het met verschillende functies voor adolescenten en volwassenen, en met adolescenten die een hogere *CL* per standaard gewicht hadden dan volwassenen. Bovendien hadden adolescente mannen in dit aparte covariatenmodel 21% hogere *CL* dan adolescente vrouwen met hetzelfde standaardgewicht, terwijl bij volwassenen de *CL* afnam met toenemende leeftijd. Deze resultaten suggereren dat er duidelijke verschillen zijn in vancomycine *CL* bij volwassenen met overgewicht en obesitas *versus* adolescenten met overgewicht en obesitas, wat impliceert dat de dosering van vancomycine niet direct geëxtrapoleerd kan worden tussen deze populaties.

In **Hoofdstuk 4** werd een popPK-model ontwikkeld om de PK van vancomycine te

kwantificeren bij patiënten met overgewicht of obesitas en verschillende graden van nier(dis)functie. Vancomycine CL bleek lineair toe te nemen met TBW en met de nierfunctie (CKD-EPI) in een machtsrelatie. Bovendien bleek de CL 15,5% lager te zijn bij IC-patiënten. Op basis van dit model werden AUC-gerichte doseringsaanbevelingen voor deze populatie voorgesteld. Om een beoogde AUC_{24} tussen 400 en 600 mg · h/L in de eerste 48 uur te bereiken, zijn twee laaddoses in de eerste 48 uur van de behandeling vereist voor zowel continue infusie als intermitterende doseringsschema's. Onderhoudsdoseringen bleken te moeten worden aangepast. Onderhoudsdoses bleken te moeten worden aangepast voor TBW, nierfunctie en IC-opnamestatus. Met deze richtlijn ligt de mediane AUC_{24} vanaf het begin van de behandeling ruim binnen de doelstelling, waardoor mogelijk minder dosisaanpassingen nodig zijn bij TDM.

Sectie III

In **Hoofdstuk 5** werd een PBPK-benadering gebruikt om correlaties te onderzoeken tussen plasmaklaring (CL_p) en kenmerken van het geneesmiddel en de proefpersoon bij proefpersonen met overgewicht of obesitas, voor geneesmiddelen die worden gemetaboliseerd via het levermetabolisme. We vonden dat body mass index (BMI) en relatieve obesitas-geïnduceerde veranderingen in enzymactiviteit sterk gecorreleerd zijn met obesitas-gerelateerde CL_p veranderingen. Geneesmiddelen die binden aan α 1-zuur glycoproteïne (AAG) hebben kleinere CL_p veranderingen vergeleken met geneesmiddelen die binden aan humaan serumalbumine (HSA). Lagere extrac-tieratio's (ER) bij personen met normaal gewicht corresponderen met grotere CL_p veranderingen vergeleken met geneesmiddelen met een hogere ER bij personen met normaal gewicht. De allometrische exponent voor perfecte CL_p schaling varieerde van -3,84 tot 3,34, wat illustreert dat geen enkele schalingsmethode (d.w.z. lineaire schaling, 0,75 allometrische schaling of geen schaling) in alle situaties goed zal presteren. In plaats daarvan moet er rekening worden gehouden met verschillende medicijneigenschappen en de ernst van obesitas om nauwkeurig te kunnen schalen.

Hoofdstuk 6 gaat verder met het onderzoek dat is gestart in **Hoofdstuk 5**, waarbij een vergelijkbare PBPK-workflow wordt gebruikt die zich richt op geneesmiddelen die worden geëlimineerd via glomerulaire filtratie (GF) en actieve nierafscheiding (ATS). In dit hoofdstuk werd speciale aandacht besteed aan het onderzoeken van de

invloed van door obesitas veroorzaakte veranderingen in ATS op de totale CL_r onder verschillende scenario's van verandering door obesitas. We vonden dat CL_r door GF en ATS toenam met BMI, zij het in verschillende mate, afhankelijk van de eigenschappen van het geneesmiddel. Wanneer de BMI lager was dan 30 kg/m^2 en de transporteractiviteit onveranderd bleef, verschilde de CL_r tussen proefpersonen met normaal gewicht en met obesitas minder dan 30% en waren beide schaalmethoden systematisch nauwkeurig. Voor personen met een hogere BMI moet rekening worden gehouden met de eigenschappen van het geneesmiddel bij het definiëren van scenario's voor systematische nauwkeurigheid van de schaling.

Appendices



List of Publications

Publications related to this thesis

- **Zhang T**, Calvier EAM, Krekels EHJ, Knibbe CAJ. The Impact of Drug Properties and Severity of Obesity on Renal Drug Clearance Through Glomerular Filtration and Active Tubular Secretion: A Systematic Analysis Using PBPK Modeling. *Pharm Res.* 2025 Jul;42(7):1079-1088. doi: 10.1007/s11095-025-03885-5.
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Publications not related to this thesis

- **Zhang T**, Chen G, Liu C, et al. A Phase I Study Comparing the Pharmacokinetics, Safety, and Immunogenicity of Proposed Biosimilar GB242 and Reference Infliximab in Healthy Subjects. *BioDrugs*. 2019;33(1):93-100.
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Tan Zhang
Leiden, March 2026

Curriculum Vitæ

Tan Zhang was born in Ningxia, China, in 1993. In 2012, she was admitted to Southwest University, China, where she pursued a Bachelor of Science in Pharmacy and a Bachelor of Literature in Foreign Languages. She successfully completed both programs in 2016, earning dual degrees.

Following her undergraduate studies, she continued her academic journey at Peking University, where she enrolled in the Clinical Pharmacy program under the supervision of Prof. Dr. Yi Fang. Concurrently, she joined the Phase I Clinical Trial Research Laboratory of the National Drug Clinical Trial Organization at Peking University People's Hospital, where she worked as a research assistant. In this role, she was actively involved in the execution of early-phase clinical trials, gaining experience in pharmacokinetics and drug safety assessments. It was during this period that she developed a strong interest in pharmacometrics, particularly its applications in clinical practice, drug development, and clinical trial design.

After obtaining her Master of Science in Clinical Pharmacy in 2019, she joined the Division of Systems Pharmacology and Pharmacy at the Leiden Academic Center for Drug Research (LACDR), Leiden University, to further specialize in pharmacometrics and quantitative pharmacology. Under the supervision of Prof. dr. Catherijne A.J. Knibbe and Dr. Elke H.J. Krekels, she contributed to research projects focused on model-informed dose optimization and individualization of drug clearance predictions in the obese population.



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