

1 Title: A repository describing an aging population to inform physiologically based
2 pharmacokinetic models considering anatomical, physiological and biological age-
3 dependent changes.
4

5 Authors: Felix Stader^{1,2,3,\$}, Marco Siccardi⁴, Manuel Battegay^{1,3}, Hannah Kinvig⁴, Melissa A.
6 Penny^{2,3} & Catia Marzolini^{1,3}
7

8 Affiliation: 1. Division of Infectious Diseases and Hospital Epidemiology
9 Departments of Medicine and Clinical Research
10 University Hospital Basel
11 Basel, Switzerland
12

13 2. Infectious Disease Modelling Unit
14 Department of Epidemiology and Public Health
15 Swiss Tropical and Public Health Institute
16 Basel, Switzerland
17

18 3. University of Basel
19 Basel, Switzerland
20

21 4. Department of Molecular and Clinical Pharmacology
22 Institute of Translational Medicine
23 University of Liverpool
24 Liverpool, UK
25

26 \$ corresponding author
27 E-mail: Felix.Stader@unibas.ch
28 Phone: +41 61 284 8738
29

30 keywords: Aging, elderly, PBPK, modelling, population database
31

32 article type Original Research Article

33 **1 Abstract**

34

35 **Background**

36 Aging is characterized by anatomical, physiological and biological changes which can impact drug
37 kinetics. Elderly are often excluded from clinical trials and knowledge about drug kinetics and drug-drug
38 interaction (DDI) magnitudes are sparse. Physiologically based pharmacokinetic (PBPK) modelling can
39 overcome this clinical limitation but detailed descriptions of the population characteristics are essential
40 to adequately inform models.

41

42 **Objective**

43 The objective of this work was to develop and verify a population database for aging Caucasians
44 considering anatomical, physiological and biological system parameters required to inform a PBPK
45 model with included population variability.

46

47 **Methods**

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

50

51 **Results**

52 A total of 362 studies were found of which 318 studies were included in the analysis as they reported
53 rich data for anthropometric parameters and specific organs (e.g. liver). Continuous functions could be
54 derived for most system parameters describing a Caucasian population from 20 to 99 years with
55 variability. Areas with sparse data have been identified like tissue composition, but knowledge gaps
56 were filled with plausible, qualified assumptions. The developed population was implemented in Matlab®
57 and estimated system parameters from 1,000 virtual individuals were in accordance to independent
58 observed data showing the robustness of the developed population.

59

60 **Conclusion**

61 The developed repository for aging subjects provides a singular specific source for key system
62 parameters needed for PBPK modelling and can in turn be used to investigate drug kinetics and DDI
63 magnitudes in elderly.

64 **2 Key Points**

65 The developed repository provides a singular, specific source of age-dependent anatomical,
66 physiological and biological system parameters required to inform physiologically based
67 pharmacokinetic (PBPK) models. The parameters and associated developed equations can be
68 implemented into existing PBPK frameworks and can be used to overcome sparse clinical data in aging
69 subjects older than 65 years to investigate age-dependent changes in drug kinetics and drug-drug
70 interaction (DDI) magnitudes *in silico*. These parameterized and informed PBPK models for elderly can
71 provide more rational frameworks for dose-adjustments to overcome DDIs.

72 **3 Introduction**

73 In recent years the number of elderly people worldwide has increased substantially [1]. An “elderly” is
74 defined as being above the age of 65 years [2], which is in line with the age of retirement in most Western
75 countries. Older individuals are prone to multi-morbidities and hence polypharmacy and in turn for drug-
76 drug interactions (DDIs) [3-5], however there is no clear pharmacological or clinical definition of “elderly”
77 [6]. Often, elderly subjects are excluded from clinical trials resulting in a general lack of knowledge about
78 the efficacy, safety and kinetics of a drug at different ages [7]. There are certain age-dependent
79 anatomical, physiological and biochemical changes influencing drug kinetics including decreased kidney
80 weight [8], reduced renal blood flow [9], reduced glomerular filtration rate (GFR) [10] and reduction in
81 liver volume and blood flow [11-13]. For other parameters like enzyme and transporter abundance, or
82 the concentration of plasma binding proteins, data are limited, contradictory or missing. In addition, it is
83 difficult to investigate aging, because other environmental and behavioral factors like diseases, food and
84 smoking can have effects themselves or enhance the aging process [14].

85

86 Physiologically based pharmacokinetic modelling can help to overcome the lack of clinical data and to
87 understand drug absorption, distribution, metabolism and elimination at different ages. Furthermore,
88 PBPK models predict DDI magnitudes in aging individuals and support more rational identification of
89 dose adjustments to overcome DDIs. To develop a PBPK model, system data (where system refers to
90 the population of interest – e.g. elderly) are required to inform the PBPK model. To generate reliable
91 predictions, a comprehensive description of system characteristics is essential to fully represent the
92 population of interest. To date only two databases have been published to inform PBPK models for
93 elderly, of which one does not distinguish between ethnicities [15] and the other does not consider
94 population variability and provides no descriptive functions of physiological and anatomical parameters
95 [16].

96

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

102 **4 Methods**

103 **4.1 Data source**

104 A structured literature search was performed using the MEDLINE database for age-dependency of
105 anatomical, physiological and biological parameters required to inform a PBPK model for aging subjects.
106 Keywords used were “aging”, “elderly” or “geriatric” plus the parameter of interest (Supplement S-Table
107 1 and S-Figure 1 for the investigated compartments of a PBPK model). No restrictions were applied
108 regarding the language or the publication year of the article. Abstracts were screened, and studies
109 included if the study population were Caucasians, at least age has been reported in addition to the
110 parameter of interest, and subjects were healthy or their disease / organ function was deemed unlikely
111 to affect the parameter of interest like the effect of chronic liver disease on brain blood flow [17]. Studies
112 performed with North Americans and Australians were considered if at least 80% of the study population
113 were of European heritage. Studies including subjects over the age of 65 years should report at least a
114 mean age in age decades. The reference list of chosen articles was manually screened to identify further
115 references.

116 **4.2 Data analysis**

117 Data analysis was performed in Matlab® 2015b. ~~The parameter of interest was analyzed in age decades.~~
118 Data were converted to consistent units and a normal distribution was assumed for each parameter to
119 make published data comparable. If a study reported median, minimum and maximum, data were
120 converted to the arithmetic mean and standard deviation according to Hozo *et al.* [18] and if the
121 interquartile range was given, the conversion was done according to Wan *et al.* [19].

122

123 Collated data were separated into a development and verification dataset. Studies in the development
124 dataset were required to report age, sex, body height, body weight and the ethnicity in addition to the
125 parameter of interest as necessary covariates to describe correlations. Otherwise, studies with less
126 reported covariates were used in the verification dataset. If at least three different studies covering the
127 entire age range with at least one value in each age decade and all required covariates for the
128 development dataset were available for a parameter of interest, the data was randomly separated into
129 a development and a verification dataset. In the case of missing covariates like anthropometric

130 parameters in the verification dataset or cardiac output for regional blood flow analysis, the covariates
131 have been estimated by the derived equations following the approach by Williams & Leggett [20]. The
132 body surface area was calculated according to DuBois & DuBois [21].

133

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

142

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

151

152 The derived equations for all parameters necessary to describe a white population have been
153 implemented in Matlab® and 1,000 virtual men and women have been created and the estimated system
154 parameters have been compared to the independent verification dataset. Normal distribution with the
155 derived CV (Tab. 1) was used to describe variability of the parameter of interest. Furthermore, it was
156 analyzed if the sum of organ weights and regional blood flows do not exceed body weight and cardiac
157 output.

158 **5 Results**

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

170 **5.1 Age and sex distribution**

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

179 **5.2 Body height and body weight**

180 Anthropometric data of 106,698 Caucasians have been analyzed in the developmental dataset [24-70]
181 and the derived equation has been verified with data from 14,096 subjects [71-86]. The mean body
182 height of Caucasians aged 20 to 59 years was 178 cm for men and 166 cm for women with a gender-
183 independent CV of 3.8%. Body height declined 2% per age decade from the age of 60 years (Figure 2).
184 The difference between men and women was constant at all age ranges. Location was found to be a

185 significant variable during regression, with lower height observed in Southern Europe, and an exclusion
186 of data reported from Portugal, Spain and Italy led to a non-significance of location.

187

188 The mean body weight of a Caucasian aged 20 to 49 years was 79.9 kg for men and 64.1 kg for women
189 with a CV of 15.7% (Figure 2). Body weight increased in subjects in the 5th and 6th age decade about
190 4% and decreased afterwards about 10% in each age decade. In women, the decline started one age
191 decade later than in men. In contrast to body height, location was not significant for body weight, but
192 publication year was with a significant increase since 2000.

193 **5.3 Liver**

194 **5.3.1 *Liver weight***

195 Liver is the major organ of metabolism. Liver weight was analyzed from over 3,000 subjects [29, 41, 51,
196 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
197 a CV of 23.7% till the age of 65 years. Thereafter, liver weight decreased by 10 to 15% in women per
198 age decade reaching 1.03 kg at the age of 100 years. The decrease in men was around 20% per age
199 decade reaching 1.01 kg on average in 90 years old individuals (Figure 3).

200

201 **5.3.2 *Liver blood flow***

202 Absolute total liver blood flow decreased by 60% between 60 and 90 years in men and women, but
203 relative to cardiac output the changes were only significant between 90 and 100 years of age [13, 89].
204 The age-dependent changes in total liver blood flow might come from changes of the splanchnic blood
205 flow [77, 89-94] explaining observed differences in the first pass effect between young and old subjects
206 [95-97]. The hepatic arterial blood flow appears to be constant with age [20, 89, 98].

207

208 **5.3.3 *In-vitro-in-vivo extrapolation factors***

209 PBPK models are informed by *in-vitro-in-vivo* extrapolation meaning that for instance the *in vivo*
210 clearance is extrapolated from measured *in vitro* data. Hepatic scaling factors like the hepatocellularity
211 (HPGL) or microsomal proteins per gram liver (MPPGL) are needed [99]. Barter *et al.* reported age-
212 dependent equations for HPGL [100] and MPPGL [101] with the oldest individuals in the analysis being
213 between the mid-seventies and the early eighties.

214

215 **5.3.4 Hepatic enzyme activity**

216 Studies concerning the age-dependency of hepatic CYP enzyme activity are sparse and contradictory.
217 The biggest challenge is the high variability in hepatic CYP enzyme abundance [102, 103] and the small
218 sample size generally used for analysis [104, 105]. In a recent large meta-analysis investigating hepatic
219 CYP abundance to inform PBPK models, age was only a significant covariate for CYP2C9 [103]. It is
220 worthwhile mentioning, that the different genotypes known for CYP2C9 increase the sample size needed
221 to identify age-dependency even further. A significant age-dependency was detected for CYP1A2,
222 CYP2D6 and CYP2E1 in a different study, but not for CYP2C9 [106]. In a third study, CYP1A2 activity
223 was reported to be independent of age [107]. Consistent between different studies, CYP3A4 activity is
224 reported to be independent of age [108-110].

225

226 Posalek *et al.* investigated drug clearances in elderly for probe substrates like caffeine (CYP1A2),
227 warfarin (CYP2C9), phenytoin (CYP2C19), desipramine (CYP2D6) and midazolam (CYP3A4) and
228 found a clearance decrease of 30 to 40% in 70 years old subjects compared to young individuals, which
229 can be explained by the decline in liver volume and blood flow rather than hepatic CYP enzyme activity
230 [111]. In addition inflammation affects CYP enzyme activity [112] making it difficult to analyze data from
231 non-healthy elderly.

232

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

237

238 **5.3.5 Hepatic drug transporter activity**

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

244 activity; however, these data are currently not available. Comparable to hepatic enzymes, it is therefore
245 recommended to use the same activity in elderly as in young subjects.

246 **5.4 Kidney**

247 **5.4.1 *Kidney weight***

248 The literature search yielded nine different studies with a total of 1,620 data points measuring kidney
249 weight after autopsy [29, 41, 42, 51, 52, 55, 69, 78, 85] (Figure 4A). The average kidney weight in young
250 males and females was 0.318 kg with a CV of 19.3% and 0.259 kg with a CV of 23.2%, respectively.
251 The reduction in kidney weight increased with age starting from 5% at the age of 70 years to 15% at the
252 age of 80 years to 25% up to the age of 100 years in both genders.

253

254 **5.4.2 *Kidney blood flow***

255 Absolute kidney blood flow decreased by 5 to 10% per age decade till the age of 65 years and thereafter
256 decreased by 25% per age decade (Figure 4B) [77, 90, 94, 117-125]. Kidney blood flow relative to
257 cardiac output was 19.7% in young men and decreased to 11.9% at the age of 85 years. The decrease
258 was 5 to 20% per age decade. In women, the average kidney blood flow relative to cardiac output was
259 16.5% and stayed constant till the age of 70 years. Thereafter, it decreased to 9.2% at the age of 85
260 years.

261

262 **5.4.3 *Glomerular filtration rate***

263 Only studies using inulin or ⁵¹Cr-EDTA as a biomarker for glomerular filtration rate have been considered
264 in this work [117-123, 125-129]. Equations to estimate the glomerular filtration rate like Cockcroft-Gault
265 [10] and the modification of diet in renal disease [130] use serum creatinine, which is problematic
266 considering senile sarcopenia in aging subjects [131]. The average glomerular filtration rate was
267 between 130 – 140 mL/min in men aged between 20 and 50 years and around 120 mL/min in women
268 of the same age. In the 5th age decade, glomerular filtration rate declined in men to 115 mL/min, which
269 was like the value in women (112 mL/min). Afterwards, the decline in glomerular filtration rate was
270 roughly 10% per age decade independent of gender reaching 50% of the value of a young adult at the
271 age of 90 years (Figure 4C).

272 **5.5 Adipose**

273 **5.5.1 *Adipose weight***

274 Adipose weight is usually measured via X-ray absorptiometry and bioelectric impedance analysis. Data
275 from 18 different studies from 12,323 subjects were available for the development dataset [25, 26, 36,
276 37, 41, 42, 45-48, 57, 59, 60, 62, 65, 68, 73, 132]. In young men, adipose weight was on average 17.8
277 kg with a CV of 24%. It increased by 5 to 10% per age decade to 22.9 kg at the age of 70 years. The
278 CV increased to 28%. In young women, adipose weight was found to be 17.3 kg with a CV of 29%.
279 Between 20 and 70 years, adipose weight increased to 25.2 kg with a CV of 37% in women and
280 decreased again to 21.9 kg with a CV of 37% at the age of 85 years.

281

282 **5.5.2 *Adipose blood flow***

283 Adipose blood flow increased from 5% in young to 9% in aged males and from 8% in young to 10% in
284 aged females [133, 134].

285 **5.6 Muscle**

286 **5.6.1 *Muscle weight***

287 Data from 11 different studies with 5,542 participants were available to analyze muscle weight, which
288 was measured by X-ray absorptiometry and bioelectrical impedance analysis [26, 41, 42, 45, 50, 64, 73,
289 79, 81, 83, 132]. The average muscle weight was 32.0 kg in men aged 20 to 65 years and 19.8 kg in
290 women of the same age. Muscle weight decreased by 10% per age decade between 65 and 100 years.
291 The CV was 11.8% and was similar for males and females.

292

293 **5.6.2 *Muscle blood flow***

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

296 **5.7 Brain**

297 **5.7.1 *Brain weight***

298 Brain weight was analyzed by using data from eight different studies with 2,425 participants [29, 41, 42,
299 51, 52, 55, 78, 139] and was found to be independent of age. The average brain weight was 1.39 kg in
300 males and 1.28 kg in females with a gender-independent CV of 9%.

301

302 **5.7.2 *Brain blood flow***

303 The literature search yielded 12 different studies with 956 participants for brain blood flow [140-151].
304 brain blood flow relative to cardiac output was 11.8% in men and 15.6% in women below the age of 40
305 years and increased to 15.6% in men and 16.3% in women in the 4th age decade and was constant
306 thereafter.

307 **5.8 Heart**

308 **5.8.1 *Heart weight***

309 Heart weight was analyzed using data from 10 different studies measuring heart weight after autopsy
310 [29, 41, 42, 53, 55, 61, 69, 78, 152, 153] and increased in both, males and females, from 0.325 kg and
311 0.241 kg at the age of 25 to 0.390 kg and 0.317 kg in the 9th age decade.

312

313 **5.8.2 *Heart blood flow***

314 Blood flow to the heart relative to cardiac output increased from 5.5% at the age of 25 years to 12% at
315 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
316 women [154-159].

317

318 **5.8.3 *Cardiac output***

319 Cardiac output is the volume of blood being ejected by the heart per minute. Data from 12 studies
320 involving 645 subjects were used to analyze cardiac output [39, 63, 70, 74, 77, 84, 90, 94, 135, 138,
321 160, 161]. Cardiac output decreased from 352 L/h in 30 years old males and 312 L/h in young females
322 between 5 and 10% every age decade to 258 L/h in aged males and 201 L/h in aged females (Figure
323 5). The CV was similar between both genders with a value of 21.1%.

324 **5.9 Blood**

325 **5.9.1 *Blood weight***

326 Blood weight was analyzed from seven different studies with 382 male and 179 female participants [27,
327 30, 31, 44, 66, 75, 162]. In young males, blood weight was 5.8 kg with a CV of 10% and decreased to
328 5.0 kg at the age of 90 years (Figure 6). In young women, blood weight was lower with 3.8 kg, but stayed
329 constant over different age decades. At the age of 70 years, female blood weight was still 3.7 kg. The
330 CV was like in men.

331

332 **5.9.2 *Hematocrit***

333 Blood parameters that have been analyzed were hematocrit and the concentration of albumin and alpha-
334 acidic glycoprotein (Figure 6). Data of 1,752 subjects aged 21 till 90 years were available to analyze
335 hematocrit [122, 142, 163-168]. Sex was the only significant covariate. Mean values were 0.443 ± 0.064
336 for men and 0.410 ± 0.063 for women.

337

338 **5.9.3 *Plasma binding protein concentration***

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

341

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

347 **5.10 Other organs**

348 Other organs like spleen and pancreas are not described in detail here, but the descriptive equations to
349 describe an aging Caucasian population can be found in Table 1 and more detailed information can be
350 found in the Supplement (S-Table 2, 3 and 4).

351 **5.11 Tissue composition**

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

365 **5.12 Parameters affecting drug absorption**

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

369

370 **5.12.1 *Gastric pH***

371 One study compared gastric pH in fasted and fed state between 24 young, healthy volunteers aged 21
372 to 35 years [194] and 79 subjects aged 65 to 83 years [195]. The study reported a significant age-
373 dependent difference between the median pH in fasted state (interquartile range) with 1.72 (1.08 – 2.34)
374 in the young group and 1.28 (0.90 – 5.60) in the aged group. The variability appeared to be much greater
375 in older individuals, but the difference in sample size need to be kept in mind. Another study in young
376 subjects below the age of 65 years found a median fasted pH of 1.45 [196]. To conclude, it is doubtful
377 if there is an age-dependency of gastric pH in fasted state and more data need to be generated and
378 included in the meta-analysis to judge the age effect properly. Gastric pH in fed state was not
379 significantly different between young and elderly subjects [194, 195], but the decline of gastric pH from

380 fed to fasted state was exponential with a half-life of 1.8 hours (CV: 65%) in young and was linear with
381 a half-life of 3.0 hours (CV: 80%) in aging subjects [195]. 8% of Caucasians are achlorhydric meaning
382 they do not secrete hydrochloric acid in the gastric juice [197] and thus having a gastric pH at fasted state
383 of 7.1 [195]. In Japanese, the number of achlorhydric subjects increases with age [198], but this appears
384 not to be the case in healthy aging Caucasians [195].

385

386 **5.12.2 Gastric emptying time**

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

397

398 **5.12.3 Small intestinal transit time**

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

401

402 **5.12.4 Passive permeability**

403 The mucosal area is reported to decline with age [211, 212], but enterocytes and villi appear to be
404 unchanged [212]. Malnutrition, disease and drug intake could alter the mucosa and need to be carefully
405 considered when investigating age-dependency. Passive permeability was reported to be impaired in
406 aging subjects [211], but two studies investigating mannitol and lactulose, two carbohydrates which are
407 passively absorbed, showed no difference in passive permeability between young controls and aging
408 subjects after correcting the data for the age-dependent decline in glomerular filtration rate [213, 214].

409 It is therefore assumed that neither the surface area available for passive diffusion nor the rate of passive
410 diffusion differ in aging subjects compared to young individuals.

411

412 **5.12.5 Intestinal enzyme and drug transporter abundance**

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

415 **6 Discussion**

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

420

421 Two previous databases have been described in the literature for aging individuals. Thompson *et al.*
422 gathered extensive data from the literature, but the authors did not considered different ethnic groups
423 and combined data from Caucasians, Latin-Americans and Asians [15]. However, it is known that
424 ethnicity can have a significant impact on system parameters, for instance hepatic enzyme abundance,
425 and therefore on clearance prediction [215]. Schlender *et al.* published recently a database for elderly
426 individuals further processing the data from Thompson *et al.* for Caucasians only [16]. A limitation of this
427 study is that only values for organ weight and blood flow for each age decade were considered making
428 it difficult to extrapolate to other ages of interest. Furthermore, population variability of system
429 parameters was not considered by Schlender *et al.*, which is an essential element for reasonable
430 predictions of drug kinetics using PBPK models [216].

431

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

440

441 A few limitations need to be acknowledged. Data from individuals over the age of 85 are sparse (S-
442 Table 2 in the Supplement) meaning the derived equations could be less robust and extrapolation to
443 older ages might be difficult. However, data for centenarians have been included for some system
444 parameters [78] and were adequately estimated by the derived functions. Clinical studies are usually
445 not performed in the very old making it impossible to verify the described population by analyzing drug

446 kinetics. It is therefore recommended to use the described repository with caution at older ages. This
447 holds particularly true for regional blood flows to adipose, heart, muscle and skin, because almost no
448 geriatric data are currently available in the literature.

449

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

455

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

462

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

475

476

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

490

491 A challenge when studying older individuals is that the definition of elderly is not universal. The WHO
492 specifies elderly as being above the age of 65 years [2], which is in accordance with the age of retirement
493 in most Western countries, but a clear pharmacological or clinical age-cut off is missing [6]. For some
494 patient groups, like people infected with HIV, the age cut-off is even as early as 50 years [220]. We
495 compared organs parameters important for drug disposition for 50 and 70 years old men and women
496 with 30 years old subjects (Figure 8). There is a progressive decline in relevant system parameters,
497 such as adipose weight, liver and kidney blood flow, with age. However, it is challenging to conclude a
498 “pharmacological” or “clinical” age cut-off for elderly based on the age-dependent changes in anatomical
499 and physiological parameters, because it is unknown when those changes affect drug kinetics
500 significantly. No study has been undertaken to compare pharmacokinetics of a drug between different
501 age decades and correlate those data to age-dependent changes of organ parameters. Furthermore,
502 elderly subjects included in clinical trials can have diseases influencing the parameter of interest. It is
503 therefore a challenge to define “healthy” in terms of an aged person.

504

505 Despite the limitations, in this work it was possible to derive descriptive, continuous functions to generate
506 a virtual population from 20 to 99 years in accordance to observed, independent data. Elderly are a
507 growing vulnerable patient population with a high frequency of co-morbidities and in turn polypharmacy.

508 However, aging subjects are often excluded from clinical trials and knowledge concerning drug kinetics
509 and DDI magnitudes are scarce. The developed population database can be implemented into existing
510 PBPK frameworks and can in turn be used to predict drug kinetics and DDI magnitudes in aging subjects
511 overcoming the lack of clinical data and providing a rational framework for dose optimization to
512 overcome DDIs.

513 **7 Conclusions**

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

520

521 **8 Funding.**

522 This study was supported by the Swiss National Foundation (Grant number 166204), the OPO
523 Foundation and the Isaac Dreyfus Foundation.

524

525 **9 Conflict of Interest**

526 Felix Stader, Marco Siccardi, Manuel Battegay, Hannah Kinvig, Melissa A. Penny, and Catia Marzolini
527 have no conflict of interest to declare.

528 **10 References**

529

530 1. United Nations. World Population Ageing. 2015 [cited 23/01/2018]; Available from:
 531 [http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.](http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf)
 532 [pdf](http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf)

533 2. World Health Organisation. Definition of an older or elderly person. 2010 [cited 23/02/2018];
 534 Available from: <http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html>

535 3. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert
 536 Opinion on Drug Safety. 2014;13(1):57-65.

537 4. Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug–drug interactions, and
 538 potentially inappropriate medications in older adults with human immunodeficiency virus
 539 infection. Journal of the American Geriatrics Society. 2014;62(3):447-53.

540 5. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity
 541 and implications for health care, research, and medical education: a cross-sectional study. The
 542 Lancet. 2012;380(9836):37-43.

543 6. Singh S, Bajorek B. Defining ‘elderly’ in clinical practice guidelines for pharmacotherapy.
 544 Pharmacy Practice. 2014;12(4):489-98.

545 7. Watts G. Why the exclusion of older people from clinical research must stop. BMJ: British
 546 Medical Journal (Online). 2012;344.

547 8. Dunnill M, Halley W. Some observations on the quantitative anatomy of the kidney. The Journal
 548 of Pathology. 1973;110(2):113-21.

549 9. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP. Senescence and
 550 the renal vasculature in normal man. Circulation Research. 1974;34(3):309-16.

551 10. Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron.
 552 1976;16(1):31-41.

553 11. Koff R, Garvey A, Burney S, Bell B. Absence of an age effect on sulfobromophthalein retention
 554 in healthy men. Gastroenterology. 1973;65(2):300-2.

555 12. Marchesini G, Bua V, Brunori A, Bianchi G, Pisi P, Fabbri A, et al. Galactose elimination capacity
 556 and liver volume in aging man. Hepatology. 1988;8(5):1079-83.

557 13. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. The effect of age
 558 upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989;9(2):297-301.

559 14. Safar M. Ageing and its effects on the cardiovascular system. Drugs. 1990;39(1):1-8.

560 15. Thompson CM, Johns DO, Sonawane B, Barton HA, Hattis D, Tardif R, et al. Database for
 561 physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and
 562 health-impaired elderly. Journal of Toxicology and Environmental Health, Part B. 2009;12(1):1-
 563 24.

564 16. Schlender J-F, Meyer M, Thelen K, Krauss M, Willmann S, Eissing T, et al. Development of a
 565 whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics
 566 of drugs in elderly individuals. Clinical Pharmacokinetics. 2016;55(12):1573-89.

567 17. O'Carroll R, Ebmeier K, Dougall N, Murray C, Goodwin G, Hayes P, et al. Regional cerebral
 568 blood flow and cognitive function in patients with chronic liver disease. The Lancet.
 569 1991;337(8752):1250-3.

570 18. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range,
 571 and the size of a sample. BMC Medical Research Methodology. 2005;5(13):1-10.

572 19. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the
 573 sample size, median, range and/or interquartile range. BMC Medical Research Methodology.
 574 2014;14(1):135-59.

575 20. Williams L, Leggett R. Reference values for resting blood flow to organs of man. Clinical Physics
 576 and Physiological Measurement. 1989;10(3):187-217.

577 21. DuBois D, DuBois EF. Fifth paper the measurement of the surface area of man. Archives of
 578 Internal Medicine. 1915;15(5):868-81.

579 22. Burnham KP, Anderson DR. Model selection and multimodel inference: a practical information-
 580 theoretic approach: Springer Science & Business Media; 2003.

581 23. European Union. Eurostat - Population. 2013 [cited 23/02/2017]; Available from:
 582 <http://ec.europa.eu/eurostat/data/database>

583 24. Bundesamt für Statistik (Schweiz). Permanent resident population by age,sex and category of
 584 citizenship. 2016 [cited 01/05/2017]; Available from:
 585 <https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung.assetdetail.299701.html>

- 586 25. Bedogni G, Pietrobelli A, Heymsfield SB, Borghi A, Manzieri AM, Morini P, et al. Is body mass
587 index a measure of adiposity in elderly women? *Obesity Research*. 2001;9(1):17-20.
- 588 26. Bosy-Westphal A, Mast M, Eichhorn C, Becker C, Kutzner D, Heller M, et al. Validation of air-
589 displacement plethysmography for estimation of body fat mass in healthy elderly subjects.
590 *European Journal of Nutrition*. 2003;42(4):207-16.
- 591 27. Brown E, Hopper Jr J, Hodges Jr J, Bradley B, Wennesland R, Yamauchi H. Red cell, plasma,
592 and blood volume in healthy women measured by radiochromium cell-labeling and hematocrit.
593 *Journal of Clinical Investigation*. 1962;41(12):2182-90.
- 594 28. Statistisches Bundesamt der Bundesrepublik Deutschland. Mikrozensus - Fragen zur
595 Gesundheit. Körpermaße der Bevölkerung. 2013 [cited 31/05/2017]; Available from:
596 https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermaesse5239003099004.pdf?__blob=publicationFile
597
- 598 29. Calloway N, Foley C, Lagerbloom P. Uncertainties in geriatric data. II. Organ size. *Journal of*
599 *the American Geriatrics Society*. 1965;13(1):20-8.
- 600 30. Chien S, Usami S, Simmons R, McAllister F, Gregersen M. Blood volume and age: repeated
601 measurements on normal men after 17 years. *Journal of Applied Physiology*. 1966;21(2):583-
602 8.
- 603 31. Cohn JE, Shock NW. Blood volume studies in middle-aged and elderly males. *American Journal*
604 *of Medical Sciences*. 1949;217:388-91.
- 605 32. Corish CA, Kennedy NP. Anthropometric measurements from a cross-sectional survey of Irish
606 free-living elderly subjects with smoothed centile curves. *British Journal of Nutrition*.
607 2003;89(1):137-45.
- 608 33. De Groot C, Perdigo A, Deurenberg P. Longitudinal changes in anthropometric characteristics
609 of elderly Europeans. SENECA Investigators. *European Journal of Clinical Nutrition*.
610 1996;50(Spl2):S9-15.
- 611 34. Delarue J, Constans T, Malvy D, Pradignac A, Couet C, Lamisse F. Anthropometric values in
612 an elderly French population. *British Journal of Nutrition*. 1994;71(2):295-302.
- 613 35. Dey DK, Rothenberg E, Sundh V, Bosaeus I, Steen B. Height and body weight in the elderly. I.
614 A 25-year longitudinal study of a population aged 70 to 95 years. *European Journal of Clinical*
615 *Nutrition*. 1999;53(12):905-14.
- 616 36. Dey D, Bosaeus I, Lissner L, Steen B. Body composition estimated by bioelectrical impedance
617 in the Swedish elderly. Development of population-based prediction equation and reference
618 values of fat-free mass and body fat for 70- and 75-y olds. *European Journal of Clinical Nutrition*.
619 2003;57(8):909-16.
- 620 37. Dey DK, Bosaeus I, Lissner L, Steen B. Changes in body composition and its relation to muscle
621 strength in 75-year-old men and women: a 5-year prospective follow-up study of the NORA
622 cohort in Göteborg, Sweden. *Nutrition*. 2009;25(6):613-9.
- 623 38. Eiben G, Dey D, Rothenberg E, Steen B, Björkelund C, Bengtsson C, et al. Obesity in 70-year-
624 old Swedes: secular changes over 30 years. *International Journal of Obesity*. 2005;29(7):810-
625 7.
- 626 39. Farinatti PT, Soares PP. Cardiac output and oxygen uptake relationship during physical effort
627 in men and women over 60 years old. *European Journal of Applied Physiology*.
628 2009;107(6):625-31.
- 629 40. Gallagher D, Visser M, De Meersman RE, Sepúlveda D, Baumgartner RN, Pierson RN, et al.
630 Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *Journal of Applied*
631 *Physiology*. 1997;83(1):229-39.
- 632 41. Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue
633 mass measurement allows modeling of REE and metabolically active tissue mass. *American*
634 *Journal of Physiology-Endocrinology And Metabolism*. 1998;275(2):E249-E58.
- 635 42. Gallagher D, Allen A, Wang Z, Heymsfield SB, Krasnow N. Smaller organ tissue mass in the
636 elderly fails to explain lower resting metabolic rate. *Annals of the New York Academy of*
637 *Sciences*. 2000;904(1):449-55.
- 638 43. Gavriilidou N, Pihlsgård M, Elmståhl S. Anthropometric reference data for elderly Swedes and
639 its disease-related pattern. *European Journal of Clinical Nutrition*. 2015;69(9):1066-75.
- 640 44. Gibson JG, Evans WA. Clinical studies of the blood volume. II. The relation of plasma and total
641 blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in
642 ninety normal humans. *Journal of Clinical Investigation*. 1937;16(3):317-28.
- 643 45. Gillette-Guyonnet S, Nourhashemi F, Lauque S, Grandjean H, Vellas B. Body composition and
644 osteoporosis in elderly women. *Gerontology*. 2000;46(4):189-93.
- 645 46. Gnudi S, Sitta E, Fiumi N. Relationship between body composition and bone mineral density in
646 women with and without osteoporosis: relative contribution of lean and fat mass. *Journal of*
647 *Bone and Mineral Metabolism*. 2007;25(5):326-32.

- 648 47. Henche SA, Torres RR, Pellico LG. An evaluation of patterns of change in total and regional
649 body fat mass in healthy Spanish subjects using dual-energy X-ray absorptiometry (DXA).
650 *European Journal of Clinical Nutrition*. 2008;62(12):1440-8.
- 651 48. Horber FF, Gruber B, Thomi F, Jensen EX, Jaeger P. Effect of sex and age on bone mass, body
652 composition and fuel metabolism in humans. *Nutrition*. 1997;13(6):524-34.
- 653 49. Launer LJ, Harris T. Weight, height and body mass index distributions in geographically and
654 ethnically diverse samples of older persons. *Age and Ageing*. 1996;25(4):300-6.
- 655 50. Legrand D, Adriaensen W, Vaes B, Matheï C, Wallemacq P, Degryse J. The relationship
656 between grip strength and muscle mass (MM), inflammatory biomarkers and physical
657 performance in community-dwelling very old persons. *Archives of Gerontology and Geriatrics*.
658 2013;57(3):345-51.
- 659 51. Molina DK, DiMaio VJ. Normal organ weights in men: part II—the brain, lungs, liver, spleen, and
660 kidneys. *The American Journal of Forensic Medicine and Pathology*. 2012;33(4):368-72.
- 661 52. Molina DK, DiMaio VJ. Normal organ weights in women: Part II - the brain, lungs, liver, spleen,
662 and kidneys. *The American Journal of Forensic Medicine and Pathology*. 2015;36(3):182-7.
- 663 53. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, et al. Gender
664 differences and aging: effects on the human heart. *Journal of the American College of
665 Cardiology*. 1995;26(4):1068-79.
- 666 54. Perissinotto E, Pisent C, Sergi G, Grigoletto F, Enzi G. Anthropometric measurements in the
667 elderly: age and gender differences. *British Journal of Nutrition*. 2002;87(2):177-86.
- 668 55. Puggaard L, Bjørnsbo KS, Kock K, Lüders K, Thobo-Carlsen B, Lammert O. Age-related
669 decrease in energy expenditure at rest parallels reductions in mass of internal organs. *American
670 Journal of Human Biology*. 2002;14(4):486-93.
- 671 56. Ravaglia G, Morini P, Forti P, Maioli F, Boschi F, Bernardi M, et al. Anthropometric
672 characteristics of healthy Italian nonagenarians and centenarians. *British Journal of Nutrition*.
673 1997;77(1):9-17.
- 674 57. Ravaglia G, Forti P, Maioli F, Boschi F, Cicognani A, Gasbarrini G. Measurement of body fat in
675 healthy elderly men: a comparison of methods. *The Journals of Gerontology Series A: Biological
676 Sciences and Medical Sciences*. 1999;54(2):M70-M6.
- 677 58. Rea I, Gillen S, Clarke E. Anthropometric measurements from a cross-sectional survey of
678 community dwelling subjects aged over 90 years of age. *European Journal of Clinical Nutrition*.
679 1997;51(2):102-6.
- 680 59. Santana H, Zoico E, Turcato E, Tosoni P, Bissoli L, Olivieri M, et al. Relation between body
681 composition, fat distribution, and lung function in elderly men. *The American Journal of Clinical
682 Nutrition*. 2001;73(4):827-31.
- 683 60. Schutz Y, Kyle U, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians
684 aged 18-98 y. *International Journal of Obesity*. 2002;26(7):953-60.
- 685 61. Smith HL. The relation of the weight of the heart to the weight of the body and of the weight of
686 the heart to age. *American Heart Journal*. 1928;4(1):79-93.
- 687 62. Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body
688 composition and fat distribution in healthy women as measured by dual-energy X-ray
689 absorptiometry. *Metabolism*. 1995;44(3):369-73.
- 690 63. Tanner J. The construction of normal standards for cardiac output in man. *Journal of Clinical
691 Investigation*. 1949;28(3):567-82.
- 692 64. Tichet J, Goxe D, Sallé A, Berrut G, Ritz P. Prevalence of sarcopenia in the French senior
693 population. *The Journal of Nutrition Health and Aging*. 2008;12(3):202-6.
- 694 65. Vache C, Rousset P, Gachon P, Gachon A, Morio B, Boulier A, et al. Bioelectrical impedance
695 analysis measurements of total body water and extracellular water in healthy elderly subjects.
696 *International Journal of Obesity*. 1998;22(6):537-43.
- 697 66. Wennesland R, Brown E, Hopper Jr J, Hodges Jr J, Guttentag O, Scott K, et al. Red cell, plasma
698 and blood volume in healthy men measured by radiochromium (Cr51) cell tagging and
699 hematocrit: influence of age, somatotype and habits of physical activity on the variance after
700 regression of volumes to height and weight combined. *Journal of Clinical Investigation*.
701 1959;38(7):1065-77.
- 702 67. Whimster WF, Macfarlane AJ. Normal lung weights in a white population. *American Review of
703 Respiratory Disease*. 1974;110(4):478-83.
- 704 68. Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJ, Eriksson JG. Body mass index during
705 childhood and adult body composition in men and women aged 56–70 y. *The American Journal
706 of Clinical Nutrition*. 2008;87(6):1769-75.
- 707 69. de la Grandmaison GL, Clairand I, Durigon M. Organ weight in 684 adult autopsies: new tables
708 for a Caucosoid population. *Forensic Science International*. 2001;119(2):149-54.

- 709 70. Starr I, Donal J, Margolies A, Shaw R, Collins L, Gamble C. Studies of the heart and circulation
710 in disease; estimations of basal cardiac output, metabolism, heart size, and blood pressure in
711 235 subjects. *Journal of Clinical Investigation*. 1934;13(4):561-92.
- 712 71. Bartali B, Benvenuti E, Corsi AM, Bandinelli S, Russo CR, Di Iorio A, et al. Changes in
713 anthropometric measures in men and women across the life-span: findings from the InCHIANTI
714 study. *Sozial-und Präventivmedizin*. 2002;47(5):336-48.
- 715 72. Chouker A, Martignoni A, Dugas M, Eisenmenger W, Schauer R, Kaufmann I, et al. Estimation
716 of liver size for liver transplantation: the impact of age and gender. *Liver Transplantation*.
717 2004;10(5):678-85.
- 718 73. Clarys J, Martin A, Drinkwater D. Gross tissue weights in the human body by cadaver dissection.
719 *Human Biology*. 1984;56(3):459-73.
- 720 74. Cournand A, Riley R, Breed E, Baldwin ED, Richards Jr D, Lester M, et al. Measurement of
721 cardiac output in man using the technique of catheterization of the right auricle or ventricle.
722 *Journal of Clinical Investigation*. 1945;24(1):106-16.
- 723 75. Davy KP, Seals DR. Total blood volume in healthy young and older men. *Journal of Applied*
724 *Physiology*. 1994;76(5):2059-62.
- 725 76. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, Cantet C, Albarède JL, Vellas B, et al. Body
726 composition in French women 75+ years of age: the EPIDOS study. *Mechanisms of Ageing and*
727 *Development*. 2003;124(3):311-6.
- 728 77. Ho C, Beard J, Farrell P, Minson C, Kenney W. Age, fitness, and regional blood flow during
729 exercise in the heat. *Journal of Applied Physiology*. 1997;82(4):1126-35.
- 730 78. Ishii T, Sternby NH. Pathology of centenarians. I. The cardiovascular system and lungs. *Journal*
731 *of the American Geriatrics Society*. 1978;26(3):108-15.
- 732 79. Janssen I, Heymsfield SB, Wang Z, Ross R. Skeletal muscle mass and distribution in 468 men
733 and women aged 18–88 yr. *Journal of Applied Physiology*. 2000;89(1):81-8.
- 734 80. Kasiske B, Umen A. The influence of age, sex, race, and body habitus on kidney weight in
735 humans. *Archives of Pathology & Laboratory Medicine*. 1986;110(1):55-60.
- 736 81. Kemmler W, Teschler M, Goisser S, Bebenek M, von Stengel S, Bollheimer LC, et al.
737 Prevalence of sarcopenia in Germany and the corresponding effect of osteoarthritis in females
738 70 years and older living in the community: results of the FORMoSA study. *Clinical Interventions*
739 *in Aging*. 2015;10:1565-73.
- 740 82. Kumar NT, Liestøl K, Løberg EM, Reims HM, Mæhlen J. Postmortem heart weight: relation to
741 body size and effects of cardiovascular disease and cancer. *Cardiovascular Pathology*.
742 2014;23(1):5-11.
- 743 83. Masanes Toran F, Culla A, Navarro-Gonzalez M, Navarro-Lopez M, Sacanella E, Torres B, et
744 al. Prevalence of sarcopenia in healthy community-dwelling elderly in an urban area of
745 Barcelona (Spain). *The Journal of Nutrition, Health & Aging*. 2012;16(2):184-7.
- 746 84. Mezzani A, Grassi B, Giordano A, Corrà U, Colombo S, Giannuzzi P. Age-related prolongation
747 of phase I of $\dot{V}O_2$ on-kinetics in healthy humans. *American Journal of Physiology*.
748 2010;299(3):R968-R76.
- 749 85. Nyengaard J, Bendtsen T. Glomerular number and size in relation to age, kidney weight, and
750 body surface in normal man. *The Anatomical Record*. 1992;232(2):194-201.
- 751 86. Sprogøe-Jakobsen S, Sprogøe-Jakobsen U. The weight of the normal spleen. *Forensic Science*
752 *International*. 1997;88(3):215-23.
- 753 87. Thompson EN, Williams R. Effect of age on liver function with particular reference to
754 bromsulphalein excretion. *Gut*. 1965;6(3):266-9.
- 755 88. Meyer W, Peter B, Solth K. The weight of organs in the older age groups (70-92 years) and their
756 relation to age and body weight. *Virchows Archiv für pathologische Anatomie und Physiologie*
757 *und für klinische Medizin*. 1963;337:17-32.
- 758 89. Carlisle K, Halliwell M, Read A, Wells P. Estimation of total hepatic blood flow by duplex
759 ultrasound. *Gut*. 1992;33(1):92-7.
- 760 90. Minson CT, Wladkowski SL, Cardell AF, Pawelczyk JA, Kenney WL. Age alters the
761 cardiovascular response to direct passive heating. *Journal of Applied Physiology*.
762 1998;84(4):1323-32.
- 763 91. Nakamura T, Moriyasu F, Ban N, Nishida O, Tamada T, Kawasaki T, et al. Quantitative
764 measurement of abdominal arterial blood flow using image-directed Doppler ultrasonography:
765 superior mesenteric, splenic, and common hepatic arterial blood flow in normal adults. *Journal*
766 *of Clinical Ultrasound*. 1989;17(4):261-8.
- 767 92. Vanis L, Gentilcore D, Lange K, Gilja OH, Rigda RS, Trahair LG, et al. Effects of variations in
768 intragastric volume on blood pressure and splanchnic blood flow during intraduodenal glucose
769 infusion in healthy older subjects. *American Journal of Physiology*. 2012;302(4):R391-R9.

- 770 93. Zoli M, Iervese T, Abbati S, Bianchi G, Marchesini G, Pisi E. Portal blood velocity and flow in
771 aging man. *Gerontology*. 1989;35(2-3):61-5.
- 772 94. Dunbar SL, Kenney WL. Effects of hormone replacement therapy on hemodynamic responses
773 of postmenopausal women to passive heating. *Journal of Applied Physiology*. 2000;89(1):97-
774 103.
- 775 95. Robertson D, Waller D, Renwick A, George C. Age-related changes in the pharmacokinetics
776 and pharmacodynamics of nifedipine. *British Journal of Clinical Pharmacology*. 1988;25(3):297-
777 305.
- 778 96. Castleden CM, George CF. The effect of ageing on the hepatic clearance of propranolol. *British
779 Journal of Clinical Pharmacology*. 1979;7(1):49-54.
- 780 97. Greenblatt DJ, Harmatz JS, Shapiro L, Engelhardt N, Gouthro TA, Shader RI. Sensitivity to
781 triazolam in the elderly. *New England Journal of Medicine*. 1991;324(24):1691-8.
- 782 98. Tygstrup N, Winkler K, Mellemegaard K, Andreassen M. Determination of the hepatic arterial
783 blood flow and oxygen supply in man by clamping the hepatic artery during surgery. *Journal of
784 Clinical Investigation*. 1962;41(3):447-54.
- 785 99. Howgate E, Rowland Yeo K, Proctor N, Tucker G, Rostami-Hodjegan A. Prediction of in vivo
786 drug clearance from in vitro data. I: impact of inter-individual variability. *Xenobiotica*.
787 2006;36(6):473-97.
- 788 100. Barter ZE, Bayliss MK, Beaune PH, Boobis AR, Carlile DJ, Edwards RJ, et al. Scaling factors
789 for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus
790 on values of human micro-somal protein and hepatocellularity per gram of liver. *Current Drug
791 Metabolism*. 2007;8(1):33-45.
- 792 101. Barter ZE, Chowdry JE, Harlow JR, Snawder JE, Lipscomb JC, Rostami-Hodjegan A.
793 Covariation of human microsomal protein per gram of liver with age: absence of influence of
794 operator and sample storage may justify interlaboratory data pooling. *Drug Metabolism and
795 Disposition*. 2008;36(12):2405-9.
- 796 102. Rowland-Yeo K. Abundance of cytochrome P450 in human liver: a meta-analysis. *British
797 Journal of Clinical Pharmacology*. 2004;57(5):687-8.
- 798 103. Achour B, Barber J, Rostami-Hodjegan A. Expression of hepatic drug-metabolizing cytochrome
799 p450 enzymes and their intercorrelations: a meta-analysis. *Drug Metabolism and Disposition*.
800 2014;42(8):1349-56.
- 801 104. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human
802 liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic
803 chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *Journal of
804 Pharmacology and Experimental Therapeutics*. 1994;270(1):414-23.
- 805 105. Achour B, Russell MR, Barber J, Rostami-Hodjegan A. Simultaneous quantification of the
806 abundance of several cytochrome P450 and uridine 5'-diphospho-glucuronosyltransferase
807 enzymes in human liver microsomes using multiplexed targeted proteomics. *Drug Metabolism
808 and Disposition*. 2014;42(4):500-10.
- 809 106. Parkinson A, Mudra D, Johnson C, Dwyer A, Carroll K. The effects of gender, age, ethnicity,
810 and liver microsomes and inducibility in cultured human hepatocytes. *Toxicology & Applied
811 Pharmacology*. 2004;199(3):193-209.
- 812 107. Simon T, Becquemont L, Hamon B, Nouyrigat E, Chodjania Y, Poirier J, et al. Variability of
813 cytochrome P450 1A2 activity over time in young and elderly healthy volunteers. *British Journal
814 of Clinical Pharmacology*. 2001;52(5):601-4.
- 815 108. Schwartz JB. Erythromycin breath test results in elderly, very elderly, and frail elderly persons.
816 *Clinical Pharmacology & Therapeutics*. 2006;79(5):440-8.
- 817 109. Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic
818 CYP3A. *Biochemical Pharmacology*. 1992;44(2):275-83.
- 819 110. Schmucker DL, Woodhouse KW, Wang RK, Wynne H, James OF, McManus M, et al. Effects
820 of age and gender on in vitro properties of human liver microsomal monooxygenases. *Clinical
821 Pharmacology & Therapeutics*. 1990;48(4):365-74.
- 822 111. Polasek TM, Patel F, Jensen BP, Sorich MJ, Wiese MD, Doogue MP. Predicted metabolic drug
823 clearance with increasing adult age. *British Journal of Clinical Pharmacology*. 2013;75(4):1019-
824 28.
- 825 112. Morgan E. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug
826 metabolism and pharmacokinetics. *Clinical Pharmacology & Therapeutics*. 2009;85(4):434-8.
- 827 113. Court MH. Interindividual variability in hepatic drug glucuronidation: studies into the role of age,
828 sex, enzyme inducers, and genetic polymorphism using the human liver bank as a model
829 system. *Drug Metabolism Reviews*. 2010;42(1):209-24.

- 830 114. Herd B, Wynne H, Wright P, James O, Woodhouse K. The effect of age on glucuronidation and
831 sulphation of paracetamol by human liver fractions. *British Journal of Clinical Pharmacology*.
832 1991;32(6):768-70.
- 833 115. Villesen HH, Banning A-M, Petersen RH, Weinelt S, Poulsen JB, Hansen SH, et al.
834 Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly
835 patients. *Therapeutics and Clinical Risk Management*. 2007;3(5):961-7.
- 836 116. Burt HJ, Riedmaier AE, Harwood MD, Crewe HK, Gill KL, Neuhoff S. Abundance of hepatic
837 transporters in Caucasians: a meta-analysis. *Drug Metabolism and Disposition*.
838 2016;44(10):1550-61.
- 839 117. Bauer JH, Brooks CS, Burch RN. Renal function and hemodynamic studies in low-and normal-
840 renin essential hypertension. *Archives of Internal Medicine*. 1982;142(7):1317-23.
- 841 118. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow,
842 and tubular excretory capacity in adult males. *Journal of Clinical Investigation*. 1950;29(5):496-
843 507.
- 844 119. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. *Journal*
845 *of the American Society of Nephrology*. 1993;3(7):1371-7.
- 846 120. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: impact
847 of hypertension and cardiac function. *Kidney International*. 1997;51(4):1196-204.
- 848 121. Ghose K, Burch A. Measurement of renal functions by double isotope techniques in elderly
849 patients during tenoxicam therapy. *Archives of Gerontology and Geriatrics*. 1989;9(2):115-22.
- 850 122. Goldring W, Chasis H, Ranges HA, Smith HW. Relations of effective renal blood flow and
851 glomerular filtration to tubular excretory mass in normal man. *Journal of Clinical Investigation*.
852 1940;19(5):739-50.
- 853 123. McDonald RK, Solomon DH, Shock NW. Aging as a factor in the renal hemodynamic changes
854 induced by a standardized pyrogen. *Journal of Clinical Investigation*. 1951;30(5):457-62.
- 855 124. Miller JH, McDonald RK, Shock NW. The renal extraction of p-aminohippurate in the aged
856 individual. *Journal of Gerontology*. 1951;6(3):213-6.
- 857 125. Fuiano G, Sund S, Mazza G, Rosa M, Caglioti A, Gallo G, et al. Renal hemodynamic response
858 to maximal vasodilating stimulus in healthy older subjects. *Kidney International*.
859 2001;59(3):1052-8.
- 860 126. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function - measured and
861 estimated glomerular filtration rate. *New England Journal of Medicine*. 2006;354(23):2473-83.
- 862 127. Christensson A, Elmståhl S. Estimation of the age-dependent decline of glomerular filtration
863 rate from formulas based on creatinine and cystatin C in the general elderly population. *Nephron*
864 *Clinical Practice*. 2011;117(1):c40-c50.
- 865 128. Van Den Noortgate NJ, Janssens WH, Delanghe JR, Afschrift MB, Lameire NH. Serum cystatin
866 C concentration compared with other markers of glomerular filtration rate in the old old. *Journal*
867 *of the American Geriatrics Society*. 2002;50(7):1278-82.
- 868 129. DeSanto N, Anastasio P, Coppola S, Barba G, Jadanza A, Capasso G. Age-related changes in
869 renal reserve and renal tubular function in healthy humans. *Child Nephrology and Urology*.
870 1991;11(1):33-40.
- 871 130. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to
872 estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Annals of*
873 *Internal Medicine*. 1999;130(6):461-70.
- 874 131. Musso CG, Oreopoulos DG. Aging and physiological changes of the kidneys including changes
875 in glomerular filtration rate. *Nephron Physiology*. 2011;119(Suppl. 1):p1-p5.
- 876 132. Zoico E, Di Francesco V, Guralnik J, Mazzali G, Bortolani A, Guariento S, et al. Physical
877 disability and muscular strength in relation to obesity and different body composition indexes in
878 a sample of healthy elderly women. *International Journal of Obesity*. 2004;28(2):234-41.
- 879 133. Lesser GT, Deutsch S. Measurement of adipose tissue blood flow and perfusion in man by
880 uptake of ⁸⁵Kr. *Journal of Applied Physiology*. 1967;23(5):621-30.
- 881 134. Andersson J, Karpe F, Sjöström L-G, Riklund K, Söderberg S, Olsson T. Association of adipose
882 tissue blood flow with fat depot sizes and adipokines in women. *International Journal of Obesity*.
883 2012;36(6):783-9.
- 884 135. Proctor DN, Newcomer SC, Koch DW, Le KU, MacLean DA, Leuenberger UA. Leg blood flow
885 during submaximal cycle ergometry is not reduced in healthy older normally active men. *Journal*
886 *of Applied Physiology*. 2003;94(5):1859-69.
- 887 136. Amery A, Bossaert H, Verstraete M. Muscle blood flow in normal and hypertensive subjects:
888 influence of age, exercise, and body position. *American Heart Journal*. 1969;78(2):211-6.
- 889 137. Johnson JM, Brengelmann GL, Rowell LB. Interactions between local and reflex influences on
890 human forearm skin blood flow. *Journal of Applied Physiology*. 1976;41(6):826-31.

- 891 138. Proctor DN, Koch DW, Newcomer SC, Le KU, Leuenberger UA. Impaired leg vasodilation during
892 dynamic exercise in healthy older women. *Journal of Applied Physiology*. 2003;95(5):1963-70.
- 893 139. Spann W, Dustmann H. Weight of the human brain and its dependence on age, body length,
894 cause of death and occupation. *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*.
895 1964;56(5):299-317.
- 896 140. Bertsch K, Hagemann D, Hermes M, Walter C, Khan R, Naumann E. Resting cerebral blood
897 flow, attention, and aging. *Brain Research*. 2009;1267:77-88.
- 898 141. Chen JJ, Rosas HD, Salat DH. Age-associated reductions in cerebral blood flow are
899 independent from regional atrophy. *Neuroimage*. 2011;55(2):468-78.
- 900 142. Davis SM, Ackerman RH, Correia JA, Alpert NM, Chang J, Buonanno F, et al. Cerebral blood
901 flow and cerebrovascular CO₂ reactivity in stroke-age normal controls. *Neurology*.
902 1983;33(4):391-.
- 903 143. Devous M, Stokely E, Chehabi H, Bonte F. Normal distribution of regional cerebral blood flow
904 measured by dynamic single-photon emission tomography. *Journal of Cerebral Blood Flow &
905 Metabolism*. 1986;6(1):95-104.
- 906 144. Hagstadius S, Risberg J. Regional cerebral blood flow characteristics and variations with age
907 in resting normal subjects. *Brain and Cognition*. 1989;10(1):28-43.
- 908 145. Leenders K, Perani D, Lammertsma A, Heather J, Buckingham P, Jones T, et al. Cerebral blood
909 flow, blood volume and oxygen utilization. *Brain*. 1990;113(1):27-47.
- 910 146. Lu H, Xu F, Rodrigue KM, Kennedy KM, Cheng Y, Flicker B, et al. Alterations in cerebral
911 metabolic rate and blood supply across the adult lifespan. *Cerebral Cortex*. 2011;21(6):1426-
912 34.
- 913 147. Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS. Decreases in regional cerebral blood flow
914 with normal aging. *Journal of Cerebral Blood Flow & Metabolism*. 1991;11(4):684-9.
- 915 148. Parkes LM, Rashid W, Chard DT, Tofts PS. Normal cerebral perfusion measurements using
916 arterial spin labeling: reproducibility, stability, and age and gender effects. *Magnetic Resonance
917 in Medicine*. 2004;51(4):736-43.
- 918 149. Scheinberg P, Blackburn I, Rich M, Saslaw M. Effects of aging on cerebral circulation and
919 metabolism. *AMA Archives of Neurology & Psychiatry*. 1953;70(1):77-85.
- 920 150. Shaw TG, Mortel KF, Meyer JS, Rogers RL, Hardenberg J, Cutaia MM. Cerebral blood flow
921 changes in benign aging and cerebrovascular disease. *Neurology*. 1984;34(7):855-.
- 922 151. Shin W, Horowitz S, Ragin A, Chen Y, Walker M, Carroll TJ. Quantitative cerebral perfusion
923 using dynamic susceptibility contrast MRI: evaluation of reproducibility and age-and gender-
924 dependence with fully automatic image postprocessing algorithm. *Magnetic Resonance in
925 Medicine*. 2007;58(6):1232-41.
- 926 152. Molina DK, DiMaio VJ. Normal organ weights in men: part I - the heart. *The American Journal of
927 Forensic Medicine and Pathology*. 2012;33(4):362-7.
- 928 153. Molina DK, DiMaio VJ. Normal organ weights in women: part I - the heart. *The American Journal of
929 Forensic Medicine and Pathology*. 2015;36(3):176-81.
- 930 154. Baliga RR, Rosen SD, Camici PG, Kooner JS. Regional myocardial blood flow redistribution as
931 a cause of postprandial angina pectoris. *Circulation*. 1998;97(12):1144-9.
- 932 155. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of
933 myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission
934 tomography. *Journal of the American College of Cardiology*. 1989;14(3):639-52.
- 935 156. Chan SY, Brunken RC, Czernin J, Porenta G, Kuhle W, Krivokapich J, et al. Comparison of
936 maximal myocardial blood flow during adenosine infusion with that of intravenous dipyridamole
937 in normal men. *Journal of the American College of Cardiology*. 1992;20(4):979-85.
- 938 157. Duvernoy CS, Meyer C, Seifert-Klauss V, Dayanikli F, Matsunari I, Rattenhuber J, et al. Gender
939 differences in myocardial blood flow dynamics: lipid profile and hemodynamic effects. *Journal
940 of the American College of Cardiology*. 1999;33(2):463-70.
- 941 158. Leight L, Defazio V, Talmers FN, Regan TJ, Hellems HK. Coronary blood flow, myocardial
942 oxygen consumption, and myocardial metabolism in normal and hyperthyroid human subjects.
943 *Circulation*. 1956;14(1):90-9.
- 944 159. Senneff MJ, Geltman EM, Bergmann SR. Noninvasive delineation of the effects of moderate
945 aging on myocardial perfusion. *Journal of Nuclear Medicine*. 1991;32(11):2037-42.
- 946 160. Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation*.
947 1955;12(4):557-66.
- 948 161. Lewis WH. Changes with age in the cardiac output in adult men. *American Journal of
949 Physiology*. 1938;121(2):517-27.
- 950 162. Smith RH. Normal blood volumes in men and women over sixty years of age as determined by
951 a modified Cr⁵¹ method. *The Journal of the American Society of Anesthesiologists*.
952 1958;19(6):752-6.

- 953 163. Smith WW, Wikler NS, Fox AC. Hemodynamic studies of patients with myocardial infarction.
954 Circulation. 1954;9(3):352-62.
- 955 164. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals - sexagenarians
956 through centenarians. Clinical Chemistry. 1992;38(6):1167-85.
- 957 165. Zauber NP, Zauber AG. Hematologic data of healthy very old people. Jama.
958 1987;257(16):2181-4.
- 959 166. Timiras ML, Brownstein H. Prevalence of anemia and correlation of hemoglobin with age in a
960 geriatric screening clinic population. Journal of the American Geriatrics Society.
961 1987;35(7):639-43.
- 962 167. Sklaroff D. Isotopic determination of blood volume in the normal aged. American Journal of
963 Roentgenology. 1956;75:1082-3.
- 964 168. Jernigan JA, Gudat JC, Blake JL, Bowen L, Lezotte DC. Reference values for blood findings in
965 relatively fit elderly persons. Journal of the American Geriatrics Society. 1980;28(7):308-14.
- 966 169. Veering BT, Burm A, Souverijn J, Serree J, Spierdijk J. The effect of age on serum
967 concentrations of albumin and alpha 1-acid glycoprotein. British Journal of Clinical
968 Pharmacology. 1990;29(2):201-6.
- 969 170. Routledge P, Stargel W, Kitchell B, Barchowsky A, Shand D. Sex-related differences in the
970 plasma protein binding of lignocaine and diazepam. British Journal of Clinical Pharmacology.
971 1981;11(3):245-50.
- 972 171. Paxton J, Briant R. Alpha 1-acid glycoprotein concentrations and propranolol binding in elderly
973 patients with acute illness. British Journal of Clinical Pharmacology. 1984;18(5):806-10.
- 974 172. Denko CW, Gabriel P. Age and sex related levels of albumin, ceruloplasmin, alpha 1 antitrypsin,
975 alpha 1 acid glycoprotein, and transferrin. Annals of Clinical & Laboratory Science.
976 1981;11(1):63-8.
- 977 173. Blain P, Mucklow J, Rawlins M, Roberts D, Routledge P, Shand D. Determinants of plasma
978 alpha 1-acid glycoprotein (AAG) concentrations in health. British Journal of Clinical
979 Pharmacology. 1985;20(5):500-2.
- 980 174. Champion EW, Delabry LO, Glynn RJ. The effect of age on serum albumin in healthy males:
981 report from the Normative Aging Study. Journal of Gerontology. 1988;43(1):M18-M20.
- 982 175. Fu A, Nair KS. Age effect on fibrinogen and albumin synthesis in humans. American Journal of
983 Physiology-Endocrinology And Metabolism. 1998;275(6):E1023-E30.
- 984 176. Gardner M, Scott R. Age-and sex-related reference ranges for eight plasma constituents derived
985 from randomly selected adults in a Scottish new town. Journal of Clinical Pathology.
986 1980;33(4):380-5.
- 987 177. Garry PJ, Hunt WC, Van der Jagt DJ, Rhyne RL. Clinical chemistry reference intervals for
988 healthy elderly subjects. The American Journal of Clinical Nutrition. 1989;50(5):1219-30.
- 989 178. Gersovitz M, Munro HN, Udall J, Young VR. Albumin synthesis in young and elderly subjects
990 using a new stable isotope methodology: response to level of protein intake. Metabolism.
991 1980;29(11):1075-86.
- 992 179. Pickart L. Increased ratio of plasma free fatty acids to albumin during normal aging and in
993 patients with coronary heart disease. Atherosclerosis. 1983;46(1):21-8.
- 994 180. Reed A, Cannon D, Winkelman J, Bhasin Y, Henry R, Pileggi V. Estimation of normal ranges
995 from a controlled sample survey. I. Sex and age-related influence on the SMA 12/60 screening
996 group of tests. Clinical Chemistry. 1972;18(1):57-66.
- 997 181. Wallace S, Whiting B. Factors affecting drug binding in plasma of elderly patients. British Journal
998 of Clinical Pharmacology. 1976;3(2):327-30.
- 999 182. Boddy K, King PC, Hume R, Weyers E. The relation of total body potassium to height, weight,
1000 and age in normal adults. Journal of Clinical Pathology. 1972;25(6):512-7.
- 1001 183. Bruce A, Andersson M, Arvidsson B, Isaksson B. Body composition. Prediction of normal body
1002 potassium, body water and body fat in adults on the basis of body height, body weight and age.
1003 Scandinavian Journal of Clinical and Laboratory Investigation. 1980;40(5):461-73.
- 1004 184. Cornish B, Ward L, Thomas B, Jebb S, Elia M. Evaluation of multiple frequency bioelectrical
1005 impedance and Cole-Cole analysis for the assessment of body water volumes in healthy
1006 humans. European Journal of Clinical Nutrition. 1996;50(3):159-64.
- 1007 185. Fülöp T, Worum I, Csongor J, Foris G, Leövey A. Body composition in elderly people.
1008 Gerontology. 1985;31(1):6-14.
- 1009 186. Hume R, Weyers E. Relationship between total body water and surface area in normal and
1010 obese subjects. Journal of Clinical Pathology. 1971;24(3):234-8.
- 1011 187. Schoeller DA. Changes in total body water with age. The American Journal of Clinical Nutrition.
1012 1989;50(5):1176-81.

- 1013 188. St-Onge M-P, Wang Z, Horlick M, Wang J, Heymsfield SB. Dual-energy X-ray absorptiometry
1014 lean soft tissue hydration: independent contributions of intra-and extracellular water. *American*
1015 *Journal of Physiology-Endocrinology and Metabolism*. 2004;287(5):E842-E7.
- 1016 189. Steen B. Body composition and aging. *Nutrition Reviews*. 1988;46(2):45-51.
- 1017 190. Chumlea WC, Guo SS, Zeller CM, Reo NV, Baumgartner RN, Garry PJ, et al. Total body water
1018 reference values and prediction equations for adults. *Kidney International*. 2001;59(6):2250-8.
- 1019 191. Gill KL, Gardner I, Li L, Jamei M. A bottom-up whole-body physiologically based
1020 pharmacokinetic model to mechanistically predict tissue distribution and the rate of
1021 subcutaneous absorption of therapeutic proteins. *The AAPS Journal*. 2016;18(1):156-70.
- 1022 192. Snyder W, Cook M, Nasset E, Karhausen L, Howells GP, Tipton I. Report of the Task Group on
1023 Reference Man: Pergamon Press; 1975.
- 1024 193. Valentin J. Basic anatomical and physiological data for use in radiological protection: reference
1025 values: ICRP Publication 89. *Annals of the ICRP*. 2002;32(3):1-277.
- 1026 194. Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, et al.
1027 Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharmaceutical Research*.
1028 1990;7(7):756-61.
- 1029 195. Russell TL, Berardi RR, Barnett JL, Dermentzoglou LC, Jarvenpaa KM, Schmaltz SP, et al.
1030 Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women.
1031 *Pharmaceutical Research*. 1993;10(2):187-96.
- 1032 196. Fallingborg J, Christensen L, Ingeman-Nielsen M, Jacobsen B, Abildgaard K, Rasmussen H.
1033 pH-profile and regional transit times of the normal gut measured by a radiotelemetry device.
1034 *Alimentary Pharmacology & Therapeutics*. 1989;3(6):605-14.
- 1035 197. Jamei M, Turner D, Yang J, Neuhoff S, Polak S, Rostami-Hodjegan A, et al. Population-based
1036 mechanistic prediction of oral drug absorption. *The AAPS Journal*. 2009;11(2):225-37.
- 1037 198. Morihara M, Aoyagi N, Kaniwa N, Kojima S, Ogata H. Assessment of gastric acidity of Japanese
1038 subjects over the last 15 years. *Biological and Pharmaceutical Bulletin*. 2001;24(3):313-5.
- 1039 199. Evans MA, Triggs EJ, Cheung M, Broe GA, Creasey H. Gastric emptying rate in the elderly:
1040 implications for drug therapy. *Journal of the American Geriatrics Society*. 1981;29(5):201-5.
- 1041 200. Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Harding PE, Shearman DJ. Changes in
1042 gastric emptying rates with age. *Clinical Science*. 1984;67(2):213-8.
- 1043 201. Gainsborough N, Maskrey V, Nelson M, Keating J, Sherwood R, Jackson S, et al. The
1044 association of age with gastric emptying. *Age and Ageing*. 1993;22(1):37-40.
- 1045 202. Madsen JL. Effects of gender, age, and body mass index on gastrointestinal transit times.
1046 *Digestive Diseases and Sciences*. 1992;37(10):1548-53.
- 1047 203. Graff J, Brinch K, Madsen JL. Gastrointestinal mean transit times in young and middle-aged
1048 healthy subjects. *Clinical Physiology*. 2001;21(2):253-9.
- 1049 204. Kupfer R, Heppell M, Haggith J, Bateman D. Gastric emptying and small-bowel transit rate in
1050 the elderly. *Journal of the American Geriatrics Society*. 1985;33(5):340-3.
- 1051 205. Chaw C, Yazaki E, Evans D. The effect of pH change on the gastric emptying of liquids
1052 measured by electrical impedance tomography and pH-sensitive radiotelemetry capsule.
1053 *International Journal of Pharmaceutics*. 2001;227(1):167-75.
- 1054 206. Moore JG, Tweedy C, Christian PE, Datz FL. Effect of age on gastric emptying of liquid-solid
1055 meals in man. *Digestive Diseases and Sciences*. 1983;28(4):340-4.
- 1056 207. Goo R, Moore J, Greenberg E, Alazraki N. Circadian variation in gastric emptying of meals in
1057 humans. *Gastroenterology*. 1987;93(3):515-8.
- 1058 208. Henderson JM, Heymsfield SB, Horowitz J, Kutner MH. Measurement of liver and spleen
1059 volume by computed tomography. Assessment of reproducibility and changes found following
1060 a selective distal splenorenal shunt. *Radiology*. 1981;141(2):525-7.
- 1061 209. Fischer M, Fadda HM. The effect of sex and age on small intestinal transit times in humans.
1062 *Journal of Pharmaceutical Sciences*. 2016;105(2):682-6.
- 1063 210. Husebye E, Engedal K. The patterns of motility are maintained in the human small intestine
1064 throughout the process of aging. *Scandinavian Journal of Gastroenterology*. 1992;27(5):397-
1065 404.
- 1066 211. Bender AD. Effect of age on intestinal absorption: implications for drug absorption in the elderly.
1067 *Journal of the American Geriatrics Society*. 1968;16(12):1331-9.
- 1068 212. Warren P, Pepperman M, Montgomery R. Age changes in small-intestinal mucosa. *The Lancet*.
1069 1978;312(8094):849-50.
- 1070 213. Saltzman JR, Kowdley KV, Perrone G, Russell RM. Changes in small-intestine permeability with
1071 aging. *Journal of the American Geriatrics Society*. 1995;43(2):160-4.
- 1072 214. Valentini L, Ramming S, Haas V, Postrach E, Werich M, Fischer A, et al. Small intestinal
1073 permeability in older adults. *Physiological Reports*. 2014;2(4):1-10.

1074 215. Barter ZE, Tucker GT, Rowland-Yeo K. Differences in cytochrome p450-mediated
1075 pharmacokinetics between chinese and caucasian populations predicted by mechanistic
1076 physiologically based pharmacokinetic modelling. *Clinical Pharmacokinetics*.
1077 2013;52(12):1085-100.

1078 216. Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual
1079 variability in pharmacokinetics using virtual human populations and integrating general
1080 knowledge of physical chemistry, biology, anatomy, physiology and genetics: a tale of 'bottom-
1081 up'vs 'top-down'recognition of covariates. *Drug Metabolism and Pharmacokinetics*.
1082 2009;24(1):53-75.

1083 217. Abduljalil K, Jamei M, Rostami-Hodjegan A, Johnson TN. Changes in individual drug-
1084 independent system parameters during virtual paediatric pharmacokinetic trials: introducing
1085 time-varying physiology into a paediatric PBPK model. *The AAPS Journal*. 2014;16(3):568-76.

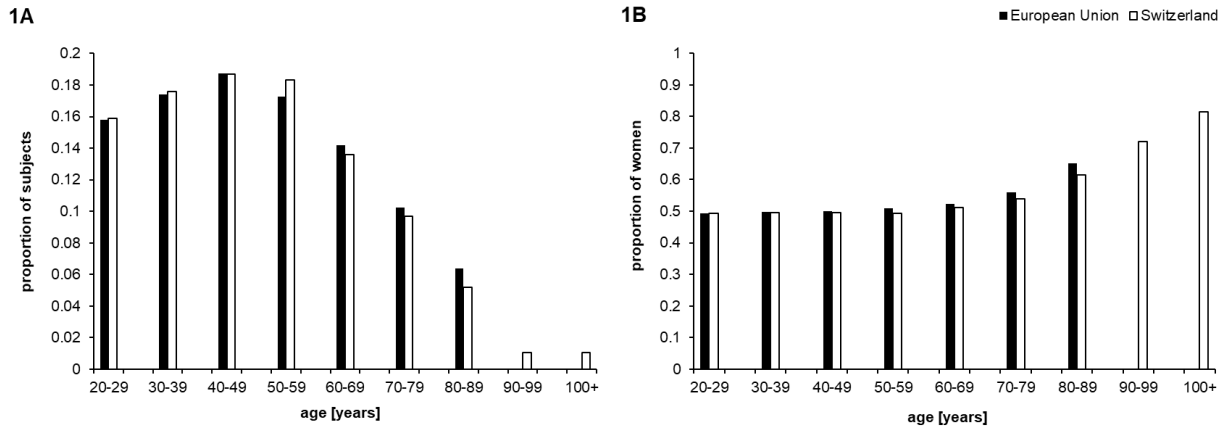
1086 218. Ludin H. Radiologic estimation of kidney weight. *Acta Radiologica Diagnosis*. 1967;6(6):561-74.

1087 219. McLachlan M, Wasserman P. Changes in sizes and distensibility of the aging kidney. *The British*
1088 *Journal of Radiology*. 1981;54(642):488-91.

1089 220. Centers for Disease Control and Prevention. HIV among people aged 50 and over. 2018 [cited
1090 26/02/2018]; Available from: <https://www.cdc.gov/hiv/group/age/olderamericans/index.html>
1091

1092

1093 **11 Figures**

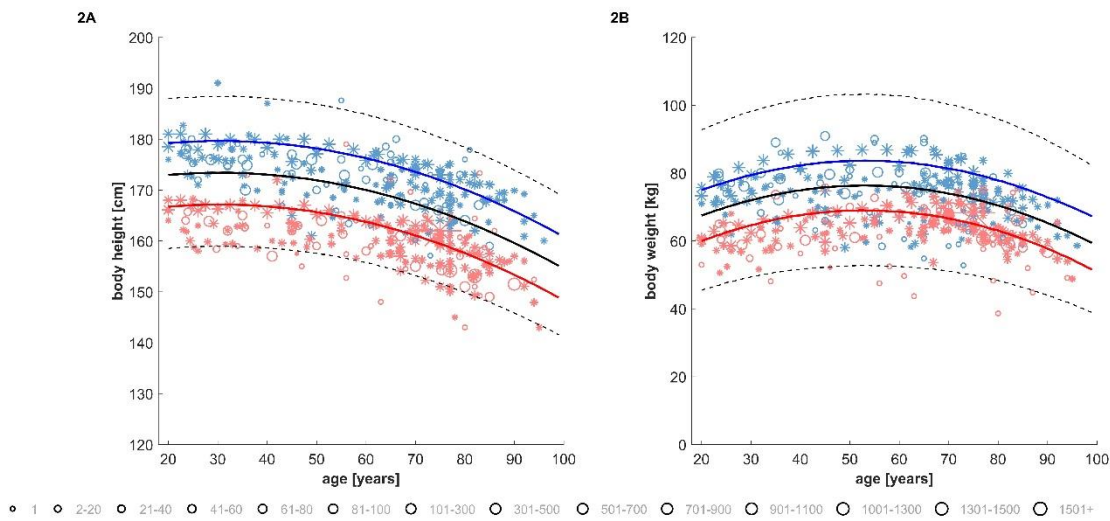


1094

1095 Figure 1: Proportion of subjects (1A) and proportion of women (1B) per age decade. Data are from the
 1096 28-member states of the European Union (black bars) and Switzerland (white bars)
 1097

1098

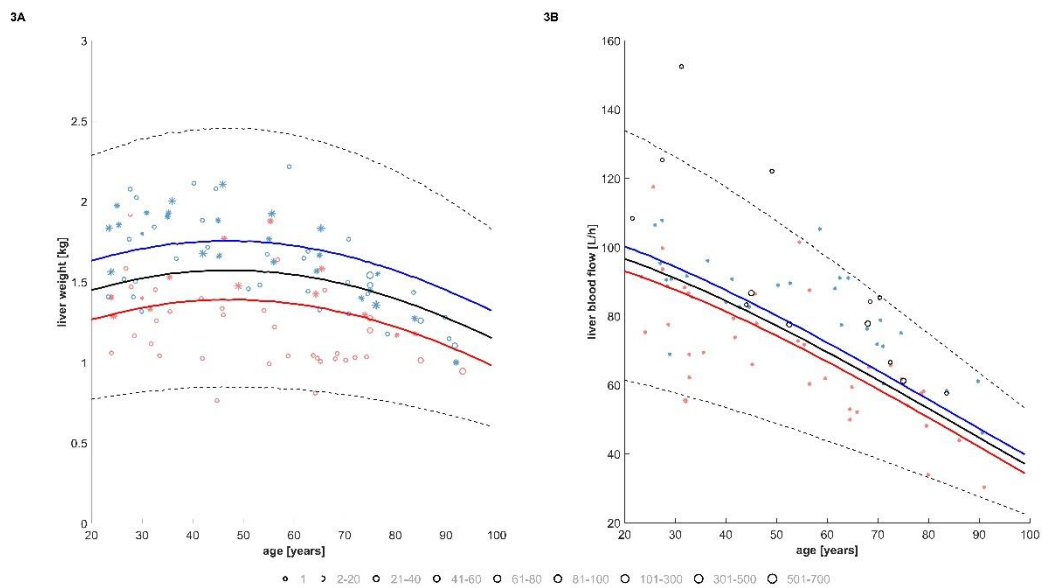
1099



1100

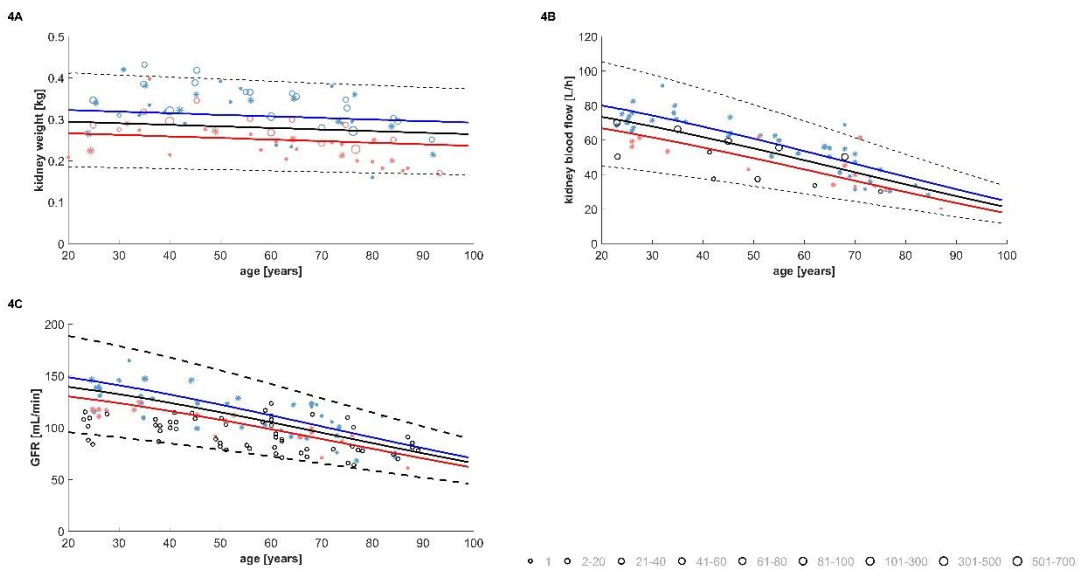
1101 Figure 2: Body height (2A) and body weight (2B) per age decade in an aging population. The blue, red
 1102 and black lines represent the predicted mean of virtual males, virtual females and from all virtual
 1103 subjects, respectively. The dashed lines represent the 5 and 95% percentile of the predictions. Stars
 1104 show observed data from the development and circles represent overserved data from the independent
 1105 verification dataset. The size of the stars and circles indicates the size of the studied population

1106



1107

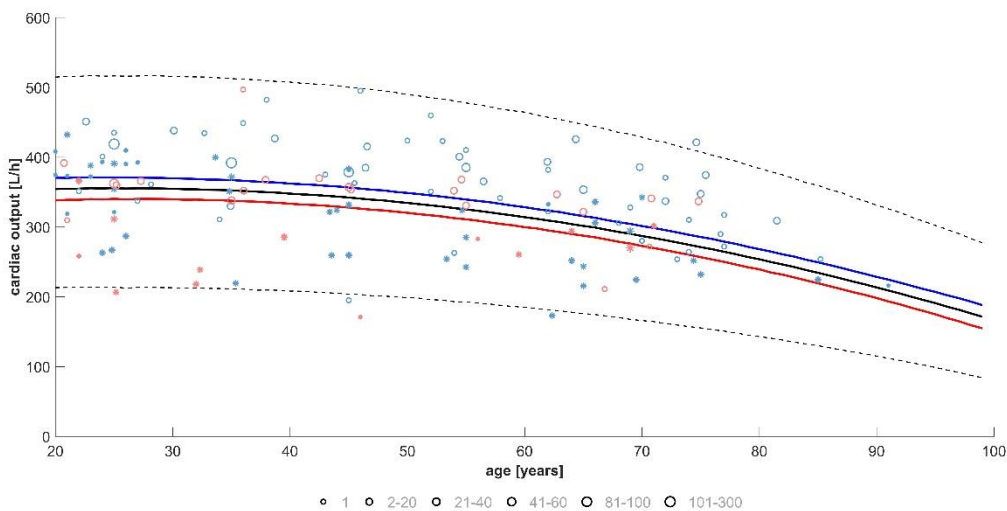
1108 Figure 3: Liver weight (3A) and liver blood flow (3B) per age decade in an aging population. The blue,
1109 red and black lines represent the predicted mean of virtual males, virtual females and from all virtual
1110 subjects, respectively. The dashed lines represent the 5 and 95% percentile of the predictions. Stars
1111 show observed data from the development and circles represent observed data from the independent
1112 verification dataset. Black circles represent data from an undefined gender population. The size of the
1113 stars and circles indicates the size of the studied population
1114
1115
1116



1117

1118 Figure 4: Kidney weight (4A), kidney blood flow (4B) and glomerular filtration rate (4C) per age decade
1119 in an aging population. The blue, red and black lines represent the predicted mean of virtual males,
1120 virtual females and from all virtual subjects, respectively. The dashed lines represent the 5 and 95%
1121 percentile of the predictions. Stars show observed data from the development and circles represent
1122 observed data from the independent verification dataset. Black circles represent data from an undefined
1123 gender population. The size of the stars and circles indicates the size of the studied population

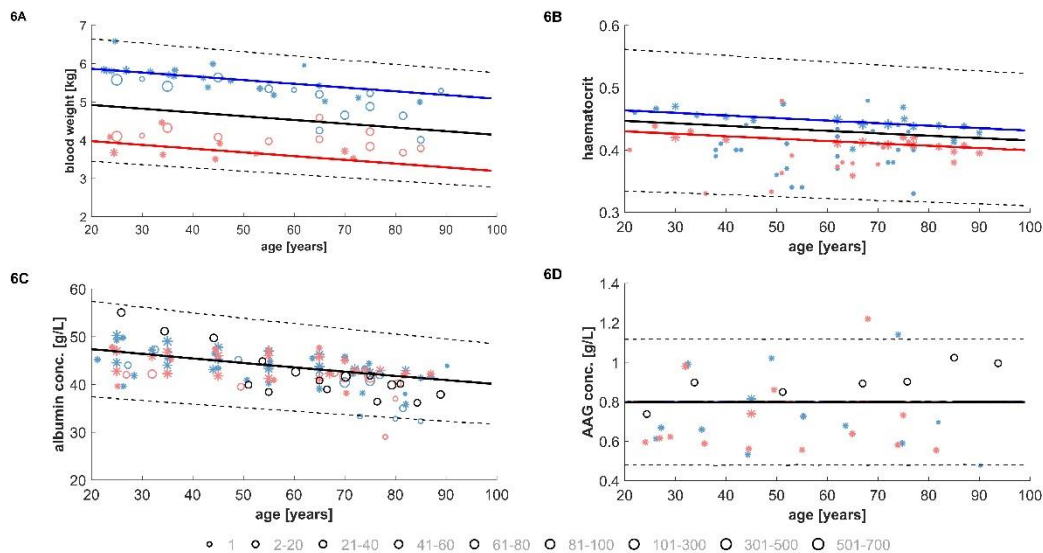
1124



1125

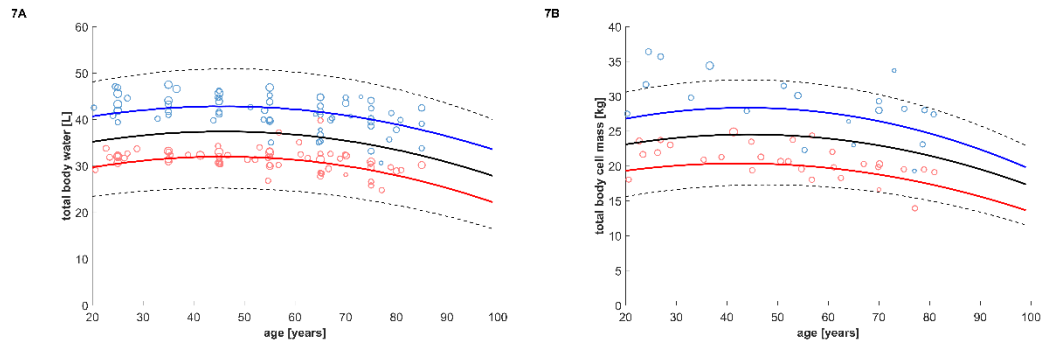
1126 Figure 5: Cardiac output per age decade in an aging population. The blue, red and black lines represent
1127 the predicted mean of virtual males, virtual females and from all virtual subjects, respectively. The
1128 dashed lines represent the 5 and 95% percentile of the predictions. Stars show observed data from the
1129 development and circles represent observed data from the independent verification dataset. The size of
1130 the stars and circles indicates the size of the studied population
1131

1132



1133

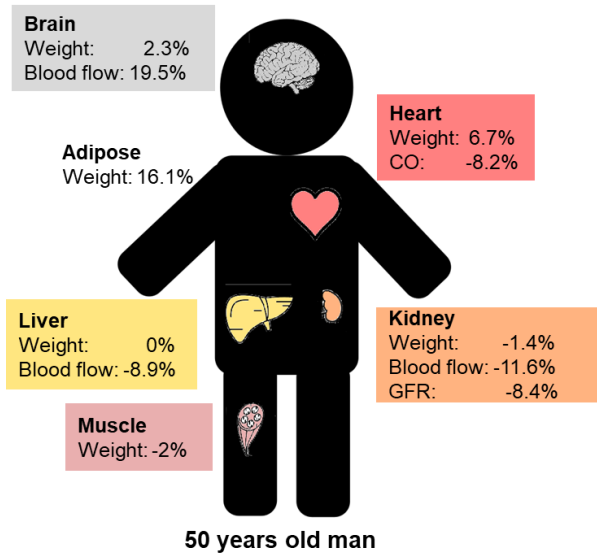
1134 Figure 6: Blood weight (6A), hematocrit (6B), albumin (6C) and alpha-acid glycoprotein (6D)
1135 concentration per age decade in an aging population. The blue, red and black lines represent the
1136 predicted mean of virtual males, virtual females and from all virtual subjects, respectively. The dashed
1137 lines represent the 5 and 95% percentile of the predictions. Stars show observed data from the
1138 development and circles represent overserved data from the independent verification dataset. Black
1139 circles represent data from an undefined gender population. The size of the stars and circles
1140 indicates the size of the studied population



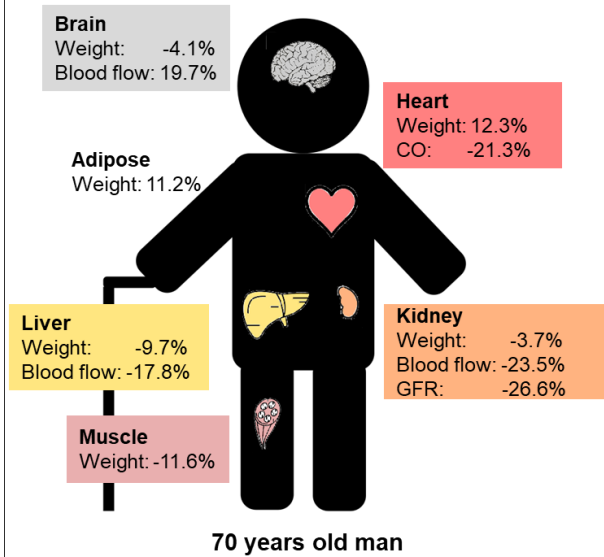
1141

1142 Figure 7: Total body water (7A) and total body cell mass (7B) per age decade in an aging population.
 1143 The blue, red and black lines represent the predicted mean of virtual males, virtual females and from all
 1144 virtual subjects, respectively. The dashed lines represent the 5 and 95% percentile of the predictions.
 1145 Stars show observed data from the development and circles represent observed data from the
 1146 independent verification dataset. The size of the stars and circles indicates the size of the studied
 1147 population

8A



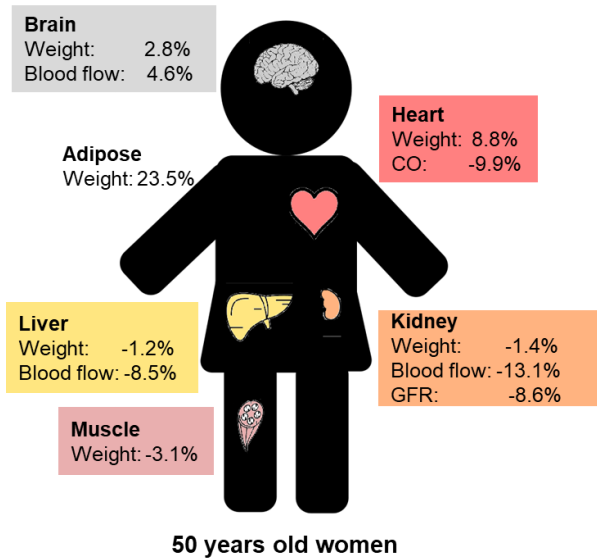
8B



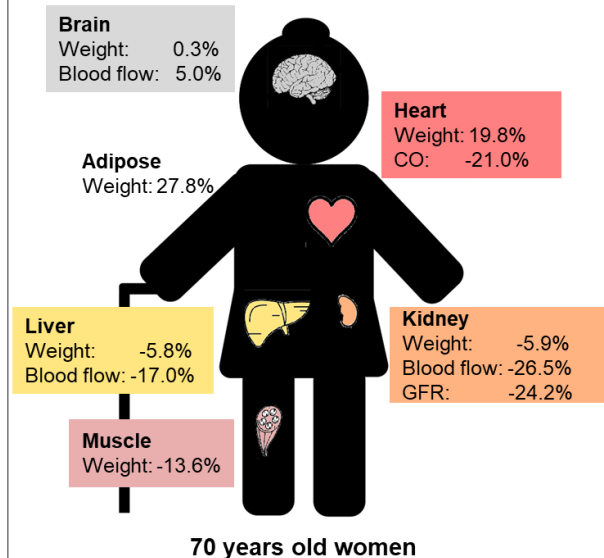
1148

1149

8C



8D



1150

1151 Figure 8: Comparison of a 50 and 70 years old man (8A and 8B) and women (8C and 8D) with a 30
 1152 years old subject, who was arbitrarily chosen to represent a young individual. Blood flow is relative to
 1153 cardiac output and all values are relative to a 30 years old man and women, respectively

1154 **12 Tables**

1155

1156 Table. 1: Descriptive equations and population variability for anatomical, physiological and biological
 1157 parameters necessary to inform a PBPK model. Virtual subjects from 20 to 99 years can be generated.
 1158 Blood flows are relative to cardiac output and the variability is only propagated from cardiac output. *m*
 1159 indicates male and *f* female, when there was a gender-related difference in the CV

Parameter	Unit	Descriptive equation	CV [%]
Body height	cm	$-0.0039 \times Age^2 + 0.238 \times Age - 12.5 \times Sex + 176$	3.8
Body weight	kg	$-0.0039 \times Age^2 + 1.12 \times Body\ height + 0.611 \times Age - 0.424 \times Sex - 137$	15.2
Lung weight	kg	$e^{(0.028 \times Body\ height + 0.0077 \times Age - 5.6)}$	0
Adipose weight	kg	$0.68 \times Body\ weight - 0.56 \times Body\ height + 6.1 \times Sex + 65$	29.6
Bone weight	kg	$e^{(0.024 \times Body\ height - 1.9)}$	13.2
Brain weight	kg	$e^{-0.0075 \times Age + 0.0078 \times Body\ height - 0.97}$	9.0
Gonad weight	kg	$-0.00034 \times Body\ weight - 0.00022 \times Age - 0.03 \times Sex + 0.072$	34.8
Heart weight	kg	$0.34 \times BSA + 0.0018 \times Age - 0.36$	17.9 (m), 22.7 (f)
Kidney weight	kg	$-0.00038 \times Age - 0.056 \times Sex + 0.33$	19.3 (m), 23.2 (f)
Muscle weight	kg	$17.9 \times BSA - 0.0667 \times Age - 5.68 \times Sex - 1.22$	11.8
Skin weight	kg	$e^{(-0.0058 \times Age - 0.37 \times Sex + 1.13)}$	8.3
Thymus weight	kg	0.0221	44.8
Gut weight	kg	$3E^{-06} \times Body\ height^{2.49}$	7.3
Spleen weight	kg	$e^{1.13 \times BSA - 3.93}$	51.7
Pancreas weight	kg	0.103	27.8
Liver weight	kg	$e^{(0.87 \times BSA - 0.0014 \times Age - 1.0)}$	23.7
Blood weight	kg	$e^{(0.067 \times BSA - 0.0025 \times Age - 0.38 \times Sex + 1.7)}$	10.4
Cardiac output (CO)	L/h	$159 \times BSA - 1.56 \times Age + 114$	21.1
Adipose blood flow	% of CO	$(0.044 + 0.027 \times Sex) \times Age + 2.4 \times Sex + 3.9$	
Bone blood flow	% of CO	5	
Brain blood flow	% of CO	$e^{-0.48 \times BSA + 0.04 \times Sex + 3.5}$	
Gonad blood flow	% of CO	$-0.03 \times Sex + 0.05$	
Heart blood flow	% of CO	$-0.72 \times Body\ height - 10 \times Sex + 134$	
Kidney blood flow	% of CO	$-8.7 \times BSA + 0.29 \times Body\ height - 0.081 \times Age - 13$	
Muscle blood flow	% of CO	$-6.4 \times Sex + 17.5$	
Skin blood flow	% of CO	5	
Thymus blood flow	% of CO	1.5	
Gut blood flow	% of CO	$2 \times Sex + 14$	

Parameter	Unit	Descriptive equation	CV [%]
Spleen blood flow	% of CO	3	
Pancreas blood flow	% of CO	1	
Liver blood flow	% of CO	$-0.108 \times Age + 1.04 \times Sex + 27.9$	
Albumin	g/L	$-0.0709 \times Age + 47.7$	7.9
GFR	mL/min	$e^{-0.0079 \times Age + 0.5 \times BSA + 4.2}$	14.7

1160