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ORIGINAL RESEARCH ARTICLE

Repository Describing an Aging Population to Inform Physiologically Based Pharmacokinetic Models Considering Anatomical, Physiological, and Biological Age-Dependent Changes

Felix Stader[1,2,3] · Marco Siccardi[4] · Manuel Battegay[1,3] · Hannah Kinvig[4] · Melissa A. Penny[2,3] · Catia Marzolini[1,3]

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Abstract

Background Aging is characterized by anatomical, physiological, and biological changes that can impact drug kinetics. The elderly are often excluded from clinical trials and knowledge about drug kinetics and drug–drug interaction magnitudes is sparse. Physiologically based pharmacokinetic modeling can overcome this clinical limitation but detailed descriptions of the population characteristics are essential to adequately inform models.

Objective The objective of this study was to develop and verify a population database for aging Caucasians considering anatomical, physiological, and biological system parameters required to inform a physiologically based pharmacokinetic model that included population variability.

Methods A structured literature search was performed to analyze age-dependent changes of system parameters. All collated data were carefully analyzed, and descriptive mathematical equations were derived.

Results A total of 362 studies were found of which 318 studies were included in the analysis as they reported rich data for anthropometric parameters and specific organs (e.g., liver). Continuous functions could be derived for most system parameters describing a Caucasian population from 20 to 99 years of age with variability. Areas with sparse data were identified such as tissue composition, but knowledge gaps were filled with plausible qualified assumptions. The developed population was implemented in Matlab® and estimated system parameters from 1000 virtual individuals were in accordance with independent observed data showing the robustness of the developed population.

Conclusions The developed repository for aging subjects provides a singular specific source for key system parameters needed for physiologically based pharmacokinetic modeling and can in turn be used to investigate drug kinetics and drug–drug interaction magnitudes in the elderly.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40262-018-0709-7) contains supplementary material, which is available to authorized users.

✉ Felix Stader
Felix.Stader@unibas.ch

1 Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital Basel, Basel, Switzerland

2 Infectious Disease Modelling Unit, Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland

3 University of Basel, Basel, Switzerland

4 Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Key Points

The developed repository provides a singular specific source of age-dependent anatomical, physiological, and biological system parameters required to inform physiologically based pharmacokinetic models.

The parameters and associated developed equations can be implemented into existing physiologically based pharmacokinetic frameworks and can be used to overcome sparse clinical data in subjects older than 65 years of age to investigate age-dependent changes in drug kinetics and drug–drug interaction magnitudes in silico.

These parameterized and informed physiologically based pharmacokinetic models for the elderly can provide more rational frameworks for dose adjustments to overcome drug–drug interactions.

1 Introduction

In recent years, the number of elderly people worldwide has increased substantially [1]. An "elderly" individual is defined as being above the age of 65 years [2], which is in line with the age of retirement in most Western countries. Older individuals are prone to multi-morbidities and hence polypharmacy and consequently drug–drug interactions (DDIs) [3–5]; however, there is no clear pharmacological or clinical definition of "elderly" [6]. Often, elderly subjects are excluded from clinical trials, resulting in a general lack of knowledge about the efficacy, safety, and kinetics of a drug at different ages [7]. There are certain age-dependent anatomical, physiological, and biochemical changes influencing drug kinetics including decreased kidney weight [8], reduced renal blood flow [9], reduced glomerular filtration rate [10], and reductions in liver volume and blood flow [11–13]. For other parameters such as enzyme and transporter abundance, or the concentration of plasma-binding proteins, data are limited, contradictory, or missing. In addition, it is difficult to investigate aging because other environmental and behavioral factors such as diseases, food, and smoking can have effects themselves or enhance the aging process [14].

Physiologically based pharmacokinetic (PBPK) modeling can help to overcome the lack of clinical data and to understand drug absorption, distribution, metabolism, and elimination at different ages. Furthermore, PBPK models predict DDI magnitudes in aging individuals and support more rational identification of dose adjustments to overcome DDIs. To develop a PBPK model, system data (where system refers to the population of interest, e.g., elderly) are required to inform the PBPK model. To generate reliable predictions, a comprehensive description of system characteristics is essential to fully represent the population of interest. To date, only two databases have been published to inform PBPK models for the elderly, of which one does not distinguish between ethnicities [15] and the other does not consider population variability and provides no descriptive functions of physiological and anatomical parameters [16].

The objective of this work was to collate and analyze data from the literature with the view to create a new comprehensive description of system characteristics for PBPK modeling and to address shortcomings of previous databases. The work focuses on parameters to inform a PBPK model for aging people that considers population variability, and to develop continuous functions describing physiological parameters of interest between 20 and 99 years of age for a Caucasian population.

2 Methods

2.1 Data Source

A structured literature search was performed using the MEDLINE database for age dependency of anatomical, physiological, and biological parameters required to inform a PBPK model for aging subjects. Keywords used were 'aging', 'elderly', or 'geriatric' plus the parameter of interest [S-Table 1 and S-Figure 1 of the Electronic Supplementary Material (ESM) for the investigated compartments of a PBPK model]. No restrictions were applied regarding the language or the publication year of the article. Abstracts were screened, and studies included if the study population were Caucasians, at least age had been reported in addition to the parameter of interest, and subjects were healthy or their disease/organ function was deemed unlikely to affect the parameter of interest such as the effect of chronic liver disease on brain blood flow [17]. Studies performed with North Americans and Australians were considered if at least 80% of the study population were of European heritage. Studies including subjects over the age of 65 years should at least report a mean age per age decade. The reference list of chosen articles was manually screened to identify further references.

2.2 Data Analysis

Data analysis was performed in Matlab® 2015b. Data were converted to consistent units and a normal distribution was assumed for each parameter to make published data comparable. If a study reported the median, minimum, and maximum, data were converted to the arithmetic mean and standard deviation according to Hozo et al. [18] and if the

interquartile range was given, the conversion was performed according to Wan et al. [19].

Collated data were separated into a development and verification dataset. Studies in the development dataset were required to report age, sex, body height, body weight, and ethnicity in addition to the parameter of interest as necessary covariates to describe correlations. Otherwise, studies with less reported covariates were used in the verification dataset. If at least three different studies covering the entire age range with at least one value in each age decade and all required covariates for the development dataset were available for a parameter of interest, the data were randomly separated into a development and a verification dataset. In the case of missing covariates such as anthropometric parameters in the verification dataset or cardiac output for regional blood flow analysis, the covariates have been estimated by the derived equations following the approach by Williams and Leggett [20]. The body surface area was calculated according to DuBois and DuBois [21].

We performed a weighted linear regression to derive descriptive continuous equations for the parameter of interest from 20 to 99 years considering age, sex, anthropometric parameters, location of the study, publication year, and methods of measurement as independent variables. Location was used as an independent variable to investigate if studies conducted in Europe, North America, and Australia can be combined without bringing a bias into the data. Publication year has been used to investigate differences in key parameters (e.g., body weight) over the last century and if different methods used at different times have an impact. Data obtained by different methods have only been pooled when there was no significant difference between methods.

Linear, polynomial, and exponential functions were investigated during the regression analysis. Covariates with a p value below 0.01 have been considered as significant. Visual and numerical regression diagnostic analyses were performed. The corrected Aikake's information criterion was used for numerical diagnostics to select the best fitted function [22]. Variability for each parameter was calculated as the weighted coefficient of variance (CV) of the development dataset for each individual mean and standard deviation and it was visually investigated whether age has an impact on variability. The variability of a parameter of interest is estimated by the variability of the covariates describing the parameter of interest and, if necessary, additional random variability to fully capture the observed variability.

The derived equations for all parameters necessary to describe a white population have been implemented in Matlab® and 1000 virtual men and women have been created and the estimated system parameters have been compared to the independent verification dataset. Normal distribution with the derived CV (Table 1) was used to describe the variability of the parameter of interest. Furthermore, it was analyzed if the sum of organ weights and regional blood flows does not exceed body weight and cardiac output.

3 Results

A total of 362 studies were found of which 318 studies were included in the analysis. Studies were mostly excluded because the age or ethnicity of the study population was insufficiently defined. Rich data were found for anthropometric parameters, adipose tissue, brain, heart, kidney, and liver. Data for some regional blood flows, such as to the bone, and in the general composition of tissues were difficult to obtain from the literature. Although including data for centenarians, most of the data were found for ages up to the mid-80s, identifying a general knowledge gap for very old individuals. Derived equations and the population variability expressed as the CV can be found in Table 1. Detailed information on the number of subjects in each age decade used in the development dataset (S-Table 2 of the ESM), the number of total studies in the development and verification dataset, the methods used to measure the parameter of interest, and the study location and the references (S-Table 4 of the ESM) can be found for each investigated parameter in the supplement.

3.1 Age and Sex Distribution

Data regarding age and sex distribution were taken from Eurostat [23] for all 28 member states of the European Union and the Federal Office for Statistics of Switzerland [24] (Fig. 1). The number of subjects in each age decade was found to be uniform between 20 and 59 years. The number of subjects declined from the age of 60 years, with only 2% of the Swiss population being above 90 years of age. A Weibull distribution with $\alpha = 1.55$ and $\beta = 61.73$ best described the age distribution. The proportion of women was found to be 50% of the population in Europe till the age of 69 years and increased to over 80% for very old Swiss subjects above the age of 100 years. In all the following equations, age is expressed in years and sex is either 0 for men or 1 for women.

3.2 Body Height and Body Weight

Anthropometric data of 106,698 Caucasians have been analyzed in the developmental dataset [24–70] and the derived equation has been verified with data from 14,096 subjects [71–86]. The mean body height of Caucasians aged 20–59 years was 178 cm for men and 166 cm for women with a sex-independent CV of 3.8%. Body height declined 2% per age decade from the age of 60 years (Fig. 2). The difference between men and women was

Table 1 Descriptive equations and population variability for anatomical, physiological, and biological parameters necessary to inform a physiologically based pharmacokinetic model. Virtual subjects from 20 to 99 years of age can be generated. Blood flows are relative to cardiac output (CO) and their variability is only propagated from CO

Parameter	Unit	Descriptive equation	CV [%]
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	$-0.0039 \times \text{Age}^2 + 1.12 \times \text{Body height} + 0.611 \times \text{Age} - 0.424 \times \text{Sex} - 137$	15.2
Lung weight	kg	$e^{(0.028 \times \text{Body height} + 0.0077 \times \text{Age} - 5.6)}$	0
Adipose tissue weight	kg	$0.68 \times \text{Body weight} - 0.56 \times \text{Body height} + 6.1 \times \text{Sex} + 65$	29.6
Bone weight	kg	$e^{(0.024 \times \text{Body height} - 1.9)}$	13.2
Brain weight	kg	$e^{-0.0075 \times \text{Age} + 0.0078 \times \text{Body height} - 0.97}$	9.0
Gonad weight	kg	$-0.00034 \times \text{Body weight} - 0.00022 \times \text{Age} - 0.03 \times \text{Sex} + 0.072$	34.8
Heart weight	kg	$0.34 \times \text{BSA} + 0.0018 \times \text{Age} - 0.36$	17.9 (m), 22.7 (f)
Kidney weight	kg	$-0.00038 \times \text{Age} - 0.056 \times \text{Sex} + 0.33$	19.3 (m), 23.2 (f)
Muscle weight	kg	$17.9 \times \text{BSA} - 0.0667 \times \text{Age} - 5.68 \times \text{Sex} - 1.22$	11.8
Skin weight	kg	$e^{(-0.0058 \times \text{Age} - 0.37 \times \text{Sex} + 1.13)}$	8.3
Thymus weight	kg	0.0221	44.8
Gut weight	kg	$3E^{-06} \times \text{Body height}^{2.49}$	7.3
Spleen weight	kg	$e^{1.13 \times \text{BSA} - 3.93}$	51.7
Pancreas weight	kg	0.103	27.8
Liver weight	kg	$e^{(0.87 \times \text{BSA} - 0.0014 \times \text{Age} - 1.0)}$	23.7
Blood weight	kg	$e^{(0.067 \times \text{BSA} - 0.0025 \times \text{Age} - 0.38 \times \text{Sex} + 1.7)}$	10.4
CO	L/h	$159 \times \text{BSA} - 1.56 \times \text{Age} + 114$	21.1
Adipose tissue blood flow	% of CO	$(0.044 + 0.027 \times \text{Sex}) \times \text{Age} + 2.4 \times \text{Sex} + 3.9$	
Bone blood flow	% of CO	5	
Brain blood flow	% of CO	$e^{-0.48 \times \text{BSA} + 0.04 \times \text{Sex} + 3.5}$	
Gonad blood flow	% of CO	$-0.03 \times \text{Sex} + 0.05$	
Heart blood flow	% of CO	$-0.72 \times \text{Body height} - 10 \times \text{Sex} + 134$	
Kidney blood flow	% of CO	$-8.7 \times \text{BSA} + 0.29 \times \text{Body height} - 0.081 \times \text{Age} - 13$	
Muscle blood flow	% of CO	$-6.4 \times \text{Sex} + 17.5$	
Skin blood flow	% of CO	5	
Thymus blood flow	% of CO	1.5	
Gut blood flow	% of CO	$2 \times \text{Sex} + 14$	
Spleen blood flow	% of CO	3	
Pancreas blood flow	% of CO	1	
Liver blood flow	% of CO	$-0.108 \times \text{Age} + 1.04 \times \text{Sex} + 27.9$	
Albumin	g/L	$-0.0709 \times \text{Age} + 47.7$	7.9
GFR	mL/min	$e^{-0.0079 \times \text{Age} + 0.5 \times \text{BSA} + 4.2}$	14.7

BSA body surface area, *CV* coefficient of variance, *GFR* glomerular filtration rate, *m* indicates male and *f* indicates female, when there was a sex-related difference in the CV

constant at all age ranges. Location was found to be a significant variable during regression, with a lower height observed in Southern Europe, and an exclusion of data reported from Portugal, Spain, and Italy that led to a non-significance of location.

The mean body weight of a Caucasian aged 20–49 years was 79.9 kg for men and 64.1 kg for women with a CV of 15.7% (Fig. 2). Body weight increased in subjects in the fifth and sixth age decade by about 4% and decreased afterwards by about 10% in each age decade. In women, the decline started one age decade later than in men. In contrast to body height, location was not significant for body weight, but publication year was with a significant increase since 2000.

3.3 Liver

3.3.1 Liver Weight

Liver is the major organ of metabolism. Liver weight was analyzed from over 3000 subjects [29, 41, 51, 52, 55, 69, 72, 78, 87, 88] and was found to be on average 1.78 kg in men and 1.49 kg in women with a CV of 23.7% till the age

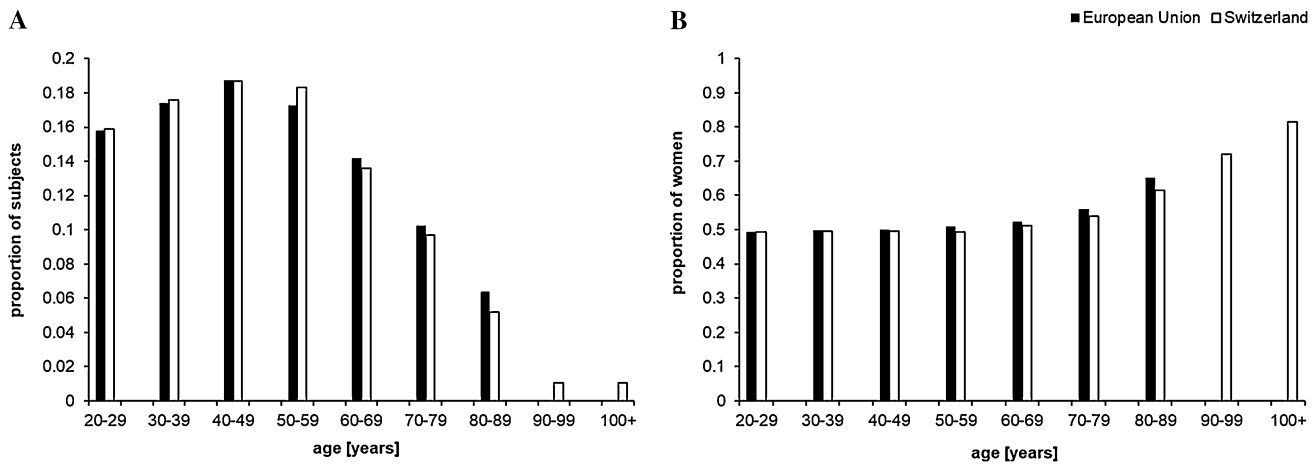

Fig. 1 Proportion of subjects (**a**) and proportion of women (**b**) per age decade. Data are from the 28 member states of the European Union (black bars) and Switzerland (white bars)

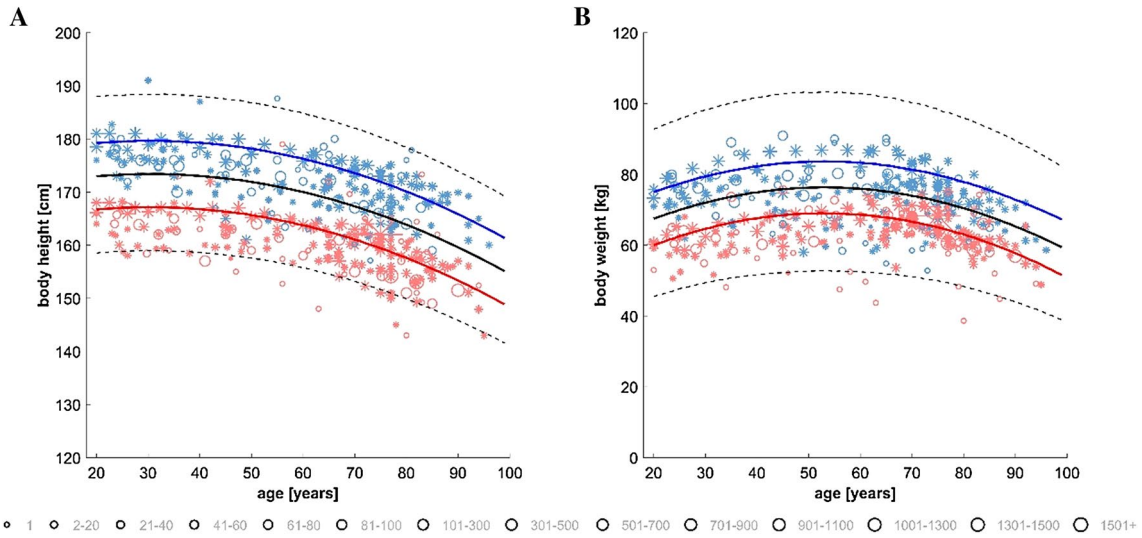

Fig. 2 Body height (**a**) and body weight (**b**) per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. The size of the stars and circles indicates the size of the studied population

of 65 years. Thereafter, liver weight decreased by 10–15% in women per age decade reaching 1.03 kg at the age of 100 years. The decrease in men was around 20% per age decade reaching 1.01 kg on average in 90-year-old individuals (Fig. 3).

3.3.2 Liver Blood Flow

Absolute total liver blood flow decreased by 60% between 60 and 90 years of age in men and women, but relative to cardiac output the changes were only significant between 90 and 100 years of age [13, 89]. The age-dependent changes in total liver blood flow might come from changes of the splanchnic blood flow [77, 89–94], explaining observed differences in the first-pass effect between young and old subjects [95–97]. The hepatic arterial blood flow appears to be constant with age [20, 89, 98].

3.3.3 In Vitro–In Vivo Extrapolation Factors

Physiologically based pharmacokinetic models are informed by in vitro-in vivo extrapolation, meaning that for instance the in vivo clearance is extrapolated from measured in vitro data. Hepatic scaling factors such as hepatocellularity or microsomal proteins per gram of liver are needed [99]. Barter et al. reported age-dependent equations for hepatocytes

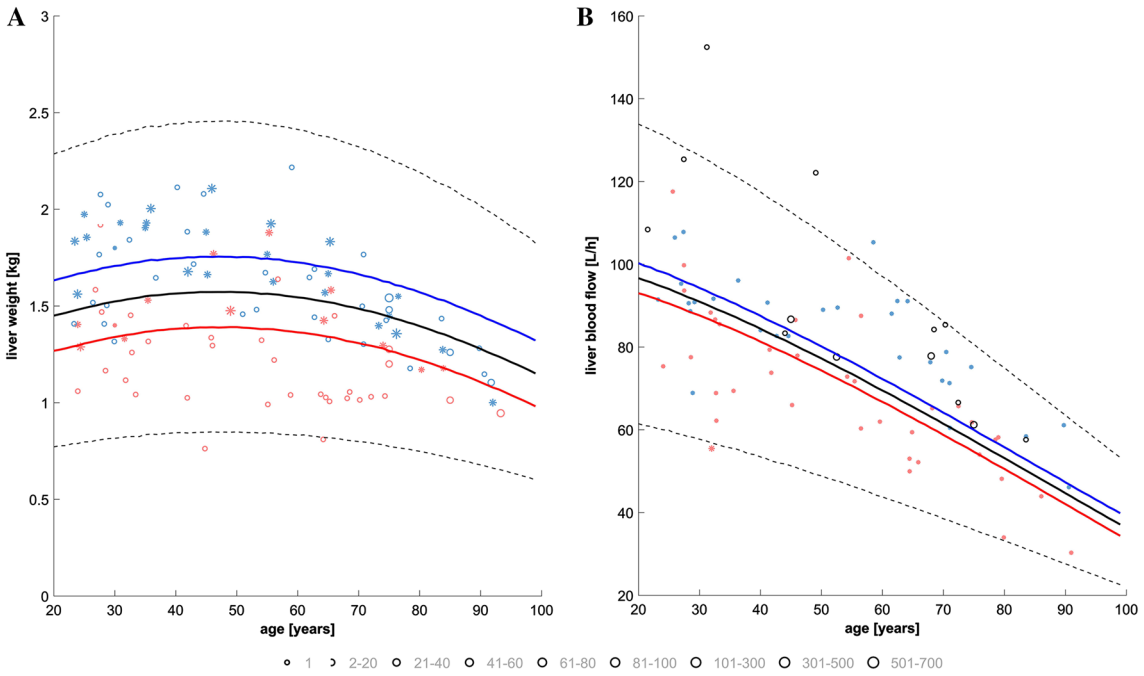

Fig. 3 Liver weight (**a**) and liver blood flow (**b**) per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. Black circles represent data from an undefined sex population. The size of the stars and circles indicates the size of the studied population

per gram of liver [100] and microsomal proteins per gram of liver [101] with the oldest individuals in the analysis being between the mid-70s and the early 80s.

3.3.4 Hepatic Enzyme Activity

Studies concerning the age dependency of hepatic cytochrome P450 (CYP) enzyme activity are sparse and contradictory. The biggest challenge is the high variability in hepatic CYP enzyme abundance [102, 103] and the small sample size generally used for analysis [104, 105]. In a recent large meta-analysis investigating hepatic CYP abundance to inform PBPK models, age was only a significant covariate for CYP2C9 [103]. It is worthwhile mentioning that the different genotypes known for CYP2C9 increase the sample size needed to identify age dependency even further. A significant age dependency was detected for CYP1A2, CYP2D6, and CYP2E1 in a different study, but not for CYP2C9 [106]. In a third study, CYP1A2 activity was reported to be independent of age [107]. Cytochrome P450 3A4 activity is consistently reported to be independent of age between different studies [108–110].

Polasek et al. investigated drug clearances in the elderly for probe substrates such as caffeine (CYP1A2), warfarin (CYP2C9), phenytoin (CYP2C19), desipramine (CYP2D6), and midazolam (CYP3A4) and found a clearance decrease of 30–40% in 70-year-old subjects compared with young individuals, which can be explained by the decline in liver volume and blood flow rather than hepatic CYP enzyme activity [111]. In addition, inflammation affects CYP enzyme activity [112], making it difficult to analyze data from the non-healthy elderly.

UGT enzyme activity is reported to be independent of age in the literature [106, 113–115]. Taken together, this lack of evidence and data to inform age dependency necessitates a more judicious approach assuming no age-dependent hepatic enzyme activity and thus assuming the same values in aging subjects as in young individuals.

3.3.5 Hepatic Drug Transporter Activity

Recently, a compact meta-analysis about hepatic drug transporter abundance to inform a PBPK model was published and age was tested as a covariate in the analysis and was reported to be not significant for any hepatic drug transporter [116]. In a PBPK model, we are interested in activity rather than abundance because the activity of enzymes and drug transporters can explain the observed data. If the abundance of transporters does not change, there might still be an age-dependent difference in transport activity; however, these data are currently not available. Comparable to hepatic

enzymes, it is therefore recommended to use the same activity in the elderly as in young subjects.

3.4 Kidney

3.4.1 Kidney Weight

The literature search yielded nine different studies with a total of 1620 data points measuring kidney weight after autopsy [29, 41, 42, 51, 52, 55, 69, 78, 85] (Fig. 4a). The average kidney weight in young male and female individuals was 0.318 kg with a CV of 19.3% and 0.259 kg with a CV of 23.2%, respectively. The reduction in kidney weight increased with age starting from 5% at the age of 70 years to 15% at the age of 80 years to 25% up to the age of 100 years in both sexes.

3.4.2 Kidney Blood Flow

Absolute kidney blood flow decreased by 5–10% per age decade till the age of 65 years and thereafter decreased by 25% per age decade (Fig. 4b) [77, 90, 94, 117–125]. Kidney blood flow relative to cardiac output was 19.7% in young men and decreased to 11.9% at the age of 85 years. The decrease was 5–20% per age decade. In women, the average kidney blood flow relative to cardiac output was 16.5% and stayed constant till the age of 70 years. Thereafter, it decreased to 9.2% at the age of 85 years.

3.4.3 Glomerular Filtration Rate

Only studies using inulin or ^{51}Cr-EDTA as a biomarker for the glomerular filtration rate have been considered in this work [117–123, 125–129]. Equations to estimate the glomerular filtration rate such as the Cockcroft–Gault [10] and the Modification of Diet in Renal Disease [130] use serum creatinine, which is problematic considering senile sarcopenia in aging subjects [131]. The average glomerular filtration rate was between 130 and 140 mL/min in men aged between 20 and 50 years and around 120 mL/min in women of the same age. In the fifth age decade, the glomerular filtration rate declined in men to 115 mL/min, which was like the value in women (112 mL/min). Afterwards, the decline in the glomerular filtration rate was roughly 10% per age decade independent of sex reaching 50% of the value of a young adult at the age of 90 years (Fig. 4c).

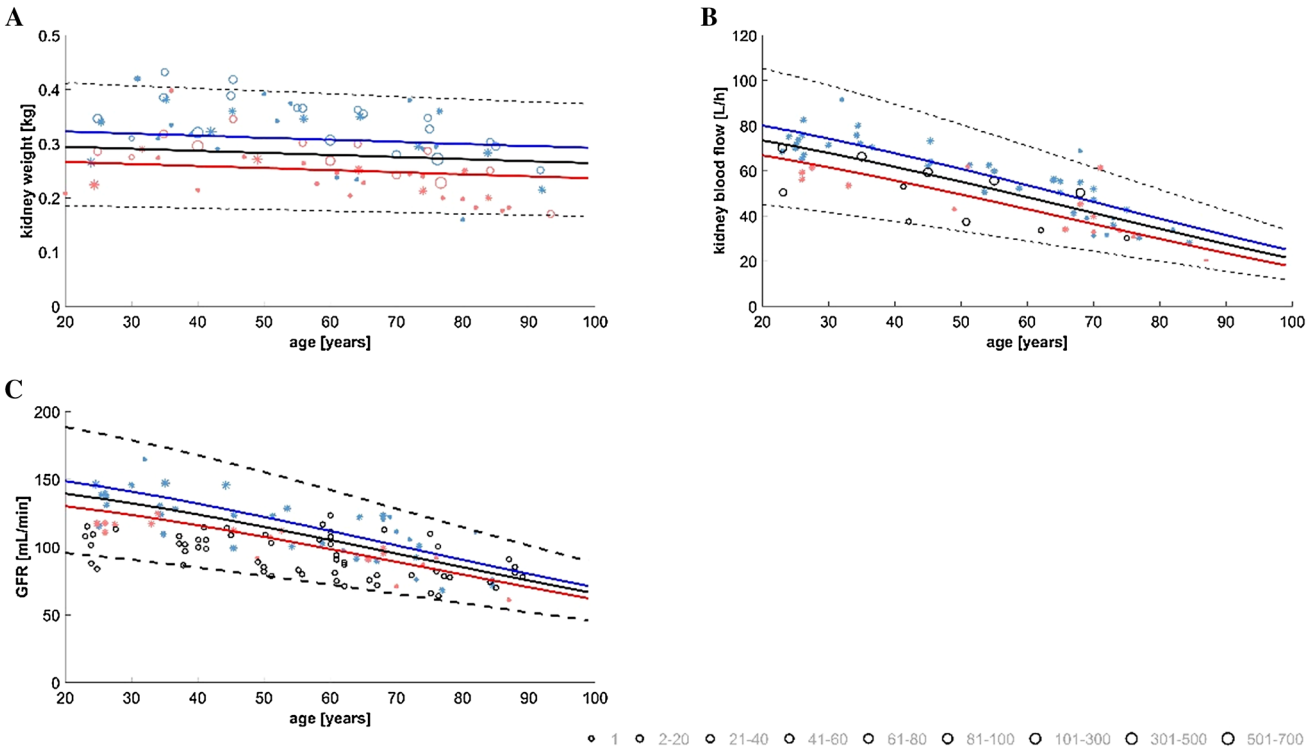

Fig. 4 Kidney weight (**a**), kidney blood flow (**b**), and glomerular filtration rate (**c**) per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. Black circles represent data from an undefined sex population. The size of the stars and circles indicates the size of the studied population

3.5 Adipose Tissue

3.5.1 Adipose Tissue Weight

Adipose tissue weight is usually measured via X-ray absorptiometry and bioelectric impedance analysis. Data from 18 different studies from 12,323 subjects were available for the development dataset [25, 26, 36, 37, 41, 42, 45–48, 57, 59, 60, 62, 65, 68, 73, 132]. In young men, adipose tissue weight was on average 17.8 kg with a CV of 24%. It increased by 5–10% per age decade to 22.9 kg at the age of 70 years. The CV increased to 28%. In young women, adipose tissue weight was found to be 17.3 kg with a CV of 29%. Between 20 and 70 years of age, adipose tissue weight increased to 25.2 kg with a CV of 37% in women and decreased again to 21.9 kg with a CV of 37% at the age of 85 years.

3.5.2 Adipose Tissue Blood Flow

Adipose tissue blood flow increased from 5% in young male individuals to 9% in aged male individuals and from 8% in young female individuals to 10% in aged female individuals [133, 134].

3.6 Muscle

3.6.1 Muscle Weight

Data from 11 different studies with 5542 participants were available to analyze muscle weight, which was measured by X-ray absorptiometry and bioelectrical impedance analysis [26, 41, 42, 45, 50, 64, 73, 79, 81, 83, 132]. The average muscle weight was 32.0 kg in men aged 20–65 years and 19.8 kg in women of the same age. Muscle weight decreased by 10% per age decade between 65 and 100 years. The CV was 11.8% and was similar for male and female individuals.

3.6.2 Muscle Blood Flow

Only sparse data concerning muscle blood flow have been found in the literature, which do not cover all age decades but suggest 17.5% of cardiac output in men and 11.1% in women [135–138].

3.7 Brain

3.7.1 Brain Weight

Brain weight was analyzed by using data from eight different studies with 2425 participants [29, 41, 42, 51, 52, 55, 78, 139] and was found to be independent of age. The average brain weight was 1.39 kg in male individuals and 1.28 kg in female individuals with a sex-independent CV of 9%.

3.7.2 Brain Blood Flow

The literature search yielded 12 different studies with 956 participants for brain blood flow [140–151]. Brain blood flow relative to cardiac output was 11.8% in men and 15.6% in women below the age of 40 years and increased to 15.6% in men and 16.3% in women in the fourth age decade and was constant thereafter.

3.8 Heart

3.8.1 Heart Weight

Heart weight was analyzed using data from ten different studies measuring heart weight after autopsy [29, 41, 42, 53, 55, 61, 69, 78, 152, 153] and increased in both male and female individuals, from 0.325 kg and 0.241 kg at the age of 25 years to 0.390 kg and 0.317 kg in the ninth age decade.

3.8.2 Heart Blood Flow

Blood flow to the heart relative to cardiac output increased from 5.5% at the age of 25 years to 12% at the age of 85 years in men and from 4.3% at the age of 25 years to 11.3% at the age of 70 years in women [154–159].

3.8.3 Cardiac Output

Cardiac output is the volume of blood being ejected by the heart per minute. Data from 12 studies involving 645 subjects were used to analyze cardiac output [39, 63, 70, 74, 77, 84, 90, 94, 135, 138, 160, 161]. Cardiac output decreased from 352 L/h in 30-year-old male individuals and 312 L/h in young female individuals between 5 and 10% every age decade to 258 L/h in aged male individuals and 201 L/h in aged female individuals (Fig. 5). The CV was similar between both sexes with a value of 21.1%.

3.9 Blood

3.9.1 Blood Weight

Blood weight was analyzed from seven different studies with 382 male and 179 female participants [27, 30, 31, 44, 66, 75, 162]. In young male individuals, blood weight was 5.8 kg with a CV of 10% and decreased to 5.0 kg at the age of 90 years (Fig. 6). In young women, blood weight was lower with 3.8 kg, but stayed constant over different age decades.

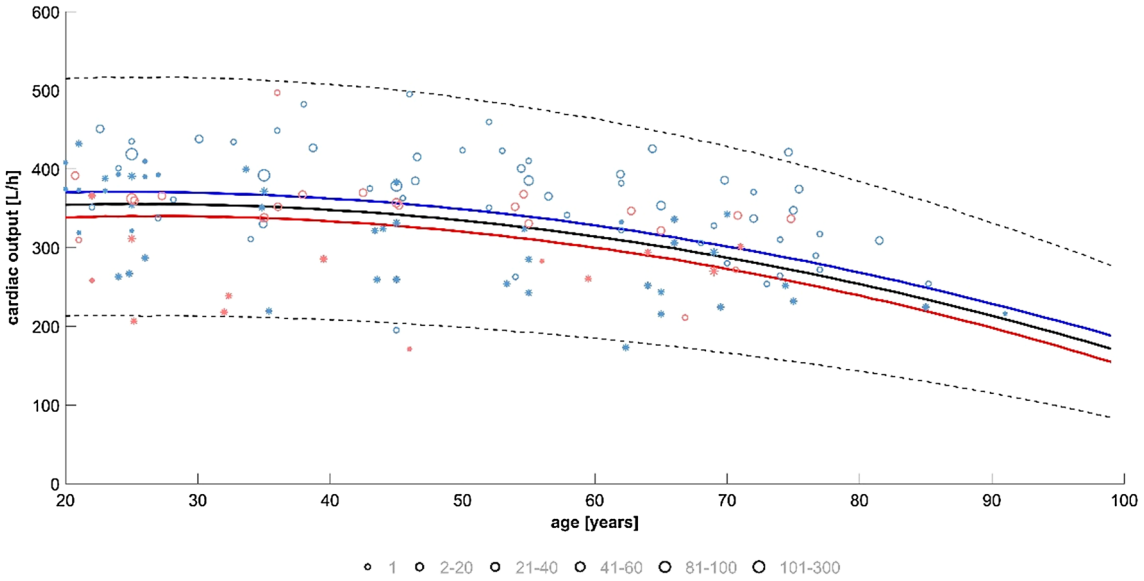

Fig. 5 Cardiac output per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. The size of the stars and circles indicates the size of the studied population

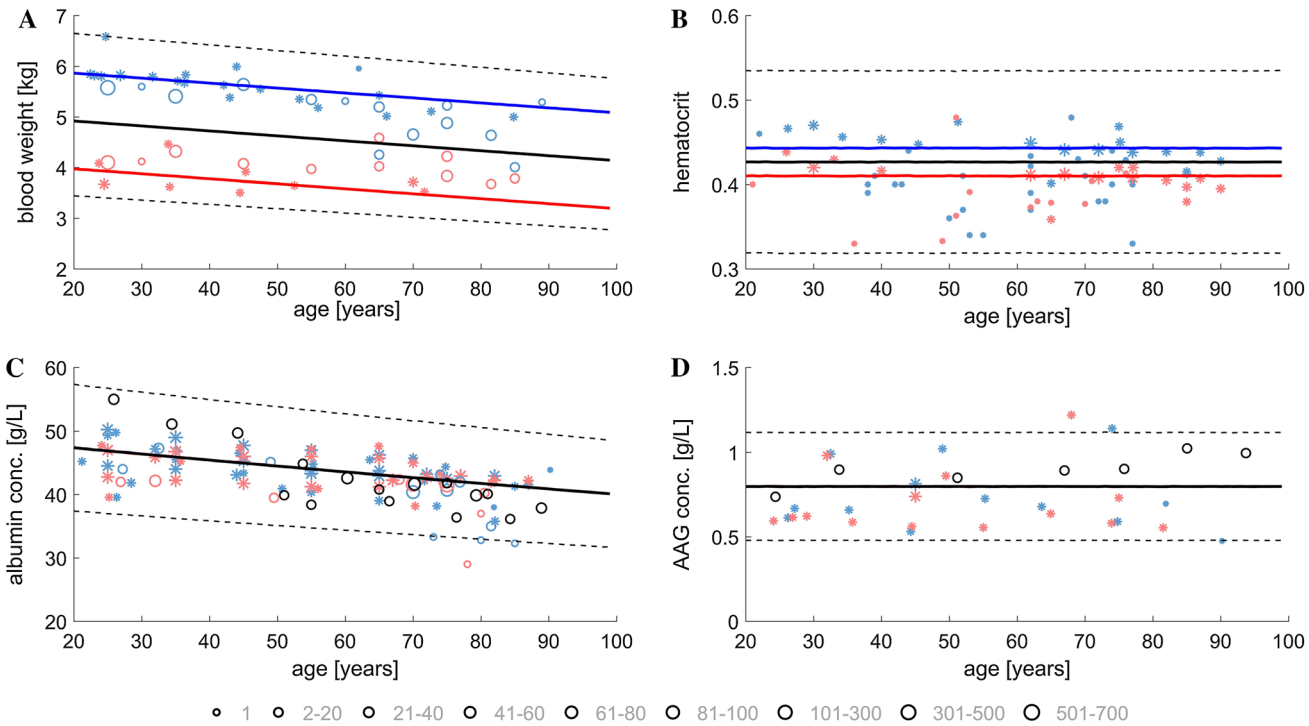

Fig. 6 Blood weight (**a**), hematocrit (**b**), albumin (**c**), and alpha-acid glycoprotein (**d**) level per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. Black circles represent data from an undefined sex population. The size of the stars and circles indicates the size of the studied population

At the age of 70 years, female blood weight was still 3.7 kg; the CV was the same as in male individuals.

3.9.2 Hematocrit

Hematocrit and the level of albumin and alpha-acidic glycoprotein were the blood parameters analyzed (Fig. 6). Data of 1752 subjects aged 21–90 years were available to analyze hematocrit [122, 142, 163–168]. Sex was the only significant covariate. Mean values were 0.443 ± 0.064 for men and 0.410 ± 0.063 for women.

3.9.3 Plasma-Binding Protein Level

Alpha-acidic glycoprotein showed no significant covariate when analyzing data of 472 subjects aged 24–90 years from five different studies [169–173]. The mean value was 0.798 g/L with a CV of 24.3%.

Regression analysis of albumin yielded age as a significant covariate [169, 174–181] with an overall CV of 7.9%. Albumin level declined about 1.5% in each age decade. Malnutrition and acute illnesses, both occurring often in the elderly, can have a significant impact on the analysis of age-dependent albumin levels [172, 174, 179]. Therefore, only data from apparently healthy subjects have been used in the analysis.

3.10 Other Organs

Other organs such as the spleen and pancreas are not described in detail here, but the descriptive equations to describe an aging Caucasian population can be found in Table 1 and more detailed information can be found in the ESM (S-Tables 2–4). Organs that have not been considered in the model are combined in a remaining organ compartment. Their weight and blood flow are calculated as the sum of all organ weights/regional blood flows subtracted from the body weight/cardiac output (S-Figure 2 of the ESM).

3.11 Tissue Composition

Tissue composition is an important parameter to predict the distribution of drugs into tissues in a PBPK model. Data regarding the composition of lipids and proteins of tissues are generally sparse in humans and no age dependency was found in the literature, but total body water, total extracellular water, and total body cell mass have been reported in aging subjects [26, 37, 65, 182–190]. Age-independent fraction of tissue volumes [191] coupled with age-dynamic tissue volumes has been used to calculate the vascular and interstitial space of tissues (representing the extracellular water) and the intracellular space minus the intracellular water (representing the cell mass). Organ densities to convert organ weight obtained from the derived functions to volumes have been used from the International Commission on Radiological Protection database [192, 193]. The weighted mean of the organ density and the fraction of tissue compositions of investigated organs was used for the remaining organ. The values of all tissues have been summed and compared against the observed data (Fig. 7). The prediction of total body water and total cell mass was well in agreement with the observed data, leading to the conclusion that the assumptions made were adequate to inform a PBPK model.

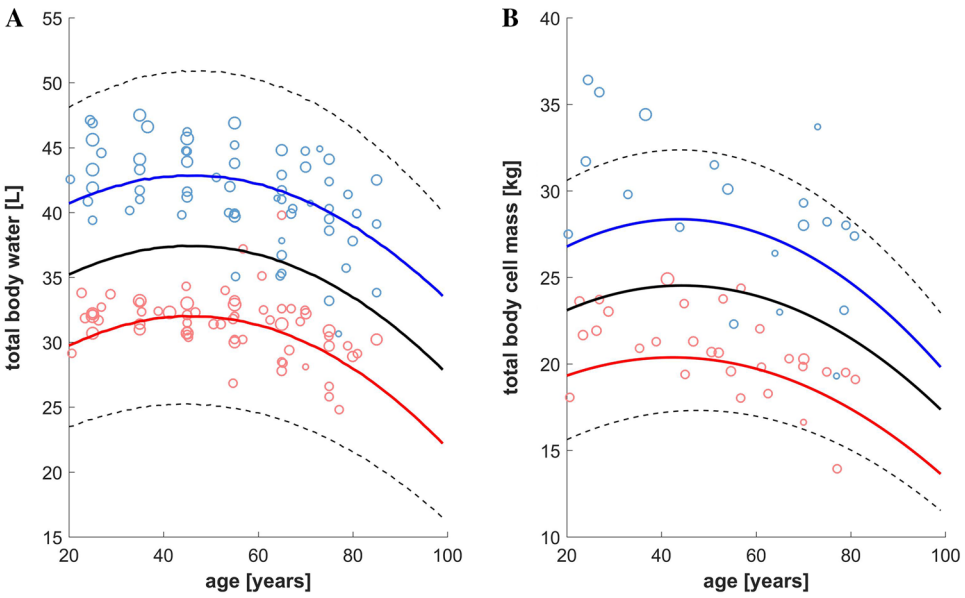

Fig. 7 Total body water (**a**) and total body cell mass (**b**) per age decade in an aging population. The blue, red, and black lines represent the predicted mean of virtual male individuals, virtual female individuals, and from all virtual subjects, respectively. The dashed lines represent the 5 and 95% percentiles of the predictions. Stars show observed data from the development and circles represent observed data from the independent verification dataset. The size of the stars and circles indicates the size of the studied population

3.12 Parameters Affecting Drug Absorption

Physiological parameters having an impact on drug absorption are gastric pH, gastric emptying and small intestine transit time, the surface area available for absorption, and intestinal enzyme and drug transporter abundance.

3.12.1 Gastric pH

One study compared gastric pH in the fasted and fed state between 24 young healthy volunteers aged 21–35 years [194] and 79 subjects aged 65–83 years [195]. The study reported a significant age-dependent difference between the median pH in the fasted state (interquartile range) with 1.72 (1.08–2.34) in the young group and 1.28 (0.90–5.60) in the aged group. The variability appeared to be much greater in older individuals, but the difference in sample size needs to be kept in mind. Another study in young subjects below the age of 65 years found a median fasted pH of 1.45 [196]. To conclude, it is doubtful if there is an age dependency of gastric pH in the fasted state and more data need to be generated and included in the meta-analysis to judge the age effect properly. Gastric pH in the fed state was not significantly different between young and elderly subjects [194, 195], but the decline of gastric pH from the fed to the fasted state was exponential with a half-life of 1.8 h (CV: 65%) in young subjects and was linear with a half-life of 3.0 h (CV: 80%) in aging subjects [195]. Eight percent of Caucasians are achlorhydric, meaning they do not secret hydrochloric acid in the gastric juice [197] and thus have a gastric pH at a fasted state of 7.1 [195]. In Japanese individuals, the number of achlorhydric subjects increases with age [198], but this appears not to be the case in healthy aging Caucasians [195].

3.12.2 Gastric Emptying Time

Reports in the literature about gastric emptying time are contradictory. Some studies report a slower gastric emptying time [199, 200] in aging subjects, some report no changes [201, 202], and some report a faster rate [203, 204]. Many influencing factors exist for gastric emptying time such as gastric pH [205], particle size [203], and food [202, 203, 206], making it difficult to analyze age dependency. Furthermore, gastric emptying has a circadian rhythm, making a difference if the study is conducted in the morning or in the evening [207]. Two studies have investigated gastric emptying time after fluid and food intake in young controls and aging subjects [206, 208]. Both studies used the same marker and the same method and both started in the morning. Gastric emptying time was different between fluids and food but did not show any age dependency, which was verified by the regression analysis. Therefore, it is recommended to use the same gastric emptying time in aging subjects as in young individuals.

3.12.3 Small Intestine Transit Time

Small intestine transit time appears to be independent of age and a fixed value can be used to inform a PBPK model [209, 210].

3.12.4 Passive Permeability

The mucosal area is reported to decline with age [211, 212], but enterocytes and villi appear to be unchanged [212]. Malnutrition, disease, and drug intake could alter the mucosa and need to be carefully considered when investigating age dependency. Passive permeability was reported to be impaired in aging subjects [211], but two studies investigating mannitol and lactulose, two carbohydrates that are passively absorbed, showed no difference in passive permeability between young controls and aging subjects after correcting the data for the age-dependent decline in the glomerular filtration rate [213, 214]. It is therefore assumed that neither the surface area available for passive diffusion nor the rate of passive diffusion differs in aging subjects compared to young individuals.

3.12.5 Intestinal Enzyme and Drug Transporter Abundance

Data regarding intestinal enzyme and drug transporter abundance are generally sparse and therefore age dependency cannot be analyzed sufficiently.

4 Discussion

The described population database for aging subjects summarizes anatomical, physiological, and biological system parameters required to inform PBPK modeling. Descriptive continuous functions for systems parameters from the age of 20–99 years have been derived and verified with observed data extracted from the peer-reviewed literature. Population variability was considered for each parameter.

Two previous databases have been described in the literature for aging individuals. Thompson et al. gathered extensive data from the literature, but the authors did not consider different ethnic groups and combined data from Caucasians, Latin-Americans, and Asians [15]. However, it is known that ethnicity can have a significant impact on system parameters, for instance hepatic enzyme abundance, and therefore on clearance prediction [215]. Schlender et al. recently published a database for elderly individuals further processing the data from Thompson

et al. for Caucasians only [16]. A limitation of this study is that only values for organ weight and blood flow for each age decade were considered, making it difficult to extrapolate to other ages of interest. Furthermore, population variability of system parameters was not considered by Schlender et al., which is an essential element for reasonable predictions of drug kinetics using PBPK models [216].

One notable novelty of the presented repository for Caucasian subjects is the derived continuous functions that allow prediction for a population from 20 to 99 years of age. The advantage of continuous functions is the creation of only one population with one distinct value at a certain age. If two separated populations would have been built with one representing young subjects from 20 to 65 years and one representing elderly individuals from 65 to 99 years, there would be two separated equations calculating system parameters at the age of 65 years, which might lead to un-physiological steps. Another advantage for the prediction of monoclonal antibody kinetics or long-term drug therapies could be to introduce time-varying physiology [217], meaning that subjects age during the time of the simulation.

A few limitations need to be acknowledged. Data from individuals over the age of 85 years are sparse (S-Table 2 of the ESM), meaning the derived equations could be less robust and extrapolation to older ages might be difficult. However, data for centenarians have been included for some system parameters [78] and were adequately estimated by the derived functions. Clinical studies are usually not performed in very old individuals, making it impossible to verify the described population by analyzing drug kinetics. It is therefore recommended to use the described repository with caution at older ages. This holds particularly true for regional blood flows to adipose tissue, heart, muscle, and skin because almost no geriatric data are currently available in the literature.

Another area with sparse data, where more research is needed in the future, is tissue composition, as it is important to predict the distribution into tissues accurately. It was shown that the assumptions used in this work are plausible for total body water and cell mass (Fig. 7); however, an exception for single tissues cannot be excluded and data for lipid composition in the elderly were generally not found in the literature.

The analysis of system parameters to inform a PBPK model for aging Caucasians was complicated by the fact that some studies combine age groups together, meaning individuals aged 65–100 years might have been included, but only a mean age is given. This can lead to a bias in the data and hinders the characterization of age-dependent changes. Reports that insufficiently described age should generally be excluded unless no other data are available. Furthermore, ethnicity, particular in European studies, is not always clearly defined and needs to be assumed from the given study location.

Predictions of system parameters become more robust when model parameters are correlated with each other and co-variability can be described [218, 219]. To obtain such descriptive correlations, studies need to report important covariates, which is unfortunately not always the case. Weighted regression analysis has been used to correlate parameters and to receive a more robust aging population. Linear regression can only describe linear relationships; however, using data transformation such as the logarithm might compensate. Using regression, it is easy to overfit and model the noise in the data rather than the relationship between the parameters. In this work, the corrected Akaike's information criterion was used to select the best performing function among those tested, which is in contrast to the coefficient of determination that exhibits no bias to higher parameterized models. Another limitation of the regression analysis is its sensitivity towards outliers. Visual inspection of the estimated mean and variability of each parameter compared to observed data in this work did show an adequate fit for all investigated parameters (Figs. 2, 3, 4, 5, 6, 7).

The evaluation of variability was further complicated by being unable to set boundaries for publication year and study location. For a few parameters, for instance blood weight, data were only available from specific regions (e.g., USA) and from the 1950s. Both location and publication year have therefore been used as independent variables during regression and their impact has been quantified when sufficient data were available. Body height and body weight are key parameters to describe a population adequately and data from 106,698 individuals were available. Location was found to have an impact on body height, with a lower height correlated with Southern Europe. Otherwise, location was not a significant covariate for any variable and therefore combining data of studies conducted in Europe, USA, and Australia appears not to bring a bias into the data. However, the derived equations should not be used to predict aging African or Asian individuals as aging processes might be different. Publication year had a significant impact on body weight, showing a weight increase particularly in the last 10 years. Consequently, the developed population will require constant updates to include future potential changes such as body weight.

A challenge when studying older individuals is that the definition of elderly is not universal. The World Health Organization specifies elderly as being above the age of 65 years [2], which is in accordance with the age of retirement in most Western countries, but a clear pharmacological or clinical age cut-off is missing [6]. For some patient groups, such as people infected with human immunodeficiency virus, the age cut-off is even as early as 50 years [220]. We compared organ parameters important for drug

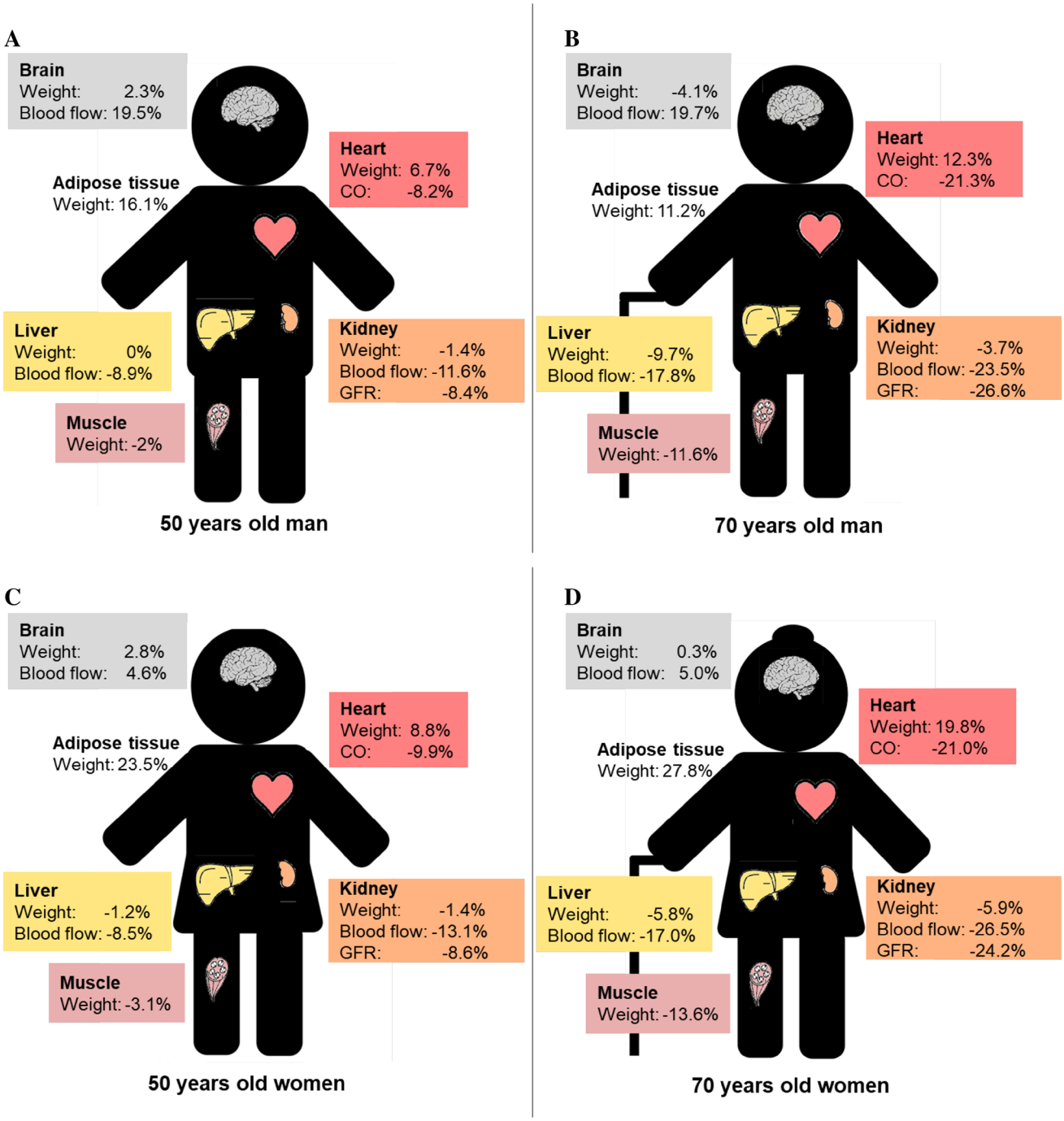

Fig. 8 Comparison of a 50-year old man and a 70-year-old man (**a**, **b**) and a 50-year-old woman and 70-year-old woman (**c**, **d**) with a 30-year-old subject, who was arbitrarily chosen to represent a young individual. Blood flow is relative to cardiac output and all values are relative to a 30-year-old man and woman, respectively

disposition for men and women aged 50 and 70 years with subjects aged 30 years (Fig. 8). There is a progressive decline in relevant system parameters, such as adipose tissue weight, liver, and kidney blood flow, with age. However, it is challenging to conclude a 'pharmacological' or 'clinical' age cut-off for the elderly based on the age-dependent changes in anatomical and physiological parameters because it is unknown when those changes affect drug kinetics significantly. No study has been undertaken to compare the pharmacokinetics of a drug between different age decades and correlate those data to age-dependent changes of organ parameters. Furthermore, elderly subjects included in

clinical trials can have diseases influencing the parameter of interest. It is therefore a challenge to define 'healthy' in terms of an aged person.

Despite the limitations, in this work, it was possible to derive descriptive continuous functions to generate a virtual population from 20 to 99 years of age in accordance with observed independent data. The elderly are a growing vulnerable patient population with a high frequency of comorbidities and in turn polypharmacy. However, aging subjects are often excluded from clinical trials and knowledge concerning drug kinetics and DDI magnitudes is scarce. The developed population database can be implemented into existing PBPK frameworks and then be used to predict drug kinetics and DDI magnitudes in aging subjects, thereby overcoming the lack of clinical data and providing a rational framework for dose optimization to prevent DDIs.

5 Conclusions

The population database for aging subjects presented in this work can be implemented into existing PBPK frameworks and allows the prediction of drug kinetics and DDI magnitudes in the elderly. It provides descriptive continuous functions for anatomical and physiological parameters from 20 to 99 years of age necessary to inform PBPK models and provides a view of the current literature concerning metabolizing enzymes and drug transporters in aging individuals. Furthermore, population variability is considered for all system parameters providing a framework for realistic pharmacokinetic predictions.

Compliance with Ethical Standards

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Conflict of interest Felix Stader, Marco Siccardi, Manuel Battegay, Hannah Kinvig, Melissa A. Penny, and Catia Marzolini have no conflicts of interest directly relevant to the contents of this study.

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