Review

Prediction of winter vitamin D status and requirements in the UK population based on 25(OH) vitamin D half-life and dietary intake data

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ABSTRACT

On a population basis, there is a gradual decline in vitamin D status (plasma 25(OH)D) throughout winter. We developed a mathematical model to predict the population winter plasma 25(OH)D concentration longitudinally, using age-specific values for 25(OH)D expenditure (25(OH)D_3 $t_{1/2}$), cross-sectional plasma 25(OH)D concentration and vitamin D intake (VDI) data from older (70+ years; n = 492) and younger adults (18–69 years; n = 448) participating in the UK National Diet and Nutrition Survey. From this model, the population VDI required to maintain the mean plasma 25(OH)D at a set concentration can be derived. As expected, both predicted and measured population 25(OH)D (mean (95%CI)) progressively declined from September to March (from 51 (40–61) to 38 (36–41) nmol/L (predicted) vs 38 (27–48) nmol/L (measured) in older people and from 59 (54–65) to 34 (31–37) nmol/L (predicted) vs 37 (31–44) nmol/L (measured) in younger people). The predicted and measured mean values closely matched. The predicted VDIs required to maintain mean winter plasma 25(OH)D at 50 nmol/L at the population level were 10 (0–20) to 11 (9–14) and 11 (6–16) to 13 (11–16) μg/d for older and younger adults, respectively dependent on the month. In conclusion, a prediction model accounting for 25(OH)D_3 $t_{1/2}$, VDI and scaling factor for the 25(OH)D response to VDI, closely predicts measured population winter values. Refinements of this model may include specific scaling factors accounting for the 25(OH)D response at different VDIs and as influenced by body composition and specific values for 25(OH)D_3 $t_{1/2}$ dependent on host factors such as kidney function. This model may help to reduce the need for longitudinal measurements.

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Contents

1. Introduction

The plasma concentration of 25 hydroxy vitamin D (25(OH)D) reflects the supply from oral intake (in the form of vitamin D_2 and D_3 and 25(OH)D_3)) and vitamin D3 from endogenous cutaneous synthesis. In temperate climates (>30°N and >30°S), no cutaneous synthesis of vitamin D takes place in the winter months [1]. Therefore, the winter plasma concentration of 25(OH)D is mainly a function of an individual's post-summer status, their expenditure of 25(OH)D and their vitamin D supply through diet. In populations living in a temperate climate, there is a gradual decline in the mean vitamin D status from late autumn throughout winter [1–4], indicating that, on average, the daily vitamin D intake is less than its daily expenditure. The impact of this circannual cycling of 25

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(OH)D is uncertain [5], but many advocate that a decrease in plasma 25(OH)D below the threshold of sufficiency (50 nmol/L) or deficiency (30 nmol/L), as defined by The Institute of Medicine (IOM) [6], should be avoided throughout the year to prevent a winter increase in plasma parathyroid hormone and bone resorption, although the threshold at which this occurs is disputed [5–9].

Here we present a mathematical model to predict longitudinally the population plasma 25(OH)D concentration during winter. Plasma 25(OH)D concentrations and vitamin D intake (VDI) data from older (70+ years) and younger adults (18–69 years) participating in the population based UK National Diet and Nutrition Survey (NDNS) [10,11] and age-specific values for vitamin D expenditure measured as 25(OH)D half-life (25(OH)D$_3$ $t_{1/2}$) [12,13]. This model was further applied to estimate mathematically the required vitamin D intake to maintain the population mean plasma 25(OH)D at a set concentration.

2. Methods

A subset of data from the National Diet and Nutrition Survey (NDNS) rolling programme (NDNS years 1–3; 2008/9–2010/11) and the NDNS of people age 65 years and over (1994/1995) was extracted from the full data sets available from the UK Data Service. The dataset included 25(OH)D concentration, month of blood collection, age and dietary intakes of vitamin D (VDI) for each participant. Special permission to include the month of blood collection was granted (personal communication Public Health England NDNS project board). Only data of individuals of 18 years of age and over were selected. Further information about the survey, how to access the data and to obtain permission for their use, can be found at https://www.noo.org.uk/data_sources/Nutrition/NDNS and http://www.data-archive.ac.uk. Recruitment of participants to NDNS, methods of data collection, measurement of 25(OH)D concentration and dietary intake of vitamin D are described elsewhere [10,11] and available online (http://webarchive.nationalarchives.gov.uk/20130402145952/ http://transparency.dh.gov.uk/category/statistics/ndns/) and http://www.data-archive.ac.uk.

In brief, NDNS participants were randomly selected from the UK population; data were collected from each individual once, i.e. on a cross-sectional basis. The survey was designed to be nationally representative. Visits took place throughout the year and the dates of visits and blood collections were recorded. Written and verbal consent was obtained from all participants. To ensure anonymity, the NDNS dataset only contains details about the month of blood collection not the day; therefore they were all assigned a value 1, i.e. all September dates were entered in the model as September 1. A venous blood sample was collected non-fasting and the plasma 25(OH)D concentration was measured using Diasorin (DiaSorin Ltd, Dartford, UK) Liaison chemiluminesence immune assay (NDNS year 1–3; 2008/9–2010/11) or Diasorin Radio − immune assay (NDNS: people age 65 years and over (1994/1995)) in lithium heparin plasma. Cross-calibration of the two Diasorin assays showed good agreement and no systematic bias (https://www.gov.uk/government/statistics/national-diet-and-nutrition-survey-results-from-years-1-to-4-combined-of-the-rolling-programme-for-2008-and-2009-to-2011-and-2012). The laboratory performing these assays was DEQAS accredited.

Participants completed a 4-day weighed food diary of all food and drink consumed using standardised house hold scales as described in detail in the above referenced NDNS report and this is considered to represent habitual nutrient intakes on a population level [14]. Vitamin D intake was assessed as Vitamin D (<2002) or the Vitamin D equivalents to include 25(OH)D3 from animal tissues (>2002) using British food composition tables (http://www.ifr.ac.uk/fooddatabanks/nutrients.htm#.Unn_QobTQil).

The data set was split by age into a subset of older (70+ years) and younger adults (18–69 years). For initial inspection of the data to determine the yearly peak and nadir in the plasma concentration of 25(OH)D and potential seasonal variation in vitamin D intake, data for all months were used. For data modelling, only data of individuals who provided a blood sample between September and March and had completed a food diary were used (70+ years; n = 492) and younger adults (18–69 years; n = 448).

2.1. Mathematical model to predict the population plasma 25(OH)D concentration in winter

The following mathematical model was developed as modification of the algorithm proposed by Diffey [15,16]. Only autumn and winter values (October to March) were modelled, with plasma concentrations obtained in September to April as starting value as explained below. The contribution of cutaneous vitamin D synthesis was assigned a value of zero. The resulting model gives the prediction plasma concentration of 25(OH)D at any time point (t) after a measured value was obtained (which was defined as t = 0) and contains 2 main components. The first component accounts for the decline in plasma 25(OH)D due to its expenditure, assuming first order kinetics. Age-specific mean values for 25(OH)D$_3$ $t_{1/2}$ were used, as experimentally obtained with a stable isotope technique with LC–MS/MS quantification[12,13]. The second term accounts for the daily increment in plasma 25(OH)D derived from an individual's dietary intake of vitamin D and the subsequent exponential decline of this component, as reflected by the sum of the geometric series. It accounts for the plasma 25(OH)D response to vitamin D intake (R (oral)), using a fixed dose-response rate (the scaling factor) and the release of 25(OH)D into plasma of the fraction stored in tissues.

$$\text{Plasma } 25(OH)D_{(t)} = [\text{Plasma } 25(OH)D_{(t=0)} \times e^{-kt}]$$
$$+ (0.168 \times VDI) \times \left(\frac{(1 - e^{-kt})}{(1 - e^{-k})}\right)$$

In which:

$$k = \frac{ln2}{25(OH)D3t1/2}$$

in which 25(OH)D$_3$ $t_{1/2}$ is the age specific 25(OH)D$_3$ half-life.
t = the number of days since t = 0
VDI is the daily vitamin D intake calculated as the mean of the 4 recorded days
(0.168* VDI)*((1-e^{-kt})/(1-e^{-k})) reflects the daily increment in plasma 25(OH)D due to VDI and the subsequent exponential decline of this component. The latter was described by the sum of the geometric series ((1-e^{-kt})/(1-e^{-k})) in which k was used as defined above.
The conversion factor of 0.168 (R(oral)) was derived from:

$$R(oral) = S \times (1-f) \times 2^{-t/\beta} + (f \times 2^{-t/Y}) = 0.168$$

In which:
S was set as = 0.023; S is the scaling factor for the 25(OH)D plasma response to VDI and was derived from the median conversion factor from 9 dose-response studies [15].
f is the fraction of vitamin D taken up and stored in tissues = 0.15
β is 25(OH)D$_3$ $t_{1/2}$ as defined above
Y is tissue half-life of vitamin D = 250 days
The plasma 25(OH)D concentration was expressed in nmol/L; 25(OH)D$_3$ $t_{1/2}$ in days; VDI in μg/d.
The plasma 25(OH)D concentration for each participant as measured in NDNS was included in the model as the starting value

(t = 0) and the predicted values were progressively calculated for each day thereafter, i.e. if a blood sample was collected in September, predicted data were derived from this month onwards; if collected in November, predicted values were derived for the months thereafter only. As a consequence, the number of individuals included in the model progressively increased at each month.

The following assumptions were made:

(ii) A linear relationship between the increment in plasma 25(OH)D and VDI was assumed within the range of vitamin D intakes observed in this survey. Therefore a fixed value for S was used. This was based on the *meta*-regression analyses presented in the IOM report, describing a biphasic response with a different dose-response below and over 25 μg/d (1000 IU/d) [6]. This can be explained by the metabolic conversion of vitamin D to 25(OH)D, changing from first to zero order kinetics due to saturation of the hepatic 25-hydroxylase [17]. We also did not account for the potential difference in the response to food based or supplemental supply of vitamin D [18]. (ii) A constant supply of vitamin D into the blood stream from the diet and subsequent conversion in 25(OH)D was assumed; therefore no allowance was made for the delay between ingestion and plasma appearance of plasma 25(OH)D and/or peaks in vitamin D intake during specific time slots and days. (iii) The plasma 25(OH)D decreases exponentially starting at t = 0. During this process, the daily increment in plasma 25(OH)D derived from dietary VDI was added as constant at t = 1, 2, 4, days, etc and subsequently is assumed to decline exponentially in parallel to the plasma concentration of 25(OH)D. Therefore, this algorithm is only valid for integer values of t. (iv) Vitamin D intake as assessed by 4 day diary reflects habitual daily intake and there is no seasonal variation in vitamin D intake during the year. This assumption was confirmed by inspection of NDNS data (see results). (v) The term in the original model by Diffey [15], reflecting cutaneous vitamin D synthesis was assigned a value of zero during the selected autumn and winter months. This term was therefore removed from the algorithm. This may have underestimated the vitamin D supply since some cutaneous synthesis may occur in September [1] with extensive duration of exposure. In addition, NDNS participants were not asked to refrain from overseas travel or sunbed use prior to blood sampling. No detailed data on these exposures are available prior to 2008 and thus could not be incorporated into the model. This in accordance with the principle of assumed minimal sun exposure on the population level, applied by IOM [6].

2.2. Mathematical model to predict the population vitamin D intake requirement to maintain plasma 25(OH)D concentration at 50 nmol/L in winter

The daily mean dietary vitamin D intake (in the absence of any cutaneous synthesized vitamin D), required to maintain the mean population plasma 25(OH)D at a given concentration from September to March was derived from the above model. To illustrate the principle of this model, the threshold for sufficiency as defined by the IOM was chosen, but any threshold may be modelled. The plasma 25(OH)D concentration was set to be equal to 50 nmol/L at the end of each month, and can be expressed as the following algorithm:

$$VDI = \left(\frac{50 - \text{Plasma } 25(OH)D_{t=0} \times e^{-kt}}{[0.168 \times (1 - e^{-kt})/(1 - e^{-k})]} \right)$$

This model used the observed value as the plasma concentration at time zero and the subsequently predicted value in the previous integer of t as derived from the previous model. It assumes an intake of vitamin D at the predicted requirement on each of the preceding days.

3. Results

The yearly peak and nadir in the plasma concentration of 25(OH)D as measured in NDNS were in September and March, respectively in both age groups (not presented). The mean (95% CI) vitamin D intake was 3.8 (3.1, 4.5) and 4.0 (3.0, 4.9) μg/d for the group of 70y+ and 18–69 y, respectively and was stable throughout the year (not presented).

The mean (95% CI) measured values in NDNS participants declined from 51 (40–61) nmol/L in September to 38 (27–48) nmol/L in March in the older adults and from 59 (54–65) to 37 (31–44) nmol/L) in younger adults (Fig. 1). There was some deviation from the expected profile, likely due the variation in number of participants and the cross-sectional nature of the data. The 95% CIs of the measured concentrations were higher than the predicted values, as may be expected from cross-sectional population data. The predicted values declined from 51 (40–61) to 38 (36–41) nmol/L in older people and 59 (54–65) to 34 (31–37) nmol/L in younger people). The widths of the 95% CI of the predicted plasma 25(OH)D concentrations were influenced by the progressive increase in the number of individuals that could be included in the model each month and were therefore wider in September than in March.
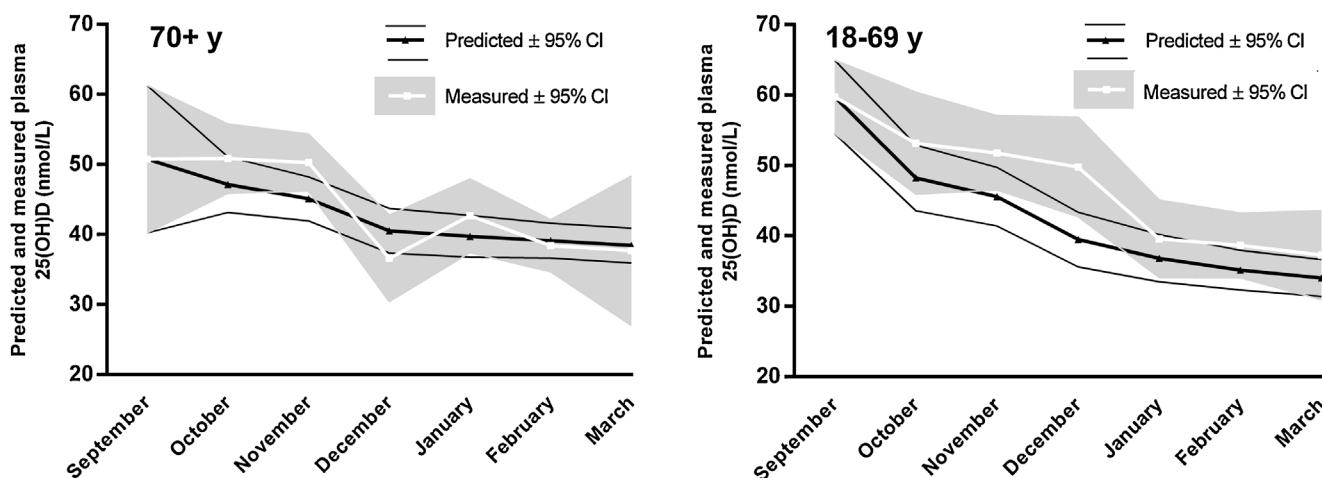

Fig 1. Measured (mean and 95% CI; white line and grey shading) plasma 25(OH)D concentrations in NDNS for people 70 years of age and over (left) and 18–69 years of age (right) and mathematically predicted (mean and 95% CI; black solid line) mean plasma 25(OH)D concentrations in the population in winter.
Data are presented in. The number of plasma 25(OH)D measurements varied by month (n = 63–205).

The predicted mean plasma 25(OH)D concentrations, with consideration of vitamin D intakes and the measured values, fell within the 95% CI of the measured values, although the predicted mean was consistently slightly lower than measured values for the younger group (Fig. 1).

The predicted VDIs required to maintain mean winter plasma 25(OH)D at 50 nmol/L at the population level were 10 (0–20) to 11 (9–14) µg/d and 11 (6–16) to 13 (11–16) µg/d for the group of 70y+ and 18–69 y, respectively, dependent on the month (Fig. 2).

4. Discussion

The predicted longitudinal mean plasma 25(OH)D concentration during winter months, derived from the mathematical model closely matched values as measured in the UK population on a cross-sectional basis. The mathematically estimated vitamin D intake, required to maintain the population mean plasma 25(OH)D at 50 nmol/L during winter assuming minimal sun exposure, was 10–11 µg/d and 11–13 µg/d for the older and younger people, respectively. These values are similar to the mean values estimated to be associated with a population mean of 50 nmol/L during winter as derived from *meta*-regression analyses [19,20]. This analysis utilised the dose-response from several randomised controlled trials in populations living at latitudes where there is minimal vitamin D synthesis during the winter months [19,20].

As expected, the 95% CI of the predicted plasma 25(OH)D concentration was narrower than the population distribution. As a consequence and additionally due the inherent assumption of the model that the intake of vitamin D was at the predicted requirement to maintain a set 25(OH)D concentration on each of the preceding days, also the predicted VDI had a relatively narrow 95% CI. Therefore, although this model may aid the estimation of the mean vitamin D requirement in the population, for the assessment of the vitamin D intakes to meet the requirement of majority of the people, the variability in the population needs to be taken into account [6,19,20].

The model includes a term to account for the expenditure of 25(OH)D. In contrast to the model proposed by Diffey [15] and several others that used adapted or slightly different models [19,21,22,18], the values used in this paper were experimentally determined in healthy older and younger participants [13,23]. A further alteration to the original model included the incorporation of a term that accounts for a continuous influx of vitamin D and 25(OH)D from dietary sources, whereas Diffey's algorithm assumed a single bolus intake. This alteration possibly provides a more realistic profile of 25(OH)D concentrations in observational, population based studies.

Although the longitudinally predicted values closely corresponded to the cross-sectional values obtained during the winter months, comparisons with longitudinally collected samples will be required to validate this mathematical model. Since this model includes variables reflecting vitamin D status, 25(OH)D half-life, vitamin D intake, and a scaling factor for the relationship between vitamin D intake and the corresponding change in the plasma 25(OH)D concentration, the predicted values depend on the accuracy and precision of these measured variables and how they are influenced by population specific factors. This and other models [15,19,20,24] rely on a fixed dose-response rate (the scaling factor), determined from 9 studies [15], which included a wide range of vitamin D intakes. However, the response of plasma 25(OH)D is known to be non-linear and the relative increment in plasma 25(OH)D decreases with an increasing vitamin D dose. In addition, it has also been suggested that the response may depend on the source of oral vitamin D [18]. Determination of scaling factors at corresponding vitamin D intakes and sources may therefore be more appropriate. Further refinement of this model may be needed to account for the 25(OH)D response as influenced by body size and composition and vitamin D status at baseline [25–27]. Further, there may be considerable differences in the dose-response between individuals and population groups, potentially determined by genetic factors associated with ethnic origin [28]. Further research is also required to obtain specific values for $25(OH)D_3$ half-life dependent on host factors such as age, physiological stage, ethnicity and kidney function. Also other dietary factors may be expected to influence $25(OH)D_3$ half-life, as shown in animal models. To date, the limited studies in humans have not shown an influence of calcium intake on $25(OH)D_3$ half-life or vitamin D status [13,29].

Despite these limitations, this prediction model may improve the sensitivity of statistical analyses of data obtained in studies in which participants were included or investigated longitudinally during different seasons and months of the year. Examples of these type of studies are randomised controlled trials with vitamin D, where participants are enrolled in the trial in different seasons. In these studies the response to supplementation may depend on the plasma 25(OH)D concentration at baseline, which may be influenced by season. In longitudinal studies, the investigation of the association between vitamin D status and health outcomes provides a challenge due to its anticipated change with season that may coincide with the progression of disease processes and/or
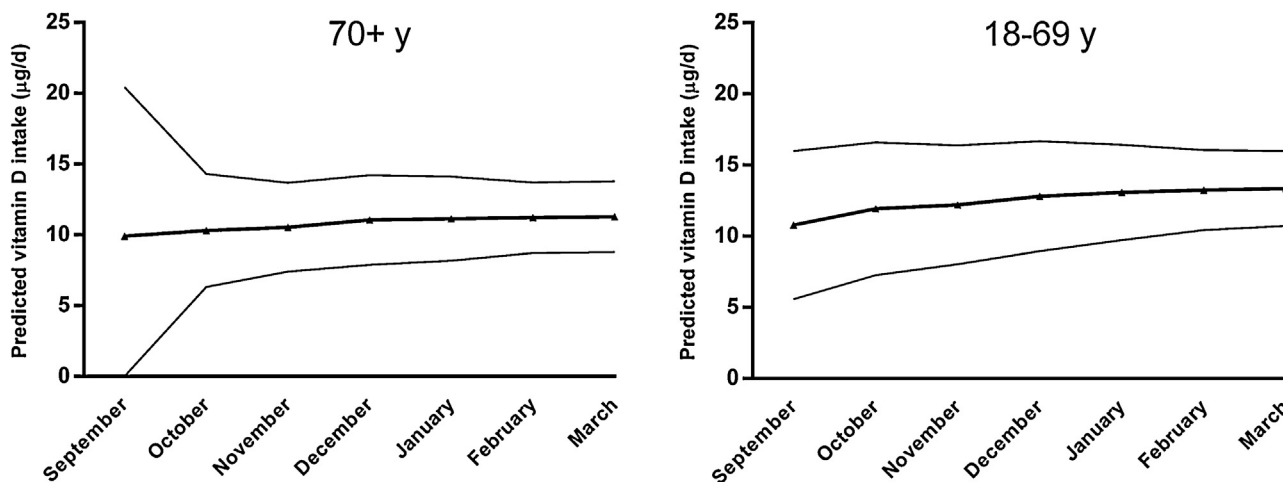

Fig. 2. Mathematically predicted (mean and 95% CI) daily dietary vitamin D intake required to maintain the mean plasma concentration of 25(OH)D at 50 nmol/L on a population basis for people 70+ years of age and over (left) and 18–69 years of age (right) in winter.

physiological changes inducing changing the concentration of 25 (OH)D and other vitamin D metabolites and hormones, for example during pregnancy. This model may provide an approach to correct for variations in vitamin D status as caused by the month or season of sampling.

There are several limitations to this study. This model can only be used for the prediction of vitamin D status and requirements of relatively large groups and populations as it cannot sufficiently account for individual differences. The published values for 25(OH) D half-life were obtained in a relatively small number of participants, and therefore are unlikely to be fully representative of the UK population. The model also does not account for the known time-lag (weeks to months) to reach a new steady state of the 25(OH)D concentration after the start of vitamin D supplementation.

In conclusion, we developed a mathematical model to predict longitudinally the mean plasma 25(OH)D concentration on a population basis during winter, which closely matched values obtained cross-sectionally in the NDNS survey. This mathematical model can be used to calculate the mean estimated vitamin D intake required to maintain the population mean plasma 25(OH)D concentration at a predetermined concentration.

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