ORIGINAL RESEARCH ARTICLE

Repository Describing the Anatomical, Physiological, and Biological Changes in an Obese Population to Inform Physiologically Based Pharmacokinetic Models

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Abstract

Background Obesity is associated with physiological changes that can affect drug pharmacokinetics. Obese individuals are underrepresented in clinical trials, leading to a lack of evidence-based dosing recommendations for many drugs. Physiologically based pharmacokinetic (PBPK) modelling can overcome this limitation but necessitates a detailed description of the population characteristics under investigation.

Objective The purpose of this study was to develop and verify a repository of the current anatomical, physiological, and biological data of obese individuals, including population variability, to inform a PBPK framework.

Methods A systematic literature search was performed to collate anatomical, physiological, and biological parameters for obese individuals. Multiple regression analyses were used to derive mathematical equations describing the continuous effect of body mass index (BMI) within the range 18.5–60 kg/m^2 on system parameters.

Results In total, 209 studies were included in the database. The literature reported mostly BMI-related changes in organ weight, whereas data on blood flow and biological parameters (i.e. enzyme abundance) were sparse, and hence physiologically plausible assumptions were made when needed. The developed obese population was implemented in Matlab® and the predicted system parameters obtained from 1000 virtual individuals were in agreement with observed data from an independent validation obese population. Our analysis indicates that a threefold increase in BMI, from 20 to 60 kg/m^2, leads to an increase in cardiac output (50%), liver weight (100%), kidney weight (60%), both the kidney and liver absolute blood flows (50%), and in total adipose blood flow (160%).

Conclusion The developed repository provides an updated description of a population with a BMI from 18.5 to 60 kg/m^2 using continuous physiological changes and their variability for each system parameter. It is a tool that can be implemented in PBPK models to simulate drug pharmacokinetics in obese individuals.

1 Introduction

Obesity is a disease characterized by an abnormal or excessive fat accumulation and commonly defined by a body mass index (BMI) ≥ 30 kg/m^2 [1]. In 2016, almost 40% of the adult world population was overweight (i.e. BMI 25–29.9 kg/m^2) and 13% were obese, with the latest publications showing that these percentages are continuously rising [1].

Key Points

This repository provides an extensive collection of anatomical, physiological, and biological parameters of a White obese population up to a body mass index of 60 kg/m^2.

The equations and population variability derived for each parameter can be used to inform a physiologically based pharmacokinetic framework.

This repository can be used in future work to fill gaps in pharmacological research questions related to obesity, such as drug pharmacokinetics and drug–drug interactions.

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Worldwide obesity is an important healthcare problem that has been associated with numerous comorbidities (i.e. cardiovascular diseases, type 2 diabetes mellitus, respiratory dysfunction, cancer, non-alcoholic liver disease) and an increased risk of mortality [2, 3].

Obesity is also linked to anatomical, physiological and biological remodelling, which can lead to changes in drug pharmacokinetics. For instance, a greater volume of distribution is related to increased adipose tissue and lean mass; different metabolism is linked to greater hepatic blood flow, increased liver weight, and alteration of enzyme abundance; and higher excretion is connected to a greater glomerular filtration rate (GFR) and renal blood flow [4]. Obese subjects are underrepresented in clinical studies, leading to a lack of information supporting dose selection in this special population. Thus, to ensure safe and efficacious treatments, it is important to evaluate the effect of physiological changes related to obesity on pharmacokinetics. Physiologically based pharmacokinetic (PBPK) modelling makes use of prior knowledge on system and drug parameters to simulate virtual clinical trials, which can fill the existing knowledge gaps and provide a better understanding of drug disposition in obese subjects.

A comprehensive description of the system parameters of the population of interest is necessary to inform a PBPK model. More often, all these anatomical, physiological and biological parameters are gathered from literature into vast repositories [5, 6], and for obese subjects, only one has been previously published [7]. This database gives a good description of the most important system parameters; however, it does not report continuous physiological changes and their corresponding variability. Furthermore, recent findings on key parameters are missing. Hence, the objective of this study was to develop and verify a comprehensive database of White obese individuals, including population variability on system parameters and continuous functions describing physiological parameters of interest for a BMI up to 60 kg/m².

2 Methods

2.1 Data Source

A systematic literature search was performed using both the PubMed and Google Scholar databases without any restrictions on language or date of publication. Anatomical, physiological and biological parameters of interest were searched combining three keywords: the first related to obesity (e.g., 'obese', 'obesity', 'BMI', 'overweight'), the second was specific to the organ or parameter (e.g., 'kidney', 'renal', 'albumin'), and the last specfied the type of parameter (e.g., 'weight', 'volume', 'blood flow', 'hemodynamics').

The studies issued from the literature search were screened and included in the final analysis if they met the following inclusion criteria: (1) adult individuals aged between 20 and 50 years; (2) predominantly White; (3) BMI > 18.5 kg/m²; and (4) concurrent comorbidity had to be mild or deemed unlikely to affect the parameter of interest. The reference list of the identified articles was further screened to find additional references.

2.2 Data Extraction

Data were generally taken from tables or the Results section of articles. In addition, GetData Graph Digitizer® was used to extract numerical values that were reported graphically. Organ weights were kindly provided from previously published works, by Dr. Michaud, Department of Forensic Medicine, University of Geneva, Switzerland [8]; Dr. Ahn, Department of Applied Mathematics and Statistics, Stony Brook University, US [9]; Dr.Brodsky, Department of Pathology, Ohio State University, US [10]; and Dr. Fritsch, Department of Pathology and Laboratory Medicine, University of Wisconsin-Madison, US [11]. Furthermore, cardiac output data were kindly provided by Dr. Dini, Cardiovascular and Thoracic Department, University of Pisa, Italy [12], while GFR data were kindly provided by Dr. Chew-Harris, Department of Medicine, University of Otago, New Zealand [13] and Dr. Navis, Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, The Netherlands [14, 15]. Organ data were sometimes expressed as volumes, in which case they were transformed into organ weight based on their relative density [16]. For each study, mean and standard deviation (SD) were collected; if the measure of dispersion was reported as median, minimum, and maximum, then the value was converted following the approach of Hozo et al., however if the interquartile range was given then the method reported by Wan et al. was applied [17, 18]. Data collected were subsequently divided into a development and verification dataset. A study was included in the development dataset when the most important anthropometric parameters (sex, age, height, and weight) as well as the parameter of interest were published, otherwise the study was added to the verification dataset. In the case of several rich-data studies, these were randomly separated between the development and verification datasets.

When covariates were missing, these were estimated using our derived equations, as done by Williams and Leggett [19]; primary covariates, such as anthropometric variables, were derived only for the verification dataset, while secondary covariates, such as cardiac output or adipose tissue weight, were also derived for the development dataset. The body surface area (BSA) was calculated according to the Ashby–Thompson equation (not using the mostly commonly used DuBois and DuBois equation) because it was

developed using a new technology (three-dimensional photonic scanner), a richer dataset (268 vs. 9 individuals) and wider BMI range (17.8–77.8 vs. 15.3–41.5 kg/m^2), and the authors found it improved the BSA prediction in individuals with a BMI ≥ 40 [20].

2.3 Data Analysis

Mathematical functions were derived for each parameter of interest by the mean of weighted linear regression. Linear, polynomial and exponential functions were tested to find the equation that best described the parameter trend. Generally, the regression was performed using sex, age, weight, height, BMI, and BSA as covariates; however, additional covariates were tested if an effect on the parameter of interest was described in the literature (e.g., relationship between blood volume and adipose tissue weight). Covariates were considered significant when their p value was lower than 0.01. To select the best fitted function, we used visual and numeric diagnostics (R^2 and Akaike's information criterion) together with physiological plausibility. The developed equations were implemented in a Matlab$^®$ script and were used to generate the virtual population parameter values [21]. The first validation consisted of visually comparing the prediction of 1000 males and females with a BMI ranging from 18.5 to 60 kg/m^2 against the independent verification dataset, while the second validation consisted of verifying that the sum of organ weights and blood flows did not exceed body weight and cardiac output. The observed parameters' variability, expressed as coefficient of variance (CV), was initially estimated as the sum of the covariates' variability; however, if the CV was not fully captured, an additional random variability with normal distribution was added. The latter was calculated as the observed CV minus the predicted CV, except for the gonads and the pancreas, where the CV was derived from the work of Giwercman et al. [22] and de la Grandmaison et al. [23], respectively. For some parameters, the data were heteroscedastic, however since the increased variability at a higher BMI was overall well-predicted by the variability of the dependent variables, a fixed CV was used rather than a CV depending on BMI (Figs. 1, 2, 3, 4, 5, 6).

3 Results

Overall, 346 articles were screened, of which 209 met the inclusion criteria and were included in the analysis. Studies were excluded from the analysis if the patients' age and BMI were outside the accepted range, if the most important anthropometric data such as weight or BMI were missing, and if the patients had comorbidities impacting the parameter of interest. Information regarding organ weights, obtained from autopsies or magnetic resonance imaging (MRI), were generally available in the literature, while measurements of regional blood flow and biological parameters, which require more sophisticated methodologies, were limited. Most of the collected parameters were measured in individuals with a BMI up to 60 kg/m^2 (as shown in Figs. 1, 2, 3, 4, 5, 6), leaving a knowledge gap for higher BMI values. Table 1 lists the derived equations for each organ and the corresponding population variability expressed as CV.

3.1 Body Composition

Body composition data were obtained from the National Health and Nutrition Examination Survey (NHANES) database [24]. Values collected from 1999 to 2018, using dual energy X-ray absorptiometry (DEXA), were analysed and a total of 3620 data points were selected and randomly divided into development and verification datasets. Following the approach of Kyle et al. [25], the fat mass and fat-free mass were normalized by the square of body height and converted into fat mass index (FMI) and fat-free mass index (FFMI). It was found that, for the same BMI, FFMI was higher in males compared with females, and vice versa for FMI, consistent with previous data showing sex differences in body composition (Fig. 1a, b) [26]. Further details regarding the changes in total body water (TBW) and tissue composition are given in Sect. 3.13.
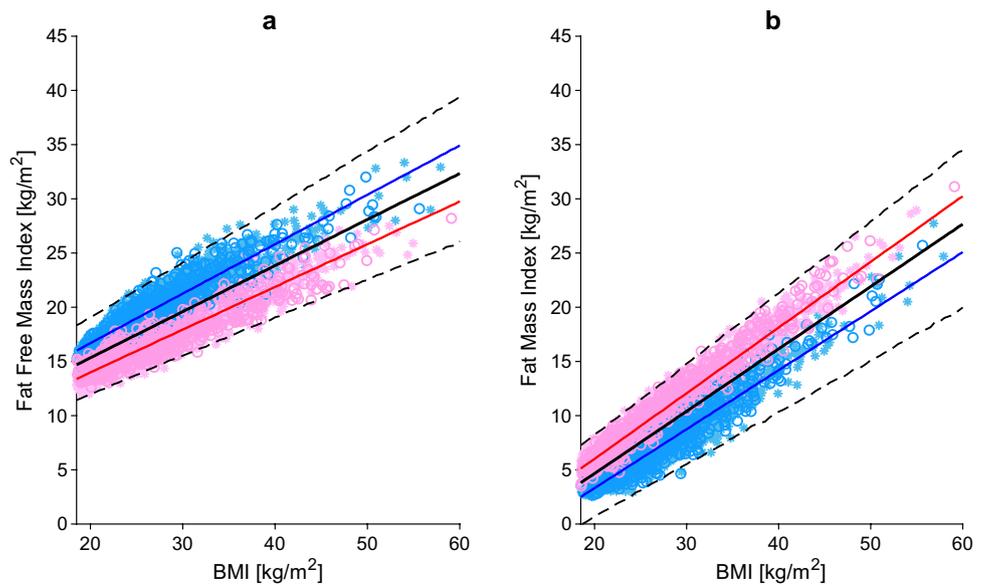
3.2 Adipose Tissue

3.2.1 Adipose Tissue Weight

The adipose tissue weight was derived from the FMI, which was calculated as the difference between BMI and FFMI. The accuracy of the prediction was verified against data from the NHANES database [24]. The adipose tissue weight was found to increase linearly with BMI, with women having higher adipose tissue weight compared with men with the same BMI. The difference in adipose tissue weight between the two sexes halved from 6 to 3.2 kg when changing from a BMI of 20 kg/m^2 to a BMI of 60 kg/m^2 (Fig. 2a). Overall, the percentage of adipose tissue doubled from 20% in individuals with a BMI of 20 kg/m^2 to 45.5% in individuals with a BMI of 60 kg/m^2.
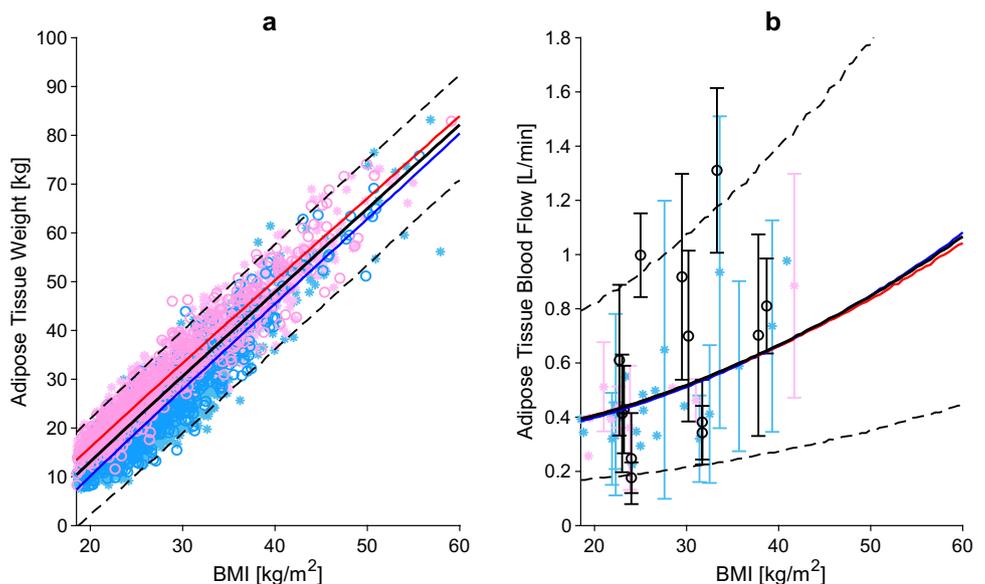
3.2.2 Adipose Tissue Blood Flow

Only a few studies measured the adipose tissue blood flow in obese individuals. The methods used by the authors to quantify the blood flow were ^{133}Xe, ^{85}Kr or ^{15}O-labelled water. Eight of the studies, reporting on data from a total of 173 subjects, were used as the development dataset [27–34],

Fig. 1 Fat-free mass index (**a**) and fat mass index (**b**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male and female data points are represented in light blue and pink, respectively. *BMI* body mass index

Fig. 2 Adipose tissue weight (**a**) and adipose tissue blood flow (**b**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male, female and mixed-sex data points are represented in light blue, pink and black, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *SD* standard deviation


while the remaining six studies, including a total of 139 individuals, composed the verification dataset [35–41]. The data analysis found that the absolute adipose tissue blood flow (expressed as mL/min/100 g) was lower in obese compared with lean individuals, confirming a lower perfusion of the adipose tissue. However, the total adipose tissue blood flow was found to be 160% higher in obese individuals with a BMI of 60 kg/m^2 compared with lean individuals with a BMI of 20 kg/m^2, explained by the greater adipose tissue mass (Fig. 2b).

3.3 Liver

3.3.1 Liver Weight

The main organ responsible for drug metabolism is the liver, and accurately predicting its weight is critical for in vitro-in vivo extrapolation. The data from a total of 1937 subjects were collected and used as the development dataset [9, 10, 23, 42–47]. The goodness of the equation, derived from the regression, was compared against the verification dataset composed of 164 data points [11, 48, 49]. In males

Fig. 3 Liver weight (**a**) and liver blood flow (**b**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male, female and mixed-sex data points are represented in light blue, pink and black, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *SD* standard deviation
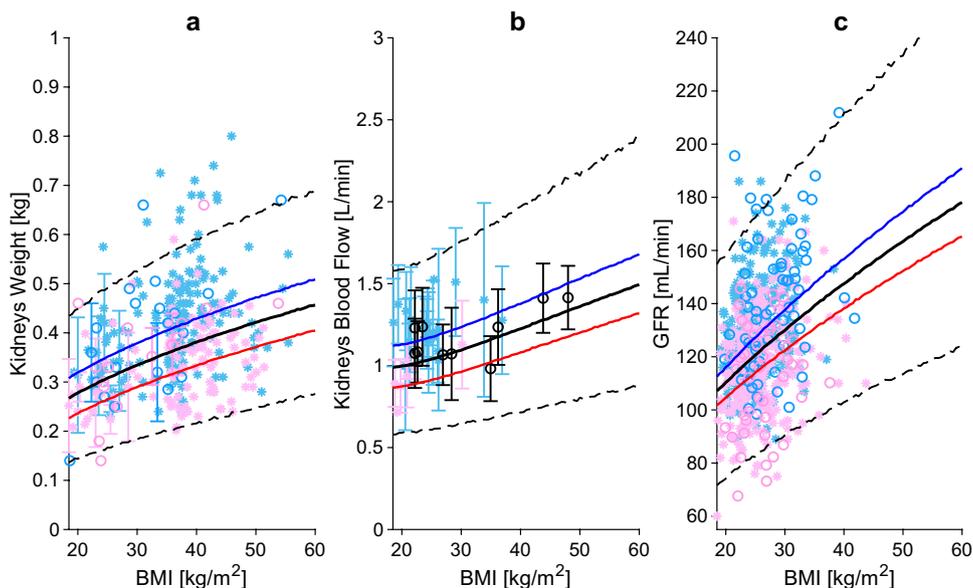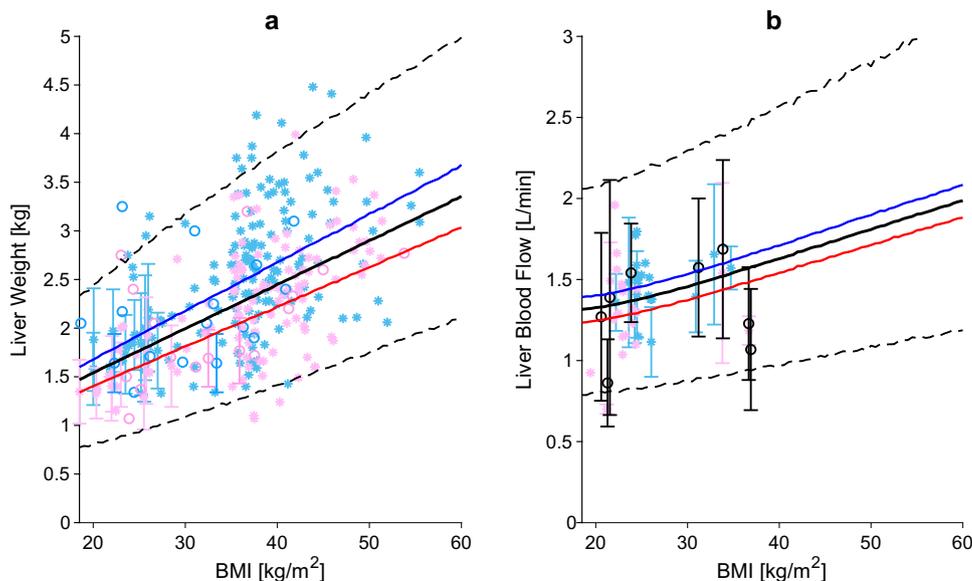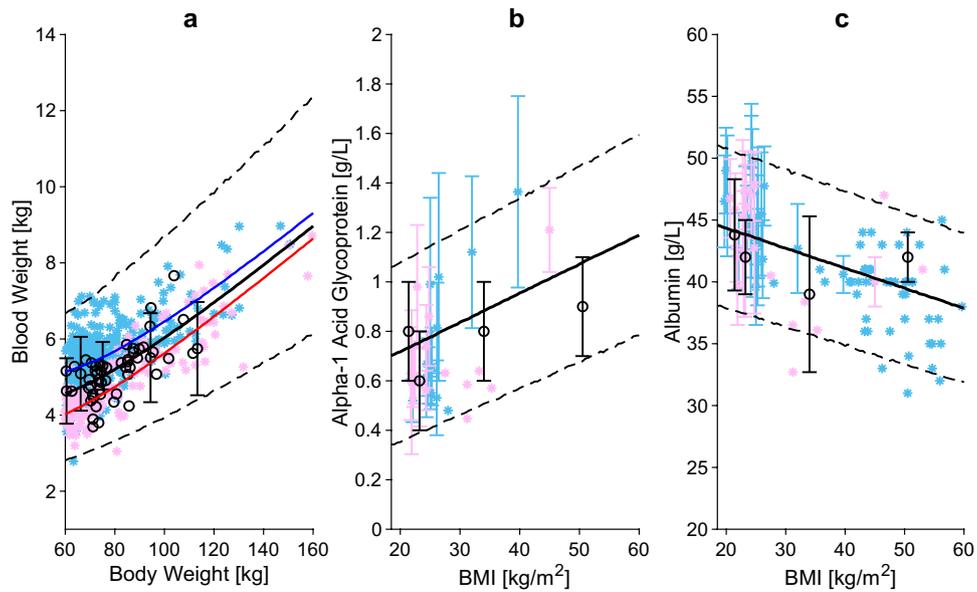
Fig. 4. Kidney weight (**a**), kidney blood flow (**b**), and GFR (**c**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male, female and mixed-sex data points are represented in light blue, pink and black, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *GFR* glomerular filtration rate, *SD* standard deviation

and females with a BMI of 20 kg/m^2, the liver weight was 1.7 kg and 1.4 kg, respectively, and increased to a weight of 3.6 kg and 3.0 kg, respectively, in individuals with a BMI of 60 kg/m^2 (Fig. 3a). It is known from the literature that there is a strong association between obesity and steatosis, with percentages in the severely obese ranging from 85 to 98% [50, 51]. Furthermore, additional studies showed that the liver fat content can be as much as 40% of the total liver weight [52, 53]. Thus, it is important to emphasize that a higher liver mass does not coincide with higher metabolic active liver parenchyma.

Fig. 5. Blood weight versus body weight (**a**), α1-acid glycoprotein (**b**), and albumin (**c**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male, female and mixed-sex data points are represented in light blue, pink and black, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *SD* standard deviation
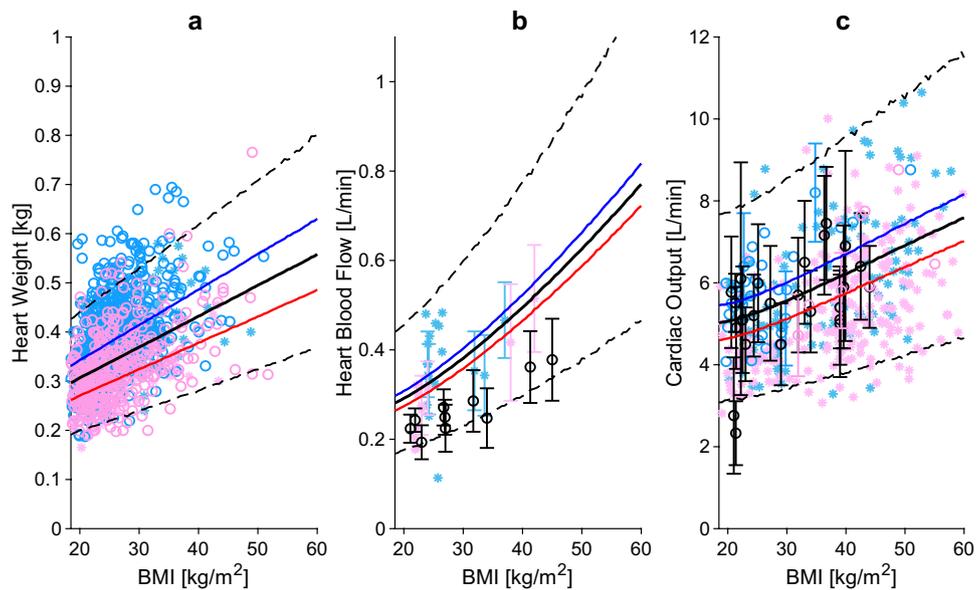
Fig. 6 Heart weight (**a**), heart blood flow (**b**), and cardiac output (**c**) relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represent the 99% normal range. Asterisks represent observed data from the development and circles represent observed data from the independent verification dataset. Male, female and mixed-sex data points are represented in light blue, pink and black, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *SD* standard deviation

Table 1 Descriptive equations and population variability for anatomical, physiological, and biological parameters necessary to inform a physiologically based pharmacokinetic model

Parameter	Unit	Descriptive equation	CV (%)
BMI	kg/m^2	Random uniform distribution	
FFMI	kg/m^2	$30.86 - 3.09 \times \text{Sex} - 0.13 \times \text{Body height} + 0.14 \times \text{Body weight}$	8.58
FMI	kg/m^2	$\text{FFMI} - \text{BMI}$	
Body height	cm	$-0.0039 \times \text{Age}^2 + 0.238 \times \text{Age} - 12.5 \times \text{Sex} + 176$	3.8
Body weight	kg	$\text{BMI} \times (\text{Body height}/100)^2$	
Lungs weight	kg	$-2.16 + 0.02 \times \text{Body height}$	18.38
Adipose weight	kg	$\text{FMI} \times (\text{Body height}/100)^2$	
Lean body weight	kg	$\text{Body weight} - \text{Adipose weight}$	
Bone weight	kg	$-9.5 + 0.1 \times \text{Body height} + 0.03 \times \text{Body weight} - 0.023 \times \text{Adipose weight precentage}$	5.78
Brain weight	kg	$e^{(-0.00075 \times \text{Age} + 0.0078 \times \text{Body height} - 0.97)}$	9
Gonads weight	kg	$0.039 - 0.028 \times \text{Sex}$	17.78
Heart weight	kg	$0.037 + 0.0012 \times \text{Age} + 0.0049 \times \text{Lean body weight}$	9.32
Kidneys weight	kg	$-0.11 - 0.48 \times \text{Sex} + 0.003 \times \text{Age} + 0.18 \times \text{BSA}$	13.15
Muscle weight	kg	$1.4 - 1.53 \times \text{Sex} - 0.051 \times \text{Age} + 0.5 \times \text{Lean body weight}$	2.96
Skin weight	kg	$\text{BSA} \times (2.07 - 0.11 \times \text{Sex}) \times 1.05$	13.37
Thymus weight	kg	$0.0027 + 0.0002 \times \text{Body weight}$	32.64
Stomach weight	kg	0.257	22.5
SIL	cm	$\dfrac{136.86 - 8.09 \times \text{Sex} + 0.87 \times \text{Age} + 2.93 \times \text{Body height} + 0.29 \times \text{Body weight} - 91.2}{1.09}$	17.7
Jejunum weight	kg	$\dfrac{\text{SIL} \times 0.4 \times \pi \times 2.43 \times 0.15 \times 1.04}{1000}$	
Ileum weight	kg	$\dfrac{\text{SIL} \times 0.6 \times \pi \times 1.92 \times 0.15 \times 1.04}{1000}$	
Duodenum weight	kg	$(\text{Jejunum weight} + \text{Ileum weight}) \times \dfrac{0.042}{0.958}$	
LIL	cm	$0.52 \times \text{Body height} + 18.5$	11.26
Large intestine weight	kg	$\dfrac{\text{LIL} \times \pi \times 4 \times 0.25 \times 1.04}{1000}$	
Gut weight	kg	$\text{Stomach weight} + \text{Jejunum weight} + \text{Ileum weight} + \text{Duodenum weight} + \text{Large intestine weight}$	
Spleen weight	kg	$e^{(-3.46 - 0.017 \times \text{Sex} + 0.93 \times \text{BSA})}$	36.71
Pancreas weight	kg	$0.089 - 0.02 \times \text{Sex} + 0.0023 \times \text{BMI}$	23.27
Liver weight	kg	$0.36 + 0.023 \times \text{Lean body weight} + 0.01 \times \text{Adipose weight}$	17.49
Blood weight	kg	$2.58 + 0.057 \times \text{Body weight} - 0.061 \times \text{Adipose weight percentage}$	9.08
HR	Beats/min	Truncated normal distribution, mu = 80, sigma = 13.2, min = 60, max = 100	
EDV	mL/beat	$43.13 + 12.96 \times \text{Blood weight}$	8.05
EF	–	$0.65 - 0.0018 \times \text{BMI}$	
CO	L/min	$\text{HR} \times \text{EDV} \times \text{EF}/1000$	
Adipose blood flow	% of CO	$\exp^{(2.50 - 0.043 \times \text{BMI} + 0.033 \times \text{Adipose weight})}$	
Bone blood flow	% of CO	5	
Brain blood flow	% of CO	$\text{BMI} < 25 = 12 \text{ and } \text{BMI} \geq 25 = 12 - 0.13 \times (\text{BMI} - 25)$	
Gonads blood flow	% of CO	$-0.03 \times \text{Sex} + 0.05$	
Heart blood flow	% of CO	$3.41 + 0.29 \times \text{Sex} + 0.11 \times \text{BMI}$	
Kidneys blood flow	% of CO	$20.57 - 1.76 \times \text{Sex}$	
Muscle blood flow	% of CO	$e^{(3.01 - 0.22 \times \text{Sex} - 0.012 \times \text{BMI})}$	
Skin blood flow	% of CO	$5.68 - 0.034 \times \text{BMI}$	
Thymus blood flow	% of CO	1.5	
Gut blood flow	% of CO	$(18.52 + 3.04 \times \text{Sex}) - (0.20 + 0.06 \times \text{Sex}) \times \text{BMI} + (0.0009 + 0.0004 \times \text{Sex}) \times \text{BMI}^2$	
Spleen blood flow	% of CO	3	
Pancreas blood flow	% of CO	$5.18 - 0.95 \times \text{BSA}$	
Liver blood flow	% of CO	$25.53 + 1.30 \times \text{Sex}$	
Albumin	g/L	$47.58 - 0.16 \times \text{BMI}$	7.2
AAG	g/L	$0.48 + 0.012 \times \text{BMI}$	25.39
Haematocrit	–	$0.45 - 0.04 \times \text{Sex}$	6.8
GFR	mL/min	$13.02 - 0.51 \times \text{Age} + 0.93 \times \text{Adipose weight percentage} + 93.56 \times \text{Kidneys blood flow}$	0

Table 1 (continued)

Blood flows are relative to cardiac output. Virtual individuals with a BMI ranging from 18.5 to 60 kg/m^2 can be generated

AAG α1-acid glycoprotein, *BMI* body mass index, *BSA* body surface area, *CO* cardiac output, *CV* coefficient of variation, *EDV* end diastolic volume, *EF* ejection fraction, *FFMI* fat-free mass index, *FMI* fat mass index, *GFR* glomerular filtration rate, *HR* heart rate, *LIL* large intestine length, *Sex* 0 = male, 1 = female, *SIL* small intestine length

3.3.2 Liver Blood Flow

The literature search yielded 11 studies examining liver blood flow in a total of 336 individuals (Fig. 3b) [33, 54–63]. The analysis showed that the liver blood flow relative to cardiac output remains constant across BMI values, but when expressed as an absolute value, it increases up to 50% in an obese individual with a BMI of 60 kg/m^2 in comparison with an individual with a BMI of 20 kg/m^2.

3.3.3 In vitro-in vivo Extrapolation Factors

In vitro-in vivo extrapolation factors are critical physiological parameters that are used in PBPK modelling to scale in vitro data to human. Microsomal proteins per gram liver (MPPGL), hepatocytes per gram liver (HPGL), or homogenate proteins per gram liver (HomPPGL) are essential hepatic scaling factors needed to extrapolate human clearance. Unfortunately, no information on how obesity affects these scaling factors is available in literature. It is known that BMI is strongly correlated with fatty liver infiltration, a medical condition called steatosis that can vary from simple non-alcoholic fatty liver disease (NAFLD) without inflammation to non-alcoholic steatohepatitis (NASH) with active hepatic inflammation [64–67]. Considering that in obese subjects a substantial part of the liver is only accumulated fat and therefore not all the liver volume is metabolically active, using MPPGL, HPGL and HomPPGL values derived from biopsies of healthy-weight individuals could result in an overprediction of clearance. Sinha et al. proposed scaling in vitro clearance values using only the volume of metabolic active liver, also called lean liver volume (LLV) [68, 69]. We applied the same approach and calculated the LLV by subtracting from the predicted liver volume the fat fraction, which was derived from the correlation plot between liver volume and fat content reported in the study by Hedderich et al. [52].

3.3.4 Hepatic Enzyme and Transporter Activity

Only a few studies describing the cytochrome P450 (CYP) enzyme abundance and activity in obese subjects were available in the literature. Two studies looked at the impact of obesity on CYP3A4 expression and found that both BMI and liver fat content have a negative impact on enzyme abundance, leading to lower levels in both liver and intestine [70, 71]. Krogstad et al. investigated the ex vivo activities of several CYP enzymes using biopsies obtained from patients with a wide range of body weights. The authors found that only hepatic CYP3A activity was significantly negatively correlated to body weight, while CYP2B6, CYP2C8, CYP2D6, CYP2C9, CYP2C19 and CYP1A2 activities were not [72]. The decrease in CYP3A4 abundance was obtained from the slope of the correlation plot between BMI and CYP3A4 expression published by Ulvestad et al. [70].

Clinical studies showed that clearance of CYP2E1 substrates is higher in the obese, however it is unclear which parameter is driving this pharmacokinetic change as activity or expression data are lacking [73, 74].

Some uridine 5′-diphosphate-glucuronosyltranferases (UGT) substrates, such as acetaminophen, oxazepam and lorazepam, have been studied in vivo and the results of the clinical trials show a higher clearance in obese compared with non-obese individuals [75]. These findings are in agreement with ex vivo UGT expression values in mouse [76], however in vitro data showing a positive correlation between body weight and UGT protein abundance in humans are missing.

One study examined the effect of obesity on human hepatic uptake transporters. Organic anion transporting polypeptides (OATP) 1B1, OATP1B3 and OATP2B1, as well as the sodium-dependent uptake transporter, were studied in a cohort of individuals with different body weights and only the abundance of OATP1B1 was found to decrease with body weight, while the others remained unchanged [77].

3.4 Kidney

3.4.1 Kidney Weight

The kidney weight equation was derived using data from 1451 subjects collected from six studies [9, 10, 45, 47, 78, 79], and validated against an additional dataset of 168 subjects (Fig. 4a) [11, 48, 49]. Overall, kidney weight increased in both sexes by 17.5% per every 10 BMI bands, up to a BMI of 35 kg/m^2, after which the increase was about 8%.

3.4.2 Kidney Blood Flow

Obesity does alter renal function. While organ weight increases across BMI values, the number of glomeruli does not, leading to greater glomerular size and planar surface area. These structural changes occur together with haemodynamic alterations such as higher plasma blood flow and GFR

[80]. Based on the data collected from 18 studies describing the changes in renal blood flow [15, 58, 59, 61, 62, 81–93], we found that absolute kidney blood flow positively correlates with BMI (Fig. 4b), while blood flow relative to cardiac output remains constant at around 20% in males and 18.5% in females.

3.4.3 Glomerular Filtration Rate

The GFR is an important parameter with a key role for the passive elimination of drugs. GFR can be calculated using creatinine-based equations, such as the Cockcroft–Gault formula or the Modification of Diet in Renal Disease (MDRD) equation, but their predictivity is biased in the obese due to higher urine creatinine excretion [94]. For this reason, only data derived using Tc-DTPA and ^{125}I-iothalamate were considered for both the development [15] and validation datasets [95, 96]. In healthy-weight male and female individuals, GFR was found to be 119 and 107 mL/min, respectively, increasing up to 145 and 130 mL/min, respectively, in obese individuals, and reaching 166 and 145 mL/min, respectively, in the morbidly obese (Fig. 4c).

3.5 Blood

3.5.1 Blood Weight

Obesity is linked to an increase in lean body weight and adipose tissue weight, which translates into higher metabolic demand, resulting in greater blood volume (Fig. 5a) [97]. Even if the absolute blood volume is higher in obese subjects, the ratio between blood volume and body weight does not remain constant but decreases. This is explained by the fact that adipose tissue is not highly perfused and therefore requires less blood than the lean mass. Analysis of the blood volume data compiled from the literature [61, 98–105] resulted in a positive correlation with total body weight, with morbidly obese patients with a BMI of 60 kg/m² having twice the amount of blood compared with a lean subject with a BMI of 20 kg/m2. Additionally, in agreement with previous observations, we found that the increase in blood weight became less prominent at higher adipose tissue percentages [104].

3.5.2 Haematocrit

Haematocrit was evaluated using a dataset of 764 individuals, with the analysis resulting in sex being the only significant covariate [84, 98–102, 106–108]. Males had a mean haematocrit of 0.45, while females had a mean haematocrit of 0.41.

3.5.3 Plasma Protein Concentration

α-Acidic glycoprotein (AAG) levels of 455 individuals with different grades of obesity were collected from 12 studies and were subsequently analysed [109–121]. AAG concentrations increased from 0.73 to 1.01 g/L in healthy-weight individuals compared with morbidly obese subjects (Fig. 5b).

A negative correlation was found between albumin concentration and BMI, with a constant decline of about 0.41% at each BMI value (Fig. 5c) [109–114, 117, 122–130].

3.6 Heart

3.6.1 Heart Weight

Higher blood volume and cardiac output in obese subjects are the main causes leading to heart hypertrophy (Fig. 6a) [131, 132]. We investigated the change in heart weight across BMI values by analysing the data of 1203 subjects collected from four published studies [8, 9, 133, 134] and found that age and lean body weight were the two covariates that best described the increase in heart weight. In morbidly obese individuals, the heart reached a weight of 0.55 kg, 85% heavier than in a subject with a BMI of 20 kg/m².

3.6.2 Heart Blood Flow

Data from 499 subjects and 11 different scientific articles were gathered from the literature [135–145]. Both absolute and relative values of heart blood flow were increased in obese subjects compared with lean-weight subjects. The latter changed from 5.9% in healthy-weight individuals to 7.3% in obese individuals (Fig. 6b).

3.6.3 Cardiac Output

Cardiac output represents the volume of blood pumped by the heart per unit of time. It is calculated as the product of end diastolic volume, ejection fraction, and heart rate. Data from Dini et al. [12] were analysed as the development dataset and subsequently compared against data from another 15 studies [9, 61, 97, 105, 146–156]. Heart rate was found to not change with obesity in accordance with other studies [132]. Furthermore, end diastolic volume increased proportionally to blood volume, while ejection fraction decreased slightly across BMI values. Multiplication of the three parameters leads to an increase in cardiac output of about 10% every 10 BMI bands, starting from 5.1 L/min in healthy-weight subjects to 5.9 L/min in obese individuals, and up to 7.5 L/min in morbidly obese individuals with a BMI of 60 kg/m² (Fig. 6c).

3.7 Gastrointestinal Tract

3.7.1 Gastrointestinal Tract Weight

Only one study compared stomach weight between lean and obese individuals, with the authors of that study reporting no differences between the two groups [157]. With regard to small and large intestine weight, no information was available in the literature. Studies regarding small bowel length were conducted but controversial conclusions were found. Despite this, the latest studies performed with more subjects found no correlations between intestinal length and body weight [158, 159]. Small bowel length was derived using the equation proposed by Tacchino et al. [159], while large bowel length was obtained using the equation proposed by the ICRP [16]. Intestinal weight was then calculated assuming that the intestine has a cylindrical shape and using intestinal length, diameter and thickness data [160, 161].

3.7.2 Gastrointestinal Blood Flow

Small intestine blood flow was found to not increase with obesity [162, 163], therefore absolute blood flow was kept constant across BMI values. No data regarding obese stomach and colon blood flows are currently available in the literature, therefore the absolute blood flow was assumed to not change across BMI values as for the small intestine.

3.7.3 Gastric pH

Only a few studies investigated the change in gastric pH. Two studies found the obese group to have a slightly lower gastric pH compared with the lean group (median values were 2.3 vs. 2.8, and 1.3 vs. 3.7, respectively) [164, 165], while a third study reported no difference (1.69 vs. 1.65) [166]. However, when comparing their results with gastric pH in young healthy volunteers measured in other studies (median values 1.72 and 1.45), we found no correlation with BMI [167–169] and therefore used the same gastric pH in lean subjects as in obese individuals.

3.7.4 Gastrointestinal Transit Time

Gastric and small bowel transit times have been studied over the years using different methods and a variety of test meals, leading to conflicting conclusions. Some articles reported a faster transit time [170, 171], while others reported a similar transit time [172–177], and some even reported a delayed transit time [178, 179], in obese compared with lean individuals. However, more recent papers all point to the same conclusions, i.e. both gastric transit time and small bowel transit time are similar between the two groups [172–174].

3.7.5 Passive Permeability

Passive permeability was reported to be higher in obese individuals [180], however the method used to investigate the change was based on urine excretion of orally administered mannitol and lactulose without correction for the obesity-dependent increase in GFR. Therefore, it is not clear whether the higher concentration of mannitol and lactulose in urine are related to higher absorption or higher excretion.

3.8 Brain Weight and Blood Flow

Obesity can cause a small reduction in brain volume. One study observed an up to 2.4% reduction in grey matter volume in obese patients [181, 182]. Unfortunately, data gathered from the literature were insufficient to derive a descriptive equation, therefore the equation from Stader et al. [5] was taken and verified against the data of Young et al. [9]. On the other hand, only one study examined brain blood flow in obese individuals and it was found to decrease by 0.34 mL/100 g/min per BMI [183].

3.9 Muscle

3.9.1 Muscle Weight

The total skeletal muscle weight was calculated from the DEXA instrument data obtained from the NHANES database [24], following the approach proposed by Kim et al. [184]. A total of 3620 data points were analysed and compared against 413 MRI data [185]. The increase in muscle weight was about 24.7% for each 10 BMI units, up to a BMI of 40 kg/m^2, and 13.8% afterwards.

3.9.2 Muscle Blood Flow

Eleven studies investigated muscle blood flow in healthy and obese individuals, and a total of 361 data points were used for deriving the descriptive function [28, 41, 186–194]. The analysis revealed a decrease in blood flow relative to cardiac output, from 15.7 and 12.6% in healthy-weight males and females, respectively, to 13.4 and 10.7% in obese subjects and up to 11.9 and 9.5% in morbidly obese individuals, respectively.

3.10 Skeleton Weight and Blood Flow

The skeleton weight equation was derived from the body bone mineral content data gathered from the NHANES database [24] and verified against dissected skeleton weight data [195]. In accordance with the study by Dolan et al., skeleton weight increased proportionally with body height and body weight but decreased with higher percentages of

adipose mass [196]. On average, skeleton weight was 11 and 22% heavier in obese and morbidly obese individuals, respectively. No information regarding the effect of obesity on bone blood flow was available in the literature, therefore we assumed it was identical to the healthy population [5] and constant across BMI values.

3.11 Skin Weight and Blood Flow

Data on skin weight in obese individuals were lacking in the literature, therefore we took the equation suggested by Kerr [197] and compared it against a small dataset of 49 subjects aged between 22 and 94 years (we also included elderly patients since only a few data were available and they were not used for the development of the equation) [198]. Due to the lack of data on skin blood flow, we used the data measured in a wide cohort of Tunisian women; however, since the data were expressed as arbitrary units rather than mL/100 g/min, we applied the same slope to the calculated absolute blood flow, assuming no difference in slope between Caucasian and Berber populations [199, 200].

3.12 Other Organs

Additional organs were studied, with the following information being identified. Spleen weight increased from about 0.19 and 0.15 kg, in lean males and females, respectively, to 0.35 and 0.26 kg, respectively, in the morbidly obese [9–11, 23, 49]. Pancreas weight, which was derived using data from two studies, was found to increase about 1.2% at each BMI value [23, 201]. Lungs weight was constant across the BMI—on average, 1.38 kg in males and 1.14 kg in females [9–11, 23, 45, 78]. Only one study examined the change of thymus weight across body weight and reported a positive correlation between the two [202]. Data describing the weight change of gonads in obese subjects were missing from the literature and therefore it was assumed to be constant across body weights [16, 22].

Only two studies looked at pancreas blood flow in obese versus lean individuals and found that pancreas perfusion is lower in obese subjects [203, 204]. Calculation of pancreas blood flow is actually a novelty since it is derived from human data and not taken from the ICRP [16], which refers to the paper by Williams and Leggett, where they extrapolated pancreas blood flow from animal data [19].

Unfortunately, blood flow data were not available in the literature for spleen, thymus, and gonads and they were therefore assumed to be constant across BMI values.

Information regarding the weight of the lymphatic system in obese subjects was lacking. However, on the other hand, several studies showed that obesity can have a negative effect on the functionality of the lymphatic system [205]. In obese subjects, there was a reduction of about 30% in the capacity of the lymphatic system in removing macromolecules from adipose tissue [31].

Figure 7a, b provide an overall picture of how body composition, expressed as a percentage of organ weight, and organ haemodynamics, expressed as a percentage of cardiac output, change up to a BMI of 60 kg/m^2 in the general population.

3.13 Tissue Composition

To correctly estimate the partition coefficients of a drug, and thereby the volume of distribution, detailed information on tissue composition is essential. In the literature, information on lipid and protein fractions for each organ across different BMI values were missing; however, we found a few studies analysing the changes in TBW, extracellular body water (EBW), and intracellular body water (IBW) in obese subjects [88, 206–224]. The absolute TBW was found to increase with BMI (Fig. 8), but when normalized by body weight, obese subjects had a lower ratio compared with healthy-weight subjects. To verify the ability of the model to predict body water distribution, we multiplied the tissue composition factors [225] by the tissue volumes and compared the results against the literature data. By keeping the tissue composition factors constant across BMI values, TBW and IBW resulted in an overprediction, while EBW did not. We therefore adjusted the fractions by lowering the IBW by 0.52% for each BMI and increasing the neutral lipids by 0.52% for each BMI.

4 Discussion

PBPK modelling is increasingly used to investigate drug pharmacokinetics in special populations; thus, it is critical to develop repositories including anatomical, physiological, and biological parameters to inform PBPK frameworks and subsequently simulate drug disposition for the corresponding population.

A repository describing obese physiology was published by Ghobadi et al. in 2011 [7]; however since then, new data on anatomical, physiological, and biological parameters have been published. Additionally, in the previous work, the authors created two separate populations, one for the obese and one for the morbidly obese, therefore the continuous effect of obesity on parameters was not evaluated. Hence, we aimed to provide an updated repository on the physiological changes induced by different levels of obesity, together with continuous equations and their corresponding physiological variabilities, in order to predict system parameters within a BMI range of 18.5–60 kg/m^2.

Our analysis shows that obesity leads to a series of anatomical, physiological, and biological changes, some of
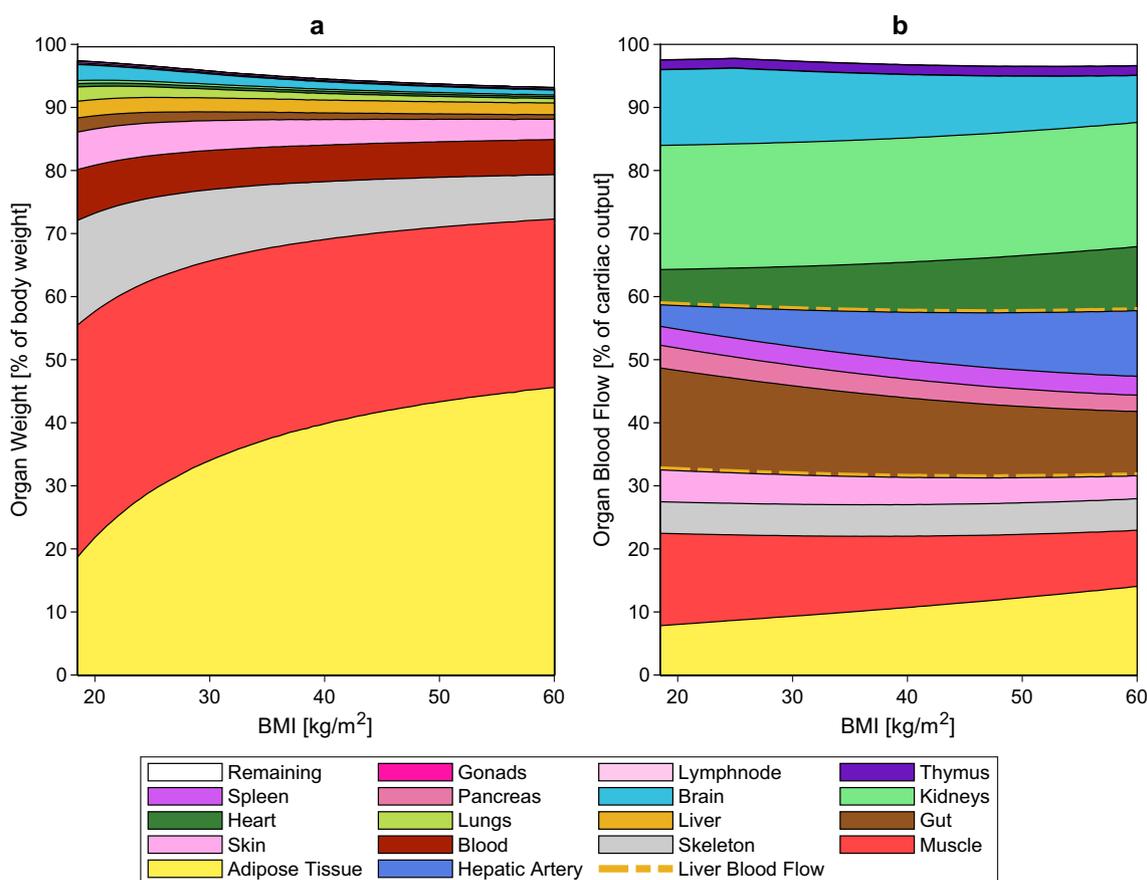
Fig. 7 Obesity-related changes in organ weights (**a**) and organ blood flows (**b**) in the general population. In panel (**b**), the area within the two dashed line corresponds to the liver blood flow. *BMI* body mass index

which are more relevant than others since they occur in organs responsible for drug elimination (liver and kidney) or absorption (gut), or in tissues critical for drug distribution (adipose and skeletal muscle tissues). The effects of obesity on the liver were found to be higher liver weight and absolute liver blood flow, lower MPPGL and HPGL, and decreased CYP3A4 enzyme abundance. Similarly, obesity resulted in higher kidney weight and greater absolute renal blood flow as well as GFR. These changes lead to higher renal excretion, as previously reported for drugs eliminated primarily by the kidneys [4]. In the long run, these changes may lead to the development of chronic kidney disease in some obese individuals [226]. Another effect of obesity impacting drug disposition is the increase in volume of distribution and half-life [227, 228]. This can be explained by the increase in adipose and skeletal muscle tissue, and lower blood perfusion of the adipose tissue; they act as reservoirs where the drug can initially accumulate and then release slowly over time. Another important parameter that influences drug distribution is tissue composition. We found that IBW was overpredicted by using constant tissue composition

factors, meaning that the fraction of IBW decreases at a higher BMI while lipid fraction in the cells tends to increase, as happens for the adipose tissue and the liver [229, 230]. However, studies investigating how each organ composition changes across different BMI values were not available in the literature.

Overall, rich datasets were available for almost all organ weights and for adipose, liver, and muscle blood flow; however, there was a paucity of data for organ weight and organ blood flow above BMI values of 60 and 40 kg/m², respectively. We therefore decided to stop the validity of the equations at a BMI of 60 kg/m². Additionally, it may not be useful to go beyond a BMI of 60 kg/m² since clinical trials in this subpopulation are difficult to find. For some parameters, limited information across the whole BMI range were reported in the literature. In particular, no data were available for MPPGL, HPGL, or HomPPGL, which are key parameters necessary to accurately perform the in vitro-in vivo calculations; even information on the abundance of enzymes and transporters were limited and sometimes contradictory. However, we filled these gaps by making physiologically
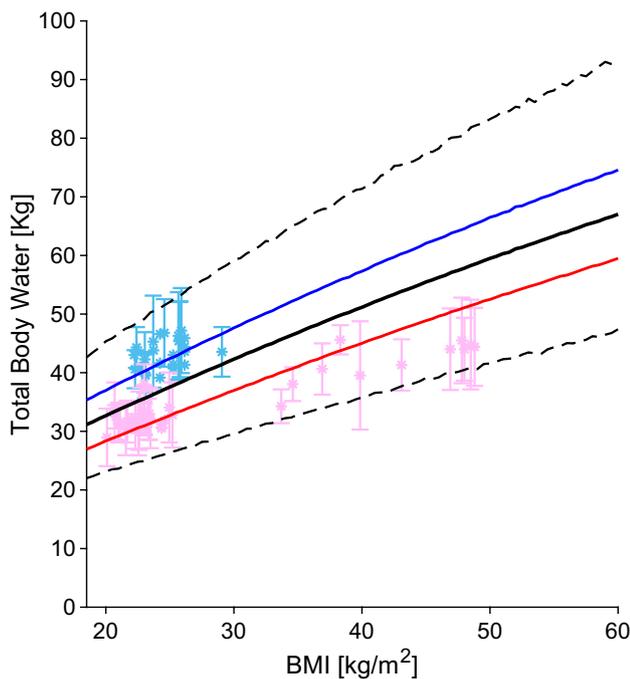
Fig. 8 Total body water relative to BMI. The blue, red and black lines represent the predicted mean of virtual male individuals, virtual female individuals and from all virtual subjects, respectively. The area within the two dashed lines represents the 99% normal range. Asterisks represent observed data from the development dataset. Male and female sex data points are represented in light blue and pink, respectively. Datapoints with multiple individuals are represented as mean ± SD. *BMI* body mass index, *SD* standard deviation

5 Conclusions

The developed repository provides up-to-date data on the anatomical, physiological, and biological changes induced by obesity. It highlights areas where knowledge gaps still exist and where further research is needed. Nonetheless, the derived continuous equations and the corresponding population variability in subjects with a BMI up to 60 kg/m^2 provide a good description of several key system parameters. Finally, this database is a valuable tool that can be added to existing PBPK models to investigate the pharmacokinetics and support informed decision making regarding optimal dosing regimens in this special population.

Declarations

Conflict of interest Mattia Berton, Sara Bettonte, Felix Stader, Manuel Battegay, and Catia Marzolini have no conflicts of interest to declare relevant to the contents of this study.

Ethics approval Not applicable.

Availability of data and material The data that support the findings of this study are available upon reasonable request to the corresponding author.

Code availability May be available upon reasonable request to the corresponding author.

Consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions MBe collected and analysed the data and wrote the first draft of the manuscript. SB contributed to the data analysis and writing of the manuscript. FS designed the study and supervised the data analysis. MBa provided clinical input. CM designed the study, supervised the data analysis and obtained the funding. All authors contributed to the critical review and approval of this manuscript.

plausible assumptions (e.g. to overcome the lack of MPPGL, HPGL, or HomPPGL in obese subjects, we kept their values constant and scaled them using only LLV. Overall, the population is robust up to a BMI of 40 kg/m^2 and less robust with a BMI between 40 and 60 kg/m^2 due to extrapolation of the organ blood flow (Figs. 1, 2, 3, 4, 5, 6).

Nowadays, the obese population represents about 13% of the worldwide population, and even if this represents a large proportion of individuals, clinical information on drug dosing, pharmacokinetics, or drug–drug interactions magnitude in this special population are still missing. This relates to the fact that obese individuals are often underrepresented in clinical trials. The current repository provides an updated description of the physiology of an obese population with a BMI up to 60 kg/m^2 by using continuous functions and physiologic variability for each parameter. It can be implemented in current PBPK models, enabling pharmacometricians to simulate difficult clinical scenarios in this special population and thereby filling the existing knowledge gaps around the magnitude of individualized drug therapy, drug disposition, and drug–drug interactions.

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