







REVIEW

Altered intravenous drug disposition in people living with cystic fibrosis: A meta-analysis integrating top-down and bottom-up data

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Abstract

Cystic fibrosis (CF) has been linked to altered drug disposition in various studies. However, the magnitude of these changes, influencing factors, and underlying mechanisms remain a matter of debate. The primary aim of this work was therefore to quantify changes in drug disposition (top-down) and the pathophysiological parameters known to affect pharmacokinetics (PKs; bottom-up). This was done through meta-analyses and meta-regressions in addition to theoretical PK simulations. Volumes of distribution and clearances were found to be elevated in people living with CF. These increases were larger in studies which included patients with pulmonary exacerbations. Differences in clearance were smaller in more recent studies and when results were normalized to body surface area or lean body mass instead of body weight. For the physiological parameters investigated, measured glomerular filtration rate and serum cytokine concentrations were found to be elevated in people living with CF, whereas serum albumin and creatinine levels were decreased. Possible pathophysiological mechanisms for these alterations relate to renal hyperfiltration, increases in free fraction, and inflammation. No differences were detected for cardiac output, body fat, fat free mass, hematocrit, creatinine clearance, and the activity of drug metabolizing enzymes. These findings imply that, in general, lower total plasma concentrations of drugs can be expected in people living with CF, especially when pulmonary exacerbations are present. Given the potential effect of CF on plasma protein binding and the variability in outcome observed between studies, the clinical relevance of adapting existing dosage regimens should be evaluated on a case-by-case basis.

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by defective functioning of the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride transporter located at the apical cell membrane of epithelial tissues.^{1,2} The hallmark of CF pathophysiology and a major cause of mortality is progressive lung function decline due to inflammation and infection.^{3,4} Additionally, CF often leads to gastrointestinal, hepatobiliary, and metabolic complications.⁵⁻⁷ Advancements in pharmacotherapy have significantly improved life expectancy for people living with CF (plwCF) over the past years, and will continue to do so as CFTR modulators are becoming more widely available.^{8,9} Because these novel drugs are added to the existing treatment schedules, they further contribute to pharmacotherapeutic complexity in patients already reporting to take a median of 10 treatments a day.^{10,11} Sufficient pharmacokinetic (PK) knowledge is therefore essential to maximize clinical effect while minimizing toxicity in this vulnerable population.

Due to the multifactorial pathophysiological mechanisms at play in CF, a first question is whether PK data obtained from healthy volunteer studies is representative enough to guide dosing in plwCF. Over the years, multiple studies have been published which investigated the impact of CF on the disposition of, primarily anti-infective, drugs. In general, slower absorption rates, equal or lower bioavailability, higher clearance (CL), and equal or increased distribution volumes (V_d) are observed in plwCF when compared to healthy volunteers.¹² The magnitude and subsequent therapeutic relevance of these changes vary considerably between studies though. Additionally, mechanistic understanding of factors driving PK alterations in plwCF is mostly below standard and founded on a posteriori hypotheses. To come to an overarching theory also applicable to less studied classes of drugs, a more profound understanding of the different pathophysiologic and disease-, study-, and drug-related factors at play is required. Additionally, leveraging the power of mechanistic modeling tools, such as physiologically-based pharmacokinetics (PBPKs), requires detailed knowledge of CF pathophysiology. These data are available in the literature but have not yet been quantitatively summarized for application in such models.

The aim of this work was therefore to estimate the overall impact of CF on intravenous (i.v.) drug disposition as well as to identify influencing drug- and pathophysiology-related factors. To achieve this, PK (top-down) and physiological (bottom-up) data, extracted from the literature, were pooled in meta-analyses and potential influencing factors subjected to meta-regressions. To our knowledge, this is the first study applying such a two-pronged approach to elucidate the effect of a disease state on drug disposition.

METHODS

Data

Data sources

A comprehensive literature search was carried out to identify clinical studies investigating i.v. drug disposition in plwCF (empirical, top-down) and studies reporting on physiological variables driving drug disposition (mechanistic, bottom-up). Due to anticipated variation in methodology across studies, only controlled studies consisting of both a CF group and a non-CF control group were evaluated. To mitigate the potential effect of body-size differences between the CF group and the control group, PK and physiological parameters known to be associated with body size were only included when reported as normalized to a body composition index. Specifically, cardiac function and renal function were included when normalized to body surface area (BSA), whereas PK parameters and body composition parameters (e.g., fat mass) were scaled to the total body weight (BW) of the subjects. Studies which included plwCF on CFTR-modulators were not included in the final analysis.

Top-down studies reporting V_d and/or CL (total, renal, and/or non-renal) after i.v. administration were drawn from previous reviews.¹²⁻¹⁵ For studies reporting the free fraction or the concentration ratio of metabolites to parent, the criterion of i.v. administration was relaxed if the same administration route (oral or i.v.) was used within the study. Bottom-up studies were collected through a structured search in Web of Science where the search string consisted of “cystic fibrosis” and the parameter of interest collated with an AND operator. The parameters of interest were: cardiac function (cardiac output, and blood flow to the liver and kidneys), renal function (measured glomerular filtration rate [mGFR], creatinine clearance, and serum creatinine), hepatic function (liver volume, density, and drug-metabolizing enzyme activities), body composition (lean body mass, fat mass, and water content), and clinical chemistry (hematocrit, serum albumin, alpha-1-acid-glycoprotein [AAG], tumor necrosis factor-alpha [TNF- α], interleukin-6 [IL-6]). Additional information on search strategies can be found in the electronic Material S1 (ESM1).

Collected study data

For each study, the following variables were collected: the number of subjects in both groups, the mean and the variation of the parameter of interest in both groups and the age of the plwCF (mean and range). Based on reported inclusion criteria regarding pulmonary exacerbations, study

subjects with CF were classified as having either stable or unstable disease symptoms. A pulmonary exacerbation is defined here as any acute respiratory condition requiring antibiotic therapy. Stable plwCF were defined as having their last treatment for a pulmonary exacerbation concluded at least 2 weeks before enrollment in the study. Both the study selection and the data collection processes were carried out by one researcher without the use of automation tools. The resulting database can be found as [ESM2](#).

Statistical methods

Meta-analysis

For each investigated parameter with an adequate number of studies ($k > 3$), a meta-analysis was carried out to obtain a pooled effect estimate. The ratio of the mean parameter value in the CF group to the mean in the control group was defined as the effect size.¹⁶ A ratio of means (ROM) larger than 1 indicates a higher mean parameter value in the CF group compared to the control group. The standard error (SE) of this ROM was calculated with [Equation 1](#).¹⁷

$$se(\theta_{\text{ratio}}) = \sqrt{\frac{(\theta_{\text{CF}})^2}{(\theta_{\text{NCF}})^2} \left(\frac{sd(\theta_{\text{CF}})^2}{n_{\text{CF}}(\theta_{\text{CF}})^2} + \frac{sd(\theta_{\text{NCF}})^2}{n_{\text{NCF}}(\theta_{\text{NCF}})^2} \right)} \quad (1)$$

Where θ , $sd(\theta)$, and n denote the study mean, the SD, and the study size, respectively. The subscripts CF and NCF denote the cystic fibrosis and control groups, respectively. When SDs were not reported, they were estimated using other measures of variation: (1) SDs were estimated from confidence intervals with the assumption of an underlying t-distribution; (2) ranges or interquartile ranges were converted to SDs as described by Wan et al.,¹⁸ which assume a normal distribution of the data. Both the ROM and the SE were log-transformed before further processing because of the asymmetric distribution properties of ratios.¹⁹ For ease of interpretation, the results were back-converted to the linear scale.

Random-effects models with inverse variance weighting were used to pool the effect sizes. Between-study heterogeneity variances (τ^2) were estimated with restricted maximum likelihood (REML) procedures.²⁰ Knapp-Hartung adjustments were used to calculate the 95% confidence interval around the pooled effect.²¹ Heterogeneity between studies is reported as a 95% prediction interval around the pooled effect. The pooled effect sizes and their respective confidence intervals should be seen as representing the average effect in the included studies, whereas the prediction interval signifies the variation between the different studies.

To assess the robustness of the results generated by the meta-analyses, two sensitivity analyses were performed.

The first sensitivity analysis evaluated the effect of correcting the overall ROM estimate for publication bias with the Duval and Tweedie Trim and Fill Method.²² The second sensitivity analysis omitted influential cases from the meta-analysis. Influential cases can be described as studies with a large contribution to the overall pooled effect and heterogeneity. Selection of influential cases was done by evaluating difference in fit ($DFFITs_k$), Cook's Distance (D_k), and Hat Value (hat_k) metrics (see [ESM1](#) for details). The results were deemed robust if the adjusted ROM of these analyses deviated less than 25% from the original ROM and if the change in ROM did not result in a different statistical significance decision (i.e., no change from statistical significance to insignificance or vice versa).

Meta-regression

A meta-regression was carried out when the meta-analysis included 10 or more studies. Exacerbation status was evaluated as influencing factor in each meta-regression. For the meta-analyses with top-down data (V_d and CL), the molecular weight (MW), lipophilicity (LogD at pH 7.4), and plasma protein binding (PPB) of the investigated drug were also evaluated as influencing factors. Sources for these drug parameters can be found in [ESM1](#). Publication year was investigated as a predictor for the top-down studies only, as ranges of publication years differed substantially between the meta-analyses of the bottom-up parameters.

The regression model fit was evaluated by the index R_*^2 and denotes the percentage of variation explained by the meta-regression model ($\tau_{\text{meta-regression}}^2$) compared to the meta-analysis (intercept) model ($\tau_{\text{meta-analysis}}^2$) ([Equation 2](#)).

$$R_*^2 = \left(1 - \frac{\tau_{\text{meta-regression}}^2}{\tau_{\text{meta-analysis}}^2} \right) * 100 \quad (2)$$

Interaction terms between drug-related predictors were evaluated through a multi-model inference procedure in which the fits of all possible models were compared according to their small sample-corrected Akaike's information criterion (AICc). When a model with an interaction term outperformed the baseline (intercept) model, the interaction term was deemed relevant.

Effect of scaling on top-down studies

The effect of scaling a PK outcome measure (V_d or CL) to a body composition index other than BW was evaluated through studies that reported the PK variable scaled

both by the standard and an alternative approach. Based on data availability, the following alternative scaling approaches were selected: linear scaling by BSA, linear scaling by lean body mass (LBM), allometric scaling by BW, and allometric scaling by LBM. Allometric scaling approaches were only evaluated for CL with an exponent of 0.75. The superiority of the alternative scaling approaches relative to scaling linearly to BW was evaluated using paired Wilcoxon tests.

Free fraction simulation

The ratio of the free fraction of a drug bound to serum albumin can be expressed using Equation 3 when assuming CF does not lead to intrinsic changes in binding affinity²³ (details in ESM1).

$$\frac{f_{u,CF}}{f_{u,NCF}} = \frac{1}{f_{u,NCF} + \frac{[Albumin]_{CF}}{[Albumin]_{NCF}} - \left(f_{u,NCF} * \frac{[Albumin]_{CF}}{[Albumin]_{NCF}}\right)} \quad (3)$$

where f_u and [Albumin] denote the free fraction of the drug and the serum albumin concentration, respectively. This equation was used to simulate the ratio of the free fraction in plwCF to the free fraction in controls for a given free fraction in controls, using the ratio of serum albumin concentrations obtained through meta-analysis of studies reporting this parameter. The results of this bottom-up simulation were visually compared to results of top-down studies investigating the free fraction of a drug in both plwCF and controls.

Activity of drug-metabolizing enzymes

The activities of drug-metabolizing enzymes were evaluated based on the results of in vivo studies measuring metabolites of selective probe substrates. Results were

only included when it is well established that only one isoenzyme is responsible for the conversion of parent to metabolite. Parameters of interest were the formation clearance of the metabolite or metabolite/parent ratio in the urine. Metabolite/parent ratios are not pure markers of enzyme activity, as they are dependent on renal function and protein binding. Therefore, the enzyme activity measurements assessed by the metabolite/parent ratios were corrected for changes of these parameters in patients with CF (Equation 4, adapted from Johnson et al.²⁴).

$$\text{Enzyme activity} = \frac{\left[\frac{\text{Metabolite}}{\text{Drug}} \right]_{\text{urine}}}{\text{mGFR} * f_u} \quad (4)$$

where mGFR is the measured glomerular filtration rate and f_u is the free fraction of the drug. For calculation of the ROM of enzyme activity, the GFR ratio is derived from the meta-analysis of studies assessing mGFR by an exogenous substrate, and f_u is substituted by Equation 3. The free fraction correction was not applied when the probe substrate does not primarily bind to albumin or the binding protein is unknown.

All calculations were performed with R version 4.1.0; the “meta” and “dmeta” packages were used for meta-analysis and meta-regression.^{25,26} The applied code is made available as ESM3.

RESULTS

Top-down data

Thirty-one studies were identified which reported BW-corrected estimates of PK parameters after i.v. administration (Table S3 in ESM1). Meta-analyses of these studies indicated, on average, larger V_d and enhanced total, renal, and non-renal CL in plwCF compared to controls (Table 1, individual forest plots in ESM1). The increase in V_d was

TABLE 1 Meta-analyses of the top-down studies in plwCF and controls

Parameter (unit)	Studies	plwCF	Ratio of means [confidence interval]	Heterogeneity (prediction interval)	Sensitivity analyses	
					Publication bias	Influential cases
Volume of distribution (L/kg)	32	326	1.16 [1.09; 1.24] ^c	(0.84; 1.62)	+6.49%	+0.06%
Total clearance (ml/min/kg)	22	220	1.39 [1.26; 1.54] ^c	(0.89; 2.18)	0.00%	-1.05%
Renal clearance (ml/min/kg)	8	70	1.30 [1.07; 1.57] ^a	(0.78; 2.14)	0.00%	-5.64%*
Non-renal clearance (ml/min/kg)	7	63	1.25 [1.08; 1.46] ^a	(0.88; 1.79)	-13.13%*	+4.05%

Notes: Ratio of means = ratio of mean parameter in people living with cystic fibrosis (plwCF) to mean parameter value in controls. Confidence and prediction intervals denote 95% intervals. All values were normalized to total body weight. Results of sensitivity analyses are presented as the deviation of the adjusted ratio of means to the original ratio of means. An asterisk indicates that the statistical conclusion (significant/nonsignificant) of the adjusted meta-analysis differs from the original. ^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$.

relatively minor (+16%, forest plot 1 in [ESM1](#)), whereas the increase in total CL can be considered moderate (+39%, forest plot 2 in [ESM1](#)). Similarly, renal and non-renal CL were found to be moderately increased (+30% and +25%, respectively, forest plots 3 and 4 in [ESM1](#)). The increase in renal CL was not found to be significantly larger than the increase in non-renal CL for the seven studies reporting estimates for both CL pathways (paired Wilcoxon test $p = 0.81$). Although the meta-analyses of V_d and total CL were robust, the meta-analyses of renal and non-renal CL were sensitive to omitting influential cases and to publication bias adjustments, respectively (Tables S5 and S6 in [ESM1](#)).

The publication year of the studies was found to be negatively associated with the CL ratio, indicating less pronounced increases in CL in more recent studies ([Figure 1c](#)). For V_d , such an association could not be inferred ([Figure 1a](#)). Both CL and V_d ratios were significantly larger in studies that included plwCF with pulmonary exacerbations compared to studies where only patients with stable symptoms were included ([Figure 1b,d](#)). It should be noted that publication year and exacerbation status were negatively correlated in both meta-analyses ($r = -0.47$ and -0.54 for V_d and CL, respectively, both $p < 0.05$). The impact of the pulmonary exacerbation status on drug disposition is simulated for a hypothetical drug based on a one-compartmental model in [Figure 2](#). None of the evaluated drug characteristics (MW, LogD, and PPB in healthy volunteers) could explain a significant portion of the

heterogeneity between studies ([ESM1](#), [Figure S1](#)) and no relevant interaction terms could be discerned through the multi-model inference procedure (Table S7 in [ESM1](#)).

Evaluation of studies reporting V_d and CL scaled linearly with BW and with another parameter indicated a trend for lower ROMs when an alternative scaling index was utilized ([Figure 3](#)). This trend only reached statistical significance ($p < 0.05$) for the linear scaling of CL with BSA or LBM.

Bottom-up data

[Table 2](#) summarizes the results of meta-analyses of studies investigating physiological variables relevant for i.v. drug disposition. No controlled studies could be identified that investigated liver size/weight/density, milligram protein per gram liver, hepatic drug-metabolizing enzyme concentrations/mRNA levels, or serum concentrations of AAG. The number of studies included and excluded for each of the investigated physiological variables is provided in [Table S4](#) of [ESM1](#).

Cardiac function

Cardiac function was assessed through studies investigating cardiac index (CI) and blood flows to the liver and

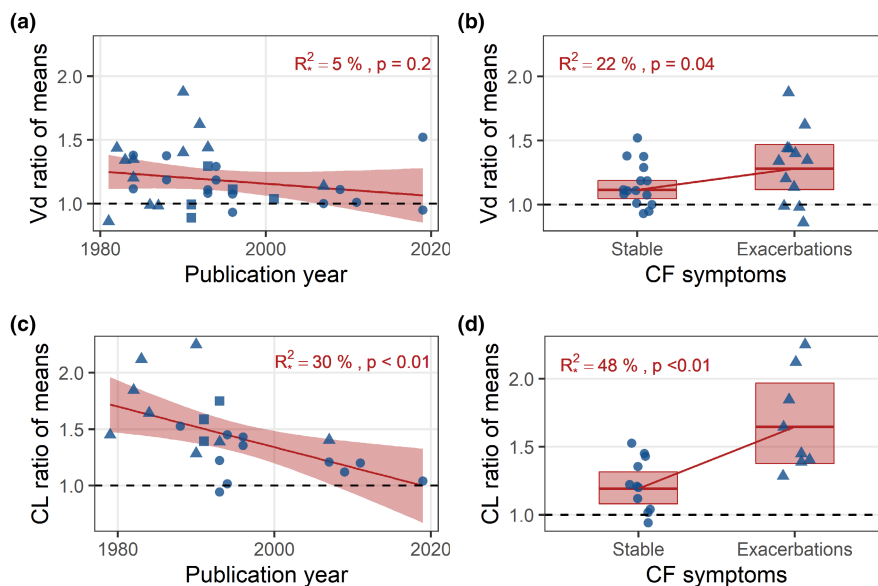


FIGURE 1 Meta-regressions between top-down pharmacokinetic (PK) parameters and study characteristics. PK parameters (volume of distribution [V_d] and total clearance [CL]) are quantified as the ratio of means (mean in cystic fibrosis [CF] group/mean in control group). Both parameters were scaled based on total body weight. Circles represent studies including people living with cystic fibrosis (plwCF) with stable disease symptoms, triangles studies including plwCF with exacerbations, and squares studies that did not report information on exacerbation status. The colored area in panels a and c signifies the area within one standard error around the meta-regression line, while in panels b and d it represents a 95% confidence interval around the mean of the subgroup.

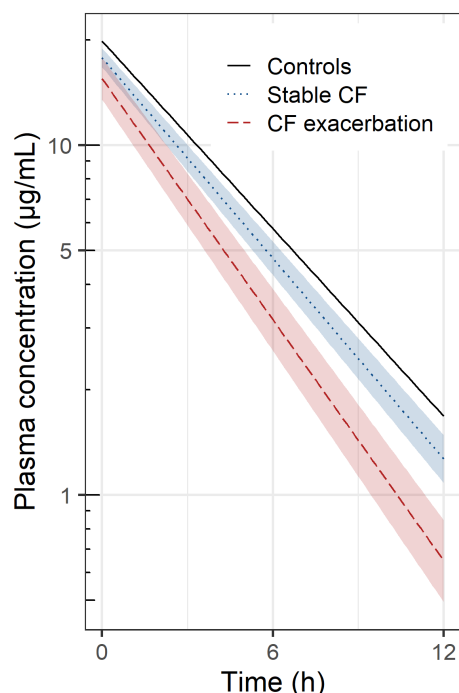


FIGURE 2 Meta-analysis derived mean pharmacokinetic (PK) profiles in people living with cystic fibrosis (plwCF) compared to controls. Total plasma concentrations after intravenous bolus administration of a 500 mg hypothetical drug with a total clearance (CL) of 1.24 ml/min/kg and a volume of distribution (V_d) of 0.36 L/kg (median CL and V_d of the included drugs in this work). A one compartment PK model is used to derive plasma concentrations using the dose, CL, and V_d as inputs (model code in [ESM3](#)). Profiles of plwCF with stable symptoms and plwCF with pulmonary exacerbations are calculated by multiplying the CL and V_d by the ratios of means found in the respective subgroup meta-analyses. For all three groups, body weight was fixed to 70 kg. Colored areas are a result of simulating the profiles with the upper and lower estimates of the confidence intervals of CL and V_d .

kidneys. The CI is the product of heart rate and stroke volume scaled to BSA. Most of the studies included aimed to measure the effect of exercise or pharmaceutical intervention on the cardiac function of plwCF with stable disease symptoms. Therefore, only values at rest or before the intervention were included in the meta-analysis. Meta-analysis of seven studies did not reveal significant alterations in cardiac output in plwCF (forest plot 5 in [ESM1](#)). Six out of seven studies included measurements of stroke volume and heart rate. Meta-analysis of this subset of studies points to significantly increased heart rates (+19%) and decreased stroke volume indices (−17%) in plwCF (forest plots 6 and 7 in [ESM1](#), respectively). The robustness of the stroke volume index estimate is low, as omitting the influential study of Bisch et al.²⁷ leads to a nonsignificant ROM (Table S6 in [ESM1](#)). The available data on specific blood flows was insufficient to pool in meta-analyses.

Renal function

Measuring the GFR by determining the renal CL of a suitable exogenous probe substrate can be considered as a fairly accurate method of renal function assessment.²⁸ Eleven studies were identified that utilized this approach and normalized the results for BSA. The probe substrates were diverse and included iothalamate ($N = 2$), iohexol ($N = 2$), inulin ($N = 5$), radiolabeled EDTA (ethylenediaminetetraacetic acid, $N = 1$), and radiolabeled DTPA (diethylenetriaminepentaacetic acid, $N = 1$). Meta-analysis of these studies showed a slight but significant increase of mGFR in plwCF (+14%, forest plot 8 in [ESM1](#)). No subgroup analysis based on disease status was carried out due to a lack of studies reporting on pulmonary exacerbations being an in- or exclusion criterium.

Four studies evaluated GFR by measuring the renal CL of creatinine. As creatinine is an endogenous metabolite and not a pure marker of glomerular filtration,²⁸ the results of these studies were not pooled with the studies investigating mGFR by an exogenous probe substrate. In contrast with the findings of the meta-analysis of mGFR, creatinine CL was not found to be different in plwCF compared to controls (forest plot 9 in [ESM1](#)). A meta-analysis of 17 studies that reported serum creatinine levels in plwCF and controls was also carried out. The results of this analysis indicate significantly lower serum levels of creatinine in plwCF (−10%, forest plot 10 in [ESM1](#)). This ROM was found to be sensitive to publication bias adjustments and omitting influential cases (Tables S5 and S6 in [ESM1](#)). No subgroup differences were detected between studies investigating plwCF with stable symptoms and plwCF with pulmonary exacerbations (Figure S2A in [ESM1](#)).

Body composition

Body composition was assessed through studies that experimentally investigated the amount of fat and/or fat-free tissue and normalized the results to total BW. Fifteen studies were identified that collected body fat measurements and seven that reported fat-free mass. Meta-analyses of these studies did not detect an overall difference in body fat or fat-free mass content (forest plots 11 and 12 in [ESM1](#), respectively). Because all but one of these studies included plwCF with stable disease symptoms, a subgroup analysis based on exacerbation status was not performed. One study was found where body water content was investigated and where results were normalized for BW. The results of this study do not indicate differences in body water content between plwCF and controls, as assessed by deuterium dilution.²⁹

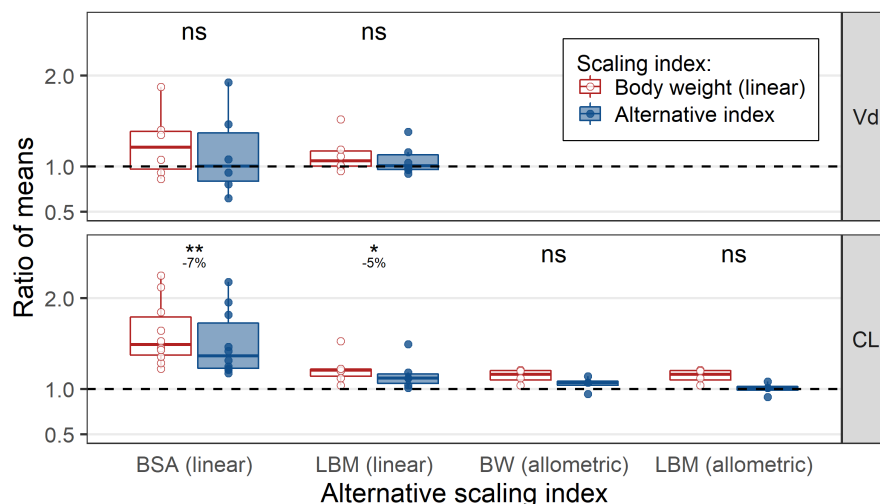


FIGURE 3 Effect of scaling volume of distribution (V_d) and total clearance (CL) to an alternative scaling index on the ratio of means. The ratio of means is defined as the ratio of the parameter mean in people living with cystic fibrosis to the parameter mean in controls. Alternative scaling indices evaluated are linear scaling by body surface area (BSA), linear scaling by lean body mass (LBM), allometric scaling by total body weight (BW), and allometric scaling by LBM. Dots and boxplots denote individual studies and are grouped by the alternative parameter scale reported in parallel to linear scaling by BW. Renal and non-renal CL are not represented due to lack of data. Open dots and boxplots represent the values scaled linearly by BW, whereas the filled points and boxplots indicate values scaled by the alternative scaling index. Statistical significance testing was carried out through paired Wilcoxon tests (ns: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$).

TABLE 2 Meta-analyses of bottom-up studies in plwCF and controls

Parameter (unit)	Studies	plwCF	Ratio of means [confidence interval]	Heterogeneity (prediction interval)	Sensitivity analyses	
					Publication bias	Influential cases
Cardiac function						
Cardiac output (L/min/m ²)	7	116	0.96 [0.85; 1.09] ^{ns}	(0.71; 1.30)	-8.21%	+2.70%
Heart rate (beats/min)	6	99	1.19 [1.10; 1.27] ^b	(1.03; 1.36)	0.00%	-0.54%
Stroke volume (ml/beat/m ²)	6	99	0.83 [0.73; 0.95] ^a	(0.61; 1.13)	-7.21%	+2.89%*
Renal function						
mGFR (ml/min/1.73 m ²)	11	111	1.14 [1.06; 1.23] ^b	(0.95; 1.36)	+3.52%	+0.02%
CrCL (ml/min/1.73 m ²)	4	47	0.98 [0.87; 1.11] ^{ns}	(0.83; 1.15)	-5.43%	+5.16%
Serum creatinine (μmol/L)	17	716	0.90 [0.84; 0.97] ^b	(0.71; 1.16)	+11.10%*	+8.28%*
Body composition						
Body fat (%)	15	357	0.92 [0.82; 1.04] ^{ns}	(0.59; 1.43)	-8.23%*	-1.45%
Fat-free mass (%)	7	139	0.99 [0.93; 1.05] ^{ns}	(0.84; 1.17)	-2.29%	-0.85%
Clinical chemistry						
Serum albumin (g/dL)	27	477	0.86 [0.82; 0.91] ^c	(0.65; 1.14)	+10.13%*	+2.18%
Hematocrit (%)	9	221	0.98 [0.88; 1.10] ^{ns}	(0.71; 1.37)	+9.54%	+6.55%
TNF-α (pg/ml)	31	697	1.54 [1.25; 1.91] ^c	(0.51; 4.64)	+22.05%	-5.08%
IL-6 (pg/ml)	23	405	3.73 [2.75; 5.05] ^c	(0.99; 14.02)	0.00%	-3.42%

Notes: Ratio of means = ratio of mean parameter in people living with cystic fibrosis (plwCF) to mean parameter value in controls. Confidence and prediction intervals denote 95% intervals. Cardiac output, stroke volume, measured glomerular filtration rate (mGFR) and creatinine clearance (CrCL) were normalized to body surface area; body fat and fat-free mass were normalized to total body weight; other parameters were not normalized to a body composition descriptor. Results of sensitivity analyses are presented as the deviation of the adjusted ratio of means to the original ratio of means. An asterisk indicates that the statistical conclusion (significant/non-significant) of the adjusted meta-analysis differs from the original. ^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$.

Abbreviations: CL, clearance; IL, interleukin; mGFR, measured glomerular filtration rate; ns, not significant; TNF, tumor necrosis factor.

Clinical chemistry

Albumin is a major plasma protein which binds most drugs to variable extents. A recent meta-analysis carried out by Causer et al.³⁰ investigated serum albumin levels in stable plwCF and found significantly lower levels in plwCF compared to controls. Their meta-analysis of six studies is appended in the current study with five studies in plwCF having pulmonary exacerbations, 11 additional studies in stable plwCF, and five studies where disease status of the plwCF was not described. Meta-analysis of 27 included studies revealed significantly lower serum albumin levels (−14%) in the plwCF compared to control groups (forest plot 13 in [ESM1](#)). This finding was no longer significant when corrected for potential publication bias (Table S5 in [ESM1](#)). One of the studies included a CF group with stable symptoms and a CF group undergoing pulmonary exacerbations. Lower serum albumin levels were found in the latter group when compared to the stable CF and control groups.³¹ Between the included studies, however, the exacerbation status of the included plwCF did not explain a significant portion of the variability (Figure S2B, [ESM1](#)).

Hematocrit is the relative percentage of red blood cells to the volume of plasma. Meta-analysis of nine studies that investigated hematocrit in plwCF and controls did not point to altered hematocrit in plwCF (forest plot 14 in [ESM1](#)).

Evidence is emerging that circulating cytokines can affect drug disposition by selectively down-regulating certain drug-metabolizing enzymes.³² A wide spectrum of cytokines and downstream markers of inflammation have been identified. For brevity, this work focused on serum

levels of TNF- α and IL-6, two cytokines with considerable evidence supporting involvement in down-regulating drug-metabolizing enzymes. Meta-analysis of 31 studies reporting TNF- α levels showed a moderate increase (+54%) in serum concentrations of this cytokine in plwCF compared to controls (forest plot 15 in [ESM1](#)). For IL-6, a large increase was detected based on 23 studies (+273%, forest plot 16 in [ESM1](#)). For studies that included plwCF with exacerbations, the circulating levels of these cytokines were not significantly different as compared to studies that included plwCF with stable disease symptoms (Figures S3C,D in [ESM1](#)).

Free fraction

Simulation of the free fraction based on the results of the meta-analysis of albumin concentrations (−12% in CF) indicates a significant increase in the free fraction in plwCF compared to controls for drugs more than 35% bound to serum albumin (inflection point of the lower 95% confidence interval of the prediction and ROM = 1 for free fraction, [Figure 4](#)). Ten studies were identified that analytically investigated the free fraction of drugs both in plwCF and controls.^{33–41} These studies included in total 10 different drugs, of which nine bind primarily to albumin. The ROM of the free fraction of most investigated albumin binding drugs (7/9) fell within the prediction interval of the simulation. Studies on dicloxacillin and S-warfarin reported ratios of free fractions that were, respectively, higher and lower than the prediction interval of the simulation.^{35,41}

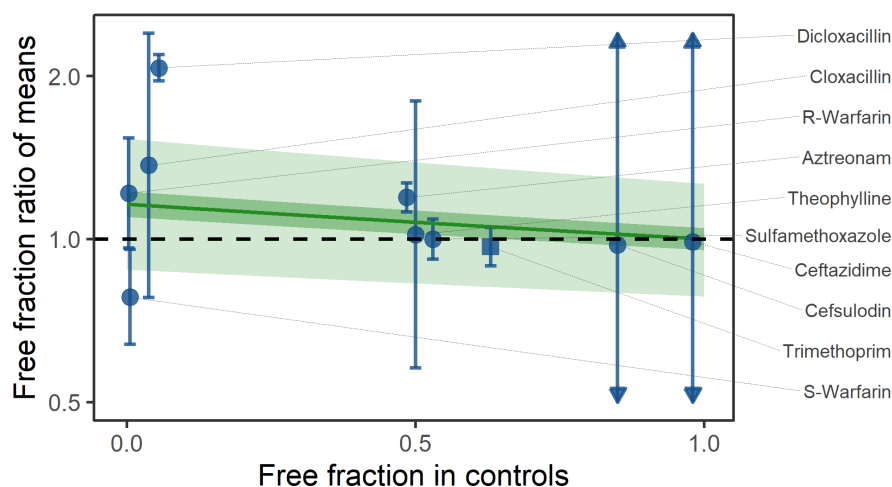


FIGURE 4 Free fraction of drugs observed in people living with cystic fibrosis and simulated based on lower albumin concentrations. The green line indicates the estimated free fraction based on the ratio of means of serum albumin derived from the meta-analysis; the confidence interval around this estimate is colored dark green and the prediction interval light green. Blue circles indicate the results of clinical studies with drugs that primarily bind to albumin, whereas blue squares are drugs that primarily bind to alpha-1-acid glycoprotein. Error bars represent 95% confidence intervals and arrows indicate results with confidence intervals larger than the represented range (ceftazidime) or lacking a measure of variation (cefsulodin). The y-axis is log-transformed.

Activity of drug-metabolizing enzymes

Few studies have directly probed *in vitro* activities or the prevalence of drug-metabolizing enzymes in plwCF. Johnson et al.⁴² determined the CYP3A4 content in duodenal biopsies of pediatric plwCF and did not observe any difference compared to healthy pediatric patients. Data on the hepatic content of CYP3A4 or other drug-metabolizing enzymes are not available. There are, however, some studies that have investigated the *in vitro* activity of enzymes present in blood. Three *in vitro* studies examined the *in vitro* acetylation activity in blood cells (erythrocytes and leukocytes), with one study reporting higher activities in erythrocytes and peripheral blood cells in plwCF, whereas two other studies could not reproduce these findings in erythrocytes⁴³ and peripheral mononuclear leukocytes,⁴⁴ respectively. One study noted significantly lower plasma esterase activities in plwCF undergoing a pulmonary exacerbation compared to controls.⁴⁵ These data are too sparse to draw conclusions about alterations of drug-metabolizing enzymes in plwCF. Therefore, studies designed to determine the activity of specific isoenzymes through selective probes and their metabolites were identified. These were a combination of caffeine phenotyping studies and studies on specific metabolites of drugs. Data from these *in vivo* studies and pooled estimates for the specific isoenzymes can be found in Table 3. Only for N-acetyl-transferase (NAT) and xanthine oxidase (XO), sufficient studies were available to pool into meta-analyses. For both these enzymes no significant alterations in activity was detected. When all results from all studies were pooled together, irrespective of the iso-enzyme, a slight but statistically insignificant increase in drug-metabolizing enzyme activity was derived. In a second analysis, the data were corrected for expected differences in free fraction and renal function. The results of this analysis did not point to overall alterations in drug metabolism.

DISCUSSION

Drug disposition in plwCF has been studied for over 40 years.^{12,14,46} Over this period, multiple hypotheses have been postulated that aim to explain increased V_d and CL. Complex interactions between pathophysiological changes and drug-dependent parameters (e.g., lipophilicity) seem to be at play. Knowledge synthesis has happened through (systematic) reviews but these are, in general, narrative in character, which inevitably introduces subjectivity in the assessment of the overall impact of CF on PK.^{12–14,47} Additionally, the vast body of work on the pathophysiology of CF is currently being underutilized in mechanistic predictions of drug disposition in

these patients. In this work, the question was investigated whether quantitative analysis of studies on PK and relevant pathophysiological phenomena in plwCF could identify the magnitude and the potential causes of altered drug disposition in this population. This was done through meta-analysis and meta-regression of clinical studies and theoretical PK simulations.

Meta-analysis of controlled clinical PK studies revealed that V_d and CL are increased in plwCF. Of the investigated pathophysiological variables, heart rate, mGFR, and cytokine levels (TNF- α and IL-6) were increased, while stroke volume, serum creatinine and serum albumin were decreased. No significant changes were found in cardiac output, creatinine CL, relative body composition (percentage fat or fat-free mass), or hematocrit.

Mechanisms for increased volumes of distribution

The increases in V_d in plwCF compared to controls are relatively minor, and the large prediction interval indicates a considerable spread between studies as well as investigated drugs. In studies with patients with pulmonary exacerbations, this increase was larger than in stable patients. The latter observation aligns with one of the included studies designed with both a stable and exacerbation CF group that investigated the disposition of ceftazidime.³⁸

The lower levels of serum albumin found in plwCF may theoretically result in increased extravasation of drugs to tissues through an increase in the free fraction in plasma. Simulations indicated that for drugs that are extensively bound to serum albumin (>35%), an increase in free fraction can be expected. Clinical estimates of the free fraction of drugs in plwCF were sparse and, in general, imprecise but seem to confirm this finding. Additionally, a recent study by Shah et al.⁴⁸ found increased free fractions for cefotiam ($\pm 50\%$ bound to serum albumin). Even though this can also be seen as supportive evidence, it was not included in the analysis because the free fraction was derived from the population PK model and not determined analytically. However, meta-regression of clinical PK studies did not indicate that drugs that are extensively bound to plasma proteins had more pronounced increases in V_d compared to drugs that are less bound to plasma proteins, suggesting that other mechanisms may be involved. This is in contrast with the results of an analysis of covariance by Bulitta and colleagues of studies investigating the PK of beta-lactam antibiotics in plwCF. They identified protein binding differences between plwCF and healthy volunteers as a factor explaining a significant portion of the variability for the differences in V_d and CL between studies or drugs.¹⁵ Another unexpected finding in the current

TABLE 3 Assessment of drug-metabolizing-enzyme activity

Enzyme	Probe (administration route)	Parameter	Age group	Uncorrected activity ROM (95% CI)	Protein binding correction	Renal function correction	Corrected activity ROM (95% CI)	References
CYP1A2	Caffeine (p.o.)	(AFMU +1X +1 U)/17U	Children	0.97	1.05	1.14	0.81	80
	Caffeine (p.o.)	(AAMU +1 X +1 U)/17U	Children	1.11	1.05	1.14	0.92	81
CYP2C9	S-Warfarin (i.v.)	CLu 7-OH S-Warfarin	Adults	1.00	1.00	1.00	1.00	35
CYP2D6	Dextromethorphan (p.o.)	DM/DX	Children	0.99	1.00	1.14	0.87	80
CYP3A4	R-Warfarin (i.v.)	CLu 10-OH R-Warfarin	Adults	0.27	1.00	1.00	0.27	34
NAT	Caffeine (p.o.)	AFMU/(AFMU +1X +1 U)	Children	0.75	1.05	1.14	0.63	80
	Caffeine (p.o.)	AFMU/(AFMU +1X +1 U)	Mixed	0.53	1.05	1.14	0.44	82
	Caffeine (p.o.)	AAMU/(AAMU +1X +1U)	Children	1.00	1.05	1.14	0.83	81
	Sulfamethoxazole (i.v.)	N4-acetyl recovery	Adults	1.75	1.12	1.14	1.37	37
			All NAT	1.01 (0.48; 2.15)			0.83 (0.41; 1.68)	
SULT	Acetaminophen (p.o.)	Sulfate recovery	Adults	1.23	1.02	1.14	1.06	83
UGT	Acetaminophen (p.o.)	Glucuronide recovery	Adults	1.13	1.02	1.14	0.97	83
	Furosemide (i.v.)	Glucuronide recovery	Adults	1.67	1.16	1.14	1.27	84
XO	Caffeine (p.o.)	1U/1X	Children	0.92	1.05	1.14	0.77	80
	Caffeine (p.o.)	1U/1X	Mixed	1.25	1.05	1.14	1.05	82
	Caffeine (p.o.)	1U/1X	Mixed	1.38	1.05	1.14	1.15	81
			All XO	1.18 (0.71; 1.96)			0.98 (0.59; 1.63)	
All				1.08 (0.89; 1.30)			0.92 (0.78; 1.08)	

Notes: All probes except dextromethorphan bind primarily to albumin in serum. All parameters are concentrations in urine, except unbound formation clearances (CL_u), which are derived based on concentrations in plasma and urine. Studies were carried out in people living with cystic fibrosis without exacerbations or who did not report exacerbation status.

Abbreviations: 1X, 1-methylxanthine; 1U, 1-methyluric acid; 17U, 1,7-dimethylurate; AFMU, 5-acetylamino-6-formyl-amino-3-methyluracil; CYP, cytochrome P450; DM, dextromethorphan; DX, dextrothorphan; i.v., intravenous; NAT, N-acetyl-transferase; p.o., oral; XO, xanthine oxidase; SULT, sulfotransferase; UGT, glucuronyltransferase; ROM, ratio of means.

work was that serum albumin levels were not found to be associated with the pulmonary exacerbation status of the included patients. This contradicts reports of lower albumin levels in plwCF undergoing active exacerbation compared to relatively stable plwCF.^{31,49}

Differences in body composition are often described as contributing to the increased V_d observed in plwCF.^{13,15} To mitigate the effects of potential differences in body mass between plwCF and healthy controls, all PK parameters were normalized to the total BW. This, however, does not correct for relative differences in body composition (e.g., more or less body fat relative to total BW), and, in several studies, results were therefore scaled to BSA or LBM. The V_d estimates in plwCF were indeed closer to those in controls when results were scaled to BSA or LBM instead of BW, although statistical significance ($p < 0.05$) was not reached. This is in line with a recent systematic review of population PK analyses in plwCF where LBM was identified as a key factor influencing variability of antibiotic PK.⁵⁰ This phenomenon can theoretically be explained by an increase in fat-free mass per unit of BW. Most drugs investigated were either charged at pH 7.4 or hydrophilic and will therefore preferentially distribute to lean tissue, leading to increased V_d when relatively more of this tissue is present. No association was found, however, between the distribution coefficient (LogD) of the studied drugs and the increase in V_d . Additionally, the meta-analysis did not indicate an increase in fat-free mass or a decrease in fat mass in plwCF. This is unexpected as lower body mass indices (BMI) have consistently been reported in national CF registries.⁵¹ A possible explanation for this discrepancy is that in some of the studies investigating body composition, control subjects were not representative of the general population as they were selected for a normal BMI (e.g., within 15–85 percentiles)^{52,53} or were matched to the plwCF in terms of weight.^{29,54,55} Comparing the results of the CF group to reference percentiles might have been a more suitable approach.

Due to the finding of unaltered hematocrit in CF, it is unlikely that the increased V_{ds} are due to changes in the blood: plasma ratio of drugs. Other possible mechanisms for a larger V_d in CF include increased capillary permeability due to endothelial damage and inflammation⁵⁶ and a larger plasma volume,⁵⁷ but these variables were not systematically assessed in this work.

Mechanisms for increased clearance

Augmented CL was found in plwCF and both renal and non-renal pathways seem to be affected. This increase in CL was most apparent in older studies or when plwCF with pulmonary exacerbations were included. This is in

line with the work of Bulitta et al. on beta-lactam antibiotics in plwCF, where it was identified that older studies reported larger increases in CL and V_d than more recent studies.¹⁵ This might be due to historical improvements in CF disease management,⁴ a selection bias toward more severely ill plwCF in older studies, or better matching of control subjects to the CF subjects in terms of age and body composition in newer studies. Either way, this should be taken into account when using older studies to guide drug therapy in plwCF.

An increase in free fraction could partly explain this phenomenon in cases where the drug either has a low CL or is to an important extent eliminated unchanged via the kidneys. However, no association between the extent of PPB and alterations in CL was observed. This might be partly explained by the fact that for hepatically cleared drugs, alterations in protein binding are only impactful on CL when the hepatic extraction ratio is small (< 0.3). The number of studies on non-renal CL was, however, insufficient to carry out a meta-regression with the extraction ratio as moderator. As with the V_d , body composition differences could be an explanation for the increase in CL observed in plwCF. Differences in CL were found to be significantly reduced when this parameter was normalized for BSA or LBM instead of BW. This might be due to BSA and LBM increasing nonlinearly with BW and BW requiring an allometric exponent of 0.75 to scale linearly to CL.⁵⁸ It follows that CL per kg might be an overestimation in patients with a lower BW (e.g., plwCF). However, which alternative scaling index is most suited in plwCF is unclear. Nevertheless, these results indicate that scaling CL to LBM or BSA can reduce the differences of this parameter between plwCF and controls.

Clearance could also be affected by blood flow to the eliminating organs. A body of clinical evidence suggests that hypoxemia and inflammation can lead to ventricular dysfunction in plwCF.⁵⁹ The findings of lower stroke volume indices in plwCF align with this theory. However, due to the higher heart rates in plwCF, the CI is unaltered. This suggests that plwCF do not typically present general changes in blood flow. However, regional disturbances such as changes due to hepatic shunting cannot be ruled out based on this data. One study that investigated hepatic and portal vein blood flows scaled to BSA did not detect differences between plwCF and matched control subjects.¹⁵ The assessment of renal blood flow by Jusko and colleagues through iodine-125 orthoiodohippurate (125I-OIH) renal CL similarly did not reveal any changes in renal blood flow.¹⁶ Some groups have assessed the liver blood flow in plwCF through indomethacin green CL,^{17,18} but this method is potentially inappropriate in plwCF because of the biliary CL of this substrate.¹⁹ Given the collected data, increased CL due to supraphysiological blood flow to the liver or kidneys in plwCF seems unlikely.

In addition to higher CL due to increases in free fraction, augmented renal CL can potentially be explained by the larger GFR observed in plwCF. As kidney involvement in CF is not well-described, it is uncertain what mechanisms drive this alteration.⁶⁰ Hyperfiltration (creatinine clearance [CrCL] >130 ml/min/1.73 m²) has been described in intensive care unit (ICU) patients and it can be hypothesized that shared characteristics between CF and ICU patients (e.g., systemic inflammatory response) might be involved.⁶¹ The findings of a study by Hong et al. of higher CrCL at the start of treatment for a pulmonary exacerbation than after a week of treatment can be seen as support for an inflammation-hyperfiltration theory.⁶² However, the findings of equal CrCL between plwCF and controls contradict the findings based on measured GFR. Reasons for this might be linked to the fact that creatinine undergoes active secretion in addition to renal filtration²⁸ or because the number of studies is too low ($k = 4$) to detect the difference. The lower creatinine levels can be attributed to a decrease in creatinine generation (e.g., less muscle mass or dietary protein) or to enhanced elimination and can therefore not be seen as evidence for augmented renal CL without correction for body mass and gender. Multiple studies have estimated GFR through serum creatinine concentrations and established formulas (e.g., Cockcroft-Gault), but no effort was made to pool the results of these studies, as there is substantial heterogeneity in formulas applied and there is controversy about which GFR estimation method is best suited in plwCF.^{63,64} It should also be noted that increases in active tubular secretion or decreases in passive re-absorption might be responsible for augmented CL. These mechanisms were, however, not evaluated in this work, as they are to a large extent substrate-specific and thus less suited to be subjected to a meta-analysis approach.

Possible mechanisms for increased non-renal CL are less apparent. It is unlikely that selective upregulation of specific isoenzymes is directly responsible for higher non-renal CL of certain drugs. In previous reviews, this hypothesis was proposed,^{14,65} but after the addition of more recent evidence and correction of metabolite/parent ratios for expected differences in protein binding and glomerular filtration, no such conclusion can be drawn. A caveat regarding the correction made for altered physiology is that relevant controlled studies on liver pathophysiology in plwCF are lacking. An increase in functional liver size could, for example, contribute to apparent increases in enzyme activities. A range of hepatobiliary irregularities have been observed in plwCF.⁶⁶ A recent study found that CF-associated liver disease affects one in three plwCF by age 25.⁶⁷ Clinical and subclinical manifestations of this disease might impact drug metabolism but no studies have been identified that aimed to investigate this question.

Significantly higher levels of proinflammatory cytokines were found in plwCF, which is in line with the general inflammation-related pathophysiology of this disease. In disease states, such as rheumatoid arthritis and inflammatory bowel disease, elevated cytokine levels have been linked to the downregulation of CYP enzymes.⁶⁸ Based on the data included in this work, a precise conclusion about the influence of inflammation on drug metabolism in plwCF cannot be drawn. It should, however, be kept in mind that the net effect of CF as a disease state is an increase in (non-renal) CL, and not a decrease. Studies are therefore needed to elucidate whether the effect of inflammation on drug metabolism is lacking or negated by other pathophysiological mechanisms in plwCF.

Limitations and future directions

Apart from the lack of controlled studies on certain physiological parameters relevant for drug disposition (liver function and AAG concentration), there are some additional limitations to this work. A first limitation is the large heterogeneity in outcome observed between studies. This is indicated by broad prediction intervals which, in nearly all meta-analyses with significant results, included an ROM of 1, implying that studies can likely be found refuting the pooled finding. This calls for caution when extrapolating the results of these meta-analyses. For example, the higher V_d and CL could be interpreted as necessitating higher and more frequent dosing in plwCF to achieve the same amount of exposure as in controls. Although this statement concurs with most included studies, some studies did not produce results supporting this rationale. As an example, Tsang and colleagues reported unaltered CL of cyclosporin in plwCF,⁶⁹ hence increasing dosing frequency could hypothetically lead to overexposure. Additionally, exposure based on unbound plasma concentration might be unaltered for some drugs due to the finding of higher free fractions in plwCF.

The heterogeneity between studies was, in some cases, partly explained by the differences in pulmonary exacerbation status of the included plwCF. The use of the absence or the presence of exacerbations as a variable classifying plwCF in a stable and unstable group came with some limitations. First, pulmonary exacerbation status only partly represents the severity of CF as assessed by a clinical scoring system (e.g., Shwachman-Kulczycki scale⁷⁶) or pulmonary function test (e.g., forced expiratory volume in 1 s). For example, based on the data presented here, no statements can be made whether stable plwCF with low pulmonary function have a different PK than stable plwCF with normal pulmonary function. Possible additional insights could have been gained if meta-regressions

were carried out with a measure of disease severity, but due to the use of different scoring systems between studies and variability of disease severity within most studies, this was deemed unfeasible. Second, the association between pulmonary exacerbation status and outcome variable can be confounded with patient characteristics driving disease progression, such as CFTR genotype, age, or medication use. Although these factors could potentially explain a part of the variation observed between studies, they were not evaluated as predictors in the meta-regression. The lack of studies reporting CFTR genotype information made it impossible to include genotype as a predicting variable. Age and sex were reported in nearly all studies, but it would have been statistically unsound to carry out a meta-regression with the mean age or ratio of women as predictors. This is because inferences made about individuals based on average group characteristics are prone to ecological bias when the group characteristic varies between individuals.⁷⁰ Multilevel meta-analyses based on individual patient data⁷¹ or population PK approaches would potentially have been able to discern the effect of covariates which vary between study subjects. Additionally, inclusion of individual demographic data would have allowed to correct for poor matching of the plwCF and control groups in certain studies. Hennig et al., for example, found no differences in tobramycin PK between plwCF and controls when results were pooled in a population PK analysis and corrected for age, fat-free mass, sex, and renal function.⁷² Such analyses would require individual patient data which were not readily available.

The data presented here can serve as a primer for further mechanistic *in silico* studies. The estimates of the physiological parameters could, for example, be used to construct a virtual CF population for PBPK modeling useful for simulation of therapeutic scenarios not yet described by dedicated studies. Cicali and colleagues recently illustrated the merit of this approach with an antipyretic efficacy PBPK model for oral ibuprofen in children with CF.⁷³ Additional clinical studies are also needed to further confirm and elucidate the impact of CF on PKs. Data on the abundance and the activity of drug-metabolizing enzymes is lacking, for example, but could confirm or rule out some of the hypotheses posed in this work regarding elevated non-renal CL. For other critical parameters, more recent follow-up studies are called for to confirm the findings presented here. This is because of the partly unknown impact of improvements in CF disease management on most pathophysiological parameters. More specifically, the newly introduced highly effective CFTR modulators have a major positive impact on lung function preservation.^{74–76} However, the effect of these therapies on the physiological variables discussed here is less well-documented. There is some evidence that plwCF tend

to gain weight after initiation of the CFTR modulation therapy, primarily through reduced respiratory cachexia (fewer exacerbations) and gastrointestinal pH normalization.^{77,78} Additionally, long-term use of CFTR modulators decreases chronic inflammation in plwCF, which could potentially reduce the differences observed here for inflammatory cytokines, serum albumin, and renal filtration. Similarly, it is uncertain whether chronic therapy with CFTR modulators will also steer PK profiles toward normality.⁷⁹

CONCLUSION

This is the first work to quantitatively analyze available PK and pathophysiological evidence for altered drug disposition in plwCF. Increased V_d and CL were found, especially in plwCF with pulmonary exacerbations. Drug characteristics, such as lipophilicity (LogD), were not identified as being associated with alterations in PKs. Pathophysiological mechanisms for altered PK are decreased serum levels of albumin, augmented GFR, and general inflammation-related mechanisms. Intrinsic changes in activity of drug-metabolizing enzymes or alterations in blood flow to the liver and kidneys are unlikely in plwCF. The collected pathophysiological parameters can serve as a primer for further clinical research and mechanistic modeling in this population. In general, the findings of this study imply that dosing recommendations for plwCF based on results of studies in healthy volunteers may lead to subtherapeutic total plasma concentrations of drugs. Scaling PK parameters to body indices, such as BSA or LBM, reduces the differences between plwCF and controls, and dosage regimens based on these indices might improve pharmacotherapy. Additionally, unbound concentrations might be less affected due to decreased serum albumin levels and the subsequent increase in free fractions. Dedicated clinical trials to find the right treatment regimens for plwCF remain necessary as the large heterogeneity in outcome observed between studies and drugs does not allow for general recommendations regarding dosage adaptations.

AUTHOR CONTRIBUTIONS

P.-J.D.S., M.V.H., E.V.B., S.V.B., J.V.B., A.V., and E.G. wrote the manuscript. P.-J.D.S., A.V., and E.G. designed the research. P.-J.D.S. performed the research. P.-J.D.S. and M.V.H. analyzed the data.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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