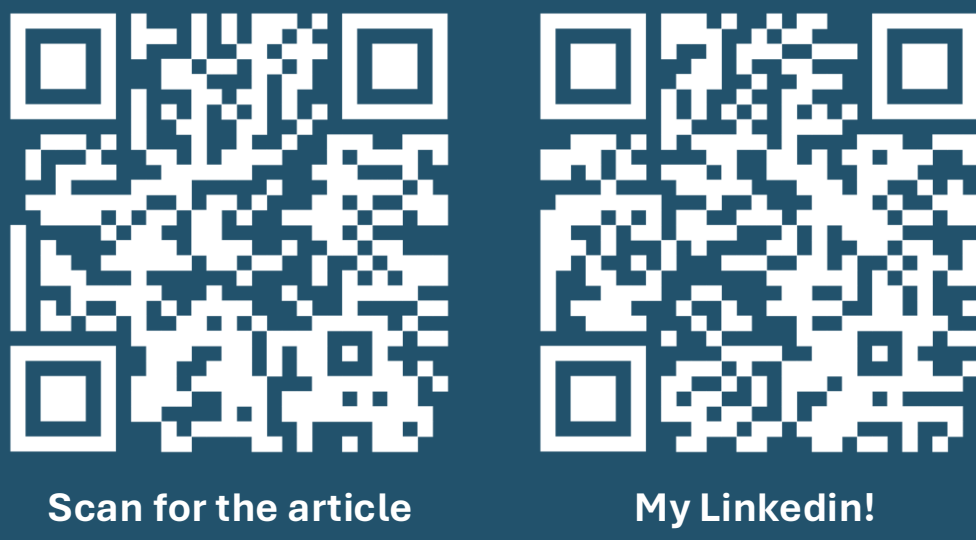


Improving Individualized Salbutamol Treatment: A Population Pharmacokinetic Model for Oral Salbutamol in Virtual Patients

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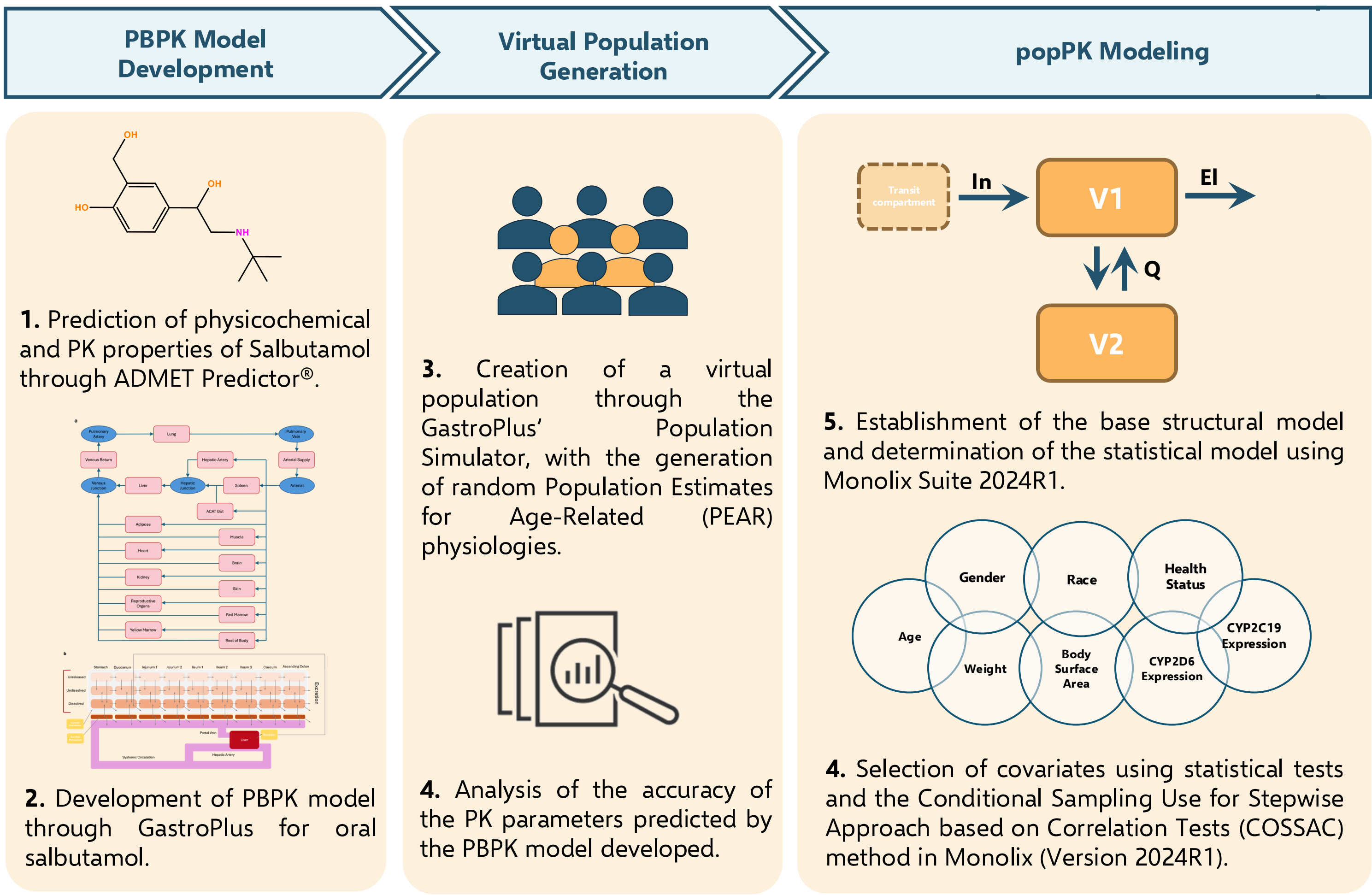
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Introduction

Although primarily administered via inhalation for its rapid and localized effect, salbutamol can also be given intravenously (IV), intramuscularly (IM), subcutaneously, and orally [1]. Salbutamol's pharmacokinetics (absorption, distribution, and elimination) and pharmacodynamics (drug response) characteristics can vary significantly depending on how these different formulations interact with patient-specific characteristics. Thus, a personalized approach becomes particularly essential when multiple administration options exist, as with salbutamol, since there will indeed be individual characteristics that benefit from the use of one formulation over another. This study aims to assess the **influence of several covariates** (age, weight, cytochrome P450 (CYP) expression, health status, and race) on the **PK parameters of oral salbutamol**, adopting a fully in silico approach, from data generation to analysis. This model is intended to support the selection of optimal formulations and dosing regimens based on individual patient profiles.

Workflow



Influence of Patient-Specific Covariates on Oral Salbutamol

Table 2. PK parameters of salbutamol across different patient subgroups defined by gender, BSA, and weight. For the M_{tt} , values are shown for male and female groups. For the V1 and Cl, values are stratified according to BSA and weight categories. The geometric mean and SD are provided for each subgroup.

Parameter	Covariate		Geometric Mean	SD
M_{it}	Gender			
	Female	Male	0.21	3.89
V1	BSA	Weight	0.30	1.37
	0.94–1.60	26.4–75.0	226	1.56
	1.60–2.37	26.4–75.0	276	1.54
CI	1.60–2.37	75.0–109	287	1.84
	0.94–1.60	26.4–75.0	77.9	1.51
	1.60–2.37	26.4–75.0	69.9	2.28
	1.60–2.37	75.0–109	68.2	1.45

Age does not affect the PK parameters of orally administered salbutamol, in contrast to salbutamol DPI [2]. The prescription of the oral regimen for children could be favoured.

Gender significantly influences M_{tt} and Cl. Metabolic differences are the major cause of differential PK between males and females [3,4].

Weight and BSA were found to affect both **V1** and **Cl**, reflecting important physiological differences. These findings highlight the importance of **dose adjustment** in populations with atypical body composition.

Virtual Population

Table 1. Demographic and clinical characteristics of patients (mean or median $\pm$ standard deviation, SD, or interquartile range, IR).

Characteristics	Total (n = 40)
Age (years)	39.5 $\pm$ 18.4
Gender (n, %)	
Female	16, 40
Male	24, 60
BSA (m ²)	1.64 $\pm$ 0.330
Weight (kg)	60.2 $\pm$ 19.8
CYP2C19 Expression (%)	1.30 $\pm$ 1.50
CYP2D6 Expression (%)	1.90 $\pm$ 1.60
Race (n, %)	
American	20, 50
Asian	10, 25
Chinese	10, 25
Health Status (n, %)	
Healthy	24, 65
Obese	4, 10
Cirrhosis A	10, 25

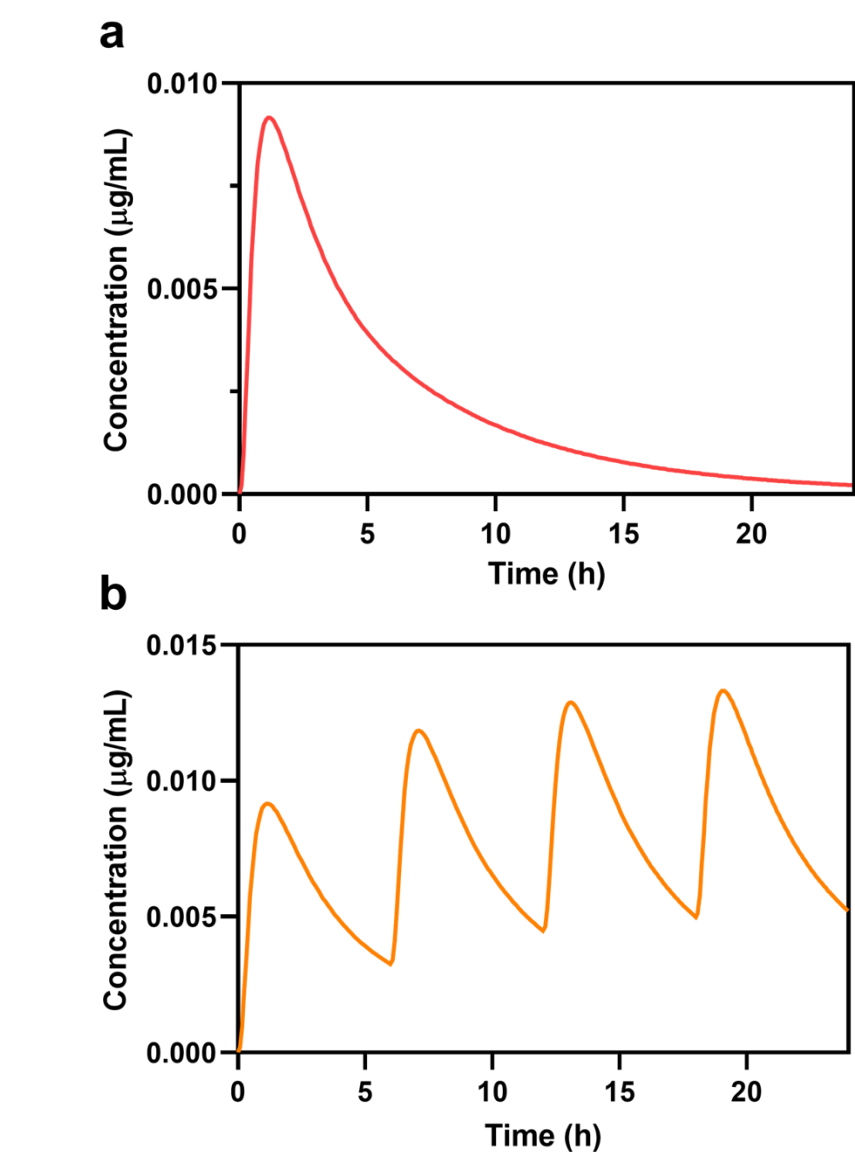


Figure 1. Simulation of single-dose treatment with 4 mg of oral salbutamol (a) and treatment with 4 mg of orally administered salbutamol every 6 hours (b) in a healthy 30-year-old American male individual.

Race was not included as a covariate in the model, as no statistical correlations with PK parameters were found. PK variations caused by race have been reported for salbutamol DPI [2], thus, **formulation choice** may need to consider **race** when tailoring treatment to individual patients.

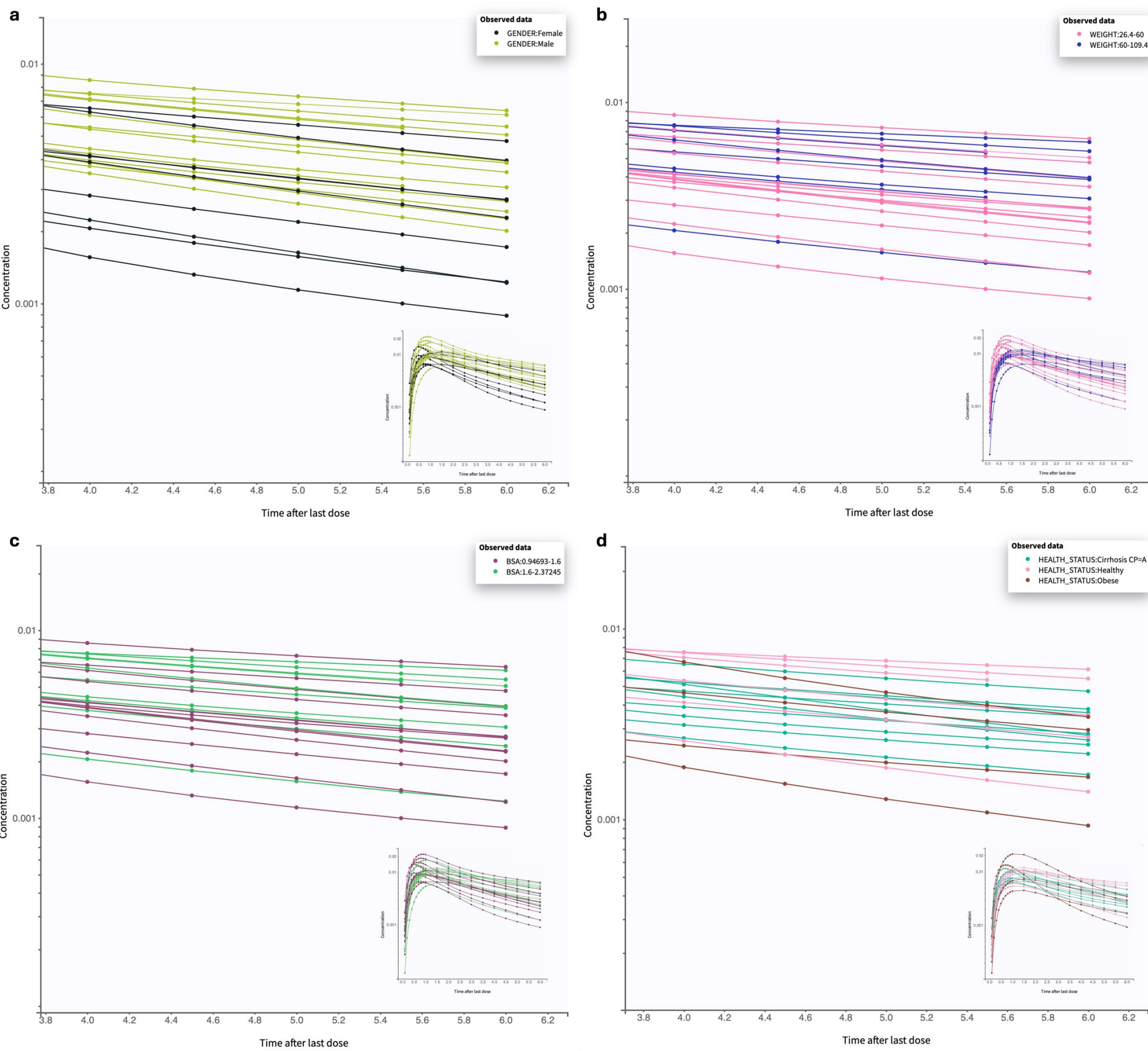


Figure 3. Analysis of covariates' effect on Cl. Evaluation of the terminal phase of the concentration-time profile of the virtual population of healthy adults (20–69 years) under oral treatment with 4 mg of salbutamol. Panel (a) shows the analysis stratified by gender, (b) by body weight, (c) by BSA, and (d) by health status, with only American individuals selected.

popPK Model

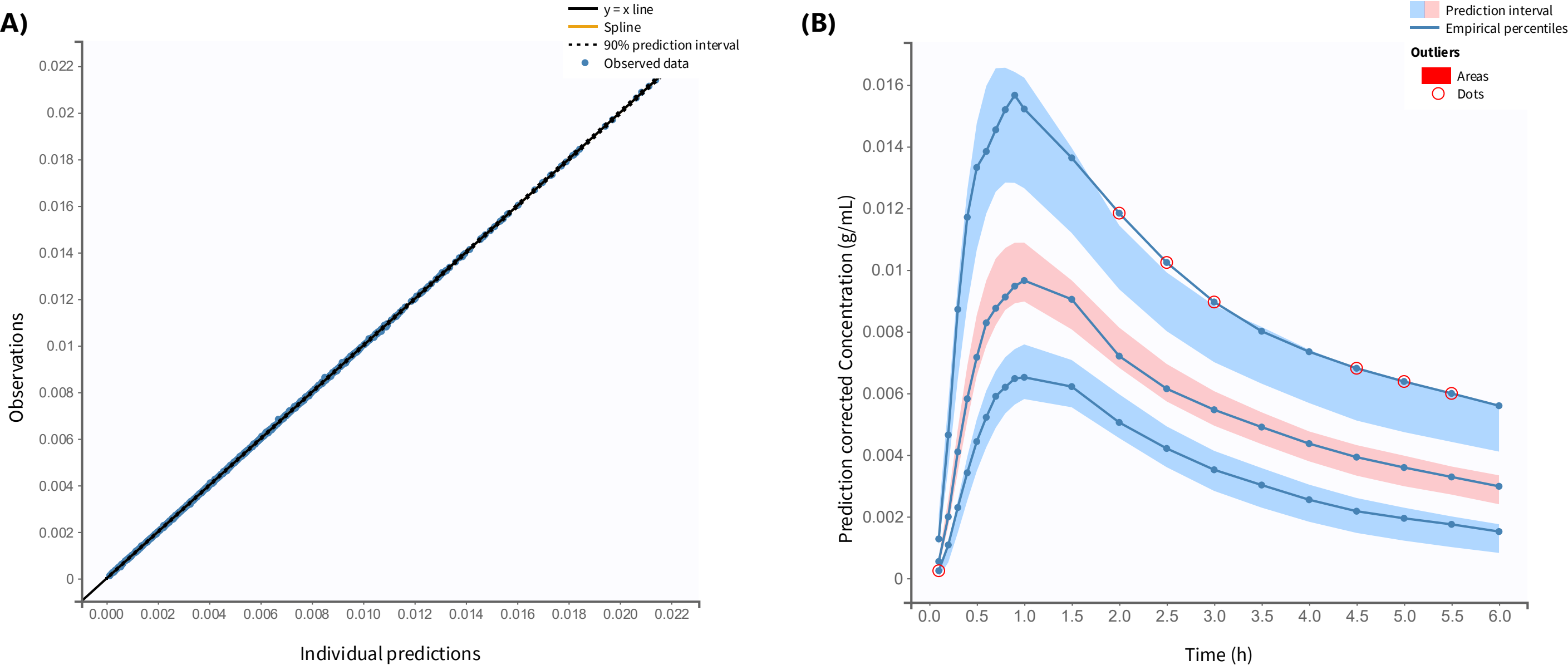


Figure 2. Goodness-of-fit plots of the final popPK model. (A) Observed salbutamol concentration ($\mu\text{g/mL}$) vs individual predictions ($\mu\text{g/mL}$) using conditional mode (EBEs) for the two-compartment model with first-order absorption, including transit compartments, and linear elimination; and (B) the VPC of the final covariate PK model, displaying the prediction intervals for the 10th, 50th, and 90th percentiles (shaded areas, from bottom to top, respectively).

Patients with **cirrhosis A** showed higher **Cl** values than **healthy subjects**.

Conclusions

This popPK study, including gender, weight, BSA, and health status as covariates, further underscores the potential of popPK modeling for personalized therapy, where drug prescriptions are informed not only by disease pathophysiology but also by patient-specific physiological, anatomical, and demographic factors.

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