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SHORT COMMUNICATION

The Influence of Normalization Weight in Population Pharmacokinetic Covariate Models

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Abstract In covariate (sub)models of population pharmacokinetic models, most covariates are normalized to the median value; however, for body weight, normalization to 70 kg or 1 kg is often applied. In this article, we illustrate the impact of normalization weight on the precision of population clearance (CL_{pop}) parameter estimates. The influence of normalization weight (70, 1 kg or median weight) on the precision of the CL_{pop} estimate, expressed as relative standard error (RSE), was illustrated using data from a pharmacokinetic study in neonates with a median weight of 2.7 kg. In addition, a simulation study was performed to show the impact of normalization to 70 kg in pharmacokinetic studies with paediatric or obese patients. The RSE of the CL_{pop} parameter estimate in the neonatal dataset was lowest with normalization to median weight (8.1%), compared with normalization to 1 kg (10.5%) or 70 kg (48.8%). Typical clearance (CL) predictions were independent of the normalization weight used. Simulations showed that the increase in RSE of the CL_{pop} estimate with 70 kg normalization was highest in studies with a narrow weight range and a geometric mean weight away from 70 kg. When, instead of normalizing with median weight, a weight outside the observed range is used, the RSE of the CL_{pop} estimate will be inflated, and should therefore not be used for model selection. Instead, established mathematical principles can be used to calculate the RSE of the typical CL (CL_{TV}) at a relevant weight to evaluate the precision of CL predictions.

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Key Points

Normalization to a weight outside the observed weight range (e.g. 70 kg normalization in a paediatric study) can increase the uncertainty of parameter estimates in pharmacokinetic covariate models.

The predictive performance of pharmacokinetic models and their covariate submodels is unaffected by weight normalization.

When normalizing outside the observed covariate range, the RSEs of the corresponding population estimates should generally not be used for model evaluation. The RSE of the typical parameter at a relevant covariate value can be used instead.

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1 Introduction

In population pharmacokinetic modelling, covariate models are built to describe between-subject variability in pharmacokinetic parameters (e.g. clearance [CL]) based on patient information (e.g. weight) [1, 2]. These covariate models can then be used to support personalized pharmacotherapy [3]. One of the most commonly identified covariates in population pharmacokinetic models is the body weight of the patient [4–8]. The relationship between drug CL and weight is often described using a power function:

$$CL_{TV} = CL_{pop} \times \left(\frac{WT_i}{WT_{norm}} \right)^{EXP_{WT}} \qquad (1)$$

$$CL_i = CL_{TV} \times e^{ETAi}, \qquad (2)$$

where CL_{TV} represents the predicted CL for a typical individual with weight equal to WT_i, CL_{pop} represents the population estimate of CL for an individual with a weight equal to the normalization weight (WT_{norm}), WT_i represents the individual's weight, EXP_{WT} represents the exponent that characterizes the influence of weight on CL, CL_i represents the individual post hoc predictions of CL for individual i, and e^{ETA} represents the post hoc estimate of the deviation of individual i from the predicted CL of a typical individual.

EXP_{WT} in this weight-based Eq. 1 can be fixed a priori (for instance to 1, 0.75 or 0.67) or estimated [9–12]. For continuous covariates other than weight, it is common to normalize to the mean or the median covariate value of the covariate in the dataset, whereas for weight, normalization to 70 kg is often chosen [2, 13–15]. The rationale for this approach is that the estimate of CL_{pop} will then represent the value of a typical 70 kg adult, which can easily be compared with other (adult) studies [2, 5, 10]. For similar reasons, a WT_{norm} of 1 kg can be chosen or, when no explicit normalization is performed, this normalization is implicitly chosen [9]. Recently, Mahmood and Tegenge investigated the impact of 70 and 1 kg weight normalization on CL_{TV} predictions and concluded that weight normalization has no impact on CL_{TV} predictions [9].

The concept of normalization has been extensively studied in linear regression [16, 17]. When normalizing the data to the mean, the relative standard error (RSE) of the intercept term is minimized, while normalizing outside of the data range can result in estimates with poor precision [16]. In this context, the power function in Eq. 1 can be considered a linear model in the log domain, with an intercept of log CL_{pop} [13]. If the same concepts apply, we might expect the RSE of the estimate of CL_{pop} to be minimal when normalizing weight to the geometric mean. Alternatively, normalizing to 1 kg or 70 kg might result in

high RSE of CL_{pop}, especially in populations with high or low weights.

As the impact of 70 kg normalization on the RSE of CL_{pop} could be considerable, especially when analysing data from neonatal or morbidly obese patients, insight into the statistical consequences of the selected normalization weight seems important among those involved in population pharmacokinetic modelling. In this article, we provide mathematical derivations of the phenomena and illustrate the impact of weight normalization on the precision of the parameter estimate of CL_{pop}. For this, we used an existing neonatal pharmacokinetic dataset, as well as simulated data of various paediatric and obese populations.

2 Methods

2.1 Case Study

A dataset from a previously published population pharmacokinetic analysis of phenobarbital in term and preterm neonates was used [18]. This dataset contained phenobarbital plasma concentrations collected during therapeutic drug monitoring from 53 neonates up to 80 h after the last phenobarbital dose. The weight of these neonates ranged from 0.45 to 4.5 kg and had a median value of 2.7 kg [18].

These data were modelled using a one-compartment model with interindividual variability on CL and volume of distribution (V) and a proportional error model. The covariate model consisted of a linear model (exponent fixed to a value of 1) for weight on V and a power model with an estimated exponent for weight on CL (Eq. 1). For three different values of WT_{norm} (1, 2.7, and 70 kg), parameter estimates were obtained using NONMEM 7.3 [19]. The collinearity of the parameter estimates was assessed using the condition number, which is defined as the square root of the ratio between the largest and smallest eigenvalue of the correlation matrix. RSEs of the parameter estimates (i.e., CL_{pop} and EXP_{WT}) in NONMEM were obtained using two different methods: calculation from the estimated variance–covariance matrix in NONMEM, and calculation calculated from 1000 bootstrap runs, which were performed using PsN 4.2.0. for each of the three models [20].

Furthermore, from these 1000 bootstrap runs, the estimates of CL_{pop} and EXP_{WT} (see Eq. 1) were used to calculate the predicted function of CL_{TV} over weight for each of the bootstrap runs over a weight range of 0.5–200 kg. For each of the three weight-normalized models, we used these functions of CL_{TV} over weight to obtain the 95% confidence interval and RSE of CL_{TV} predictions over the weight range of 0.5–200 kg for all three values of WT_{norm}.

RSE of CL_{TV} predictions over weight were also calculated using the variance–covariance matrix obtained from NONMEM [13]. For this, we log-transformed the power function of Eq. 1, which resulted in the following linear model:

$$\text{Log } CL_{TV} = \text{LogCL}_{pop} + \text{EXP}_{WT} \times \log\left(\frac{WT_i}{WT_{norm}}\right), \quad (3)$$

where LogCL_{pop} represents the estimate of the natural logarithm of CL of an individual whose weight is equal to the normalization weight. With a linear model, we can use principles from linear regression to calculate the RSE of the predictions of CL_{TV} at an arbitrary weight WT_i:

$$\begin{aligned}
\text{VAR}(\text{Log } CL_{TV}) = {} & \text{VAR}_{\text{LogCL}_{pop}} + 2 \\
& \times \text{COVAR}_{\text{LogCL}_{pop},\text{EXP}_{wt}} \\
& \times \log\left(\frac{WT_i}{WT_{norm}}\right) + \text{VAR}_{\text{EXP}_{wt}} \\
& \times \left\{\log\left(\frac{WT_i}{WT_{norm}}\right)\right\}^2
\end{aligned} \quad (4)$$

$$\text{RSE}(CL_{TV}) = \sqrt{e^{\text{VAR}(\text{LogCL}_{TV})} - 1}, \quad (5)$$

where $\text{VAR}_{\text{LogCL}_{pop}}$ represents the variance of the estimate of LogCL_{pop}, $\text{COVAR}_{\text{LogCL}_{pop},\text{EXP}_{wt}}$ represents the covariance between the estimates for LogCL_{pop} and EXP_{WT}, and $\text{VAR}_{\text{EXP}_{wt}}$ represents the variance of the estimate of EXP_{WT}. Mathematical derivation of Eqs. 4 and 5 are supplied in the electronic supplementary material.

2.2 Impact of WT_{norm} on the Relative Standard Error of CL_{pop} for Different Weight Distributions

To further study the impact of WT_{norm} in a covariate function on the RSE of the estimate of CL_{pop} with different weight distributions, we generated pharmacokinetic datasets of patient populations with six different weight distributions in R version 3.3.2. We then fitted a one-compartmental pharmacokinetic model described in the previous subsection, re-estimating all parameters.

For this purpose, three paediatric weight distributions (PEDIAT1, PEDIAT2 and PEDIAT3) and three weight distributions of adult populations including obese patients (OBESE1, OBESE2 and OBESE3) were used to generate simulated datasets (Table 2).

For each weight distribution, 250 datasets consisting of 50 patients were randomly sampled from the distributions using R software. For each patient, concentrations were simulated for 24, 72 and 120 h after a single 10 mg/kg dose. The simulated datasets were fitted with the models described in Sect. 2.1 and weight was normalized to either 70 kg or the expected geometric mean of the weight

distribution. Geometric mean was chosen as we hypothesized that this would result in the minimum RSE of CL_{pop}, as discussed in the Introduction. The proportion of successful covariance steps was compared for a statistically significant difference between the different normalization strategies, using a two-sample test for equality of proportions with continuity correction (prop.test function in R). For datasets that yielded successful covariance steps in both model fits, we calculated the ratio of the RSEs for the estimate of CL_{pop} of both model fits:

$$\text{RSE ratio} = \frac{\text{RSE } CL_{pop} \, 70\,\text{kg normalization}}{\text{RSE } CL_{pop} \, \text{Geometric mean normalization}} \quad (6)$$

3 Results

3.1 Case Study

Table 1 shows that only the RSE of the estimate of CL_{pop} varied with normalization weight. Normalizing to median weight (2.7 kg) resulted in a lower RSE of CL_{pop}, compared with 1 kg and 70 kg normalization. RSEs were 10.6, 8.0, and 48.2% for 1, 2.7 and 70 kg, respectively (Table 1). These RSE values were obtained from NONMEM's covariance step, but similar results were obtained using a bootstrap (1 kg: 10.5%; 2.7 kg: 8.1%; 70 kg: 48.8%). Additionally, there was a stronger correlation between the uncertainty of the parameter estimates of CL_{pop} and EXP_{WT} when normalizing to 1 kg or 70 kg (Table 1). Finally, increased collinearity between the parameters was observed for the 1 kg and 70 kg normalizations, as identified by a higher condition number (Table 1).

The parameter estimates of CL_{pop} varied with normalization weight (Table 1), which results from the fact that this parameter represents the typical CL of a subject whose weight is equal to the normalization weight. However, the same predicted CL_{TV} (Eq. 1) is obtained for the three model fits with different normalization weights since

$$\begin{aligned}
CL_{TV} &= 0.00615 \times \left(\frac{WT_i}{1\text{kg}}\right)^{0.665} \\
&\approx 0.0119 \times \left(\frac{WT_i}{2.7\text{kg}}\right)^{0.665} \approx 0.104 \times \left(\frac{WT_i}{70\text{kg}}\right)^{0.665}
\end{aligned}$$

This is further illustrated by Fig. 1 where the results on predicted CL_{TV} for the model with a normalization weight of 2.7 kg is shown, while the models with different normalization weights produced equivalent results. Additionally, Fig. 1a shows that the 95% bootstrap confidence interval of predicted CL_{TV} broadens the further the weight moves away from the centre of the weight distribution of the patient population in the dataset.

Table 1 Parameter estimates and relative standard errors (%) from the NONMEM covariance step for the neonatal dataset using different normalization weights

WT_{norm}	1 kg	2.7 kg (median)	70 kg
OFV	1091	1091	1091
CL_{pop} (L/h)	0.00615 (10.6%)	0.0119 (8.0%)	0.104 (48.2%)
V (L)	2.37 (4.4%)	2.37 (4.4%)	2.37 (4.4%)
EXP_{WT}	0.665 (20.3%)	0.665 (20.3%)	0.665 (20.3%)
Proportional error [%]	2.89 (23.5%)	2.89 (23.5%)	2.89 (23.5%)
Condition number	4.4	2.8	16.2
$Correlation_{CLpop,\ EXPwt}$[a]	− 0.840	0.545	0.988

[a]Correlation of the uncertainty of the parameter estimates of CL_{pop} and EXP_{WT}

OFV objective function value, *CL_{pop}* typical clearance of subject whose weight is equal to normalization weight, *V* volume of distribution, *EXP_{WT}* exponent in Eq. 1, *WT_{norm}* normalization weight in Eq. 1
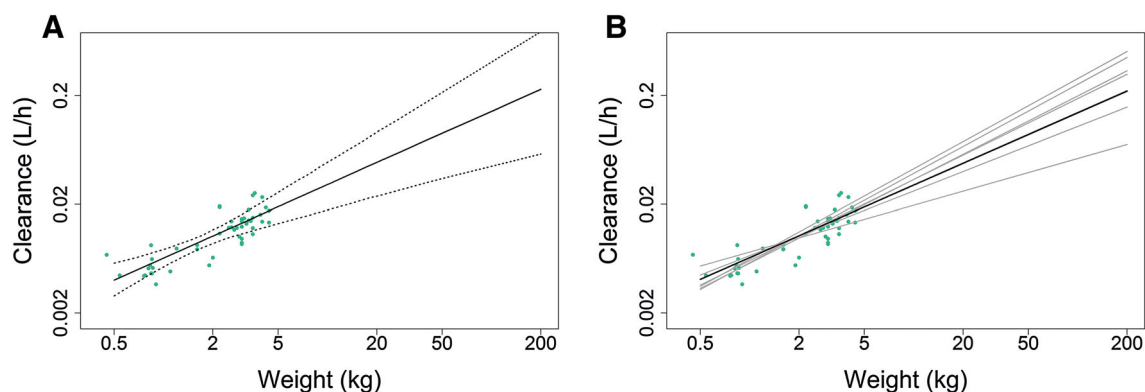

Fig. 1 Clearance predictions versus weight (0.5–200 kg) in an example neonatal dataset. (**a**) Median (solid black line) and 95% confidence interval (dotted line) of 1000 functions of CL_{TV} versus weight obtained from 1000 bootstrap runs; green dots represent the individual post hoc CL_i estimates of the studied patients. (**b**) Estimated function of CL_{TV} versus weight from the original dataset (solid black line) and illustrative set of functions of CL_{TV} versus weight (grey solid lines) obtained in six (of 1000) separate bootstrap runs; green dots represent the individual post hoc CL_i estimates of patients in the original dataset. Depicted results were obtained using a normalization weight of 2.7 kg. CL_{TV} clearance for a typical individual, CL_i clearance for individual i

Figure 1b illustrates that the CL_{TV} functions from different bootstrap samples are very similar within the range of the data, and diverge outside the weight range of the original dataset, explaining the broader confidence intervals seen in Fig. 1a.

Figure 2 shows the RSE of the predicted function of CL_{TV} over weight, as well as the RSE of the estimate of the parameter CL_{pop}. The RSE of the CL_{TV} function was calculated using either bootstrap or the variance–covariance matrix (Eq. 5), with both methods resulting in similar results (Fig. 2). Using Eq. 5, the minimum RSE of CL_{TV} (5.8%) was calculated at 1.9 kg, which is close to, but not equal to, measures of the central tendency of the weight distribution, such as the mean (2.4 kg, RSE = 6.6%), median (2.7 kg, RSE = 7.5%) or geometric mean (2.1 kg, RSE = 6.0%). The RSE of the estimate of the CL_{pop} parameter reported by NONMEM for a model with a given normalization weight matches the RSE of the CL_{TV} function at the normalization weight. The former results in the

6.4% RSE with 1.9 kg normalization, and 8.0% RSE with normalization to the median.

3.2 Impact of 70 kg Normalization in Different Paediatric and Obese Populations

Evaluation of the impact of 70 kg normalization on the RSE of CL_{pop} estimates for simulated paediatric and obese datasets with various weight distributions showed that, generally, 70 kg normalization resulted in a higher RSE of the CL_{pop} estimate compared with normalization to geometric mean weight, resulting in an RSE ratio above 1 (Table 2, Fig. 3). The results show that the degree of impact of 70 kg normalization depends on the weight distribution in the dataset. The three paediatric weight distributions had a geometric mean weight of 20 kg, but different dispersion around the geometric mean. The RSE ratio was highest (median RSE ratio = 4.3) for the lognormal distribution with a standard deviation on the logarithmic scale of 0.25 (PEDIAT1).
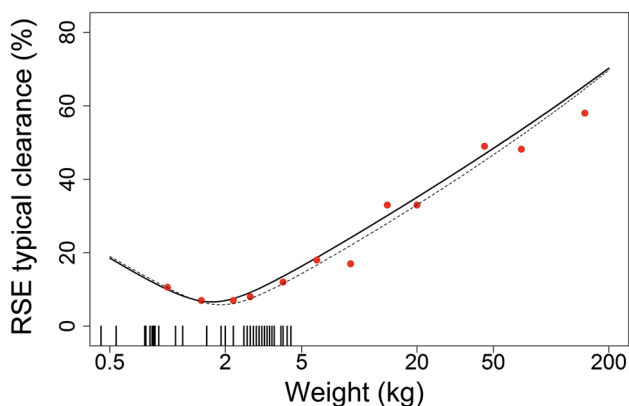
Fig. 2 Relation between weight and the RSE of both CL_{TV} and CL_{pop} in an illustrative neonatal dataset. The solid line represents the RSE of CL_{TV} predictions from 1000 bootstrap runs, the dotted line represents the RSE of CL_{TV} predictions obtained from the variance–covariance matrix (Eq. 5), and the red dots represent the RSE of the estimated CL_{pop} parameter using the corresponding normalization weight, obtained from the covariance step of a single NONMEM run. The vertical tick marks on the bottom of the graph depict the body weights of subjects in the dataset. *RSE* relative standard error, CL_{TV} clearance for a typical individual, CL_{pop} population clearance

The weight distributions of OBESE1 and OBESE2 have a similar standard deviation on a logarithmic scale, but different geometric means of the weight (162 and 118 kg, respectively). The results in Table 2 and Fig. 3 show that this results in a lower RSE ratio in OBESE2, compared with OBESE1 (median RSE ratio of 2.3 and 3.5,

respectively). Normalizing to 70 kg has only marginal impact on RSE in OBESE3 (median RSE ratio = 1.1), with a geometric mean that is closer to 70 kg than OBESE2 (97 kg vs. 118 kg), as well as a higher standard deviation on a logarithmic scale (0.35 vs. 0.2).

Table 2 shows that for both paediatric and adult populations, the impact of 70 kg normalization on the RSE of the estimate of CL_{pop} was highest for studies with a narrow weight range (low standard deviation on a logarithmic scale) and a median weight away from 70 kg.

The percentage of datasets for which a successful covariance step could be obtained in both model fits ranged from 28 to 84% in the different scenarios. The proportion of successful covariance steps was significantly higher using geometric mean normalization compared with 70 kg normalization in scenarios PEDIAT1 ($p < 0.001$) and PEDIAT2 ($p < 0.001$), but not in any of the other scenarios. The most common cause of the missing covariance steps was boundary issues due to the difficulty in estimating the variance for the interindividual variability of CL.

4 Discussion

This report illustrates the statistical principle that, when estimating the exponent in a body weight-based covariate submodel of a population pharmacokinetic model (Eq. 1),

Table 2 Characteristics of the different weight distributions and summary of the simulation results

Distribution	Geometric mean (kg)	SD on log-scale	Distance between geometric mean and 70 kg (in SD on log-scale)	Median RSE ratio CL_{pop} (Eq. 6) for 70 kg normalization	Covariance step successful with 70 kg normalization (%)	Covariance step successful with geometric mean normalization (%)	Covariate step successful in both normalizations (%)
PEDIAT1 Log-normal	20	0.25	5.0	4.3	72	57	54
PEDIAT2 Uniform 10–32 kg	20	0.33	3.9	3.5	79	63	59
PEDIAT3 Uniform 1–51 kg	20	0.83	1.5	1.7	85	85	84
OBESE1 Uniform 110–220	162	0.2	− 4.2	3.5	31	32	28
OBESE2 Uniform 80–160	118	0.2	− 2.6	2.3	47	48	45
OBESE3 Uniform 45–160	97	0.35	− 0.9	1.1	52	53	50

RSE relative standard error, *SD* standard deviation, CL_{pop} population clearance

Fig. 3 RSE ratio of CL_{pop} (Eq. 6) when using 70 kg normalization compared with geometric mean weight normalization. For each weight distribution, 250 datasets were generated and refitted. Only results of datasets for which the covariance step was successful for both the 70 kg and geometric mean weight normalization were included in this graph (Table 2). *RSE* relative standard error, CL_{pop} population clearance
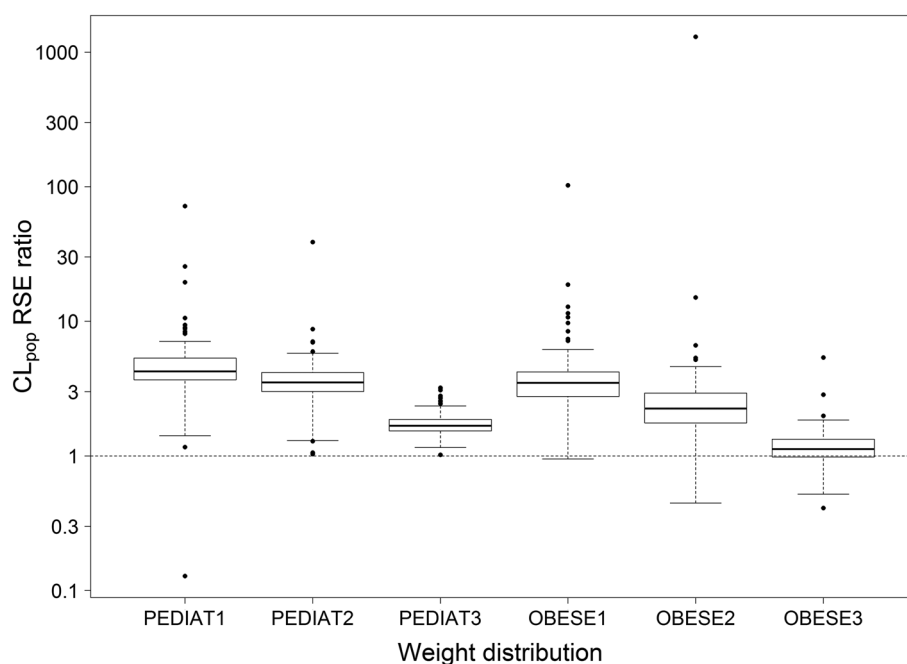
the use of a normalization weight outside the observed weight range can result in an inflated RSE of the estimate of CL_{pop}. This holds true for 70 kg normalization, but also for 1 kg normalization (which is sometimes referred to as 'no normalization') [9].

The RSE of the CL parameter CL_{pop} represents the RSE of the predicted typical CL (CL_{TV}) at a particular normalization weight, and is therefore not a universal measure for the precision of the estimate of CL (Table 2). As we show, the RSE of the predicted CL_{TV} is not constant, but dependent on the weight of the subject for whom CL_{TV} is predicted (Figs. 1 and 2). This means that the RSE of CL_{pop} represents how precisely CL can be estimated for a subject at the applied normalization weight. When estimating CL_{pop} at a normalization weight outside the observed weight range, the RSE of CL_{pop} will be inflated and cannot be used as a criterion for model selection. Our example with 70 kg normalization in a neonatal pharmacokinetic model showed, for instance, that the RSE of the CL_{pop} estimate increased sixfold compared with the estimate obtained with normalization to the median.

In linear regression, the minimum RSE is obtained by normalizing to the mean value. Because the power function becomes a linear model in the log domain, one might expect the minimum RSE at the geometric mean weight as this is equivalent to normalizing to the mean value of log of weight. The results of the case study show that this is not necessarily the case for covariate models of non-linear mixed-effects models. In our case study, we found that the minimum RSE of CL_{pop} was obtained by normalizing to 1.9 kg, rather than the mean, median or geometric mean

weight. The normalization weight with minimum RSE of CL_{pop} can be predicted by minimizing Eq. 5, although this does require that an initial model with a test normalization weight is run to obtain an estimate of the variance–covariance matrix. In our case study, we normalized to the median weight as this is the most commonly used normalization weight. This increased the RSE of CL_{pop} to 8.0%, from the minimum RSE of 6.4% at a normalization weight of 1.9 kg. However, normalizing to the median weight will likely be fit-for-purpose in most cases.

Regardless of the normalization weight that is used, Eqs. 4 and 5 can be used to calculate RSE values for any given body weight based on a variance–covariance matrix. This can be useful as normalization to 70 kg as a 'standardized individual' is sometimes advocated to improve comparisons of results from different studies [5]. In these cases, normalization to 70 kg can applied and Eqs. 4 and 5 can be used to calculate the RSE values for a relevant body weight to enable its use as a model selection criterion. Alternatively, model estimation can be performed with median weight normalization, and both the estimated CL_{pop} parameter for the median weight and the derived CL_{TV} for a 70 kg individual are reported, in which case the calculated RSE of the latter is relevant when comparing results from different studies.

The expected increase in RSE of centring to 70 kg is dependent on both the variance of the weight distribution and the distance of the mean of the distribution from the chosen normalization weight (Fig. 3). The effect seems to be largest in cases of narrow distributions with a mean covariate value far away from the centre of the data. This

especially holds true for (pre)term neonates, infants and young children and (morbidly) obese patients. In cases where the population mean is away from 70 kg but the range of weights includes 70 kg (such as scenario OBESE3), normalizing to 70 kg will likely result in an RSE increase of CL_{pop} that will not affect its application in model selection (Fig. 3).

It is important to realize that weight normalization only impacts the precision of the CL_{pop} parameter estimate, in case a covariate model according to Eq. 1 is chosen. If the exponent is fixed, the RSE of the estimate of CL_{pop} will be unaffected by normalization weight. Similarly, in this situation, the RSE of the predicted CL_{TV} will be independent of the subject's weight. Whether or not the exponent should be estimated or fixed is an ongoing discussion that is outside the scope of this paper [5, 11, 12].

In the simulation study, the calculation of the RSE ratio required that both model fits resulted in a successful covariance step. This requirement introduces the potential for selection bias as the results from the excluded datasets might have had a different impact of normalization on the RSE of CL_{pop}. However, performing a bootstrap on each of the 3000 model fits to obtain the RSE ratio independent of covariance step success was not feasible due to its computational demands.

Interestingly, the simulation study showed that in two of the six simulated scenarios, a higher percentage of runs with successful covariance steps was obtained when using geometric mean normalization instead of 70 kg normalization. Additionally, the paediatric case study showed that with normalization outside the observed weight range, collinearity between the CL_{pop} and EXP_{WT} parameter estimates is increased (Table 1). This suggests that normalization affects the stability of the parameter estimation process, which has been described for both linear models, as well as population pharmacokinetic models [15]. Although the increased stability was not observed in all simulated scenarios, it might be a reason to advocate median weight normalization over normalization outside the observed weight range.

5 Conclusions

Normalizing body weight-based covariate relationships in population pharmacokinetic models to 1 kg or 70 kg can inflate the RSE of the parameter estimate of CL_{pop} in population pharmacokinetic models. The predictive performance of the models are unaffected by normalization. However, when normalizing with a weight outside the observed weight range, the CL_{pop} RSE represents the precision of the CL_{TV} at this extrapolated weight, and this value should therefore not be used for model selection.

Instead, the precision of CL_{TV} at a relevant weight value can be calculated from the covariance matrix.

Compliance with Ethical Standards

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