European Journal of Pharmaceutical Sciences 188 (2023) 106496

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Physiologically based pharmacokinetic (PBPK) modelling of oral drug absorption in older adults – an AGePOP review

Cleo Demeester [a,b,1], Donnia Robins [c,d,1], Angela Elma Edwina [e,1], Jos Tournoy [e,f], Patrick Augustijns [b], Ibrahim Ince [a], Andreas Lehmann [c], Maria Vertzoni [d], Jan Frederik Schlender [a,2,*]

[a] Systems Pharmacology & Medicine, Pharmaceuticals, Bayer AG, Leverkusen 51373, Germany
[b] Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Gasthuisberg O&N II, Leuven, Belgium
[c] Global CMC Development, Merck KGaA, Frankfurter Straße 250, Darmstadt, Germany
[d] Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Zografou, Greece
[e] Gerontology and Geriatrics Unit, Department of Public Health and Primary care, KU Leuven – University of Leuven, Leuven, Belgium
[f] Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:
PBPK modelling
Absorption
Older people
Elderly
Peroral
In silico
Clinical pharmacology
Oral drug development

ABSTRACT

The older population consisting of persons aged 65 years or older is the fastest-growing population group and also the major consumer of pharmaceutical products. Due to the heterogenous ageing process, this age group shows high interindividual variability in the dose-exposure-response relationship and, thus, a prediction of drug safety and efficacy is challenging. Although physiologically based pharmacokinetic (PBPK) modelling is a well-established tool to inform and confirm drug dosing strategies during drug development for special population groups, age-related changes in absorption are poorly accounted for in current PBPK models. The purpose of this review is to summarise the current state-of-knowledge in terms of physiological changes with increasing age that can influence the oral absorption of dosage forms. The capacity of common PBPK platforms to incorporate these changes and describe the older population is also discussed, as well as the implications of extrinsic factors such as drug-drug interactions associated with polypharmacy on the model development process. The future potential of this field will rely on addressing the gaps identified in this article, which can subsequently supplement *in-vitro* and *in-vivo* data for more robust decision-making on the adequacy of the formulation for use in older adults and inform pharmacotherapy.

1. Introduction

Worldwide, the advanced aged population is rapidly growing in size (Division, 2019). The older adult population, typically defined as persons aged 65 years and older (European, C. and Eurostat, 2020), is expected to grow to be 31.3% of the European Union's population by 2100, up from 20.8% in 2021 (Eurostat, 2022). Even though this group receives the vast majority of drug prescriptions, current formulations are primarily based on clinical studies that include younger adults between 18 and 64 years of age. Due to factors such as multi-morbidity, frailty, and polypharmacy, older adults and especially geriatric patients are usually not enroled in clinical trials and thus underrepresented in these studies (Liu, 2022; Ruiter et al., 2019). This is a major drawback as the physiological changes associated with ageing can potentially alter the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs (Mangoni and Jackson, 2004). Therefore, it may be necessary to optimize dosing for maximum therapeutic effect and safety in this population. Older and frail adults usually receive the standard dose recommended in the Summary of Product Characteristics (SmPC) of the European Medicines Agency (EMA) which was determined from study data in a younger, more homogenous population cohort. Additionally The Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START), which form the START/STOP criteria, and the American Geriatrics Society Beer's Criteria are both lists of

* Corresponding author.
E-mail address: jan-frederik.schlender@novartis.com (J.F. Schlender).
[1] These authors contributed equally to this work.
[2] Present address: Novartis Institute of Biomedical Research, Basel, Switzerland

https://doi.org/10.1016/j.ejps.2023.106496
Received 28 March 2023; Received in revised form 6 June 2023; Accepted 14 June 2023
Available online 15 June 2023

inappropriate medications for older adults in most circumstances, in certain conditions or in combination with other drugs (American Geriatrics Society, 2019; O'Mahony et al., 2015). When dose adjustments are adviced they are frequently based on using genomics, biomarkers, or quantitative approaches. Within these quantitative approaches, population PK/PD methods often rely on scaling the exposure with age- or organ-based functions (e.g., creatinine clearance) from the studied young adult population. Since scaling factors, such as height and body weight, are not always linear with age, such extrapolations based on observations in the young may not be suitable (Schlender et al., 2018a).

A well-proven auxiliary tool for untested or under-studied scenarios is physiologically based pharmacokinetic (PBPK) modelling. When clinical data is lacking, PBPK approaches are well-established for dose guidance in paediatrics and have been mentioned in several existing regulatory guidelines (Grimstein et al., 2019; (EMA), E.M.A., 2018). PBPK modelling incorporates system-specific components such as organ volumes and perfusion rates as well as absorption, distribution, metabolism, and elimination (ADME) related protein abundance and activity. It is therefore a useful *in silico* tool that can give more insight into potential PK alterations due to changes in these parameters in older adults. Combining the system components with drug-specific parameters such as lipophilicity, receptor binding, and ionization constants, PBPK models can predict the PK of a compound in the body using mathematical relationships such as *in vitro in vivo* correlation (IVIVC). This bottom-up approach permits the investigation of the impact of intrinsic (e.g., race, age, disease) and extrinsic (e.g., smoking, diet) patient factors on ADME processes (Zhao et al., 2011). Since the physiological data is presumably representative of the population and the physiochemical data for the drug is also constant, this approach is not heavily reliant on clinical data for model development like conventional compartmental modelling and other top-down approaches. Therefore, it provides the advantage of hypothesis testing and extrapolation beyond the domain of experimentation to complex scenarios such as drug-drug interactions (DDIs) and special populations such as patients with renal impairment or geriatric patients. Furthermore, incorporating these intrinsic factors such as age and ethnicity into a PBPK model may contribute to the development of personalized medicine (Schlender et al., 2018a; Schlender et al., 2016; Schlender et al., 2018b).

Currently, several well-established PBPK modelling tools have included the changes in physiology associated with advanced age and have been used to investigate changes in PK in this target group (Schlender et al., 2016; Schlender et al., 2018b; Stader et al., 2021a; Stader et al., 2021b). However, for the most part, age-associated changes in absorption have been considered only indirectly by informing gastrointestinal-tract (GI) organ volumes and perfusion rates, while changes in other processes like distribution and especially elimination have been the primary focus. As the GI-tract is known to undergo changes with advancing age, there is a need to mechanistically understand and capture these changes in models for better predictions in this population. In this review, the latest understandings and existing gaps in modelling absorption in older adults using PBPK modelling will be discussed.

2. Current PBPK models for older people

The general workflow for developing PBPK models for the older population is depicted in Fig. 1. The approach begins with the validation of an adult PBPK model using known system- and drug-specific parameters from various data sources. An adult population has less inter-individual system variability and is therefore used as the classical first-in-human population cohort. Accordingly, a PBPK model is generally built and validated on study data of this population cohort (Kuepfer et al., 2016). Afterwards, age-associated physiological changes are incorporated (as the drug-specific parameters are constant) and the older adult prediction can be evaluated.

As a first starting point, Thompson et al. (2009) developed a database for physiological and anatomical literature sources for older adults. This database includes changes in key physiological parameters such as organ volumes, blood flows and metabolic clearances for different age ranges in this healthy population and even for older adults with health conditions like diabetes. As a valuable resource for age-inclusive model parameterization, it facilitates the model-building process for the prediction of drug exposures in older populations for use in risk assessment and dose selection. Table 1 presents an overview of published PBPK models that have been applied to successfully predict pharmacokinetics in older people.

Subsequently, Schlender et al. informed a generic whole-body PBPK framework in older adults by extending the database of Thompson et al. (Zhao et al., 2011) with additional data from the literature (Schlender et al., 2016). Multiple applications to evaluate the predictive performance have been published as well (Schlender et al., 2016, Schlender et al., 2018b). As a result, an even more robust database of anthropometric measures, organ weights, tissue weights, cardiac index, organ blood flows, glomerular filtration rate (GFR), and distribution of body water and fat mass over a lifespan is available and implemented in the open source software PK-Sim and Mobi which are part of OSP (OSP Suite, http://www.open-systemspharmacology.org) (Schlender et al., 2016; Lippert et al., 2019). When Schlender et al. (2018b) predict the PK of ciprofloxacin up to an age of 90 years, anatomical age-associated changes, as well as changes in clearance and protein-binding were distinguished. The resulting intravenous and oral population models demonstrated similar predictive power as the precursor adult model and allowed for the identification of critical parameters as a function of age using a sensitivity analysis (Schlender et al., 2018b). Using this database in OSP, Kneller and Hempel (2020) predicted risperidone and 9-hydroxyrisperidone in various cytochrome P450 (CYP) 2D6 metabolizers in older adults. Age-related changes in oral drug absorption, and GI organ volumes in older adults were, however, not accounted for in the models of Schlender et al. and Kneller et al.

Relevant information for the respective framework was also extracted from the database of Thompson et al. (2009) and implemented in the Simcyp minimal PBPK approach (Simcyp Ltd, Blades Enterprise Centre, Sheffield, UK) to inform the Geriatric population (Chetty et al., 2018). It has been successfully applied to predict PK in a variety of ethnicities including Caucasian, Japanese, and Chinese older populations (Cui et al., 2021; De Sousa Mendes and Chetty, 2019; Rhee et al. 2017; Li et al., 2019). Most of these models focus on a specific risk factor such as renal impairment whose incidence increases with age, or ethnic differences in metabolism that can be further exacerbated by advanced age. For example, in the model of Wang et al., Simcyp's internal Chinese population was used with a custom age range of up to 80 years to predict the PK of midazolam, a well-known CYP substrate (Kim et al., 2021).

Another PBPK platform is GastroPlus (Simulations Plus, Inc., Lancaster, California) wherein the Population Estimates for Age-Related (PEAR™) Physiology™ module accounts for the body weight, height, body mass index, tissue weights and volumes, and tissue perfusion rates in older adults (SimulationsPlus. Inc, 2018). Here, the underlying literature sources to inform the respective framework are not published. Using this module, Kim et al. succeeded to predict the PK of bilastine in healthy volunteers and older adults and proved that the PBPK approach can support clinical decision-making in this age group (Stader et al., 2019). While developing this model, apical and basolateral transporters in the gut were implemented to modulate both secretion and absorption. However, when scaling to older adults, it was assumed that age had no effect on these transporters, and this proved to have no negative impact on the predictive power of the model.

Similar to the previously mentioned databases, Stader et al. (2021a) also retrieved most information from the database of Thompson et al. (2009) and added additional sources in order to take age into account during PBPK model development. The repository validated in MATLAB (R2017a, Natick, Massachusetts: The MathWorks Inc.), includes equations describing anatomical, biological, and physiological parameters

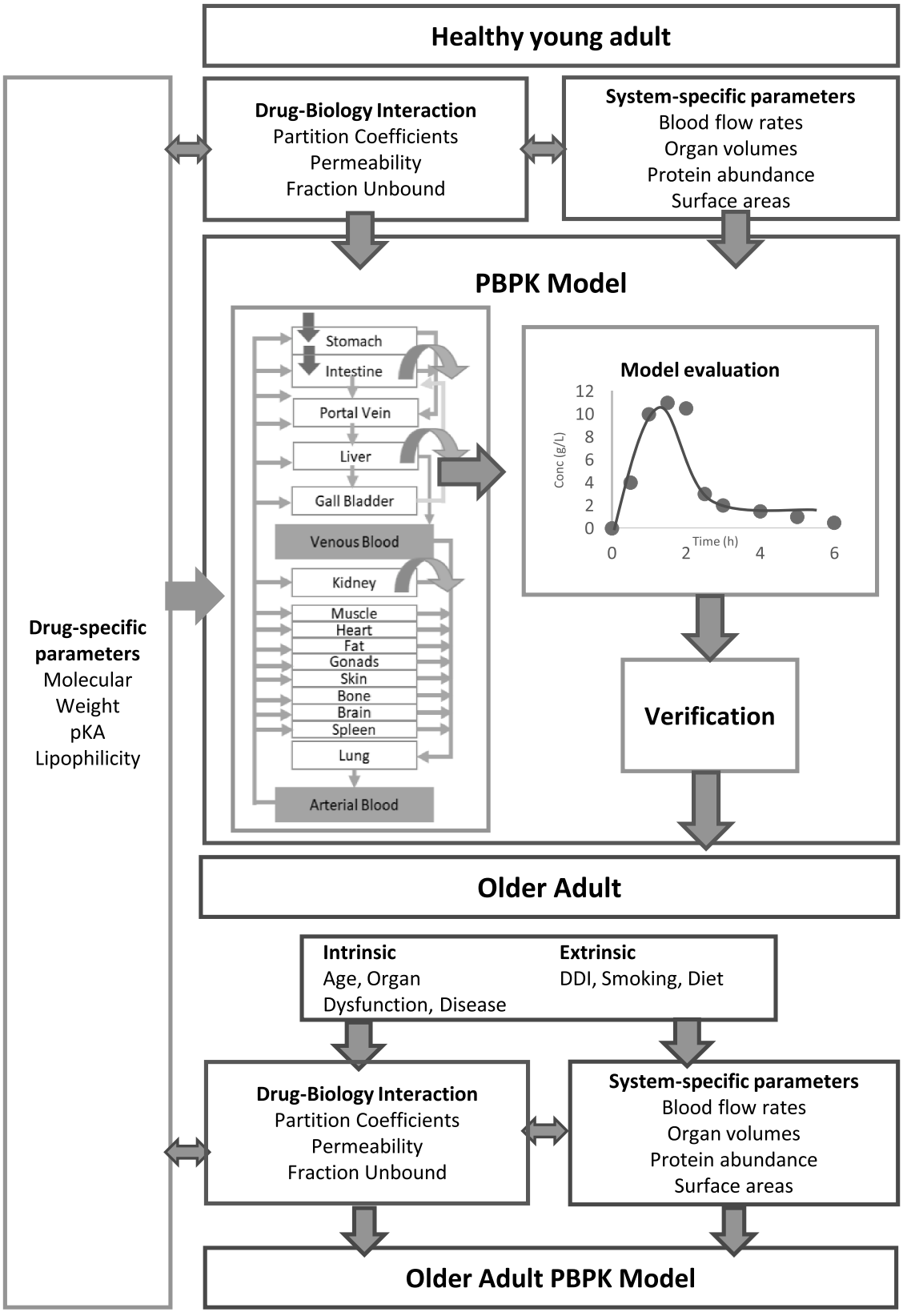

Fig. 1. Overview workflow PBPK modelling for the older population. Where absorption is given in brown, metabolism and excretion in green, and the biliary system in yellow. For older adults the intrinsic and extrinsic factors influence the system-specific parameters while drug-specific parameters remain unchanged.

Table 1
Overview of PBPK models of drugs applied in the older population.

Compound(s)	Rationale	Route	Age Adjustments*	Refs.
***OSP*®**[a]				
Morphine, Furosemide	Model qualification	IV	Anthropometrics, organ volumes, and perfusion	(Schlender et al., 2016)
Ciprofloxacin	Dose evaluation in older adults	IV, PO	Proportional decrease of tubular secretion to GFR	(Schlender et al., 2018b)
Risperidone	Polymorphism	PO		(Kneller and Hempel, 2020)
Pregabalin	Special populations	PO		(Rashid et al., 2021)
MATLAB®-based repository[b,c]				
Bictegravir	Special Population – HIV	PO		(Stader et al., 2021a)
Ritonavir, Darunavir/Ritonavir, Atazanavir/Ritonavir, Dolutegravir, Rilpivirine, Efavirenz, Etravirine, Tenofovir, Emtricitabine	Special Population – HIV, Ethnics	PO		(Stader et al., 2021b)
Simcyp Simulator®[d]				
Midazolam	Supporting dose recommendations in the older population while taking into account ethnic differences	PO	Scaling using the Simcyp general population model	(Wang et al., 2016)
Metformin	Extend the PBPK model to special populations	PO	Physiologically Based Pharmacokinetic Modelling and Prediction of Metformin Pharmacokinetics in Renal/Hepatic-Impaired Young Adults and Elderly Populations	(Rhee et al., 2017)
Caffeine, Desipramine, Midazolam, Digoxin, Warfarin, Triazolam, Omeprazole	Geriatrics model verification	IV, PO		(Chetty et al., 2018)
Caffeine, Theophylline	Incorporating the impact of ethnicity-specific drug disposition mediated by CYP1A2 in young and older Chinese adults	PO	Recalibrate the system parameters of Chinese-specific microsomal protein per gram of liver, liver weight, CYP1A2 abundance	(Li et al., 2019)
Emtricitabine, Lamivudine, Tenofovir	Supporting dose recommendations in the older population while taking into account ethnic differences	PO	Scaling using the Sim-Geriatric Population Model	(De Sousa Mendes and Chetty, 2019)
Theophylline, Midazolam, Simvastatin, Ceftazidime, Gentamicin, Vancomycin	Evaluating combined ethnic differences in metabolism and age effects on the pharmacokinetics	IV	Height, Weight, Body surface area, Cardiac output, Serum creatinine, Liver weight, Kidney weight	(Cui et al., 2021)
GastroPlus[e]				
Bilastine	Supporting dose recommendations in the older population	IV, PO	Scaling using the Population Estimates for Age-Related (PEAR) Physiology module	(Kim et al., 2021)

[a] OSP Suite, http://www.open-systemspharmacology.org.
[b] Natick, Massachusetts: The MathWorks Inc.
[c] Stader et al. (2019).
[d] Certara UK Ltd, Sheffield, UK.
[e] SimulationsPlus, Inc.
* Adjustment beyond build-in components.

representative of an ageing healthy Caucasian along with the associated population variability (Stader et al., 2021b; Stader et al., 2019). Using this database, a whole-body PBPK model was later implemented in MATLAB, to investigate the risk of toxicity of the integrase inhibitor bictegravir in ageing persons living with HIV, a chronic condition (Stader et al., 2021a). They concluded that no dose adjustment is needed due to advanced age since exposure changes were well within the indicated therapeutic window of the drug.

During the development of the repository of Stader et al. (2019), parameters influencing absorption were considered including gastric pH, gastric emptying time, small intestinal transit time, gastrointestinal surface area, and the abundance of various enzymes and transporters. Similar to the results of this review discussed in further sections, the lack of data for these parameters limited conclusions, particularly in the case of enzyme and transporter abundance and gastric pH. However, with the given evidence, the assumption and consequent recommendation in the article was to use similar values for the older population as used in the young for absorption (Stader et al., 2019). Considering that this study was restricted to healthy Caucasians, these conclusions are not necessarily valid for the entire older population, since the diversity of lifestyle factors such as comorbidities and diet described in later sections can also influence these parameters, a point also noted by Stader et al. (2021b).

3. PBPK modelling of absorption

Various mechanistic absorption frameworks have been implemented into PBPK software platforms. The absorption model of Thelen et al. (2011), (2012) implemented in PK-Sim is divided into 12 compartments of the GI tract from the stomach to the rectum. Each intestinal compartment is representative of a distinct region with corresponding physiological values such as surface area and pH and contains a mucosal compartment beside the luminal segment. Similarly, the compartmental absorption and transit (CAT) model (Yu and Amidon, 1999) has been implemented in GastroPlus and has later been extended by including various parameters, such as colon absorption, in the advanced compartmental absorption and transit (ACAT). The ACAT model consists of nine compartments including the stomach, seven for the small intestine, and finally the colon (Jamei et al., 2009a, 2009b, Wang and Flanagan, 1999). Simcyp's model is called the advanced dissolution absorption and metabolism model (ADAM) and is comparable to ACAT in its compartmentalization but differs in their parameterization of physiological processes (Thelen et al., 2011; Thelen et al., 2012). Within these frameworks, drug movement within the GI tract is described with standard ordinary differential equations (ODEs) that depend on various anatomical and physiological parameters. Extra components can be added to the Simcyp code using the embedded interface scirpting

language Lua (Ierusalimschy, 2006). While using PK-Sim with standardized ODEs, the user can additionally customise these ODEs with Mobi. Despite the fact that these PBPK frameworks rely on a large number of input parameters derived from literature values, measurements, and assumptions, the model can still be a simpler representation of the phenomena they intend to emulate. As a result, the PBPK simulation may not always fully match to the data. In this case, the PBPK software allows the user to specify which values of input parameters result in the simulation that best fits the observed data. Besides, anatomical and physiological parameters, the absorption model frameworks also have the capacity to account for food effects, transporter and efflux protein densities, and other regional factors within the GI tract (Thelen et al., 2011; Thelen et al., 2012). Many of these parameters such as pH are the same for older adults as implemented for the young, and the following section will explore the plausibility of this assumption by presenting the current scientific knowledge regarding age-associated changes in absorption-related parameters. A summary of these findings is given in Table 2.

Table 2
Incorporation of the absorption-related parameters in the PBPK modelling platforms and their adjustments for the older population.

Parameters	Software	Current incorporation in the software	Incorporated change in older population	Comment on change in the older population
Oral Cavity and Swallowing Capacity	PK-Sim	Saliva flow rate and saliva pH can be manually altered and the delivery can be customized with zero- or first-order absorption from the oral cavity.	No change.	
	GastroPlus	Saliva flow rate and saliva pH can be manually altered and the OCCAT model considers parameters for the buccal and sublingual routes.	No change.	
	Simcyp	Saliva flow rate can be manually altered but saliva pH is not incorporated.	No change.	
Gastro-Intestinal pH	PK-Sim	Stomach acid output, and the pH of the stomach, duodenum, jejunum, ileum, caecum, ascending and descending colon are incorporated and can be manually altered.	No change.	
	GastroPlus	Stomach, duodenum, jejunum, ileum, caecum ascending and descending colon are incorporated and can be manually altered.	No change.	Informed stomach and duodenum pH values with the same younger population literature values. Due to these findings, assumed that the rest of the intestinal pH's remains similar too.
	Simcyp	Stomach, duodenum, jejunum, ileum and colon are incorporated and can be manually altered.	Slower rate of return of gastric pH after food intake.	
GI Transit Times	PK-Sim	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal the gastric emptying time is altered based on a Weibull equation.	No change.	
	GastroPlus	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal, gastric emptying time is dependant on meals, the API and the caloric intake.	Indirect change of GET after meal intake.	Age is indirect influencing the GET after a meal by influencing the parameter total daily caloric intake.
	Simcyp	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal the gastric emptying time is altered based on a Weibull equation.	No change.	
GI Fluid Volumes	PK-Sim	Stomach, small and large intestinal luminal fluid are incorporated and can be manually altered.	No change.	
	GastroPlus	Stomach, small and large intestinal luminal are depending on the fluid secretion and fluid absorption and incorporated in the dynamic fluid volume model. Herein they can be manually incorporated.	No change.	
	Simcyp	Stomach, small and large intestinal luminal fluid are incorporated and can be manually altered.	No change.	
Bile Acid Synthesis	PK-Sim	No mechanistic models for bile salt concentrations or micelle-mediated solubility but *in vitro* solubility data can be implemented manually.	No change.	
	GastroPlus	Incorporates bile salt solubilization model.	No change.	Informed no change in the older population for micelle-mediated solubility and bile salt concentrations.
	Simcyp	Incorporates Simcyp *In Vitro* Analysis (SIVA) toolkit to analyse dissolution profiles and solubility data of drugs.	No change.	
Intestinal Epithelial Barrier Function	PK-Sim	Intestinal paracellular permeability and intestinal surface area are incorporated and can be manually altered.	No change.	
	GastroPlus	Paracellular pore size and intestinal surface area are incorporated and can be manually altered.	No change.	Assumed to be the same between young and older adults.
	Simcyp	Paracellular pore size and intestinal surface area are incorporated and can be manually altered.	No change.	
Active Transport and Metabolism	PK-Sim, GastroPlus, Simcyp	Active transporter concentrations and GI enzyme concentrations are incorporated and can be manually altered.	No change.	
Gut Microbiome	PK-Sim, GastroPlus, Simcyp	Not incorporated yet.		

4. Modelling absorption-related physiological changes associated with ageing

The following sections summarise the physiological and anatomical changes in the GI tract associated with ageing for critical processes that affect absorption. The capacity for PBPK platforms to take these changes into account is also described for the commercial and open-source software packages introduced earlier. OSP is the only open-source software, therefore model parameters for Simcyp and GastroPlus, when given, were retrieved from publications or the results of a questionnaire provided to representatives of all three software providers concerning parameterization of absorption in their respective geriatric models.

4.1. Oral cavity and swallowing capacity

Advanced age is associated with lower salivary flow rates, which are primarily attributed to reduced water content as exemplified by the general increase in the concentration of salivary components such as potassium, calcium, and amylase, with certain enzyme exceptions such as lactate dehydrogenase. This can contribute to the incidence of dysphagia or difficulties in swallowing, as well as xerostomia, the sensation of dry mouth, which is also often associated with drug use (Nagler and Hershkovich, 2005). Most major PBPK platforms allow changes in the flow rates, however considering that they are optimized for swallowable dosage forms, changes in saliva composition have been neglected due to the short residence time in the mouth. Although there is little to no research regarding any age-associated changes in the pH of saliva to date, most of the current modelling platforms have the capacity to define the pH of the saliva once this data becomes available.

On the other hand, if buccal and sublingual routes are considered, these changes need to be incorporated if a mechanistic model is desired. Despite having a small market share of total oral drug products, these formulations are proven solutions due to their ease of use and the ability to avoid potential degradation within the gastrointestinal tract or the first-pass effect by the liver. For example, sublingual fentanyl formulations have been extensively considered as safe effective options for cancer pain management in older adults, for which this patient group has been historically underdosed due to the perceived increased risk of side effects (Guitart et al., 2017). In another case, Emezine, the prochlorperazine buccal tablet formulation being developed by BioDelivery Sciences International for the rapid treatment of nausea and vomiting was denied approval by the FDA due to concerns about its performance in older adults (Pather et al., 2008). This decision is based on observations of a higher maximum plasma concentration and a slower absorption compared to the equivalent conventional Emezine tablet. GastroPlus has already incorporated such capabilities in its Oral Cavity Compartmental Absorption and Transit Model (OCCAT). It is dependant on the pH, production rate, and residual volume of the saliva and simulates absorption as a partition between the saliva where dissolution takes place and the upper epithelium. Applying the model for an orodispersible formulation of risperidone in dogs confirmed that despite complete dissolution in the oral cavity and potential uptake in the oral mucosa, most of the absorption still occurred in the GI tract (Chen et al., 2019). Considering the complexity of such a setup, other platforms have not yet directly integrated these routes into their software; instead depending on their expertise, users have the option to customize delivery (e.g., in OSP's Mobi) or to assume zero or first-order absorption from the oral cavity.

Nevertheless, these changes, in particular dysphagia, are still of interest to conventional peroral dosage forms such as tablets and capsules, as they can alter pharmacokinetics by delaying the release of the drug or stimulating drug release at a premature location (in the case of it becoming lodged in the oesophagus). Water volumes in the various software platforms are easily customizable but are only associated with improved swallowability when the viscosity of the fluid has been increased, leading to the addition of extra components (Salle et al., 2021). Comparably, changes such as dysphagia encourage the alteration of formulations through crushing and suspension of dosage forms in food or commercial thickeners, which also alters the dissolution and hence absorption of the drug. This is a specific situation in the older population and this predictability is currently not well-addressed in most platforms due to the lack of implementation of these altered formulation deliveries. Furthermore, since these practices are non-standardized, the dissolution profile of altered formulations introduces a lot of uncertainty, restricting the predictive power of the simulation. Nevertheless, several studies have investigated the underlying mechanisms of this reduced swallowing capacity with age both from the dynamic (the forces that move the bolus) and kinematic (the actual bolus movement) perspectives for solids and liquids (Bardan et al., 2006; Tracy et al., 1989; Shim et al., 2017). So, a meticulous, mechanistic model would require numerical solutions due to the fluid dynamics and complex movements involved, which would hinder its incorporation into PBPK platforms (Chang et al., 1999; Chang et al., 1998). To reduce the complexities, a statistical approach (e.g., the average delay in release, etc.) may be sufficient instead.

4.2. Gastro-Intestinal pH

Secretions and regional pH variations are crucial for the solubility of a drug (Hurwitz et al., 2003). For a long time, it was assumed that gastric secretion, like many other physiological functions, declines with age (Polland and Bloomfield, 1931; Bloomfield and Keefer, 1928; Vanzant et al., 1932; Baron, 1963). However, recent publications have reported that gastric acid secretion is dependant on chronic atrophic gastritis (CAG) rather than age. Therefore, when older adults with CAG were excluded from these studies, similar rates of gastric acid secretion in young adults and older adults were found (Collen et al., 1994; Goldschmiedt et al., 1991; Kekki et al., 1982). People infected with Helicobacter pylori (H. *pylori*) are associated with CAG and have shown slightly significant lower peak acid output. Therefore, also gastric acid secretion will decline with age when CAG and H. *pylori* individuals are included in the older adult population. Ageing, on the other hand, is associated with decreased pepsin output and independent of CAG, H. pylori infection, and smoking (Feldman et al., 1996; Haruma et al., 2000). Contrarily, Katelaris et al. (1993) found no difference in acid output in *H. Pylori* infected and non-infected in both young and older adults. In general, a lower gastric acid secretion can lead to a higher pH in the stomach (Russell, 1997), but also conflicting results regarding pH in older adults were found in the literature. When comparing Dressman et al. (1990) studied fasted gastric pH of 1.7 in healthy young men to Russell et al. (1993) fasted gastric pH of 1.3 in older men, it seems lower while ageing. On the other hand, Pedersen et al. (2013) found no tendency toward pH differences between the three different age groups they included. PH is an important factor for the bioavailability of poorly soluble basic compounds. For example, plasma ketoconazole concentrations were significantly lower in achlorhydric older adults with a fasted gastric pH greater than 5 compared to controlled older adults with a pH less than or equal to 4.5 after ketoconazole administration. When fasted achlorhydric older adults took ketoconazole crushed in acidic juice, the PK profile was again similar to that of the fasted control group (Hurwitz et al., 2003). Similarly, when fasted achlorhydric older adults with elevated pH took dipyridamole, they had significantly lower T_{max}, C_{max}, and absorption rate constant than the control low pH older adults (Russell et al., 1994). Furthermore, the literature showed that after a solid meal, old people needed 89 (44–167) and 154 (82–210) minutes to return to a pH of 3 and 2, respectively. Compared to 42 (26–83) and 100 (44–143) minutes in younger adults, is this considerably slower (Russell et al., 1993). Simcyp has taken this rate of return into account for their geriatric model. The rate of return to fasted gastric pH is for younger adults implemented with an exponential formula and for older adults with an age higher than 65 with a linear formula. GastroPlus and OSP

did not report or include an age-informed rate of return to fasted pH in the absorption model, respectively, meaning the return rate for young adults implemented in the software, is the same as for the older population.

Besides fasted gastric pH differences due to gastric acid secretion, significant pH differences were found in the rest of the older adults' GI tract. Older adults showed a significantly lower pH of 6.4 in the proximal colon in the fasted state compared to the pH of 7.8 in younger adults (Diakidou et al., 2009; Vertzoni et al., 2021). Additionally in the distal ileum, a significantly lower pH of 6.7 was observed in the old adults fed state compared to 8.1 in younger adults (Vertzoni et al., 2021; Reppas et al., 2015). The pH in the distal ileum in the fasted state was approximately the same for older people as for younger adults. On the other hand, older adults' pH in the duodenum showed contradictory results in the literature (Dressman et al., 1990; Russell et al., 1993; Annaert et al., 2010). When modelling an older population in OSP, Simcyp, or GastroPlus, the pH values implemented for the different GI segments are similar to the young adults. Gastroplus kept the stomach pH and the duodenum pH at the same values as for the younger population due to inconsistent literature findings. All the different software suites allow the user to change the pH manually. Additionally, OSP allows to change the stomach acid output manually, and Simcyp the gastric fluid secretion.

4.3. GI transit times

Regular gastrointestinal motility is crucial for consuming food and controlling appetite but also influences the absorption of a drug. Gastric emptying is another highly variable and disputed factor, due to its intricate nature as it not only reflects muscle function but depends on hormonal and neuronal activity as well (Bhutto and Morley, 2008; Rozé, 1980). Data published on gastric emptying rates in older adults compared to younger adults are conflicting and are studied with various methods, which makes it difficult to compare. Some studies detected slower rates in older adults while others revealed no change in gastric emptying time for both the fasted and fed states (Watson et al., 2019; Serra-Prat et al., 2009; Hellstrom et al., 2017; Gainsborough et al., 1993; Clarkston et al., 1997; Brogna et al., 2006). Nakae et al. (1999) observed that older adults differ in their response to meals with high lipid content, and this may be due to the role of lipase in the regulation of the gastric emptying inhibitor cholecystokinin (CKK). The half-emptying time of a lipid soup was 19.1 $\pm$ 3.3 min for young subjects and 28.0 $\pm$ 6.1 for older subjects, which was significantly higher. Additionally, the basal plasma CCK concentration of 10.9 $\pm$ 0.5 pg/ml of older subjects was significantly higher than 8.5 $\pm$ 0.5 pg/ml in young subjects. As non-lipid soup did not show significant differences in the gastric emptying time between the young and old subjects they state that the effect of ageing on gastric emptying time is related to the composition of the meal taken (Nakae et al., 1999). Despite the conflicting results regarding any age-associated differences between healthy older adults compared to younger ones, several comorbidities, and drugs do have an impact on gut motility. Anticholinergics, levodopa, chronic liver disease, and Parkinson's disease are all examples that are associated with delayed gastric emptying (Hurwitz et al., 1982; Pfeiffer, 2003; Pfeiffer et al., 2020). None of the software tools incorporated a difference in gastric emptying for the older adult population compared to the younger in the fasted state. Gastroplus informed that they did not change the fasted gastric emptying time for the older population due to inconsistent literature findings and concluded no significant differences were seen in both populations.

When modelling a meal, each software handles the calculation of gastric emptying time differently. In OSP and Simcyp, the rate of gastric emptying will change with a meal according to a function that is based on the Weibull equation. The Weibull function is age-independent and thus handles gastric emptying time in the same manner for young and older adults. The corresponding function in OSP is depending on a variability factor, the energy content, and the solid fraction of the meal where the log-normal variability for these are also age-independent. In Simcyp known variability in gastric emptying rate is implemented and the distribution of solid dosage forms is described by the Weibull function which is formed by a shape factor and a scale factor that depends on the formulation form and type of meal (Jamei et al., 2009b). For GastroPlus, the gastric emptying rate in the fed state is dependant on caloric intake, meals, and the active pharmaceutical ingredients (APIs). The software has an inbuilt correlation between the calories in the meal and the gastric emptying time. As the calories are defined as a percentage of the total daily calorie intake which differs for gender and age, it allows scaling to all ages and gender. The shape of the emptying profile is another input for implementing a meal. The shape can either be exponential or zero-order and is age independent.

Even less literature is available on changes in small intestinal transit time in the older population. Serra-Prat et al. (2009) discovered that the changes in the migrating motor complex in older adults were within the normal range for young people. Also, Madsen and Graff (2004) and Kagaya et al. (1997) observed similar transit times in the small intestine for both age groups. On the other hand, persons with chronic diseases such as diabetes mellitus tend to reduce motility and have therefore a slower small intestinal transit time (O'Mahony et al., 2002). The intestinal transit times are age independent in all software tools evaluated. For OSP, the small intestinal transit time follows a sigmoidal function based on literature data where fixed independent values are implemented for the factor's slope and intercept of this function. It also has a log-normal age-independent gender-distribution (Thelen et al., 2011). Simcyp's ADAM model and GastroPlus also handle inter-individual variability for intestinal transit independently of age (Jamei et al. (2009).

Additionally, there is a higher prevalence of constipation in the older population which translates to longer colonic transit times (Madsen and Graff, 2004; Kim, 2017). Other studies in presumably healthy, older adults report no significant differences in colon transit time compared to the young (Brogna et al., 1999). It is difficult to quantify the independent factor of ageing on colon transit time because constipation can also be caused by certain drugs, a lack of dietary fibre, or physical activity, an aspect that will be discussed in further sections. Altered transit rates may alter the absorption and disposition of drugs as they can lengthen or shorten the available time for processes like dissolution, passive transport, etc. Here, again, no software tool is accounting for any change in colon transit time for the older population.

4.4. GI fluid volumes

Gastrointestinal fluids facilitate the dissolution of compounds and therefore the volumes of these fluids influence the absorption. The volume of GI fluids is determined by fluid secretion and absorption along the GI tract, and additionally the intake of foods and drinks. Shin et al. (2022) studied gastric fluid volumes in older adults and observed a mean gastric fluid volume of 30.2 mL using ultrasound in fasting older adults. This is lower than the 45 mL studied in fasted healthy young with MRI, noting that body weights were not given (Schiller et al., 2005). On the other hand, Manchikanti et al. (1985) did not find a significant difference in the gastric fluid volume in geriatrics, compared to young adults. However, liquid volumes in the distal ileum and the proximal colon showed a significant difference in older adults compared to young adults in both the fasted and the fed state after aspiration (Vertzoni et al., 2021).

The fluid volumes in GastroPlus are dependant on fluid secretion and fluid absorption in the different GI organs and can manually be altered if a dynamic fluid volume model is selected. Additionally, dose volume allows you to input the amount of water you administer while taking an oral dosage, and will be added to the stomach fluid volume. GastroPlus did not collect direct data from the literature to inform fluid volumes in the older population, but instead assumed that the composition was

similar. Furthermore, there are no changes in fluid volumes in OSP or Simcyp for the incorporated older population. Previously, it was shown with PBPK modelling that fluid volumes have an impact on the absorption of particularly poorly soluble compounds and therefore it is important to incorporate this in PBPK databases (Van der Veken, 2022).

4.5. Bile acid synthesis

Bile acids (BA) play an important role in intestinal lipid absorption as they emulsify fats and lipids by forming micelles. BAs are synthesized in the liver from cholesterol via several pathways involving many CYP enzymes and conjugate with glycine or taurine to form bile salts (Ticho et al., 2019). Annaert et al. (2010) studied individual concentrations of 11 bile salts in human intestinal fluid aspirates in two different age groups. Although there was a tendency for the individual concentrations to be higher in the older group, these differences were not statistically significant. However, as they form mixed micelles, the global concentrations of the individual salts may not translate directly into changes in solubility as this also depends on the shape, composition, and size of the micelles and other environmental factors. Ultimately, when tested in the human intestinal fluids (HIF) samples for each age group, there were no statistically significant differences in solubility (Annaert et al., 2010). Additionally, Vertzoni et al. (2021) found a higher bile salt concentration in the distal ileum in fasted and fed older adults compared to previously studied values in younger adults (Reppas et al., 2015), and similar concentration values in the proximal colon (Diakidou et al., 2009). Furthermore, ageing has been linked to a decrease in bile acid synthesis and CYP7A1 expression (Bertolotti et al., 1993; Bertolotti et al., 2007).

Most PBPK modelling software tools include a variety of solubility and micellization models to account for bile salts and micellization. GastroPlus employs a bile salt solubilization model, which considers *in vitro* bile salt concentrations and the enhancement of solubility for a specific drug that can be defined by a solubilization ratio (Mithani et al., 1996; Parrott et al., 2016). They informed the older population with the same micelle-mediated solubility. Simcyp uses the Simcyp *In Vitro* Analysis (SIVA) toolkit to analyse the dissolution profiles and solubility data for drugs. Solubility data in media with known bile salt concentrations and the micellar partition coefficient for unionized and ionized species are fitted. Age-related changes in bile salts concentrations are not incorporated in the software. OSP currently does not have mechanistic models for bile salt concentration incorporated and the user needs to implement measured *in vitro* solubility data manually.

4.6. Intestinal epithelial barrier function

The results of some studies have suggested that absorption is more sensitive to age-associated changes in permeability (Annaert et al., 2010; Chow et al., 2016), which is inherently more difficult to assess than solubility and often relies on *in-vitro* or animal models for predictions. Permeability studies performed in rats have shown significant differences when assessing transcellular, paracellular and carrier-mediated routes (Annaert et al., 2010). All of the major platforms have incorporated common preclinical species including the rat, mouse and pig; but customization for these species is often limited compared to that for humans. Furthermore, when considering age-associated changes in the intestinal epithelial barrier function, there are few studies performed in humans with a large proportion being performed in rats. Despite this, if one would like to replicate these studies, many PBPK platforms do not allow for age or even weight adjustment for these preclinical species, a feature that may be helpful for better scaling to humans. On the other hand, there may be a couple of reasons for this including the fact that many of the animal studies do not report age, since young rats are considered standard in order to ensure a lack of disease.

The intestinal epithelial barrier is composed of a mucus layer, bicarbonate and anti-microbial peptide secretions, as well as structures such as the intestinal epithelial cells (villi) and tight junctions (Saffrey, 2013). As far as PBPK modelling is concerned, the latter two are of greater importance to permeability, particularly when considering the passive paracellular route. According to a histological analysis of human terminal ileum biopsies, the integrity of the tissue and villi is maintained with advanced age (Saffrey, 2013), in contrary to the 48% and 40% decrease in villi height and density respectively observed in rats (Ren et al., 2014). This translates to no change in the surface area of that part of the intestine, a parameter that is easily customizable in most PBPK platforms if necessary. On the other hand, trans-epithelial/transendothelial electrical resistance (TEER) measurements and the expression of integral tight junction proteins including the zonula occludens, occludin, and claudin-2 suggest a change in the functioning of the tight junctions (Man et al., 2015; Tran and Greenwood-Van Meerveld, 2013). All major platforms allow such changes by modifying the pore diameter, however the increase in claudin-2 expression is notoriously stimulated by the pro-inflammatory cytokine interleukin-6. This cytokine is not only elevated in advanced age but also in common geriatric syndromes and the associated inflammation (discussed further later) has been observed to affect the functioning of intestinal enzymes and transporters as well (Wu and Lin, 2019; Yang et al., 2010). Therefore, the “ageing leaky gut” poses a complex model with extensive confounding with disease, polypharmacy and the microbiome. Ultimately, there is some flexibility in the software to modify some of the parameters, but there is no standardized approach for taking these changes into account due to the limited and controversial data.

4.7. Active transport and metabolism

Active transporters use energy to transport drug molecules against a concentration gradient across epithelial membranes in the GI-tract, primarily in the small intestine. Since uptake and efflux transporters can be located on the apical or basolateral membranes of cells, they affect drug absorption and bioavailability. The most well-studied drug efflux transporter expressed in the intestine is P-glycoprotein (P-gp) and it has been implicated in the efflux of many compounds. As it is located at the apical surfaces of epithelial cells, it actively pumps any absorbed drug back into the small intestinal lumen (Clarkston et al., 1997; Brogna et al., 2006). Some observations show lymphocytic and hepatic P-gp expression increases and renal P-gp content decreases with age in older adults (Nakae et al., 1999; Hurwitz et al., 1982). Besides, Lown et al. did not detect a significant correlation with age in humans for P-gp levels in intestinal enterocytes of 25 kidney transplant recipients (Pfeiffer, 2003). This is in line with clinical studies of fexofenadine, a known substrate for P-gp, which does not show an effect of age on the oral clearance (Pfeiffer et al., 2020, Madsen and Graff, 2004). Contradictory, higher systemic exposure in older adults is found for the compounds dabigatran and digoxin, which are P-gp clinical substrates unrelated to CYP450 enzyme metabolism (Rattanacheeworn et al., 2021; Hanratty et al., 2000). Cui et al. (2022) found with covariate screening that age had a significant effect on clearance and subsequently used PBPK modelling to explore intestinal P-gp function in the older population. A change of 25.5% in the intestinal P-gp function induced by ageing could explain the exposure levels of DAB and digoxin in Chinese older adults. Furthermore, *in vitro* experiments showed that intestinal epithelial cells of older Alzheimer’s patients can also cause lower P-gp expression level compared to those with other types of dementia or without dementia (Haran et al., 2019). Currently, the implemented P-gp abundance in the GI-tract is the same for older adults as for younger adults in OSP, GastroPlus and Simcyp.

Regarding metabolism is CYP3A4 the most prominent CYP enzyme in the small intestine, where it plays an important role in the first-pass metabolism of a variety of compounds such as midazolam (Kinirons and O’Mahony, 2004; Trenaman et al., 2021). CYP3A4 abundance in the

intestine in older adults remains unclear (Kinirons and O'Mahony, 2004; Trenaman et al., 2021). Therefore, no different expression levels are implemented in the PBPK modelling software.

Additionally, calcium is absorbed via active transport across the intestinal mucosa and its absorption has been shown to be significantly reduced in ageing rats and humans (Kagaya et al., 1997; O'Mahony et al., 2002)., There is also a reduction in the absorption of vitamin B and iron via active transport (Kagaya et al., 1997).

4.8. Gut microbiome

The impact of the gut flora on drug disposition has been generally overlooked until recent years due to its localization in the distal intestine (whereas absorption primarily occurs at the proximal end), and a previous lack of understanding of its many influences on physiological processes such as its implication in the frailty-gut axis. Direct mechanisms such as drug binding, drug metabolism and even drug transport can affect absorption, and furthermore have been implicated in several drug-drug interactions (Klaassen and Cui, 2015). For example, tyrosine decarboxylase-encoding bacteria have been implicated in the treatment of Parkinson's disease as they prematurely convert levodopa to dopamine in the small intestine. Furthermore, common inhibitors such as carbidopa are not as effective against these enzymes contributing to a variation in bioavailability (van Kessel et al., 2019). It is well-known that the composition of the microbiome changes with age, due to a general decrease in diversity and higher prevalence of opportunistic species, which can contribute to the chronic, low-grade inflammation ("inflamm-ageing") commonly observed in the older population (Di Sabatino et al., 2018). It is, like other factors discussed, sensitive to genetics, diet, medication, disease and more; hence promoting variability in response between and within individuals. A great example demonstrating its importance in ageing is the biological ageing clock developed by Galkin et al. (2020), which utilized a deep neural network (DNN) and gut metagenomics to predict age with a mean absolute error of 5.91 years. Even so, incorporation into PBPK models is challenging as the microbiome can be linked to being an organism in itself, so the sheer complexity may require advanced techniques such as machine learning or constraint-based models such as the whole-body reconstruction of human metabolism developed using a joint COBRA-PBPK approach by Thiele et al. (2017). This model incorporated a copious amount of genomic, metabolomic and physiological data, and represents a fully mechanistic, highly specific, and time-intensive method. Another approach was the development of a basic PBPK model that includes the various compartments of the intestine, the gallbladder and a central compartment. Then, by varying the appropriate kinetic constants, the modelers were able to estimate the factors preceding altered systemic concentrations of the drug/metabolite due to microbial metabolism (Zimmermann-Kogadeeva et al., 2020). Although this was an exploratory analysis, it was able to demonstrate the various circumstances that gut microbial processes should be considered for absorption predictions.

5. Extrinsic population-specific factors

Besides the physiological and anatomical changes for the older population described previously, the older population comes with extrinsic specific factors that are essential to consider while developing

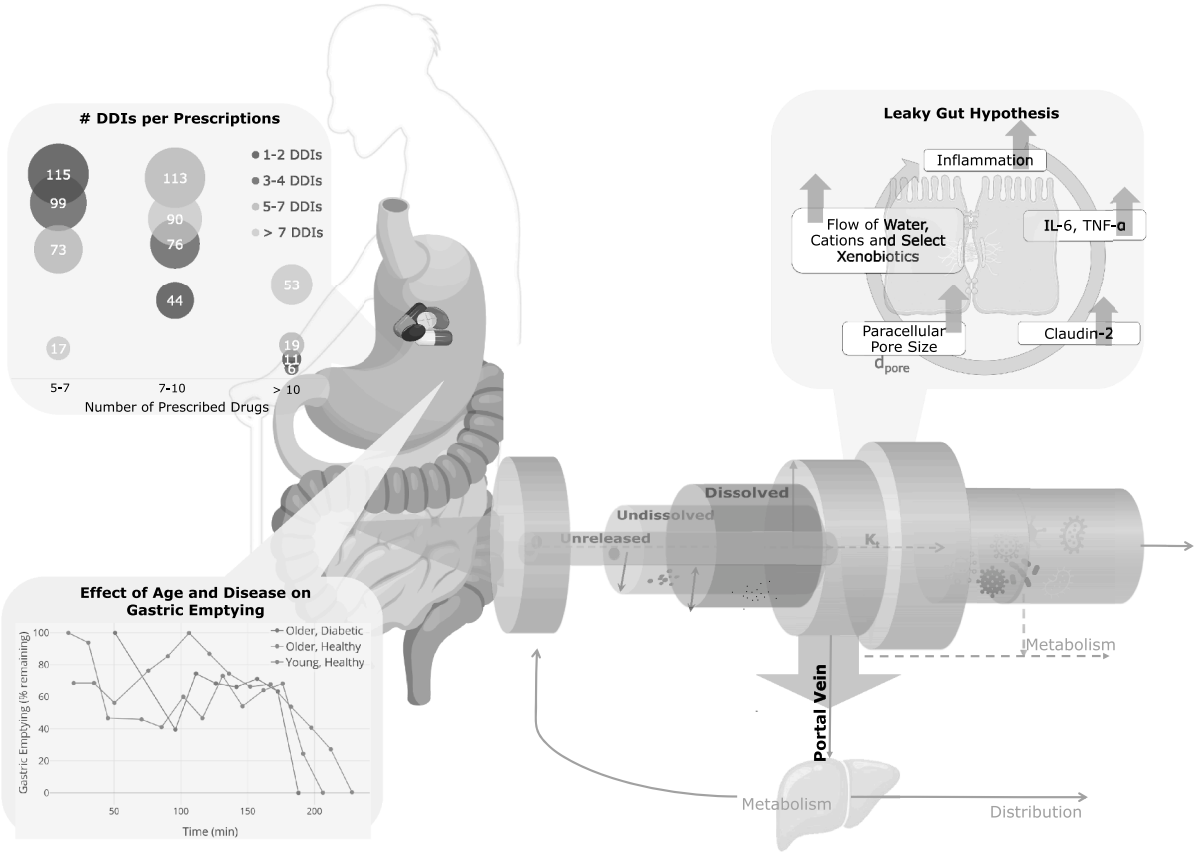

Fig. 2. Conceptual depiction of various factors essential to developing PBPK models for the older population. This includes population-level factors such as the prevalence of polypharmacy and multimorbidity, as well as compartmentalization of the gastrointestinal tract and representation of physiological processes. Data for polypharmacy concerning the number of drug-drug interactions as a function of the number of prescribed drugs were taken from an observational study at Goa Medical College from July 2011 to June 2012 (Khandeparkar and Rataboli, 2017). Data for gastric emptying are three individual profiles representing each subgroup from a research publication utilizing Alternating Current Biosusceptometry as their primary method (Watson et al., 2019).

PBPK models. These population-specific factors are described in the following sections. In Fig. 2. an overview of these factors through the gastro-intestinal tract are depicted.

5.1. Drug-drug interactions as a consequence of polypharmacy in older people

Older people are burdened with high rates of multimorbidity resulting in polypharmacy and thus, a greater risk for drug-drug interactions (DDIs). During the absorption phase, DDIs can occur via a variety of mechanisms including induction or inhibition of transporters and drug-metabolizing enzymes (DMEs), when co-medications bind to these species. Some of the major transporters and enzymes expressed in the small intestine that can affect oral drug absorption are OATP1B1, P-glycoprotein, CYP3A4 and CYP2C9 (Fritz et al., 2019; Paine et al., 2006; Estudante et al., 2013). The considerable overlap of P-gp and CYP3A4 substrates can lead to a significant increase in drug bioavailability via inhibition (Estudante et al., 2013; Malingré et al., 2001). In addition, DDIs can be mediated by drug-induced gastrointestinal physiological changes, as specified in the section: Gastric Emptying and Intestinal Motility.

Increasing efforts are being made towards understanding DDIs mediated by transporter inhibition and enzyme interactions in the intestinal wall using PBPK modelling and simulation techniques. PBPK models are considered capable of evaluating the potential risks of DDIs for a drug that can be affected by DDI (victim) and at the same time can cause DDI (perpetrator) in various populations, like erdafitinib (De Zwart et al., 2021). Simulations can predict higher exposure of erdafitinib, rivaroxaban and dabigatran with P-gp, CYP3A4 and CYP2C9 inhibitors (De Zwart et al., 2021; Willmann et al., 2021; Lang et al., 2021). More interestingly, the applicability of PBPK modelling to describe complex DDIs, attributing physicochemical, genetic polymorphisms and multiple DDIs, has been demonstrated by Türk et al. (2019). They developed whole-body PBPK models to describe drug-drug-gene-interactions (DDGI) between gemfibrozil as a perpetrator and two victim drugs, repaglinide and pioglitazone, which was mediated by CYP2C8 and OATP1B1. During this complex model development, a physicochemical interaction was demonstrated by administering gemfibrozil simultaneously, resulting in even lower itraconazole solubility, which was already intrinsically poor. The same case occurred for pioglitazone when administered together with gemfibrozil plus itraconazole.

DDIs were predicted in the above-mentioned PBPK models in the young adult population, but it has previously been demonstrated that DDI estimation can also be used in special populations. Salerno et al. (2021) successfully developed a PBPK model to predict CYP3A DDI risk in the paediatric population using solithromycin, ketoconazole and midazolam PK data, DDI information in adults and *in-vitro* data. Additionally, Cleary et al. (2021) studied the DDI risk of risdiplam, a CYP3A4 metabolised drug, in paediatrics with spinal muscular atrophy. By incorporating the intestinal and hepatic CYP3A4 ontogenies, DDI studies of healthy adults and adults with spinal muscular atrophy, and drug-related data the PBPK model assessed the DDI risk in paediatric patients. Again, midazolam was used as an interactive CYP3A drug.

Studies have been done to predict DDI magnitudes in ageing. A previously performed meta-analysis combined clinical data and PBPK modelling-simulation to detect DDI of midazolam with the presence of clarithromycin and rifampicin, and amlodipine, rosuvastatin, atorvastatin, dolutegravir with the presence of darunavir or ritonavir. This meta-analysis proposed that DDI magnitudes of those comedications are not significantly affected by age regardless of the drugs, mechanisms and the enzyme or transporter involved (Stader et al., 2021b). This result is in line with a bioavailability study comparing older people and young subjects (Briant et al., 1983). When metoprolol was co-administered with metoclopramide, an antiemetic drug known to enhance gastric motility and emptying time, the DDI magnitudes were similar between both age groups. Understanding the contribution of enzymes and transporters to bioavailability is of utmost importance in defining, controlling and improving the oral absorption of substrates. Furthermore, DDI simulations can be applied to predict the maximum inhibition or induction of transporters or enzymes when a varying dosage of victim drugs are concomitantly administered with perpetrators. Utilizing simulations, dosing intervals required to minimize the DDI risk can be selected and applied specifically for clinical trial design and for pharmacotherapy of older adults.

Another consequence of polypharmacy is an increased difficulty for older people to adhere to their prescribed regimens for the sustained amount of time needed to treat their chronic conditions. For example, a study performed in Italy investigated medication adherence for a sample of older people discharged from the hospital with regimens that included at least 4 medications. The results showed non-adherence rates of 55% by 15–30 days after discharge, and increased to 69.6%, 3 months after discharge (Pasina et al., 2014). Statistical analysis also showed a significant correlation between the number of drugs prescribed and the rates of adherence for both time points. Also, age, sex and the presence of a caregiver did not show any correlation, making polypharmacy the main culprit of all factors screened in this case. However, a systematic review showed that there are often cofactors such as cognitive function, social frailty, functional decline and caregiver burden that can also be significant (Zelko et al., 2016; Jankowska-Polańska et al., 2016). Considering that withdrawal and changes to the dosage were the primary methods, and approximately 25% of the sample did not understand the purpose of their medications, this is an issue that may be targeted on the primary care level (Pasina et al., 2014). It is important as it can lead to a discrepancy between the dose and the predicted response, something that can be simulated using PBPK/PD modelling, consequently leading to inappropriate increases in prescribed doses, which also increases the risk of DDIs. Leaders in the field have acknowledged these risks and developed tools such as the FORTA (Fit fOR The Aged) that account for these toxicity risks, compliance issues, and proven efficacy of commonly prescribed drugs to better guide pharmacotherapy in the older people (Kuhn-Thiel et al., 2014). PBPK simulations may be useful in the further development of such tools by allowing for some quantification of the associated risks.

5.2. Population parameterization

When referring to the older population or age in general, most of the time we are referring to chronological age. However, from a population modelling perspective, this does not provide sufficient information since everyone ages differently and relying solely on chronological age promotes variability, making it more difficult to observe patterns and draw inferences. For example, India has used 60 years as the minimum age for their older population (Muhammad et al., 2022), while China and South Korea have adopted 65 years as their minimum, the threshold often used in Europe and the USA (Feng et al., 2015; Ouchi et al., 2017), and Japan is considering the use of 75 years (Ouchi et al., 2017). A proportion of these differences can be attributed to demographic and socio-economic factors including access to healthcare and medicine, diet and level of urbanization as mentioned in the cited studies. Another example is the lower-than-normal minimum frequently used in studies targeting older persons living with HIV (Chen et al., 2018). The age of 50 years is predominantly used (Onen et al., 2010; High et al., 2012; Autenrieth et al., 2018; Haddow et al., 2019) with a range of 45 to 65 years observed in the literature. There may be several reasons for this, most notably the well-recognized ramifications that both the disease and its chronic treatment can have on the ageing body (High et al., 2012), as well as the recently increasing life expectancy (Wandeler et al., 2016). Therefore, it is evident that there is no single paradigm of an older person, and therefore populations should be specified accordingly.

In general, ageing can be defined as the continuous degradation of cellular function and system-signalling pathways, which then

accumulates and leads to the breakdown of systems on the organism level (Kudryashova et al., 2020; Blagosklonny, 2013). It can also be described by the "Hallmarks of ageing" framework, which considers processes such as loss of proteostasis and stem cell exhaustion, critical to defining the ageing phenotype (López-Otín et al., 2013). No matter the adopted definition, a key point that is consistent amongst them is the subsequent inability to adapt to stresses, or in other words, increased vulnerability. As a multidimensional process consisting of parameters susceptible to a varying extent by extrinsic influences such as diet or illness, there is a need to discretize the older population into more homogeneous groups when performing population modelling. In this case, PBPK modelling can be advantageous since it can theoretically capture all variability associated with observations (allowing for better parameterization of the population), provided that the key physiological processes linked to this variability have been captured in the model (Malik et al., 2017). Coupling of Bayesian statistical approaches with mechanistic models such as PBPK has shown promising results of such hierarchical framework to separate individual uncertainty about the parameters from population variability, including covariate models to cope for systematic relationships of model parameters to age, gender and body height (Krauss et al., 2015; Krauss et al., 2017). Inclusion of illness as a factor is frequently done to some extent for well-known co-morbidities such as chronic kidney disease and renal impairment in PBPK models for older people, as the influence of ageing on excretion has been well-researched (Table 1). However, it is not nearly as common for the parameters affecting absorption such as the microbiome and motility, as elaborated in previous sections.

In addition, PBPK models depend on drug-specific and physiological data and the latter is more susceptible to becoming obsolete since humans are constantly evolving, a phenomenon known as "secular trend" (Farkas and Szmodis, 2019). In other words, an older person from 100 years ago will have different characteristics from an older person of a similar age today due to a mixture of genetic and environmental factors. Therefore, the field of bio-horology, the study of the passage of time in living systems can be useful, where biomarkers from the micro to the macro scale can account for inter-individual differences in the ageing process. A popular example in this field are DNA methylation ageing clocks, which are often employed in tandem with physical, cognitive, and disease markers that are more practical for clinical use (Bell et al., 2019). The latter examples are often employed in the assessment of frailty, which can be considered the most prominent example of parameterizing ageing in order to define a category of persons with indications of an advanced biological age, independent of their chronological age (frail persons). Fig. 3 illustrates the relationship between chronological age and frailty index as a predictor for biological age based on three databases from surveys conducted in The Netherlands, Australia and Italy (Thompson et al., 2018; Hoogendijk et al., 2020; Hoogendijk et al., 2017; Biritwum et al., 2016).

Frailty is a state of reduced homoeostatic capacity caused by accumulated cellular degeneration and affects an estimated 17% of the global population over the age of 50 (O'Caoimh et al., 2021). Due to increased vulnerability as clearance and metabolic processes are weakened leading to higher drug plasma concentrations, frailty can exacerbate adverse effects that would otherwise be insignificant in non-frail or younger adults (Wynne et al., 1993). Risk factors for frailty in older people embody sociodemographic (advanced age, female sex, ethnic minority, living alone, loneliness, poor education, socioeconomic status), clinical (multimorbidity, polypharmacy, obesity, malnutrition, cognitive impairment, depression), lifestyle (physical inactivity, low protein intake, smoking, increased alcohol intake) and biological factors (inflammation, endocrine factors, micronutrient deficits) (Hoogendijk et al., 2019). Until now, no PBPK models incorporating frailty have been published, and only a small number of studies have evaluated the effect of frailty on drug absorption by means of non-compartmental PK analysis techniques. A metoclopramide PK study directly compared the AUC of intravenous and oral dosing, and identified a 14% decrease in the absolute bioavailability in frail older people compared to young, healthy subjects, with insignificant differences in bioavailability between frail and healthy older people (Wynne et al., 1993). Other studies utilized global markers, like C_{max}, T_{max} and AUC (area under the curve) values to assess oral drug absorption. For oxybutynin and brofaromine, C_{max} and AUC were significantly higher in frail, older patients than in young, healthy subjects (Hughes et al., 1992; Zeeh et al., 1996). However, these values should be carefully interpreted as AUC for an oral dosing is also determined by apparent oral clearance (CL/F), so the bioavailability is confounded by clearance.

Emerging evidence providing insights into the biology of frailty can be used to generate theories explaining the impact of frailty on drug absorption. According to Serra-Prat et al. (2013), the presence of frailty led to more rapid gastric emptying of liquids in both early and late postprandial periods compared with non-frail, older adults. They also speculated that the pathophysiology of anorexia, a marker for malnutrition, in these frail subjects may be related to the alteration of gastrointestinal physiology due to food effects (i.e., fed and fasted state effects). Food is known to affect drug absorption by delaying gastric emptying time, altering gastrointestinal pH, stimulating bile flow, increasing splanchnic blood flow, or physically interacting with drugs (Welling, 1989). Paracetamol and terbinafine PK studies show that although the delayed absorption due to food coadministration was slightly more pronounced in healthy, older people than in younger volunteers, the impact of age was insignificant because of high interindividual variability (Divoll et al., 1982; Nedelman et al., 1997). Even so, the evaluation of food effect on drug absorption in older people should be taken into account since approximately 15% of community-dwelling older people (Cederholm and Hellström, 1992) and 12–60% of hospitalized and institutionalized older people are malnourished (Elia and Stratton, 2005; Russell and Elia, 2010; Ennis et al., 2001). Furthermore, these malnourished patients often have a poor appetite (Pilgrim et al.,

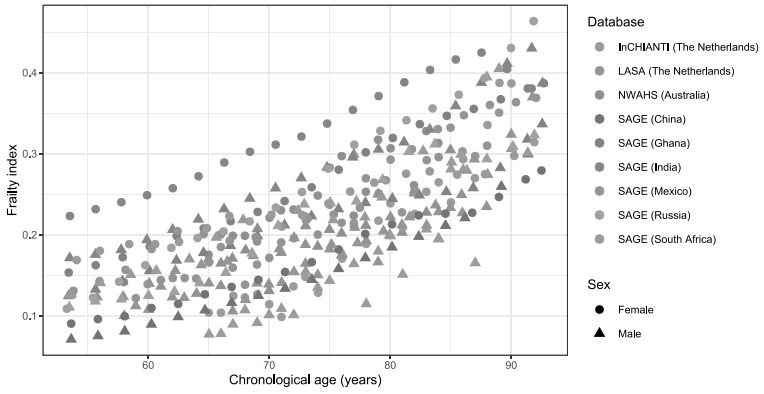

Fig. 3. The relationship between chronological age and frailty index as a predictor of biological age. The dots represent the means of the frailty indices reported in the North West Adelaide Health Study (NWAHS) (Thompson et al., 2018), the Longitudinal ageing Study Amsterdam (LASA) (Hoogendijk et al., 2017), the Invecchiare in Chianti (InCHIANTI) (Hoogendijk et al., 2020), and the Study on global AGEing and adult health (SAGE) (Biritwum et al., 2016) . Data have been grouped according to sex when reported.

2015). Therefore, complex alterations in gastrointestinal physiology due to the presence of food may occur.

Additionally, the changes of the microbiome within the gut in frail persons can possibly influence bioavailability since drugs and the microbiome have extensive bidirectional interactions as described in an earlier section (Jackson et al., 2016; Gemikonakli et al., 2021). Drug-gut microbiome interactions encompass drugs inhibiting or accelerating the growth of global or specific gut microbiota, and the microbes or microbial metabolites reacting with drugs and potentially forming active, inactive or toxic compounds (Sharma et al., 2019). Besides the alterations to gastric emptying and the microbiome, frailty seems to be correlated with inflammation as indicated by high levels of C-reactive protein, interleukin-6 and tumour necrosis factor-α (Hubbard et al., 2009). It is known that inflammation as a result of gastrointestinal pathologies (inflammatory bowel disease, coeliac disease, cholestasis, etc.) and systemic pathology states (kidney failure, liver failure, hyperthyroidism, obesity, diabetes mellitus, Alzheimer's disease, etc.) can influence the expression and function of some drug transporters within the gut (Drozdzik et al., 2020).

Due to the multifaceted nature of frailty syndrome, a variety of tools have evolved for its assessment that takes into account physical performance, self-perspectives and the judgement of the health professional (Hogan and Maxwell, 2020). Efforts have been made to standardize this through classification trees and machine learning approaches, since the current state-of-the-art allows for a lot of uncertainty to be introduced, which can hinder model development (Theou et al., 2021; Gialluisi et al., 2019). However, despite this and the observed impact on pharmacokinetics; parameterization and hence incorporation into a PBPK model, has yet to be streamlined. Also, due to the heterogeneity of this condition and the lack of clinical data, reliable population predictions will most likely remain unfeasible for the time being.

6. Inferences for modelling

Regulatory agencies have long encouraged better representation of older people in clinical studies, such as the 1993 ICH E7 recommendation to enrol at least 100 persons over the age of 65 if they are a part of the drug's target group (ICH, 1993). Despite this, exclusion criteria such as the absence of comorbidity or polypharmacy can still impede enrolment, even if the age limit is raised in the clinical studies (Kanapuru et al., 2020; Forsat et al., 2019). For example, older people constitute 61% of the cancer population, but only 35% of patients in the corresponding clinical trials, an improvement from the 25% reported in 1996 (De Stefano et al., 2022; Hutchins et al., 1999; Lewis et al., 2003). However, by relaxing just the exclusions regarding organ conditions an increase to 47% is predicted, but this also assumes that a large proportion are willing to participate (Lewis et al., 2003). In fact, this assumption is questionable since factors such as a limited capacity to understand and give informed consent, misconceptions about clinical studies and patient rights, and fear or a lack of trust; many persons in this target group may reconsider enrolment (Raheja, 2018; Brown and Topcu, 2003; Bloch and Charasz, 2014). The extent to which these factors become significant are also dependant on demographic factors such as highest level of education, transportation capabilities, insurance status, etc. and may therefore vary by region and socioeconomic status (Forsat et al., 2019; Florisson et al., 2021). Therefore, bridging the data gap would require more action besides increasing the number of clinical studies. On the other hand, PBPK models have the advantage since once the information about the relevant physiology has been incorporated, it can alleviate the need for further clinical studies in older people as it provides a basis for exploration. However, models should aim to be structurally identifiable, or in other words there should be a unique correspondence between input parameters and outputs (Theou et al., 2021). This is particularly challenging from the PBPK perspective due to the high dimensionality, intrinsically, highly correlated parameters and lack of clinical data relative to the number of unknowns. When considering the older population, these issues are further exacerbated due to multimorbidity/polypharmacy introducing more confounding between factors and the scarcity of data already discussed. The extent of identifiability can also limit the use of tools such as parameter estimation, but the impact can somewhat be offset by variation and subsequent appropriate choice of initial values (Hogan and Maxwell, 2020).

As demonstrated in previous sections, parameters that affect oral absorption in the older population are subject to a greater magnitude of variability and uncertainty compared to the standard, young population. While reviewing the various studies on physiological changes in absorption parameters before, it is important to keep in mind that this high variability, combined with a small number of studies or small sample sizes, makes drawing conclusions difficult. The variability refers to an intrinsic characteristic of the system, due to the heterogeneity of the population and lack of clinical data, which consequently limits investigational sample sizes. Therefore, it is important to take this variability into account when attempting to make predictions on the population scale (population PBPK analyses) or the virtual population will not be representative of its target, rendering the analysis invalid (Bouzom et al., 2012). Platforms discussed in this article have taken this into account on the physiological level with distributed parameters based on clinical observations or assumptions. For example, PK-Sim allows for parameters such as pH and lengths of various regions of the gastrointestinal tract to have user-defined variability by choosing from one of four distributions or models. The normal and log-normal options have customizable standard deviations and means, while the uniform is characterized by its minimum and maximum, and the constant solely by the mean. Other parameters like transit times and organ volumes have pre-defined variabilities that are editable when developing a population model. GastroPlus similarly has the capacity for users to define population variability (Babiskin and Zhang, 2015), and one of the options in Simcyp is to use a custom Lua script in order to define distributions for the population (Abduljalil et al., 2016). Along with the use of ageing clocks as described earlier, another method of handling this even with limited information about the variability is using a Bayesian-PBPK approach (Krauss et al., 2013). Standard approaches of assessment include incorporating Monte Carlo or Fuzzy models (Seng et al., 2008; Sweeney et al., 2001).

On the other hand, uncertainty refers to that which arises from errors, assumptions and other factors relating to the experimental design (Tsamandouras et al., 2015). By convention, the standard errors from experiments when available are included during model development, hence all modelling platforms are equipped for this. Along with the best practice of reporting the overall uncertainty with the results so that conclusions may be appropriately drawn, users can also take advantage of sensitivity analysis tools, which are often available in PBPK software. By quantifying the change in the dependant parameter due to a small change in an independent parameter, one can gauge the consequences of data discrepancies when there is high uncertainty. There are a variety of methods available and they can be categorized as either local or global in nature. The former provides the main effect of the parameter on the model response and cannot account for interactions nor non-linearities. On the other hand, global sensitivity analyses (GSA) are capable of this and depending on the technique can be used for a variety of "settings", such as variance cutting and factor prioritization (Saltelli et al., 2008). For example, variance-based methods such as Sobol or eFAST can estimate the contribution of the total variance in the model output by each parameter and also discretize it based on whether the particular parameter is primarily influential on its own or interacting with other parameters (Zhang et al., 2015). In the context of the advanced age population, these tests can be used to determine which parameters are driving variability in pharmacokinetics in comparison to that of the healthy, young population. PK-sim has a built-in sensitivity analysis tool that calculates the relative impact of selected input parameters on selected PK parameters (e.g. AUC or Cmax). The ratio of the relative change of the selected PK parameter and the relative variation of the

imput parameter leads to the sensitivity. Also Simcyp has built-in capabilities for the GSA methods Morris Screening and Sobol analyses. For further reference Liu et al. (2020); McNally et al. (2011) have published guidelines on the use of sensitivity analyses in PBPK models. Depending on the circumstances, it may be used to guide model refinement, by identifying the factors that are critical to model predictions and whose sensitivity may be improved (Liu et al., 2020). It is recommended that this be performed before any parameter estimation, another common, helpful function that allows for the identification of unknowns provided that there is limited confounding of variables and sufficient information concerning their corresponding uncertainties. Ultimately, the development of a model with low uncertainty, allows users to construe mechanistically any discrepancies between observations and predictions (Peters, 2012).

7. Conclusion

Despite the gaps that have been identified in this review, PBPK modelling remains a reliable approach to aid personalizing medication for this complex and unique population. Considering the above-mentioned perplexing aged-related changes and extrinsic factors, more joint efforts should be made to integrate data obtained from various *in vitro* permeability, solubility and dissolution experiments that mimic the older population, as well as clinical studies into PBPK models. This strategy allows to better predict *in vivo* clinical response. Ultimately, the outcomes from these studies may be used to support dosing recommendations and drug development in this population. This is in line with the predict-learn-confirm cycle suggesting that modelling and simulation can be employed to guide the design of confirmatory studies with a lean design and reduced sample size (Sheiner, 1997). For that reason, the PBPK approach is considered a valuable resource for drug development in this population, since there are a lot of ethical and technical hurdles to conduct a pivotal clinical study in geriatric and frail patients due to their unique characteristics (e.g., impaired cognition, multimorbidity and polypharmacy). Taking its importance into account, more trust in PBPK model use should be gained by continuously submitting PBPK models for publications and to health authorities. Overall, the older population is associated with challenges that can limit the capacity of PBPK models, however these models also provide specific solutions that aid in the management of these gaps. Like most scientific breakthroughs, moving forward will require the cooperation of multiple stakeholders including health care providers, researchers, and the older adults themselves to ensure a well-rounded solution (Liu, 2022; Lau et al., 2020). Here, we have demonstrated the potential of PBPK simulations to complement other types of studies and assist in the decision-making of these parties.

CRediT authorship contribution statement

Cleo Demeester: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Donnia Robins:** Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Angela Elma Edwina:** Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Jos Tournoy:** Funding acquisition, Conceptualization, Writing – review & editing. **Patrick Augustijns:** Funding acquisition, Conceptualization. **Ibrahim Ince:** Conceptualization, Writing – original draft. **Andreas Lehmann:** Funding acquisition, Conceptualization, Writing – original draft. **Maria Vertzoni:** Funding acquisition, Conceptualization. **Jan Frederik Schlender:** Funding acquisition, Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest that are directly relevant to the content of this article.

Data availability

No data was used for the research described in the article.

Acknowledgements

CD, DR, and AEE are supported by a Horizon 2020 research and innovation program; Marie Skłodowska-Curie grant (No. 956146). We would like to thank the OSP, GastroPlus and Simcyp Certara for their cooperation and their response to the questionnaire given in Supp 1.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2023.106496.

References

Abduljalil, K., et al., 2016. A tutorial on pharmacodynamic scripting facility in Simcyp. CPT Pharmacomet. Syst. Pharmacol. 5 (9), 455–465.
American Geriatrics Society, 2019. 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 67 (4), 674–694.
Annaert, P., et al., 2010. *Ex vivo* permeability experiments in excised rat intestinal tissue and *in vitro* solubility measurements in aspirated human intestinal fluids support age-dependent oral drug absorption. Eur. J. Pharm. Sci. 39 (1–3), 15–22.
Autenrieth, C.S., et al., 2018. Global and regional trends of people living with HIV aged 50 and over: estimates and projections for 2000-2020. PLoS ONE 13 (11), e0207005.
Babiskin, A.H., Zhang, X., 2015. Application of physiologically based absorption modeling for amphetamine salts drug products in generic drug evaluation. J. Pharm. Sci. 104 (9), 3170–3182.
Bardan, E., et al., 2006. Effect of aging on bolus kinematics during the pharyngeal phase of swallowing. Am. J. Physiol. Gastrointest. Liver Physiol. 290 (3), G458–G465.
Baron, J.H., 1963. Studies of basal and peak acid output with an augmented histamine test. Gut 4 (2), 136–144.
Bell, C.G., et al., 2019. DNA methylation aging clocks: challenges and recommendations. Genome Biol. 20 (1), 249.
Bertolotti, M., et al., 1993. Effect of aging on cholesterol 7 alpha-hydroxylation in humans. J. Lipid Res. 34 (6), 1001–1007.
Bertolotti, M., et al., 2007. Age-related changes in bile acid synthesis and hepatic nuclear receptor expression. Eur. J. Clin. Investig. 37 (6), 501–508.
Bhutto, A., Morley, J.E., 2008. The clinical significance of gastrointestinal changes with aging. Curr. Opin. Clin. Nutr. Metab. Care 11 (5), 651–660.
Biritwum, R.B., et al., 2016. Prevalence of and factors associated with frailty and disability in older adults from China, Ghana, India, Mexico, Russia and South Africa. Maturitas 91, 8–18.
Blagosklonny, M.V., 2013. Selective anti-cancer agents as anti-aging drugs. Cancer Biol. Ther. 14 (12), 1092–1097.
Bloch, F., Charasz, N., 2014. Attitudes of older adults to their participation in clinical trials: a pilot study. Drugs Aging 31 (5), 373–377.
Bloomfield, A.L., Keefer, C.S., 1928. Gastric acidity: relation to various factors such as age and physical fitness. J. Clin. Investig. 5 (2), 285–294.
Bouzom, F., et al., 2012. Physiologically based pharmacokinetic (PBPK) modelling tools: how to fit with our needs? Biopharm. Drug Dispos. 33 (2), 55–71.
Briant, R.H., et al., 1983. Bioavailability of metoprolol in young adults and the elderly, with additional studies on the effects of metoclopramide and probanthine. Eur. J. Clin. Pharmacol. 25 (3), 353–356.
Brogna, A., et al., 1999. Influence of aging on gastrointestinal transit time. An ultrasonographic and radiologic study. Investig. Radiol. 34 (5), 357–359.
Brogna, A., et al., 2006. Radioisotopic assessment of gastric emptying of solids in elderly subjects. Aging Clin. Exp. Res. 18 (6), 493–496.
Brown, D.R., Topcu, M., 2003. Willingness to participate in clinical treatment research among older African Americans and Whites. Gerontologist 43 (1), 62–72.
Cederholm, T., Hellström, K., 1992. Nutritional status in recently hospitalized and free-living elderly subjects. Gerontology 38 (1–2), 105–110.
Chang, M.W., Rosendall, B., Finlayson, B.A., 1998. Mathematical modeling of normal pharyngeal bolus transport: a preliminary study. J. Rehabil. Res. Dev. 35 (3), 327–334.
Chang, M.W., Lin, E., Hwang, J.N., 1999. Contour tracking using a knowledge-based snake algorithm to construct three-dimensional pharyngeal bolus movement. Dysphagia 14 (4), 219–227.
Chen, J., et al., 2018. Pharmacogenetic analysis of the model-based pharmacokinetics of five anti-HIV drugs: how does this influence the effect of aging? Clin. Transl. Sci. 11 (2), 226–236.
Chen, F., et al., 2019. Physiologically based pharmacokinetic modeling to understand the absorption of risperidone orodispersible film. Front. Pharmacol. 10, 1692.
Chetty, M., et al., 2018. Physiologically based pharmacokinetic modelling to guide drug delivery in older people. Adv. Drug Deliv. Rev. 135, 85–96.

Chow, E.C., et al., 2016. Using physiologically based pharmacokinetic (PBPK) modeling to evaluate the impact of pharmaceutical excipients on oral drug absorption: sensitivity analyses. AAPS J. 18 (6), 1500–1511.
Clarkston, W.K., et al., 1997. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. Am. J. Physiol. 272 (1), R243–R248. Pt 2.
Cleary, Y., et al., 2021. Model-based drug-drug interaction extrapolation strategy from adults to children: risdiplam in pediatric patients with spinal muscular atrophy. Clin. Pharmacol. Ther. 110 (6), 1547–1557.
Collen, M.J., Abdulian, J.D., Chen, Y.K., 1994. Age does not affect basal gastric acid secretion in normal subjects or in patients with acid-peptic disease. Am. J. Gastroenterol. 89 (5), 712–716.
Cui, C., et al., 2021. Development of a physiologically based pharmacokinetic (PBPK) population model for Chinese elderly subjects. Br. J. Clin. Pharmacol. 87 (7), 2711–2722.
Cui, C., et al., 2022. Assessment of aging-related function variations of P-gp transporter in old-elderly Chinese CHF patients based on modeling and simulation. Clin. Pharmacokinet. 61 (12), 1789–1800.
De Sousa Mendes, M., Chetty, M., 2019. Are standard doses of renally-excreted antiretrovirals in older patients appropriate: a PBPK study comparing exposures in the elderly population with those in renal impairment. Drugs R. D. 19 (4), 339–350.
De Stefano, N., et al., 2022. Analysis of frequency and severity of relapses in multiple sclerosis patients treated with cladribine tablets or placebo: the CLARITY and CLARITY Extension studies. Mult. Scler. 28 (1), 111–120.
De Zwart, L., et al., 2021. Prediction of the drug-drug interaction potential of the α1-acid glycoprotein bound, CYP3A4/CYP2C9 metabolized oncology drug, erdafitinib. CPT Pharmacomet. Syst. Pharmacol. 10 (9), 1107–1118.
Di Sabatino, A., et al., 2018. Frailty and the gut. Dig. Liver Dis. 50 (6), 533–541.
Diakidou, A., et al., 2009. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. Pharm. Res. 26 (9), 2141–2151.
Division, U.P., World population ageing, 2019: highlights. 2019.
Divoll, M., et al., 1982. Effect of food on acetaminophen absorption in young and elderly subjects. J. Clin. Pharmacol. 22 (11–12), 571–576.
Dressman, J.B., et al., 1990. Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm. Res. 7 (7), 756–761.
Drozdzik, M., et al., 2020. Intestinal drug transporters in pathological states: an overview. Pharmacol. Rep. 72 (5), 1173–1194.
Elia, M., Stratton, R.J., 2005. Geographical inequalities in nutrient status and risk of malnutrition among English people aged 65 y and older. Nutrition 21 (11–12), 1100–1106.
(EMA), E.M.A., Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. EMA/CHMP/458101/2016, 2018.
Ennis, B.W., Saffel-Shrier, S., Verson, H., 2001. Diagnosing malnutrition in the elderly. Nurse Pract. 26 (3), 52–60, 61-2, 65.
Estudante, M., et al., 2013. Intestinal drug transporters: an overview. Adv. Drug Deliv. Rev. 65 (10), 1340–1356.
European, C. and Eurostat, 2020. Ageing Europe: Looking At the Lives of Older People in the EU: 2020 Edition. Publications Office.
Eurostat. Population structure and ageing. 2022; Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing#Past_and_future_population_ageing_trends_in_the_EU.
Farkas, A., Szmodis, M., 2019. About the secular growth trend. Biomed. J. Sci. Tech. Res. 17 (4), 13003–13005.
Feldman, M., et al., 1996. Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. Gastroenterology 110 (4), 1043–1052.
Feng, Q., Son, J., Zeng, Y., 2015. Prevalence and correlates of successful ageing: a comparative study between China and South Korea. Eur. J. Ageing 12 (2), 83–94.
Florisson, S., et al., 2021. Are older adults insufficiently included in clinical trials?-An umbrella review. Basic Clin. Pharmacol. Toxicol. 128 (2), 213–223.
Forsat, N.P., Palmowski, A., Palmowski, Y., Boers, M., Buttgereit, F., Identifying barriers and solutions concerning the recruitment and retention of elderly people in clinical research: protocol for a Systematic Review v1. 2019.
Fritz, A., et al., 2019. Expression of clinically relevant drug-metabolizing enzymes along the human intestine and their correlation to drug transporters and nuclear receptors: an intra-subject analysis. Basic Clin. Pharmacol. Toxicol. 124 (3), 245–255.
Gainsborough, N., et al., 1993. The association of age with gastric emptying. Age Ageing 22 (1), 37–40.
Galkin, F., et al., 2020. Human gut microbiome aging clock based on taxonomic profiling and deep learning. iScience 23 (6), 101199.
Gemikonakli, G., Mach, J., Hilmer, S.N., 2021. Interactions between the aging gut microbiome and common geriatric giants: polypharmacy, frailty, and dementia. J. Gerontol. A Biol. Sci. Med. Sci. 76 (6), 1019–1028.
Gialluisi, A., et al., 2019. Machine learning approaches for the estimation of biological aging: the road ahead for population studies. Front. Med. (Lausanne) 6:, 146.
Goldschmiedt, M., et al., 1991. Effect of age on gastric acid secretion and serum gastrin concentrations in healthy men and women. Gastroenterology 101 (4), 977–990.
Grimstein, M., et al., 2019. Physiologically based pharmacokinetic modeling in regulatory science: an update from the U.S. food and drug administration's office of clinical pharmacology. J. Pharm. Sci. 108 (1), 21–25.
Guitart, J., et al., 2017. Breakthrough pain management with sublingual fentanyl tablets in patients with cancer: age subgroup analysis of a multicenter prospective study. Drugs R. D. 17 (3), 419–425.
Haddow, L.J., et al., 2019. Magnetic resonance imaging of cerebral small vessel disease in men living with HIV and HIV-negative men aged 50 and above. AIDS Res. Hum. Retrovir. 35 (5), 453–460.
Hanratty, C.G., et al., 2000. Differential pharmacokinetics of digoxin in elderly patients. Drugs Aging 17 (5), 353–362.
Haran, JP, Bhattarai, SK, Foley, SE, Dutta, P, Ward, DV, Bucci, V, McCormick, BA, 2019. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. mBio 10, e00632-19.
Haruma, K., et al., 2000. Effect of age and Helicobacter pylori infection on gastric acid secretion. J. Gastroenterol. Hepatol. 15 (3), 277–283.
Hellstrom, P.M., et al., 2017. Normal gastric emptying time of a carbohydrate-rich drink in elderly patients with acute hip fracture: a pilot study. BMC Anesthesiol. 17 (1), 23.
High, K.P., et al., 2012. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS research by the HIV and aging working group. J. Acquir. Immune Defic. Syndr. 60, S1–18. Suppl 1(Suppl 1).
Hogan, D.B., Maxwell, C.J., 2020. Frailty and unintended risks of medications. Curr. Epidemiol. Rep. 7 (1), 16–24.
Hoogendijk, E.O., et al., 2017. Development and validation of a frailty index in the longitudinal aging study Amsterdam. Aging Clin. Exp. Res. 29 (5), 927–933.
Hoogendijk, E.O., et al., 2019. Frailty: implications for clinical practice and public health. Lancet 394 (10206), 1365–1375.
Hoogendijk, E.O., et al., 2020. Operationalization of a frailty index among older adults in the InCHIANTI study: predictive ability for all-cause and cardiovascular disease mortality. Aging Clin. Exp. Res. 32 (6), 1025–1034.
Hubbard, R.E., et al., 2009. Inflammation and frailty measures in older people. J. Cell. Mol. Med. 13 (9b), 3103–3109.
Hughes, K.M., et al., 1992. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica 22 (7), 859–869.
Hurwitz, A., et al., 1982. Oral anticholinergics and gastric emptying. Clin. Pharmacol. Ther. 31 (2), 168–174.
Hurwitz, A., et al., 2003. Gastric function in the elderly: effects on absorption of ketoconazole. J. Clin. Pharmacol. 43 (9), 996–1002.
Hutchins, L.F., et al., 1999. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N. Engl. J. Med. 341 (27), 2061–2067.
ICH, et al., 1993. E7 - Studies in Support of Special Populations. Geriatrics. Available from: https://www.ich.org/page/efficacy-guidelines. Available from:
Jackson, M.A., et al., 2016. Signatures of early frailty in the gut microbiota. Genome Med 8 (1), 8.
Ierusalimschy, R. Programming in Lua. 2006; Available from: https://www.lua.org/home.html.
Jamei, M., et al., 2009a. The Simcyp population-based ADME simulator. Expert Opin. Drug Metab. Toxicol. 5 (2), 211–223.
Jamei, M., et al., 2009b. Population-based mechanistic prediction of oral drug absorption. AAPS J. 11 (2), 225–237.
Jankowska-Polańska, B., et al., 2016. The influence of frailty syndrome on medication adherence among elderly patients with hypertension. Clin. Interv. Aging 11, 1781–1790.
Kagaya, M., et al., 1997. Small bowel transit time and colonic fermentation in young and elderly women. J. Gastroenterol. 32 (4), 453–456.
Kanapuru, B., et al., 2020. Older adults in hematologic malignancy trials: representation, barriers to participation and strategies for addressing underrepresentation. Blood Rev. 43, 100670.
Katelaris, P.H., et al., 1993. Effect of age, Helicobacter pylori infection, and gastritis with atrophy on serum gastrin and gastric acid secretion in healthy men. Gut 34 (8), 1032–1037.
Kekki, M., et al., 1982. Age- and sex-related behaviour of gastric acid secretion at the population level. Scand. J. Gastroenterol. 17 (6), 737–743.
Khandeparkar, A., Rataboli, P.V., 2017. A study of harmful drug-drug interactions due to polypharmacy in hospitalized patients in Goa Medical College. Perspect. Clin. Res. 8 (4), 180–186.
Kim, C., et al., 2021. Application of a dual mechanistic approach to support bilastine dose selection for older adults. CPT Pharmacomet. Syst. Pharmacol. 10 (9), 1006–1017.
Kim, S.E., 2017. Colonic slow transit can cause changes in the gut environment observed in the elderly. J. Neurogastroenterol. Motil. 23 (1), 3–4.
Kinirons, M.T., O'Mahony, M.S., 2004. Drug metabolism and ageing. Br. J. Clin. Pharmacol. 57 (5), 540–544.
Klaassen, C.D., Cui, J.Y., 2015. Review: mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metab. Dispos. 43 (10), 1505–1521.
Kneller, L.A., Hempel, G., 2020. Modelling age-related changes in the pharmacokinetics of risperidone and 9-hydroxyrisperidone in different CYP2D6 phenotypes using a physiologically based pharmacokinetic approach. Pharm. Res. 37 (6), 110.
Krauss, M., et al., 2013. Using Bayesian-PBPK modeling for assessment of inter-individual variability and subgroup stratification. *In Silico* Pharmacol. 1, 6.
Krauss, M., et al., 2015. Bayesian population physiologically-based pharmacokinetic (PBPK) approach for a physiologically realistic characterization of interindividual variability in clinically relevant populations. PLoS ONE 10 (10), e0139423.
Krauss, M., et al., 2017. Translational learning from clinical studies predicts drug pharmacokinetics across patient populations. NPJ Syst. Biol. Appl. 3 (1), 11.
Kudryashova, K.S., et al., 2020. Aging biomarkers: from functional tests to multi-omics approaches. Proteomics 20 (5–6), e1900408.
Kuepfer, L., et al., 2016. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacomet. Syst. Pharmacol. 5 (10), 516–531.
Kuhn-Thiel, A.M., Weiß, C., Wehling, M., 2014. Consensus validation of the FORTA (Fit fOR The Aged) list: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. Drugs Aging 31 (2), 131–140.

Lang, J., et al., 2021. Reduced physiologically-based pharmacokinetic model of dabigatran etexilate-dabigatran and its application for prediction of intestinal P-gp-mediated drug-drug interactions. Eur. J. Pharm. Sci. 165, 105932.
Lau, S.W.J., et al., 2020. Geriatrics 2030: developing drugs to care for older persons-a neglected and growing population. Clin. Pharmacol. Ther. 107 (1), 53–56.
Lewis, J.H., et al., 2003. Participation of patients 65 years of age or older in cancer clinical trials. J. Clin. Oncol. 21 (7), 1383–1389.
Li, G.F., et al., 2019. Impact of ethnicity-specific hepatic microsomal scaling factor, liver weight, and cytochrome P450 (CYP) 1A2 content on physiologically based prediction of CYP1A2-mediated pharmacokinetics in young and elderly Chinese adults. Clin. Pharmacokinet. 58 (7), 927–941.
Lippert, J., et al., 2019. Open systems pharmacology community-an open access, open source, open science approach to modeling and simulation in pharmaceutical sciences. CPT Pharmacomet. Syst. Pharmacol. 8 (12), 878–882.
Liu, D., et al., 2020. Considerations and caveats when applying global sensitivity analysis methods to physiologically based pharmacokinetic models. AAPS J. 22 (5), 93.
Liu, Q., et al., 2022. Roadmap to 2030 for drug evaluation in older adults. Clin. Pharmacol. Ther. 112 (2), 210–223.
López-Otín, C., et al., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217.
Madsen, J.L., Graff, J., 2004. Effects of ageing on gastrointestinal motor function. Age Ageing 33 (2), 154–159.
Malik, P.R.V., et al., 2017. Population PBPK modelling of trastuzumab: a framework for quantifying and predicting inter-individual variability. J. Pharmacokinet. Pharmacodyn. 44 (3), 277–290.
Malingré, M.M., et al., 2001. Coadministration of cyclosporine strongly enhances the oral bioavailability of docetaxel. J. Clin. Oncol. 19 (4), 1160–1166.
Man, A.L., et al., 2015. Age-associated modifications of intestinal permeability and innate immunity in human small intestine. Clin. Sci. (Lond.) 129 (7), 515–527.
Manchikanti, L., et al., 1985. Assessment of age-related acid aspiration risk factors in pediatric, adult, and geriatric patients. Anesth. Analg. 64 (1), 11–17.
Mangoni, A.A., Jackson, S.H., 2004. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br. J. Clin. Pharmacol. 57 (1), 6–14.
McNally, K., Cotton, R., Loizou, G.D., 2011. A workflow for global sensitivity analysis of PBPK models. Front. Pharmacol. 2, 31.
Mithani, S.D., et al., 1996. Estimation of the increase in solubility of drugs as a function of bile salt concentration. Pharm. Res. 13 (1), 163–167.
Muhammad, T., et al., 2022. Decomposing rural–urban differences in successful aging among older Indian adults. Sci. Rep. 12 (1), 6430.
Nagler, R.M., Hershkovich, O., 2005. Relationships between age, drugs, oral sensorial complaints and salivary profile. Arch. Oral. Biol. 50 (1), 7–16.
Nakae, Y., et al., 1999. Effects of aging and gastric lipolysis on gastric emptying of lipid in liquid meal. J. Gastroenterol. 34 (4), 445–449.
Nedelman, J., et al., 1997. The effect of food on the pharmacokinetics of multiple-dose terbinafine in young and elderly healthy subjects. Biopharm. Drug Dispos. 18 (2), 127–138.
O'Caoimh, R., et al., 2021. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age Ageing 50 (1), 96–104.
O'Mahony, D., O'Leary, P., Quigley, E.M.M., 2002. Aging and intestinal motility. Drugs Aging 19 (7), 515–527.
O'Mahony, D., et al., 2015. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44 (2), 213–218.
Onen, N.F., et al., 2010. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. HIV Clin. Trials 11 (2), 100–109.
Ouchi, Y., et al., 2017. Redefining the elderly as aged 75 years and older: proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. Geriatr. Gerontol. Int. 17 (7), 1045–1047.
Paine, M.F., et al., 2006. The human intestinal cytochrome P450 "pie". Drug Metab. Dispos. 34 (5), 880–886.
Parrott, N.J., et al., 2016. Physiologically based absorption modeling to explore the impact of food and gastric pH changes on the pharmacokinetics of alectinib. AAPS J. 18 (6), 1464–1474.
Pasina, L., et al., 2014. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs Aging 31 (4), 283–289.
Pather, S.I., Rathbone, M.J., Senel, S., 2008. Current status and the future of buccal drug delivery systems. Expert Opin. Drug Deliv. 5 (5), 531–542.
Pedersen, P.B., et al., 2013. Characterization of fasted human gastric fluid for relevant rheological parameters and gastric lipase activities. Eur. J. Pharm. Biopharm. 85 (3), 958–965. Pt B.
Peters, S.A., 2012. Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulations: Principles, Methods, and Applications in the Pharmaceutical Industry, 2nd ed. John Wiley & Sons.John Wiley & Sons.
Pfeiffer, R.F., Isaacson, S.H., Pahwa, R., 2020. Clinical implications of gastric complications on levodopa treatment in Parkinson's disease. Parkinsonism Relat. Disord. 76, 63–71.
Pfeiffer, R.F., 2003. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 2 (2), 107–116.
Pilgrim, A.L., et al., 2015. An overview of appetite decline in older people. Nurs. Older People 27 (5), 29–35.
Polland, W.S., Bloomfield, A.L., 1931. Normal standards of gastric function. J. Clin. Investig. 9 (4), 651–658.
Raheja, D., et al., 2018. Willingness to participate in vaccine-related clinical trials among older adults. Int. J. Environ. Res. Public Health 15 (8), 1743.
Rashid, M., et al., 2021. Prediction of pharmacokinetic parameters and dose of pregabalin gastroretentive formulation in healthy adults, healthy pediatrics and renal-impaired geriatrics. J. Drug Deliv. Sci. Technol. 63, 102548.
Rattanacheeworn, P., et al., 2021. Quantification of CYP3A and drug transporters activity in healthy young, healthy elderly and chronic kidney disease elderly patients by a microdose cocktail approach. Front. Pharmacol. 12, 726669.
Ren, W.Y., et al., 2014. Age-related changes in small intestinal mucosa epithelium architecture and epithelial tight junction in rat models. Aging Clin. Exp. Res. 26 (2), 183–191.
Reppas, C., et al., 2015. Characterization of contents of distal ileum and cecum to which drugs/drug products are exposed during bioavailability/bioequivalence studies in healthy adults. Pharm. Res. 32 (10), 3338–3349.
Rhee, S.J., et al., 2017. Physiologically based pharmacokinetic modelling and prediction of metformin pharmacokinetics in renal/hepatic-impaired young adults and elderly populations. Eur. J. Drug Metab. Pharmacokinet. 42 (6), 973–980.
Rozé, C., 1980. Neurohumoral control of gastrointestinal motility. Reprod. Nutr. Dev. 20 (4b), 1125–1141, 1980.
Ruiter, R., Burggraaf, J., Rissmann, R., 2019. Under-representation of elderly in clinical trials: an analysis of the initial approval documents in the Food and Drug Administration database. Br. J. Clin. Pharmacol. 85 (4), 838–844.
Russell, C.A., Elia, M., 2010. Malnutrition in the UK: where does it begin? Proc. Nutr. Soc. 69 (4), 465–469.
Russell, T.L., et al., 1993. Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. Pharm. Res. 10 (2), 187–196.
Russell, T.L., et al., 1994. pH-related changes in the absorption of dipyridamole in the elderly. Pharm. Res. 11 (1), 136–143.
Russell, R.M., 1997. Gastric hypochlorhydria and achlorhydria in older adults. JAMA 278 (20), 1659. -1659.
Saffrey, M.J., 2013. Aging of the mammalian gastrointestinal tract: a complex organ system. Age 36 (3), 9603.
Salerno, S.N., et al., 2021. Leveraging physiologically-based pharmacokinetic (PBPK) modeling and experimental data to guide dosing modification of CYP3A-mediated drug-drug interactions (DDIs) in the pediatric population. Drug Metab. Dispos. DMD-AR-2020-000318.
Salle, J.Y., et al., 2021. Efficacy of a ready-to-drink gelled water and of a thickening powder in patients with oropharyngeal dysphagia: a crossover randomized study. SN Compr. Clin. Med. 3 (11), 2244–2250.
Saltelli, A., Ratto, M., Andres, T., Campolongo, F., Cariboni, J., Gatelli, D., Saisana, M., 2008. Global Sensitivity Analysis. The Primer. John Wiley & Sons, Ltd.
Schiller, C., et al., 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment. Pharmacol. Ther. 22 (10), 971–979.
Schlender, J.F., et al., 2016. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. Clin. Pharmacokinet. 55 (12), 1573–1589.
Schlender, J.F., et al., 2018a. Current strategies to streamline pharmacotherapy for older adults. Eur. J. Pharm. Sci. 111, 432–442.
Schlender, J.F., et al., 2018b. A physiologically-based pharmacokinetic model to describe ciprofloxacin pharmacokinetics over the entire span of life. Clin. Pharmacokinet. 57 (12), 1613–1634.
Seng, K.Y., Nestorov, I., Vicini, P., 2008. Physiologically based pharmacokinetic modeling of drug disposition in rat and human: a fuzzy arithmetic approach. Pharm. Res. 25 (8), 1771–1781.
Serra-Prat, M., et al., 2009. Effect of age and frailty on ghrelin and cholecystokinin responses to a meal test. Am. J. Clin. Nutr. 89 (5), 1410–1417.
Serra-Prat, M., et al., 2013. Gastrointestinal peptides, gastrointestinal motility, and anorexia of aging in frail elderly persons. Neurogastroenterol. Motil. 25 (4), 291–e245.
Sharma, A., Buschmann, M.M., Gilbert, J.A., 2019. Pharmacomicrobiomics: the holy grail to variability in drug response? Clin. Pharmacol. Ther. 106 (2), 317–328.
Sheiner, L.B., 1997. Learning versus confirming in clinical drug development. Clin. Pharmacol. Ther. 61 (3), 275–291.
Shim, Y.K., et al., 2017. Effects of age on esophageal motility: use of high-resolution esophageal impedance manometry. J. Neurogastroenterol. Motil. 23 (2), 229–236.
Shin, H.J., et al., 2022. Ultrasound assessment of gastric volume in older adults after drinking carbohydrate-containing fluids: a prospective, nonrandomized, and noninferiority comparative study. Can. J. Anesth./J. Can. D'anesth. 69 (9), 1160–1166.
SimulationsPlus. Inc., 2018. GastroPlus Manual Version 9.6. SimulationsPlus. Inc. Published. MayAvailable from: https://www.simulations-plus.com/software/gastroplus/
Stader, F., et al., 2019. Repository describing an aging population to inform physiologically based pharmacokinetic models considering anatomical, physiological, and biological age-dependent changes. Clin. Pharmacokinet. 58 (4), 483–501.
Stader, F., et al., 2021a. Physiologically-based pharmacokinetic modeling combined with Swiss HIV cohort study data supports no dose adjustment of bictegravir in elderly individuals living with HIV. Clin. Pharmacol. Ther. 109 (4), 1025–1029.
Stader, F., et al., 2021b. Clinical data combined with modeling and simulation indicate unchanged drug-drug interaction magnitudes in the elderly. Clin. Pharmacol. Ther. 109 (2), 471–484.
Sweeney, L.M., et al., 2001. Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo simulations. Toxicol. Sci. 62 (1), 124–139.
Türk, D., et al., 2019. Physiologically based pharmacokinetic models for prediction of complex CYP2C8 and OATP1B1 (SLCO1B1) drug-drug-gene interactions: a modeling

network of gemfibrozil, repaglinide, pioglitazone, rifampicin, clarithromycin and itraconazole. Clin. Pharmacokinet. 58 (12), 1595–1607.
Thelen, K., et al., 2011. Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part 1: oral solutions. J. Pharm. Sci. 100 (12), 5324–5345.
Thelen, K., et al., 2012. Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part II: extension to describe performance of solid dosage forms. J. Pharm. Sci. 101 (3), 1267–1280.
Theou, O., et al., 2021. A classification tree to assist with routine scoring of the clinical frailty scale. Age Ageing 50 (4), 1406–1411.
Thiele, I., et al., 2017. Quantitative systems pharmacology and the personalized drug-microbiota-diet axis. Curr. Opin. Syst. Biol. 4, 43–52.
Thompson, C.M., et al., 2009. Database for physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and health-impaired elderly. J. Toxicol. Environ. Health B Crit. Rev. 12 (1), 1–24.
Thompson, M.Q., et al., 2018. Frailty prevalence and factors associated with the Frailty Phenotype and Frailty Index: findings from the North West Adelaide Health Study. Australas. J Ageing 37 (2), 120–126.
Ticho, A.L., et al., 2019. Intestinal absorption of bile acids in health and disease. Compr. Physiol. 10 (1), 21–56.
Tracy, J.F., et al., 1989. Preliminary observations on the effects of age on oropharyngeal deglutition. Dysphagia 4 (2), 90–94.
Tran, L., Greenwood-Van Meerveld, B., 2013. Age-associated remodeling of the intestinal epithelial barrier. J. Gerontol. A Biol. Sci. Med. Sci. 68 (9), 1045–1056.
Trenaman, S.C., et al., 2021. The role of sex, age and genetic polymorphisms of CYP enzymes on the pharmacokinetics of anticholinergic drugs. Pharmacol. Res. Perspect. 9 (3), e00775.
Tsamandouras, N., Rostami-Hodjegan, A., Aarons, L., 2015. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. Br. J. Clin. Pharmacol. 79 (1), 48–55.
Van der Veken, M., et al., 2022. Gastrointestinal fluid volumes in pediatrics: a retrospective MRI study. Pharmaceutics 14 (9), 1935.
van Kessel, S.P., et al., 2019. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. Nat. Commun. 10 (1), 310.
Vanzant, F.R., et al., 1932. The normal range of gastric acidity from youth to old age: an analysis of 3,746 records. Arch. Intern. Med. 49 (3), 345–359.
Vertzoni, M., et al., 2021. Characteristics of contents of lower intestine in the 65-74 years of age range could impact the performance of safe and efficacious modified release products. J. Pharm. Sci. 110 (1), 251–258.
Wandeler, G., Johnson, L.F., Egger, M., 2016. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr. Opin. HIV AIDS 11 (5), 492–500.
Wang, J., Flanagan, D.R., 1999. General solution for diffusion-controlled dissolution of spherical particles. 1. Theory. J. Pharm. Sci. 88 (7), 731–738.
Wang, H.Y., et al., 2016. Evaluating a physiologically based pharmacokinetic model for predicting the pharmacokinetics of midazolam in Chinese after oral administration. Acta Pharmacol. Sin. 37 (2), 276–284.
Watson, L.E., et al., 2019. Gastric emptying in patients with well-controlled type 2 diabetes compared with young and older control subjects without diabetes. J. Clin. Endocrinol. Metab. 104 (8), 3311–3319.
Welling, P.G., 1989. Effects of food on drug absorption. Pharmacol. Ther. 43 (3), 425–441.
Willmann, S., et al., 2021. Applications of physiologically based pharmacokinetic modeling of rivaroxaban-renal and hepatic impairment and drug-drug interaction potential. J. Clin. Pharmacol. 61 (5), 656–665.
Wu, K.C., Lin, C.J., 2019. The regulation of drug-metabolizing enzymes and membrane transporters by inflammation: evidences in inflammatory diseases and age-related disorders. J. Food Drug Anal. 27 (1), 48–59.
Wynne, H.A., et al., 1993. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing 22 (5), 354–359.
Yang, J., et al., 2010. Pregnane X receptor is required for interleukin-6-mediated down-regulation of cytochrome P450 3A4 in human hepatocytes. Toxicol. Lett. 197 (3), 219–226.
Yu, L.X., Amidon, G.L., 1999. A compartmental absorption and transit model for estimating oral drug absorption. Int. J. Pharm. 186 (2), 119–125.
Zeeh, J., et al., 1996. Influence of age, frailty and liver function on the pharmacokinetics of brofaromine. Eur. J. Clin. Pharmacol. 49 (5), 387–391.
Zelko, E., Klemenc-Ketis, Z., Tusek-Bunc, K., 2016. Medication adherence in elderly with polypharmacy living at home: a systematic review of existing studies. Mater. Sociomed. 28 (2), 129–132.
Zhang, X.Y., et al., 2015. Sobol sensitivity analysis: a tool to guide the development and evaluation of systems pharmacology models. CPT Pharmacomet. Syst. Pharmacol. 4 (2), 69–79.
Zhao, P., et al., 2011. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin. Pharmacol. Ther. 89 (2), 259–267.
Zimmermann-Kogadeeva, M., Zimmermann, M., Goodman, A.L., 2020. Insights from pharmacokinetic models of host-microbiome drug metabolism. Gut Microbes 11 (3), 587–596.