Received: 18 September 2023 | Revised: 28 May 2024 | Accepted: 1 June 2024

DOI: 10.1111/bcp.16146

ORIGINAL ARTICLE

The pharmacokinetic differences between 10- and 15-μg daily vitamin D doses

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Funding information
Royal Golden Jubilee Ph.D. Programme, Grant/Award Number: PHD/0095/2561

Aims: The reference nutrient intake for vitamin D in people aged ≥4 years is 10 μg/day (400 IU/day) in the UK, but the recommended daily allowance is 15 μg/day (600 IU/day) for people aged 1–70 years in the USA. Here, we aim to compare the 25-hydroxyvitamin D (25(OH)D) serum concentration profiles between the 2 doses.

Methods: With world-wide trial data of adults aged ≥18 years, 45–93 kg, we constructed a minimal physiologically based pharmacokinetics model of serum concentrations of vitamin D and 25(OH)D using nonlinear mixed effects modelling. We used this model to forecast the mean, 2.5th and 97.5th percentiles for serum 25(OH)D concentrations in British adults aged ≥16 years.

Results: Our final model used bodyweight to adjust volume of each compartment and maximum clearance of 25(OH)D. No other covariate was identified. The model accurately predicted independent data from trials of a broad range of dosing regimens. We simulated British adults and showed that circulating 25(OH)D concentrations in 95% of people taking 10 μg/day for a year is predicted to reach 50 nmol/L in 32 weeks, while 97.5% of those on 15 μg/day were predicted to attain this threshold within 28 weeks.

Conclusion: Both doses are efficacious in >95% of the British population. The daily dose of 15 μg can help 97.5% of the British adults achieve 50 nmol/L serum 25(OH)D and reach the 25 nmol/L threshold in 4 weeks.

KEYWORDS
Vitamin D, Physiologically-based Pharmacokinetics Modelling, Population Pharmacokinetics

1 | INTRODUCTION

Vitamin D is crucial for maintaining bone mineralization, and it helps prevent osteopenia and osteoporosis.[1] Vitamin D deficiency is also associated with the occurrence of various health conditions, including cardiovascular diseases, diabetes mellitus type 1 and 2, chronic kidney diseases, infectious diseases, inflammatory diseases, as well as neurological and psychiatric diseases and cancer.[2–4]

The skin synthesizes vitamin D upon exposure to ultraviolet B radiation. Its stable circulating metabolite produced in the liver, 25-hydroxyvitamin D (25(OH)D), is subsequently activated in the kidneys to form calcitriol ($1,25(OH)_2D$) to exert its biological effects. Vitamin D status is assessed by the serum levels of 25(OH)D. Thresholds are controversial and vary internationally.[5] According to the UK Department of Health & Social Care (DHSC), serum 25(OH)D should not be <25 nmol/L.[6] However, deleterious effects were reported to be associated with serum 25(OH)D < 50 nmol/L.[7] This difference is explained by the need to ensure not just its calciotropic (>25 nmol) but also its noncalciotropic effects (>50 nmol/L). Others have proposed 75 nmol/L or even higher concentrations as a sufficiency target.[1,8]

Vitamin D deficiency is widespread. Among 45-year-old British adults, 15.5% were found to have 25(OH)D < 25 nmol/L in spring and winter.[9] And the percentage of US population with 25(OH)D < 30 nmol/L rose from 5% between 1988 and 1994 to 10% between 2001 and 2006.[10,11] Additionally, a study conducted on US children in 2003–2006 reported that 21% of normal-weight children had serum 25(OH)D levels <50 nmol/L.[12]

To tackle vitamin D deficiency, the UK Scientific Advisory Committee on Nutrition recommends a reference nutrient intake of 10 μg/day vitamin D in winter and spring for the general population and 10 μg/day all year round for the at-risk groups.[6] Similarly, the US National Academy of Medicine recommends a daily allowance of 15 μg/day vitamin D for 1–70-year-olds, and 20 μg/day for those older than 70 years.[8]

Notably, dosing regimens recommended from the Scientific Advisory Committee on Nutrition report do not take into consideration the pharmacokinetic (PK) properties of vitamin D and serum 25(OH)D, or their concentration/effect relationships.[6] To address the first concern, we investigate whether significant difference exists in serum 25(OH)D concentrations for 10 and 15 μg/day doses, and how they compare with the 25, 50 and 75 nmol/L thresholds for 25(OH)D proposed in the field. The pharmacokinetic/pharmacodynamic (PK/PD) relationship is outside the scope of this paper.

Previously, we reported a naïve average model for serum vitamin D_3 and 25(OH)D_3 (Figure 1). For the sake of simplicity, vitamin D_3 and 25(OH)D_3 are referred to as vitamin D and 25(OH)D in the rest of the paper. This model used baseline 25(OH)D to calculate the endogenous vitamin D synthesis rate for each trial arm. All other parameters are constant. Remarkably, it accurately predicted the mean serum 25(OH)D in adults from all around the world in all seasons for doses between 10 and 50 000 μg.[13]

In this work, we further developed this model as a nonlinear mixed effects (NLME) model in order to characterize the exposure of 25(OH)D following the 2 different vitamin D doses. Notably, the transition from a naïve average to a NLME modelling approach allowed us to take into account the interindividual variability (IIV) of PK properties of these molecules in the British population.

What is already known about this subject

- The UK recommends 10 μg/day vitamin D for people aged ≥4 years, while the USA recommends a 15-μg/day dose for 1-to-70-year-old and 20 μg/day for over 70s.

What this study adds

- A 15-μg/day dose helps 97.5% of British adults achieve serum 25(OH)D ≥ 50 nmol/L, while 10 μg/day dose is sufficient for 95% of British adults.
- For 97.5% of British adults to achieve serum 25(OH)D > 25 nmol/L, it takes a minimum of 4 weeks by 15-μg/day dosing and 6 weeks by 10-μg/day dosing.

2 | METHODS

2.1 | Clinical data compilation

Previously, we created a clinical dataset of reported adult studies from Asia, Americas, Europe and Oceania.[13] All studies involved subjects aged 18 years and over without disease or conditions that might influence the PK of vitamin D or 25(OH)D. The papers were published between January 1970 and January 2019 in English. For computational speed, we restricted the data to 90 days as most arms reach PK steady state within 90 days. The dataset includes 13 vitamin D PK arms (single dose: 70–2500 μg, up to 5 days; repeated daily dose: 20–275 μg/day, up to 120 days) and 90 25(OH)D PK arms (single dose: 1250–50 000 μg up to 270 days; repeated daily dose: 10–1250 μg/day up to 1 year). For 25(OH)D, 33 arms reported average bodyweight, ranging from 45 to 93 kg. All these data were used for model fitting. Information such as the type of trial, number of participants in each arm, dose, dosage form, quantification method, country, age, sex, weight and body mass index (BMI) are summarized in Table S1, and references are provided in Table S2 (references 1–56). All data and R scripts are provided in Data S1.

For model validation, we identified 7 adult trial arms from 3 additional published studies that reported bodyweight (references 57–59 in Table S2).

2.2 | Model structure, assumption and NLME fitting

We assumed the same structure as our previous naïve average model,[13] which is a minimal physiologically based PK (PBPK) model (Figure 1). Briefly, we assumed physiological parameters of an average 70-kg man,[14] which can be found in any of the models in nlxmir2 format in Data S1. We also lumped all nonelimination organs into a compartment called *the rest of the body*. For the compartments of arterial blood, venous blood, liver, and the rest of the body, volume was assumed to be the same for both vitamin D and 25(OH)D.[15] Upon oral administration, vitamin D first enters the GI compartment, then the liver.

Similarly to our previous work,[13] the fraction of vitamin D metabolized into 25(OH)D (F_m) was set to 0.33, as a vitamin D dose is roughly equivalent to 1/3 the dose of 25(OH)D[16]; vitamin D partition coefficient for liver over venous blood (Kp_l) was assumed to be 1.

We used the nlmixr2 R package for modelling and model equations in nlmixr2 format are provided in Data S1. Notably, the only nonlinear parameter featured in our model is the systemic clearance of 25(OH)D, which was modelled as a saturable process in function of systemic 25(OH)D concentrations. In this term $\frac{CL_{max} \times C_{25D}{}^{\gamma}}{C_{50}{}^{\gamma} + C_{25D}{}^{\gamma}} \times C_{25D}$, CL_{max} is the maximum clearance rate constant, C_{50} is the concentration of serum 25(OH)D at which 50% CL_{max} is reached, C_{25D} is the serum 25(OH)D

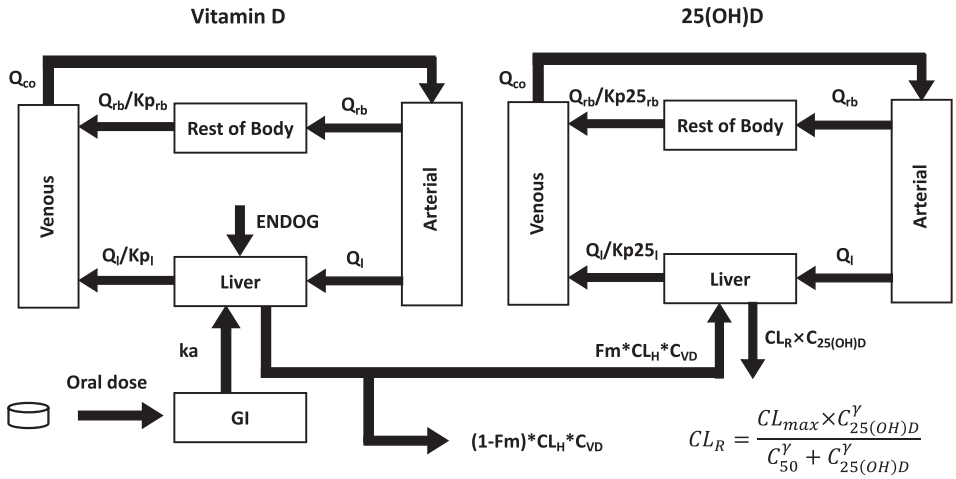

FIGURE 1 Model diagram. Orally administered vitamin D enters through the gastrointestinal tract (GI) and undergoes liver metabolism to produce 25-hydroxyvitamin D (25(OH)D), which is eventually cleared from the liver. Both vitamin D and 25(OH)D are distributed across venous blood, arterial blood, liver and the rest of the body, which lumps together all noneliminating organs. Endogenously synthesized vitamin D is assumed to enter the liver compartment at a constant rate (ENDOG). Clearance of 25(OH)D (CL_R) is the only nonlinear term in the model, with its equation listed on the right-hand side. This figure is adapted from our previous paper.[13] CL_H, hepatic clearance rate (L/h); C_{VD}, concentration of hepatic vitamin D; F_m, fraction of vitamin D metabolized into 25(OH)D; Kp_l and Kp_{25l}, distribution coefficient between venous blood and the liver for vitamin D and 25(OH)D, respectively; Kp_{rb} and Kp_{25rb}, distribution coefficient between venous blood and the rest of the body for vitamin D and 25(OH)D, respectively; Q_{co}, cardiac output (L/h); Q_l, blood flow into and out of the liver; Q_{rb}, blood flow into and out of the rest of the body.

concentration, γ is the Hill coefficient to describe the nonlinearity of the term. This term is necessary to model the saturated PK for large single doses and it is graphically shown in Figure S1. For the complete list of equations, please refer to our previous publication.[13]

We constructed a series of nested NLME models to select the best model. The goodness of fit, Akaike information criterion and Bayesian information criterion were consistently evaluated to determine the best model. We also required η shrinkage <30% throughout this process encompassing 3 steps.

First, we fitted the vitamin D data with a series of 11 nested NLME models but without covariates.

Second, we fixed the vitamin D-related PK parameters to the maximum likelihood estimates from the first step, and fitted a series of 7 nested models with different log-normally distributed random effects on 25(OH)D-related PK parameters to all 90 25(OH)D trial arms. These models do not have any covariates.

Third, for the subset of 25(OH)D PK data which also featured average weight values from the trial population (33 trial arms in total), we modified the resulting model from the second step to investigate the effect of weight as a covariate on several parameters. At this step, all model parameters except for those related to the weight model were fixed to previously estimated values. Weight was used to explain the variability in the partition coefficient between venous blood and the rest of the body for 25(OH)D (Kp_{25rb}, linear model), CL_{max} (power model) or the volume of all compartments (linear model).

2.3 | Model simulation

Given the heterogeneous dosage regimens, different serum 25(OH)D baselines and weights, a visual predictive check (VPC) was performed. Random effects and residual errors were sampled 1000 times to simulate each trial arm. We overlaid observed mean value of each time point on the predicted mean and 90% prediction intervals (Figure 3).

To simulate serum 25(OH)D concentrations for the 2 doses, we first computed the distribution of bodyweight and serum 25(OH)D baseline among all British adults. Assuming bodyweight within each age group follows Gaussian distribution, we combined bodyweight distributions for different age groups among British adults (16–49, 50–60, 65–91 years) from the latest National Diet and Nutrition Survey[17] with the percentage of people in each age group (table titled *Percentage and number of people in each age group, by ethnicity* on the UK government website)[18] to determine the bodyweight distribution among all British adults. Please refer to Supporting Information S1 for more details.

Distribution of serum 25(OH)D baseline among British adults was measured by samples from the UK biobank[19] and was sampled independently from bodyweight. Please refer to Supporting Information S2 for more details.

In our simulations, we took into account possible correlations between random effects of model parameters, as well as the quantified variance of residual errors.

2.4 | Software

Parameter estimation for NLME models was performed in R (version 4.2.2) with the nlmixr2 package (version 2.0.9) on a 30-core Linux cluster. This includes fitting NLME models in stochastic approximation expectation–maximization method, computing conditional weighted residuals (CWRES) and normalized prediction distribution errors (NPDE), and performing VPC simulation. VPC results were plotted in

vpc R package (version 1.2.2). We used rxSolve function from the rxode2 R package (version 2.1.1) to simulate the British adult population and subpopulations.

3 | RESULTS

3.1 | Vitamin D PK model development

To quantify variability among trials, we developed an NLME model based on our published naïve average model.[13] We first refitted the same vitamin D data as in our previous work (13 arms, see Section 2.1). The best vitamin D model (Model 11 in Tables S3 and S5) considers both IIV and interoccasion variability (single dose vs. repeated daily dose) in the hepatic elimination rate constant λ_H (Table S7), while all other parameters are the same as the naïve average model. The inferred λ_H values are similar. For single dose, NLME: 0.450 h^{-1}, 95% CI [0.362, 0.558] h^{-1}; naïve average (mean ± standard deviation): 0.32 ± 0.06 h^{-1}. For repeated daily dosing, NLME: 0.222 h^{-1}, 95% CI [0.179, 0.274] h^{-1}; naïve average (mean ± standard deviation): 0.210 ± 0.004 h^{-1}. Strikingly, population predictions are in excellent agreement with vitamin D data (Figure S2A: $R^2 = .984$ in the goodness-of-fit plot).

3.2 | 25(OH)D PK model development

We then fitted 25(OH)D data without covariates. For the sake of computation time, the 25(OH)D data were restricted to 90 days, as most arms reached steady state within 90 days. There are 90 arms in total, with doses ranging from 10 to 1250 μg/day. We fixed the vitamin D-related parameters to their typical values from the previous step, and some 25(OH)D-related parameters to values from our previous naïve average model, and fitted the rest of the 25(OH)D-related parameters. The best model without covariates (Table S6: Model 7) includes random effects for the partition coefficient for the rest of the body (Kp_{25rb}) and the maximum 25(OH)D clearance rate constant (CL_{max}). Population predictions are in good agreement with data (Figure S3A: $R^2 = .818$), and the individual predictions are better (Figure S3B: $R^2 = .997$). Plots of CWRES and NPDE indicated no systematic errors (Figure S3C,D). Parametric inference was good (Table S6: Model 7, Table S8).

Bodyweight was reported for 33 of the 90 25(OH)D trial arms (10–1250 μg/day). We developed Models 8–12 (Tables S4 and S6) to incorporate bodyweight as a covariate. In our final model (Model 11 in Tables S4 and S6), bodyweight is used to adjust the volume of each compartment and CL_{max}. For instance, $V_{rb} = 62.6 \times WT/70$, where $TV_{rb} = 62.6L$ for a 70 kg subject, and $CL_{max} = exp\left(TCL_{max} + \eta_{CL_{max}}\right) \times \left(\frac{WT}{70}\right)^{0.75}$, where $TCL_{max} = -3.07$ for a 70 kg subject. This reduces shrinkage in Kp_{25rb} and CL_{max} and improves model fit to data (Table S6: Model 8 vs. Model 11). Population predictions are in good agreement with observations (Figure 2A: $R^2 = .962$), and the individual predictions are better (Figure 2B: $R^2 = .998$). Although CWRES may suggest possible overpredictions for low population prediction (PRED) values (Figure 2C), there is no apparent pattern in CWRES or NPDE overall (Figure 2D–F), indicating no systematic error.

The data for model fitting cover various races, age groups, sex, and geographical locations. As the population predictions are good (Figure 2A), these factors are expected to have little influence over serum 25(OH)D as far as these data are concerned. VPCs of the model show the mean of each arm is within 90% prediction interval for the great majority of cases (Figure 3). This confirms that the model accurately describes the original data.

The parameter estimation procedure yielded good parameter inference (η shrinkage <30%). The 2 random effects are weakly correlated (correlation coefficient = −0.116 derived from Ω matrix in Table 1). Residual errors are small (additive error: 0.000741 nmol/L; proportional error: 0.0459).

To test this model, we compared model-predicted serum 25(OH)D concentrations with observed mean concentrations from trial arms that were not used to construct the model (Figure 4). Doses range between 10 to 2500 μg, and the frequency of dosing includes daily, 3 days a week, weekly and once every 2 weeks (Figure 4). Study durations vary between 16 weeks to 3 years (Figure 4). The observed mean ± standard deviation is within 68% prediction intervals in all cases except for Figure 4D which were measured in 60 elderly Lebanese participants (73 ± 2 years). The predicted mean values are similar to observed mean values, providing reassurance for model predictions.

3.3 | PK simulations for 10 *vs.* 15 μg/day

We first computed the distributions of bodyweight and serum 25(OH)D baseline (Figure S6) among all British adults. Specifically, body weight distribution was reported for age groups 16–49, 50–64, 65–91 by the UK government (Supporting Information S1). To reconcile the differences, 16- and 17-year-olds were assumed to have the same parameters to generate simulations presented in the paper. Please refer to Section 2.3, Supporting Information S1 and Supporting Information S2 for more details. We then simulated the 2 daily doses at 100% adherence for a year, and calculated 95% confidence intervals of the predicted mean, 2.5th and 97.5th percentiles (Figure 5). Interestingly, ≥2.5% of British adults are predicted to fail to reach the 50-nmol/L target at 10-μg/day dose (lower bound in Figure 5A). We replotted the results and found 10-μg/day dose is sufficient for 95% of British adults and the target is reached at approximately 32 weeks (Figure S8A). By contrast, 97.5% of British adults are predicted to reach 50 nmol/L at 15-μg/day dose within 28 weeks (lower bound in Figure 5B). Notably, the US National Academy of Medicine advises that 15-μg daily dose is required to meet the 50 nmol/L target for 97.5% US population.[8] In addition, the 15-μg/day dose is predicted to increase serum 25(OH)D more rapidly (compare Figure 5A,B). For 97.5% of the British adults to reach the UK DHSC target of 25 nmol/L, it takes 6 and 4 weeks by the 10- and 15-μg/day doses, respectively.

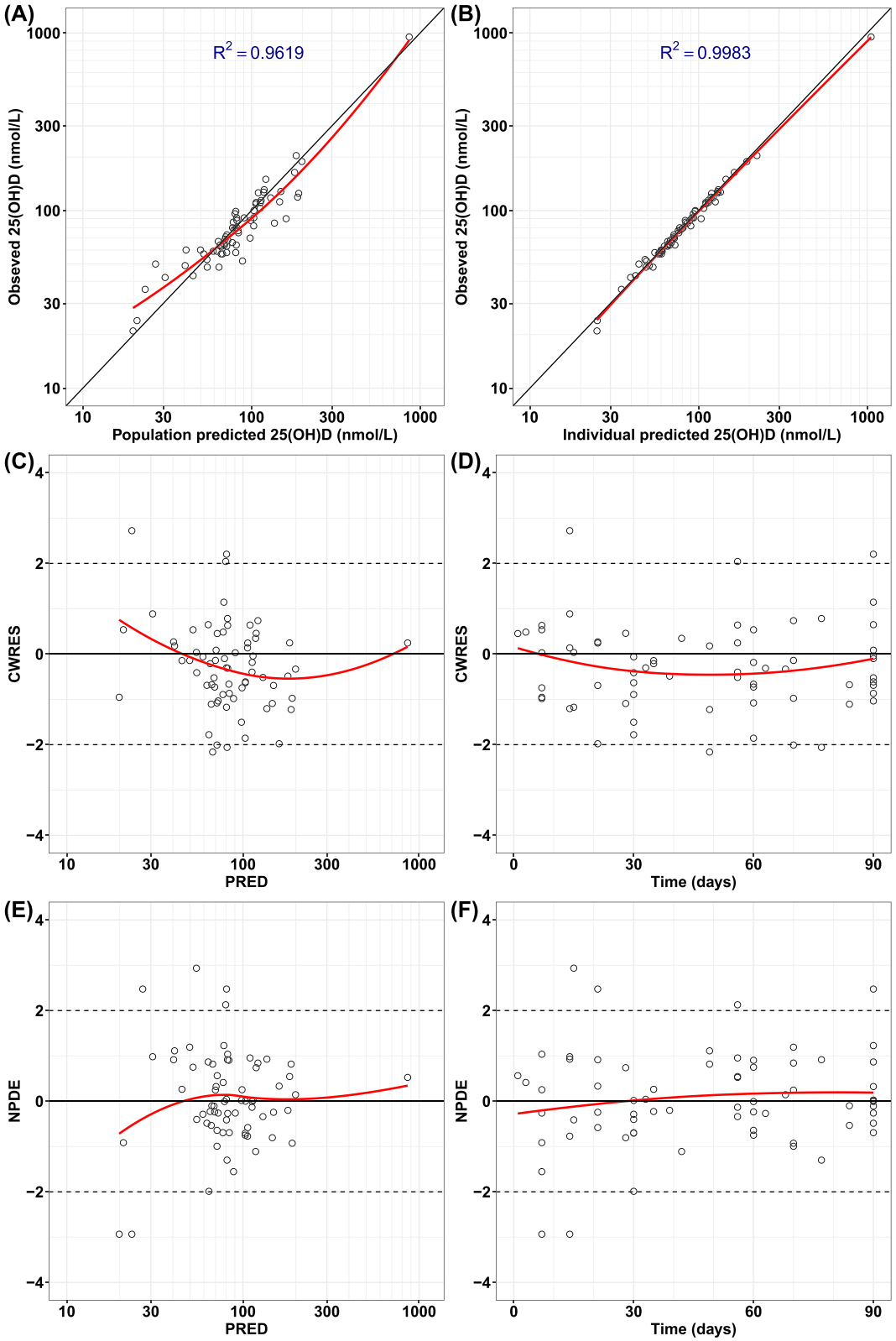

FIGURE 2 Diagnostic plots for the final model: goodness-of-fit for population (A) and individual (B) predictions. Conditional weighted residuals (CWRES) are plotted against population predictions (C) and time (D). Normalized prediction distribution errors (NPDEs) are plotted against population predictions (E) and time (F). Red curves: trendlines from a loess with $\alpha = 5/3$. 25(OH)D, 25-hydroxyvitamin D. PRED, population predictions.

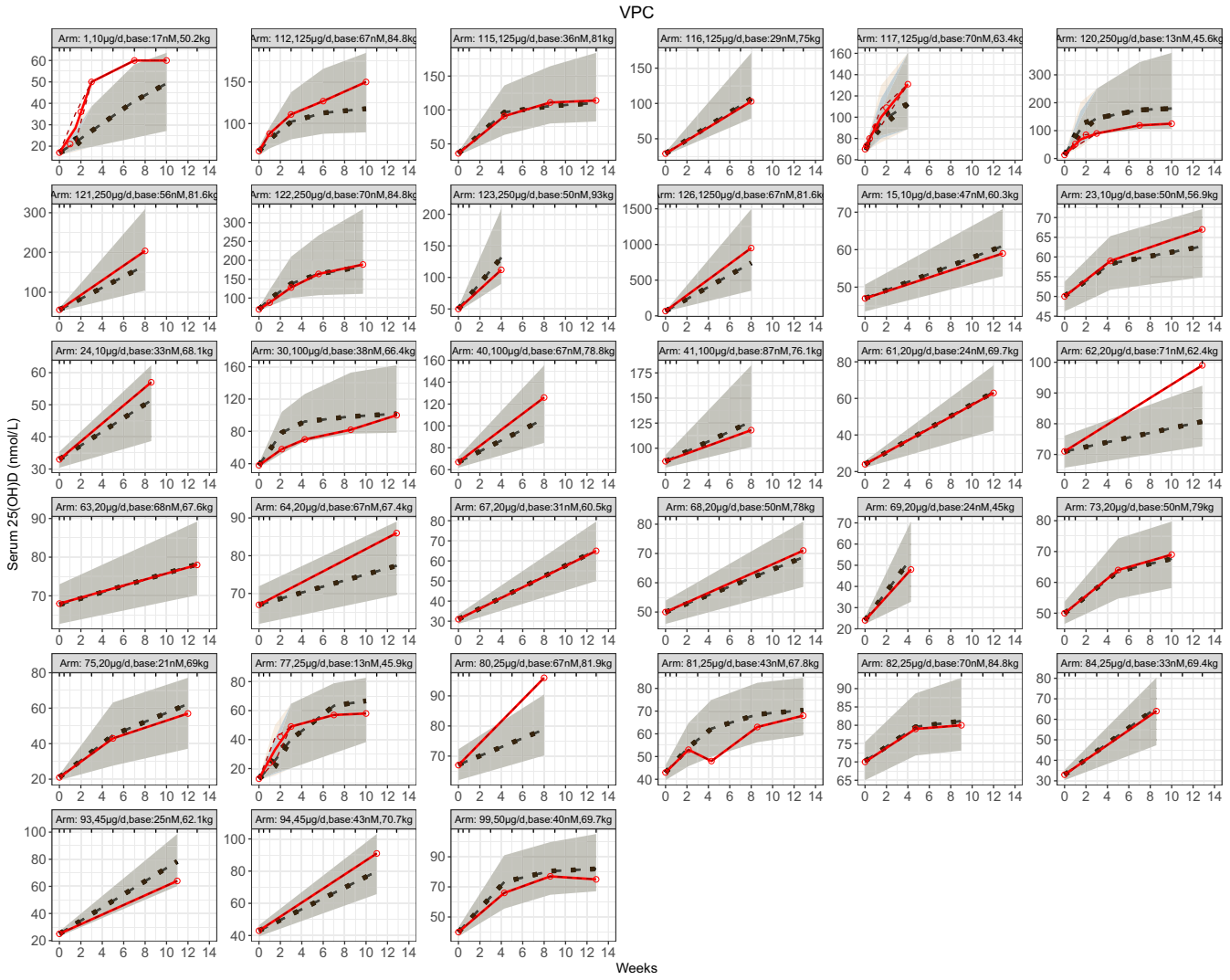

FIGURE 3 Visual predictive checks (VPCs) for each 33 arm fitted by the final model. Red line with dot: observed mean values of each arm. Grey band: 90% prediction interval. Black dotted line: predicted mean. Dose ranges from 10 to 1250 μg/day. 25(OH)D, 25-hydroxyvitamin D.

TABLE 1 Parameters of the full model with bodyweight as a covariate.

Full model (bodyweight)	Est. in natural logarithm	SE in natural logarithm	%RSE	Values in linear scale (95% CI)	IIV CV%[a]	Shrink%
Kp_{25rb}	−1.28	0.243	19	0.279 (0.173, 0.449)	114	26.1%
CL_{max}	−3.07	0.13	4.22	0.0463 (0.0359, 0.0597)	69.1	17.6%
Additive error				0.000741		
Proportional error				0.0459		
Variance–covariance matrix Ω						
	$\eta_{Kp_{25rb}}$			$\eta_{CL_{max}}$		
$\eta_{Kp_{25rb}}$	0.830			−0.116		
$\eta_{CL_{max}}$	−0.116			0.391		

Abbreviations: CI, confidence interval; CV, coefficient of variance; IIV, interindividual variability, RSE, relative standard error; SE, standard error.
[a]IIV CV% is $\sqrt{e^{\omega}-1}\times 100\%$, where ω is the variance of random effects.

We further compared the 2 doses for cases in each vitamin D status. For vitamin D deficient cases, neither dose is predicted to help 97.5% of the British adults to reach the 50-nmol/L target (Figure 6A,B), despite higher mean and lower bounds reached by the 15-μg/day dose group. The insufficient cases exhibited a clearer difference: the 2.5th percentile of the 15-μg/day dose group is just below the 50-nmol/L target at 28 weeks (Figure 6D), while 10% of the cases who receive 10-μg/day dose are predicted to fall below

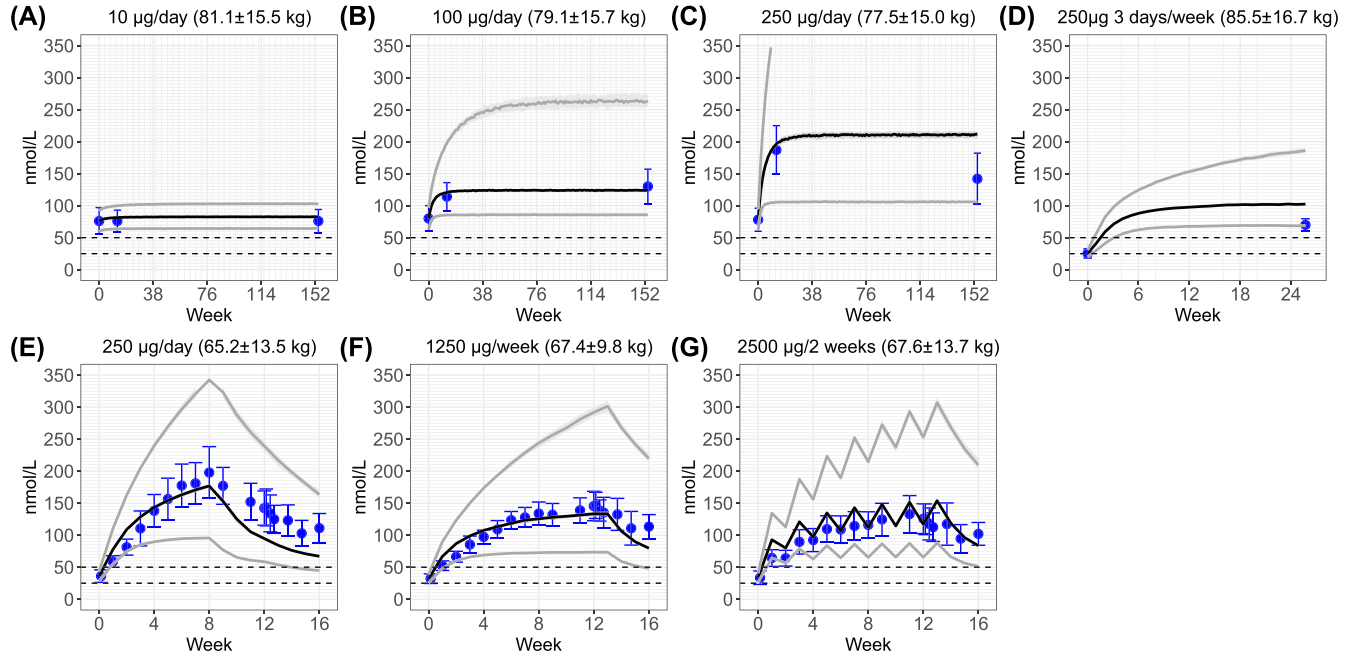

FIGURE 4 Simulation of mean serum 25-hydroxyvitamin D (25(OH)D) concentrations for adult trials of daily doses at 10 µg (A), 100 µg (B), 250 µg (C–E), 1250 µg (F) and 2500 µg (G). To produce each graph, we generated 30 simulated studies, with each study containing 2500 samples of Kp_{25rb}, CL_{max}, weight and basal serum 25(OH)D. Kp_{25rb} and CL_{max} follow a bivariate normal distribution characterized by the variance–covariance matrix from stochastic approximation expectation–maximization fitting (Table 1). We added additive residual errors (0.000794 nmol/L) for each study, and presented the predicted mean, 16th and 84th percentiles together with 68% confidence intervals around each of these percentiles. Blue dots and error bars: observed mean ± standard deviation.

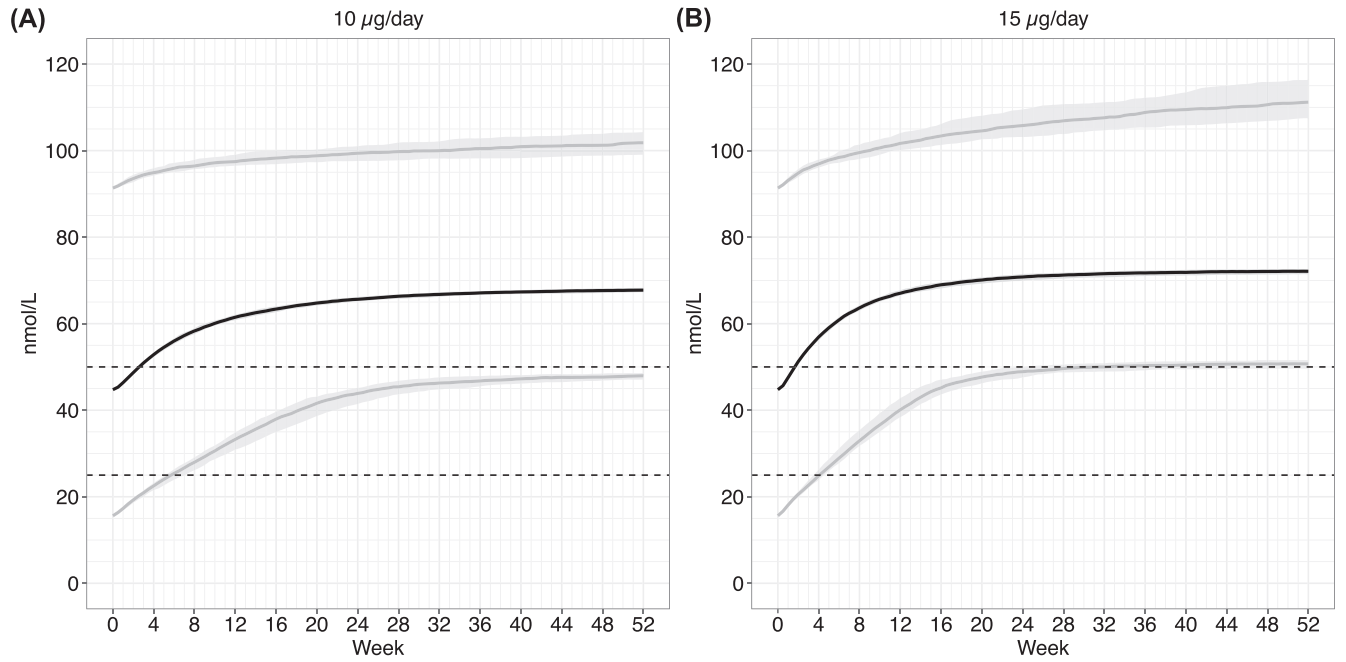

FIGURE 5 Simulation of serum 25-hydroxyvitamin D (25(OH)D) concentrations in British adults who receive continuous vitamin D daily dosing at 10 and 15 µg for 52 weeks. Baseline serum 25(OH)D follows the distribution described in Section 2. In each simulated study, random effects and additive residuals of the final model were sampled 2500 times, following the distribution of the variance–covariance matrix in Table 1. We generated 30 such studies to calculate the 95% prediction intervals (grey shaded areas) around the mean (solid black line), 2.5th and 97.5th percentiles (grey lines). The dashed lines mark the insufficiency (25 nmol/L) and sufficiency (50 nmol/L) thresholds.

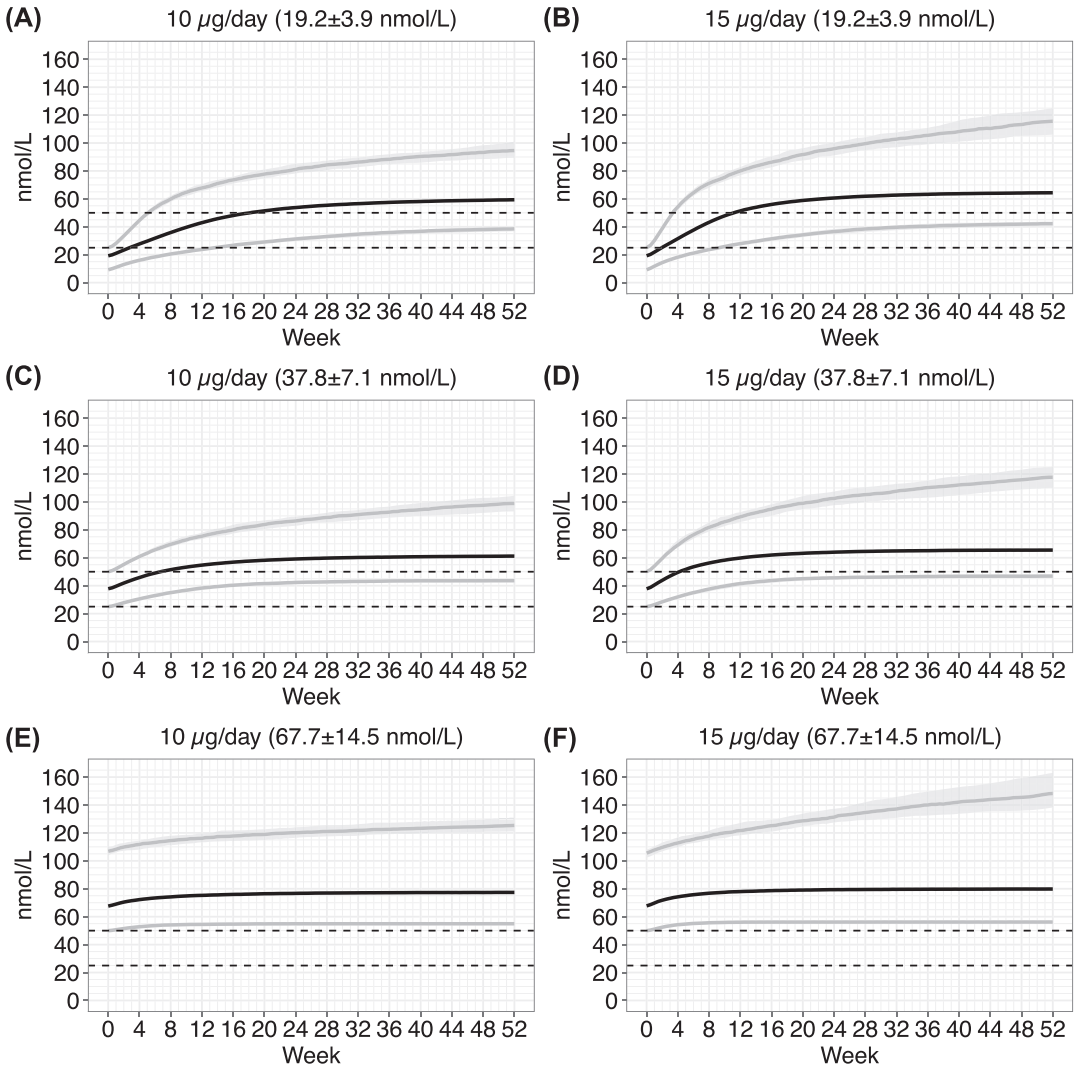

FIGURE 6 Simulation of serum 25-hydroxyvitamin D (25(OH)D) concentrations in British adults who receive continuous vitamin D daily dosing at 10 and 15 μg for 52 weeks, stratified by deficiency (A and B), insufficiency (C and D) and sufficiency (E and F). Simulations were performed in the same way as Figure 5. Mean, 2.5th percentiles and 97.5th percentiles are plotted with 95% confidence interval.

50 nmol/L throughout the entire year (Figure S7C). Among the sufficient cases, neither dose is expected to bring 97.5% of the group to reach the optimal target of 75 nmol/L (Figure 6E,F).

4 | DISCUSSION

Here we discuss differences between the 2 doses, how to evaluate the model-based inference of parameters, whether additional covariate is need, whether weight-based dose adjustment is needed, and finally how this model differs from our previous naïve average model.

4.1 | Differences between the 2 doses

The most salient finding in this work is that a 15-μg/day dose is predicted to get 97.5% of British adults to reach the 50-nmol/L target within 28 weeks (Figure 5B), and 10-μg/day dosing is predicted to be sufficient for 95% British adults and it takes 32 weeks to reach the target (Figure S8A). The difference is 2.5% of British adults, just over 1.3 million in the 2021 Census.[18] Second, both dose regimes are adequate to keep people who are sufficient (>50 nmol/L) at baseline in the sufficient range (Figure 6). Third, 15-μg/day dosing allows for quicker target attainment. As far as the UK DHSC target of 25 nmol/L is concerned, 97.5% of vitamin D deficient cases would reach the threshold within 4 weeks at the 15-μg/day dose (Figure 5B), and within 6 weeks at the 10-μg/day dose (Figure 5A). In the real world, the difference might be different due to varying compliance.

Indeed, a higher dose is required as a therapy of vitamin D deficiency (<25 nmol/L) and it is inappropriate to use a 10- or 15-μg/day dose in this case. However, according to the UK biobank study, vitamin D deficiency is prevalent among British adults (13.5%) and the great majority of cases are not diagnosed or addressed by clinical therapy. This study demonstrates that regular vitamin D prophylaxis is

not able to treat these people. Therefore, a 25(OH)D level check would be important, and represents the only effective measure to identify and properly treat this significant portion of the British population exhibiting vitamin D deficiency. Here, we simulate the PK of these 2 doses in deficient cases merely in the hope to provide clarity (Figure 6A,B).

4.2 | Does Kp < 1 make sense?

Vitamin D is lipophilic and distributes into the fat tissue. If most vitamin D is distributed in the tissue, then Kp ≥ 1. In contrast, our model inferred Kp < 1 for vitamin D, which is counterintuitive. We compared the volume of distribution (V_d) estimated by noncompartmental analysis (NCA) with what was estimated by our modelling, and concluded Kp < 1 was consistent with the PK data.

We performed NCA of vitamin D PK using all 13 trial arms and found V_d ranged between 10.0 and 16.6 L. Per definition, $V_d = \Sigma\ (V_{organ} \times K_p)$. A 70-kg man has 6.6 L of blood, 1.8 L liver and 62.6 L for the rest of the body. Our model assumed $K_{pl} = 1$ for liver and fitted $K_{prb} = 0.09$ for the rest of the body. Hence, $V_d = 6.6\ L + 1.8\ L \times 1 + 62.2\ L \times 0.09 = 14\ L$, which is consistent with the NCA results (10.0–16.6 L). In other words, $K_p < 1$ is consistent with observed vitamin D PK. Given these values, $62.2\ L \times 0.09 \div 13\ L \times 100\% = 40\%$ of vitamin D is expected to be found in the rest of the body, 13% in the liver and 47% in blood. As 25(OH)D has similar lipophilicity, $Kp_{25rb} < 1$ is expected (Table 1).

4.3 | Can BMI explain random effects?

From multiple large-scale studies, obese people were observed to tend to have lower vitamin D levels.[12] To investigate the plausibility that Kp_{25rb} is correlated with BMI, we plotted the average BMI (20–30 kg/m^2) against Kp_{25rb} or CL_{max} inferred from 25(OH)D Model 7 and Model 11, but they showed no correlation (Figures S4 & S5). First, Model 11 already uses bodyweight to adjust volume of each compartment, and BMI might not add anything independently. Second, this might be because mean values of each trial arm were used to build the model, and inference made from individual-level data might conclude differently.

For clarity, we did not find any clinical evidence to support deficiency is related to bodyweight. For simplicity, serum 25(OH)D baseline and bodyweight were assumed independent when they were sampled in all simulations. Potentially, one may use a more complex approach that first samples BMI across the British adults, then uses BMI-baseline serum 25(OH)D concentration correlation and bodyweight–BMI correlation to sample bodyweight and baseline serum 25(OH)D concentrations. In this more complex approach, the variability in bodyweight and baseline serum 25(OH)D concentration may reduce, but the reduction is expected to be small. As we need to consider the worst-case scenarios to make an informed decision on the right dose for the public, and simulations in this paper carry the largest possible variability, we believe that the results in this paper are sufficiently robust.

4.4 | Is weight-based dose adjustment needed?

At the same 25-nmol/L baseline, we simulated the 2 doses in subjects with 40, 70, 90 and 120 kg bodyweight. At 90% chance, daily dosing at 10 and 15 μg are predicted to be sufficient (≥50 nmol/L) for a subject up to 90 and 120 kg bodyweight, respectively (Figure S9). At 97.5% chance, bodyweight thresholds for sufficiency lower to 40 and 70 kg for the 2 doses, respectively (Figure S10). This suggests that weight-based dose adjustment might be needed.

4.5 | How is this model different from the naïve average model?

The structural model in this paper is the same as the minimal PBPK-naïve average model we previously published. First, only the rate of endogenous vitamin D synthesis was adjusted to match the baseline 25(OH)D for each arm, and the model employs a single set of parameters to encompass data of great diversity. This restricts captured variability to that attributable to endogenous synthesis rate. Second, the naïve average model building procedure featured only a fraction of the available data (vitamin D single dose: 70–2500 μg; 25(OH)D: 10 and 100 μg/day) and the model yielded good predictions for doses higher than the training set ($R^2 = .929$ for repeated daily dosing 12.5–1250 μg/day and $R^2 = .756$ for large single doses 1250–50 000 μg).

Here, our final model fitted 33 arms of 25(OH)D data with higher correlation: $R^2 = .962$ for population predictions (Figure S3A) and $R^2 = .998$ for individual predictions (Figure 2). Our model also successfully predicted the mean observations for independent test data under diverse dosing regimens (Figure 3).

In summary, based on a naïve average model that makes accurate predictions for a wide range of dosing regimens, we developed an NLME PBPK model to characterize the PK properties of vitamin D and its biologically relevant metabolite 25(OH)D in a semi-mechanistic fashion, taking into account the expected IIV in distribution and disposition properties of these molecules within the British population. Not everyone is expected to reach the 50 nmol/L sufficiency target at either dose. Baseline 25(OH)D levels is the main factor and should be measured before a dose is selected. Deficiency (baseline <25 nmol/L) should be treated by doses higher than a prophylaxis dose (e.g., 15 μg/day). Among the insufficient cases (baseline 25–50 nmol/L), 15-μg daily dose helps almost 97.5% of the cases achieve sufficiency, while a 10-μg daily dose is predicted to fail the target in 10% of the cases. Hence, insufficient cases may benefit from a higher, 15-μg dose. Our simulations suggest that continuous dosing at 15 μg/day is sufficient for ≥97.5% of British adults to reach 50 nmol/L, and 10 μg/day is sufficient for 95% of British adults (Figure S8). This difference corresponds, in absolute terms, to approximately 1.3 million

adults in the UK. At 100% dose adherence, it is expected to take 6 and 4 weeks for 97.5% British adults to reach the 25-nmol/L threshold at the 10- and 15-μg/day doses, respectively. These pharmacokinetic differences need to be considered in order to select a daily vitamin D deficiency prophylaxis dose for the British adults.

AUTHOR CONTRIBUTIONS

Designed the research: Tao You. Collected data: Zhonghui Huang. Checked data: Nadda Muhamad and Tao You. Performed modelling: All authors. Analysed the data: All authors. Drafted the paper: Tao You. Finalized the paper: All authors.

ACKNOWLEDGEMENTS

We are grateful for the time and useful comments made by Prof Martin Hewison (University of Birmingham) and Prof Adrian Martineau (Queen Mary University of London), which improved the manuscript. The authors would also like to thank Prof Kesara Na-Bangchang for the constructive advice. The authors would gratefully acknowledge the useful comments made by the reviewers, which helped improve the paper. NM is supported by the Royal Golden Jubilee Ph.D. Programme in Thailand (grant number PHD/0095/2561) to visit T.Y. in the UK to carry out the research. N.M. and T.Y. would like to thank Prof Andy Jones, Dr Andrew Collins and members of the Computational Biology Facilities at the University of Liverpool for providing the high-performance cluster.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

All data and R scripts needed to reproduce all results in this article and its Supporting information are available online as a zip folder on *BJCP*. A mirror copy is available at https://www.letsgobeyond.co.uk/vitamin-d.

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SUPPORTING INFORMATION

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

How to cite this article: You T, Muhamad N, Jenner J, Huang Z. The pharmacokinetic differences between 10- and 15-μg daily vitamin D doses. *Br J Clin Pharmacol*. 2024;1-10. doi:10.1111/bcp.16146