The contributions of adjusted ambient ultraviolet B radiation at place of residence and other determinants to serum 25-hydroxyvitamin D concentrations

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Summary

Background Solar ultraviolet B (UVB) radiation is the major source of vitamin D (vitD) for humans.

Objectives To describe ambient UVB radiation at wavelengths that induce vitD synthesis (vitD-UVB) in Scotland, and to examine the relationship to serum 25-hydroxyvitamin D (25OHD).

Methods We estimated the average vitD-UVB dose for each day of the year and for each postcode area in Scotland, using the Tropospheric Emission Monitoring Internet Service database. Cumulative and weighted vitD-UVB (CW-vitD-UVB) exposure at place of residence was calculated for each participant. Plasma 25OHD was assayed in 1964 healthy participants.

Results Significant seasonal and geographical variation in vitD-UVB was observed. Ambient vitD-UVB exposure at place of residence was significantly associated with plasma 25OHD (P < 0·01). An average increase in 25OHD of 1 ng mL^{-1} was observed for every 1000 kJ m^{-2} higher CW-vitD-UVB dose or for every 2·5 μg of daily supplement taken. Adequate 25OHD concentration (> 16 ng mL^{-1}) was observed in the majority when CW-vitD-UVB dose was > 6000 kJ m^{-2}, a level of ambient radiation achieved only in summer months in Scotland. When predicting vitD deficiency, dramatic improvement in the area under the curve was observed (from 0·55 to 0·70) after CW-vitD-UVB dose was added to the model, in addition to a range of other covariates.

Conclusions Ambient vitD-UVB can be a useful predictor of vitD status. Geotemporally mapped measurements of vitD-UVB can be used as a proxy for vitD status or as a covariate in epidemiological research, particularly if 25OHD is unavailable.

What's already known about this topic?

- Solar ultraviolet B (UVB) radiation is the major source of vitamin D (vitD) for humans and it is strongly associated with vitD status.
- UVB radiation at wavelengths that can induce vitD synthesis can be approximated by total UV or UVB radiation, sunshine hours or latitude, typically averaged over a large geographical region and long time period, yielding unreliable approximations.

What does this study add?

- Information on ambient UVB exposure at wavelengths required for vitD synthesis (vitD-UVB), adjusted for cloud cover and ozone layer, is a powerful yet underutilized tool to study the relationships between UVB, vitD and health outcomes.

- There was significant geographical variation in vitD-UVB, even within a small geographical area at a northern latitude.
- Measured ambient vitD-UVB dose at place of residence is a good predictor of vitD status.

The seasonality of vitamin D (vitD) status follows seasonality of ultraviolet B (UVB) radiation and attests to the key role of UVB as a source of vitD.[1] Because skin vitD synthesis is directly related to UVB exposure, there is a strong *a priori* expectation that ambient UVB dose predicts vitD status. However, there is a paucity of studies that exploit UVB measurement; this could be due, in part, to difficulties in obtaining accurate *individual* estimates, as ambient UVB dose does not directly map to latitude, sunshine, season or weather. Previous attempts using crude proxies such as sunshine hours or latitude have estimated UVB dose,[2–4] typically averaged over a large geographical region and longer time period, yielding unreliable approximations. Apart from a few rare exceptions,[5] to date, more accurate estimates of UVB relevant for vitD production have not been examined or utilized in epidemiological studies.

The amount of vitD synthesized in skin depends on two principal determinants: (i) available UVB at wavelengths relevant for vitD production and (ii) personal factors (Fig. 1).[6] While the ambient dose is easily measurable, personal characteristics and behaviours are not, because they are highly variable and difficult to capture (e.g. clothing, time spent outside or tan).[7] Therefore, an accurate estimate of ambient UVB dose at wavelengths relevant for vitD production is a critical *measurable* predictor of vitD status.[2]

Once vitD is synthesized (or ingested), it undergoes hydroxylation in the liver to form 25-hydroxyvitamin D (25OHD). The concentration of 25OHD in the circulation is currently considered to be the best biomarker of vitD status.[8] However, owing to assay costs and difficulty (practical or ethical) of obtaining blood samples, particularly if assessment at multiple time points is desired, it is not always feasible to measure circulating 25OHD.[9]

In this article, we set out to describe ambient exposure to UVB radiation at wavelengths that can induce vitD synthesis (vitD-UVB) in Scotland, and to examine the relationship between ambient vitD-UVB at the place of residence and vitD status. We also discuss the relevance and application of this novel approach for future studies.

Patients and methods

Study population

The study population consisted of 1964 individuals (43% women) recruited as control participants between February 2003 and March 2004 for a case–control study aimed at investigating factors associated with colorectal cancer in Scotland [Scottish Colorectal Cancer Study (SOCCS)]. SOCCS is described in detail elsewhere.[10,11] All participants were white and of Scottish ancestry (verified by genetic markers). Participants completed a detailed sociodemographic and lifestyle questionnaire, and a semiquantitative food frequency and supplements questionnaire. We administered the Scottish Collaborative Group Food Frequency Questionnaire (SCG-FFQ, version 6.41), which has been validated in Scotland. Nutrient content was estimated for each food item using a national nutritional database. Nutrient intake was calculated from the consumption frequencies of specified portion size for each food item from the SCG-FFQ and were standardized for total energy intake.

Residential postcode was mapped within half a degree of geographical latitude and longitude to a UVB radiation database grid (55 km south to north and 33 km east to west at the latitudes of Scotland). The final sample size (n = 1964) followed exclusion of participants (n = 284) with missing data on any of the following: residential location; level of physical activity; body mass index (BMI); plasma 25OHD level; extreme outliers of plasma vitD (> 100 ng mL^{-1}). Approval for the study was obtained from the Multicentre Research Ethics Committee for Scotland and local research ethics committees, and all participants gave written informed consent.

Plasma vitamin D measurement and deficiency categories

Blood samples were taken throughout the year (Table S1; see Supporting Information). All plasma samples were batched and assayed at the same laboratory. Total 25-OHD (25-OHD$_2$ and 25-OHD$_3$) was measured by liquid chromatography–tandem mass spectrometry, which is considered the gold-standard method.[12] The lower limit of detection for this method is 4 ng mL^{-1}; values below this limit were replaced with a value randomly sampled from the 0–4 ng mL^{-1} range from a tail of normal distribution, to improve normality. To characterize the degree of deficiency, categorical 25OHD cut-off points were set to 10, 16 and 20 ng mL^{-1} in accordance with Ross *et al.*,[13] although risk category cut-offs are still under debate.[14,15]

Genetic score

In a genome-wide association study, we extracted the genotypes for three single nucleotide polymorphisms (rs12785878,
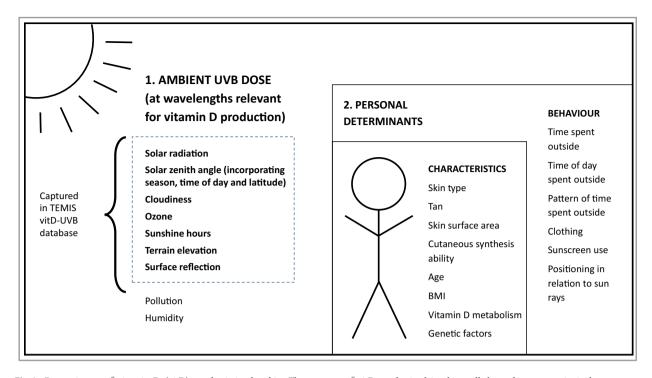
Fig 1. Determinants of vitamin D (vitD) synthesis in the skin. The amount of vitD synthesized in skin will depend on two principal parameters: (i) ambient dose of ultraviolet B (UVB) at wavelengths relevant for vitD production; and (ii) personal factors. The important difference between the two is that ambient dose is easily measurable, while personal factors are not. Personal factors include a wide range of personal characteristics [e.g. skin tone and surface area, cutaneous synthesis ability (known to decrease with age)] and behaviours (duration and timing of time spent outside, clothing, sunscreen use). These factors are often difficult and/or costly to capture accurately, owing to their constant change (clothing, tanning, time/time of day spent outside, angle of sun rays reaching skin) or are not measurable (vitD synthesis ability, deposition in fat, metabolism). The Tropospheric Emission Monitoring Internet Service (TEMIS) provides dose of UVB relevant for vitD production (vitD-UVB): daily solar radiation is measured by satellites; dose is weighted with a biological function to isolate the narrow band of wavelengths relevant for vitD production and adjusted for all main local factors: ozone, cloudiness and terrain. The main ambient factor not accounted for in the estimate is pollution; however, air pollution in Scotland is low.

rs10741657 and rs2282679) that have been associated with 25OHD concentration.[16] Genetic score has been calculated as the number of risk alleles for rs12785878 and rs2282679, variants that have been associated with circulating 25OHD in this population. Genotyping protocol has been described in detail elsewhere.[17] Approximately one-third of the cohort had no risk alleles (n = 527), 63% (n = 1021) had one or two risk alleles, and 4% (n = 65) had three or four risk alleles.

Ultraviolet B data resource

Using the Tropospheric Emission Monitoring Internet Service (TEMIS) database (www.temis.nl/uvradiation), we extracted ambient UVB dose relevant for vitD production at residential locations for every participant. Daily estimates are based on satellite UV measurements from sunrise to sunset, with a time step of 10 min. The readings are adjusted for the terrain elevation, the total ozone column and cloud cover (Fig. 1).[18]

The exposure dose is the energy associated with the radiation divided by the surface area of the receptor, expressed in kJ m^{-2}. A biological function is applied to the intensity of UV radiation, to isolate the narrow band of wavelengths relevant

for vitD production. Synthesis occurs within the UVB wavelengths, but while the action spectrum is between 260 and 315 nm, the peak conversion occurs at a very narrow range, between 295 and 297 nm.[19] The final estimate is the daily dose of UV radiation at the earth's surface that can induce vitD synthesis if absorbed by the human skin (vitD-UVB).

Because observed vitD-UVB measurement was not available prior to 2005, when this cohort was being recruited, average daily vitD-UVB dose was calculated for each day of the year using data recorded between 2005 and 2010.

Seasonal and geographical analysis of vitamin D– ultraviolet B in Scotland

Total monthly vitD-UVB exposure averaged over 5 (or 6) years (July 2005–October 2010) was calculated and is reported for eight exemplar areas selected to represent diverse geographical locations while accounting for population density: Glasgow, Edinburgh, Oban, Aberdeen, Inverness, Stornoway, Kirkwall and Lerwick. Multivariate linear regression was carried out to examine the association between total monthly vitD-UVB dose and month, location and year.

Mean monthly vitD-UVB dose was calculated for 79 grid cells that cover the entire land area of Scotland. The map of Scotland was created using Postal Boundaries Open 2012, a spatial dataset detailing the extent of the 9232 geographic postal sectors (e.g. HP21 8) covering the U.K. (last modified October 2012). Postal sectors are grouped together to form 2736 postal districts (e.g. HP21), which, in turn, group together to form 120 postal areas (e.g. HP). The data are released under the same terms as the OS OpenData licence.[20]

Individual cumulative and weighted vitamin D–ultraviolet B exposure dose

Mean daily vitD-UVB dose for each day of the year for each region was calculated using data from 2005 to 2010 for that region. A cumulative and weighted vitD-UVB (CW-vitD-UVB) dose prior to date of blood sampling was calculated for each individual based on the average estimated dose. 'Cumulative' means that daily vitD-UVB doses from a number of preceding days are added up to contribute to the final exposure estimate but using a method where daily contributions to the cumulative exposure estimate are weighted so that vitD-UVB exposures immediately prior to blood sampling contribute more than exposures from a more distant past (Fig. S1; see Supporting Information). This weighting is akin to the 'half-life' of the vitD-UVB effect and reflects the half-life of vitD in the body (whole-body vitD: 2 months; 25OHD in the circulation: 15 days).[21] Our analysis suggests a 35-day half-life of vitD-UVB effect and 135-day period are optimal parameters (see Appendix S1; see Supporting Information). The model presumes that the amount of vitD-UVB currently contributing to plasma concentration is negligible 135 days prior to sampling. The estimates are unique for every individual, because they are determined by the place of residence and date of blood sampling. For example, if a blood sample was taken on 27 January, data on daily vitD-UVB doses between 14 September and 26 January will be extracted, weighted and added up. This is illustrated in Figure S1 (see Supporting Information) and the equation below, where x is the number of days ago (starting day before and up to 135 days prior to sampling), y is the rate of disappearance of the effect of UVB in days (half-life set at 35 days) and $e^{(-\ln2/y)x}$ is the weighting formula applied.

$$\text{CW-vitD-UVB}(x) = \sum_{x=1:135} \left(\text{vitDUVB}(x)\right) * e^{-\left(\frac{\ln 2}{y}\right)x}$$

Statistical analysis

In a regression analysis after adjustment for a range of factors that have been shown to affect 25OHD concentration (age, sex, BMI, number of risk alleles, socioeconomic status, level of physical activity, dietary vitD and vitD supplement use), we tested whether cumulative and weighted vitD-UVB (CW-vitD-UVB) dose was associated with 25OHD. The proportion of

variance explained by each predictor in this population was estimated, to assess relative contributions to 25OHD levels in this population. A drawback with population variance measures is that the major determinants of population variation may not be the main *causes* of the condition; therefore, it is not possible to rank the absolute importance of factors according to their contribution to population variance.

The ability of the 25OHD-UVB proxy to predict plasma vitD status in three categories (< 10, < 16 and < 20 ng mL^{-1}) was tested using random forests prediction (RF). While logistic regression models predict the category of an observation based on linear combinations of the predictor variables, RF uses classification trees. A classification tree is fitted for each predictor variable, with each variable given a cut-off value corresponding to being vitD deficient or not. RF prediction fits many classification trees to randomly selected subsets of the data, and then combines the predictions from all the trees. The success of the prediction for each observation is calculated by combining the results of all the classification trees. The main advantage of RF over logistic regression is it has very high classification accuracy. Repeated classification trees are made from separate bootstrap samples of the training data using the classification and regression tree algorithm. Each tree provides a prediction rate for the number of individuals correctly classified below or above the cut-off point. Receiver operator curves (ROC) were constructed to measure the performance of the test, and the area under the curve (AUC) was reported. The AUC is the percentage of randomly drawn pairs classified correctly. The training dataset, on which the predictions were made, consisted of 982 observations, while the validation set, which was used for the ROCs, had the remaining 982 measurements. The analysis was carried out in the RF package in R.[22]

Results

Ambient vitamin D–ultraviolet B exposure: regional and seasonal differences

Substantial regional differences in UVB radiation dose at wavelengths that can induce vitD synthesis (vitD-UVB) were observed across Scotland and throughout the year. As expected, vitD-UVB dose was inversely related to latitude (Fig. 2 and Table S2; see Supporting Information). Location within Scotland was significantly associated with vitD-UVB radiation, despite the restricted geographical area (54·8–62·3° north and 0·25–8·25° west): for example, Edinburgh (55·9° north) received, on average, 560 kJ m^{-2} more vitD-UVB per month than Lerwick (60·2° north) (Table S3; see Supporting Information).

VitD-UVB dose had a marked seasonal pattern, and comparisons by month of the year revealed very large differences (Fig. 2 and Table S2; see Supporting Information). Both the highest daily and highest cumulative monthly vitD-UVB dose were consistently observed in the month of June and the lowest in December (2005–10): monthly vitD-UVB dose in June
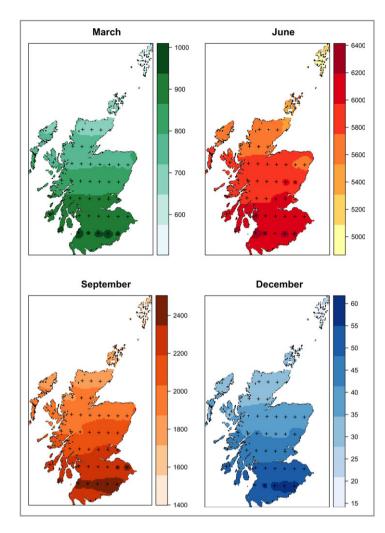
Fig 2. Average cumulative monthly ambient dose of ultraviolet B (UVB) radiation that can induce vitamin D synthesis (vitD-UVB; kJ m^{-2}) in Scotland for March, June, September and December. Colour gradient indicates regional variation in vitD-UVB dose in a given month using average monthly vitD-UVB (July 2005–October 2010). Note the very large differences in the scale between four selected months.

was approximately 100 times higher than in December. In the multivariate regression model, month remained very strongly associated with vitD-UVB dose (P < 0·01); for example, vitD-UVB in June was, on average, 5621 kJ m^{-2} higher than in January.

Association between vitamin D–ultraviolet B exposure and 25-hydroxyvitamin D in the Scottish Colorectal Cancer Study cohort

In total, 1964 healthy Scottish participants (843 women) aged 22–82 years were included in the study. The mean ± SD 25OHD was 14·14 ± 9·01 ng mL^{-1}. Peak concentrations and the highest proportion of sufficient samples were observed in August (Fig. S2a, b; see Supporting Information). In total, 510 (45% women) participants reported taking supplements; median ± SD dose was 5·00 ± 3·58 μg. For other characteristics of this population, see Zgaga *et al.*[15]

Mean ± SD CW-vitD-UVB in this cohort was 3894 ± 2745 kJ m^{-2} (median 3923 kJ m^{-2}, interquartile range 1217–6510). While ambient daily vitD-UVB radiation dose in Scotland is highest in June, CW-vitD-UVB estimate

peaks approximately 1–2 months later (Fig. S2c, d; see Supporting Information).

We observed a very strong association between plasma 25OHD and the CW-vitD-UVB exposure estimate, in both the unadjusted and adjusted analysis (P < 0·01; Table 1 and Fig. 3). CW-vitD-UVB was associated with an average 25OHD concentration increase of 1 ng mL^{-1} for every 1000 kJ m^{-2}. After adjustment for age, sex, BMI, socioeconomic class, level of physical activity, dietary vitD and supplements, the proportion of variance explained (PVE) by the CW-vitD-UVB exposure estimate was 10·9% in the whole cohort, 13·2% among those who do not take vitD supplements (n = 1455) and 6·1% among those who do take supplements (n = 510). Differences in 25OHD concentration according to the level of CW-vitD-UVB exposure were more pronounced in those who do not take supplements (Fig. S3a, b; see Supporting Information). Adequate vitD status (> 16 ng mL^{-1}, 'sufficient or at low risk of deficiency') was mostly achieved when CW-vitD-UVB was > 6000 kJ m^{-2} (a dose that is typically achieved only in summer months in Scotland) in individuals younger than 50 years of age (Fig. S3c, d; see Supporting Information).

Table 1 Multivariate linear regression models describing the personal characteristics relevant for the synthesis of vitamin D (vitD)

Model	n	Median (IQR) plasma 25OHD (ng mL^{-1})	Cumulative weighted vitD–UVB			Supplements (µg)			Dietary vitD (µg)			Genetic risk score (number of risk alleles)		
			PVE[a]	Beta coefficient (per 1000 kJ m^{-2})	P-value	PVE[a]	Beta coefficient	P-value	PVE[a]	Beta coefficient	P-value	PVE[a]	Beta coefficient	P-value
All cohort	1963	12·9 (7·8–19·0)	11·16	1·091	< 0·01	1·42	0·368	< 0·01	0·27	0·153	0·01	0·65	−0·864	< 0·01
Supplement taking														
Yes	510	15·0 (10·4–21·0)	6·89	0·815	< 0·01	0·32	0·142	0·20	0·033	−0·041	0·75	2·25	−1·561	< 0·01
No	1543	12·0 (7·0–18·0)	13·18	1·205	< 0·01	NA	NA	NA	0·49	0·252	< 0·01	0·33	−0·619	< 0·01
BMI < 25	726	13·0 (7·0–19·7)	9·04	0·730	< 0·01	2·1	0·450	< 0·01	0·27	0·165	0·17	1·56	−1·37	< 0·01
BMI ≥ 25	1237	12·5 (8·0–18·2)	12·56	1·102	< 0·01	1·19	0·336	< 0·01	0·23	0·139	0·13	0·28	−0·56	0·06
Age (years)														
< 50	246	14·8 (7·3–21·3)	22·01	0·993	< 0·01	0·03	0·078	0·79	0·05	−0·110	0·69	0·01	0·100	0·89
50–59	579	13·5 (8·1–20·9)	8·82	1·077	< 0·01	1·89	0·461	< 0·01	0·33	0·195	0·18	1·55	−1·511	< 0·01
60–69	579	13·0 (8·0–18·0)	9·51	1·096	< 0·01	1·31	0·309	< 0·01	0·48	0·161	0·15	1·04	−0·915	0·02
> 70	559	11·4 (7·0–17·0)	11·29	1·082	< 0·01	2·05	0·370	< 0·01	0·66	0·259	0·04	0·46	−0·675	0·12
Season[b]														
Winter	387	10·0 (5·0–14·0)	< 0·01	−0·175	0·84	4·69	0·618	< 0·01	0·03	0·070	0·70	0·83	−0·931	0·09
Spring	369	10·0 (6·0–16·0)	4·24	0·926	< 0·01	4·19	0·519	< 0·01	0·11	−0·097	0·49	0·04	0·177	0·72
Summer	621	16·0 (11·1–23·0)	4·38	1·851	< 0·01	0·47	0·250	0·09	0·86	0·292	0·04	0·41	−0·690	0·13
Autumn	586	13·0 (8·0–19·0)	3·13	0·701	< 0·01	0·99	0·280	0·01	0·48	0·187	0·13	1·98	−1·479	< 0·01
Male	1121	13 (8·0–19·0)	12·39	1·105	< 0·01	1·02	0·295	< 0·01	0·07	0·296	0·38	0·42	0·692	0·03
Female	842	12·9 (7·0–19·0)	9·77	1·115	< 0·01	1·95	0·472	< 0·01	0·95	0·306	0·01	0·92	−1·030	0·01
Physical activity level[c]														
1	1055	12·0 (7·0–17·05)	10·30	0·671	< 0·01	1·00	0·001	< 0·01	0·11	0·093	0·34	0·13	−0·395	0·25
2	533	13·3 (8·0–19·3)	12·40	0·796	< 0·01	2·10	0·457	< 0·01	1·34	0·409	< 0·01	2·40	−1·685	< 0·01
3	253	15·0 (9·7–21·0)	10·24	1·090	< 0·01	1·98	0·434	0·03	0·69	0·204	0·32	0·55	−0·895	0·26
4	122	15·0 (9·1–21·1)	16·45	0·842	< 0·01	0·84	0·249	0·28	0·29	−0·121	0·58	0·28	−0·562	0·56
Genetic risk score[d]														
0	527	13·7 (7·7–21·0)	12·00	0·827	< 0·01	4·38	0·687	< 0·01	0·36	0·189	0·21	NA	NA	NA
1 or 2	1021	12·7 (8·0–18·3)	10·30	0·893	< 0·01	0·54	0·208	0·01	0·29	0·145	0·09	NA	NA	NA
3 or 4	65	10·1 (70·0–17·2)	16·90	0·802	0·01	0·01	−0·076	0·91	0·01	−0·025	0·94	NA	NA	NA

Plasma 25-hydroxyvitamin D (25OHD) levels were associated with cumulative weighted vitD–ultraviolet B (UVB) exposure estimate, supplement use and dietary vitD, adjusting for age, sex, body mass index (BMI), socioeconomic class and level of physical activity. Percentage of variance explained was calculated by partitioning the sum of squares between predictors for covariates of interest. IQR, interquartile range; NA, not available. [a]Proportion of variance explained (PVE) by the exposure will depend on (i) strength of the association between exposure and the outcome, and also on (ii) the variation of the exposure in the population. Therefore, while causal relationships remain unchanged, varying exposure level in a population will strongly impact on the PVE by that exposure. Hence, it does not make sense to evaluate the contribution of exposures in absolute terms, but it can be a useful descriptive measure for relative comparisons in a population. [b]Seasons defined as December–February (winter), March–May (spring), June–August (summer) and September–November (autumn), respectively. [c]Level of physical activity (hours of running, cycling and other sports activities; four categories). [d]Genetic risk score was calculated as the number of risk alleles (associated with decreasing 25OHD) for two single nucleotide polymorphisms – rs12785878 and rs2282679.
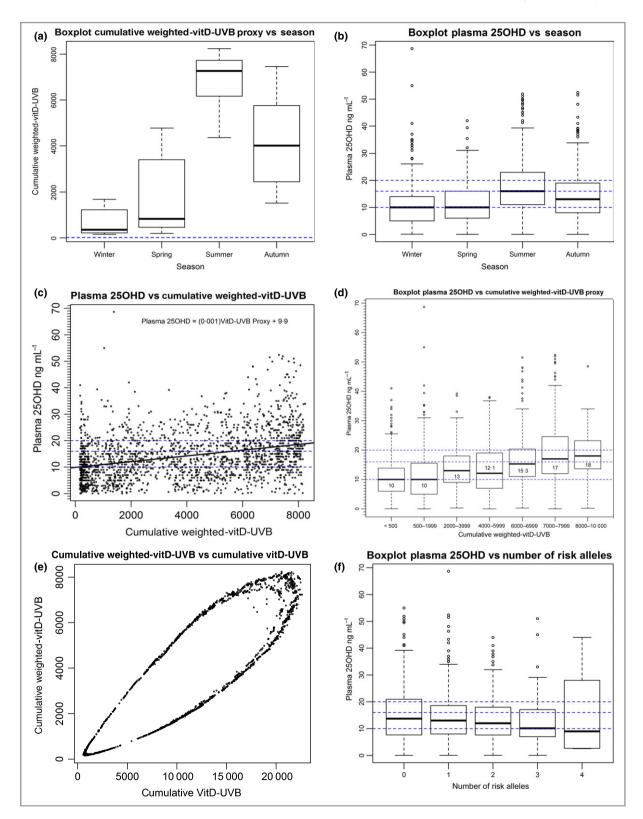
Fig 3. Relationships between season, cumulative and weighted dose of ultraviolet B (UVB) radiation that can induce vitamin D (vitD) synthesis (CW-vitD-UVB) and 25-hydroxyvitamin D (25OHD) are shown. (a) CW-vitD-UVB dose and season; (b) 25OHD concentration and season; (c) CW-vitD-UVB and 25OHD; (d) categories of CW-vitD-UVB exposure and 25OHD; (e) scatterplot of cumulative vitD-UVB vs. CW-vitD-UVB illustrates the impact of accounting for accumulation and diminution through weighing: for the same cumulative exposure, at times when UVB dose is increasing CW-vitD-UVB is going to be smaller than at times when UVB dose is increasing; (f) 25OHD concentration and number of risk alleles.

Not surprisingly, after stratification by the season of blood sample, in winter months we did not observe any association between UVB estimate and 25OHD. In contrast, the association between supplement use and plasma 25OHD was the strongest in winter ($P < 0.01$) and spring ($P < 0.01$), when skin synthesis is low, and explained 5·6% and 4·0% of the variance in 25OHD (only 0·6% in summer). VitD supplementation was associated with an average of 0·4 ng mL^{-1} greater plasma level for every 1 μg daily supplement. For every additional risk allele 25OHD concentration was, on average, 1 ng mL^{-1} lower ($P < 0.01$). Notably, vitD from dietary sources excluding supplements explained only a small proportion of the variance in plasma 25OHD (0·4%).

Stratification by age confirmed a particularly strong relationship between 25OHD and CW-vitD-UVB in those under the age of 50 years: average 25OHD levels were > 15 ng mL^{-1} higher in those with highest levels of CW-vitD-UVB exposure compared with those who had a CW-vitD-UVB < 1000 kJ m^{-2}. UVB exposure estimate explained 19% of variance in this group, while supplement use was not associated with 25OHD concentration.

Predictive ability of cumulative weighted vitamin D–ultraviolet B estimate for vitamin D deficiency

CW-vitD-UVB exposure estimate was found to make a large contribution to predicting vitD deficiency (Fig. 4). The final model (model 6) included CW-vitD-UVB exposure estimate and age, sex, BMI, number of risk alleles, socioeconomic class, level of physical activity, dietary vitD and supplements use. When evaluated in the validation dataset, improved AUC was observed for models that included CW-vitD-UVB exposure estimate, particularly for predicting severe deficiency: for a cut-off at 10 ng mL^{-1}, AUC was 0·70 (improved from 0·55); for a deficiency cut-off at 16 ng mL^{-1} AUC was 0·69 (improved from 0·60); and for a cut-off at 20 ng mL^{-1}, AUC was 0·70 (improved from 0·64). The variables with the largest determined importance in the final model are CW-vitD-UVB, supplement use and age (Fig. S4; see Supporting Information).

Discussion

We set out to examine the relationship between the dose of UVB relevant for vitD production at the place of residence and vitD status, and to determine if this exposure can be used to predict vitD status. The UVB radiation relevant for vitD production is determined daily for Europe and is readily available through TEMIS. In addition to much greater geotemporal resolution, these data offer a further improvement over UVB estimates used previously: measured daily dose of solar radiation is considered, rather than an approximation of it; wavelengths relevant for vitD production only are extracted, and adjustments are made for terrain elevation, local ozone column and
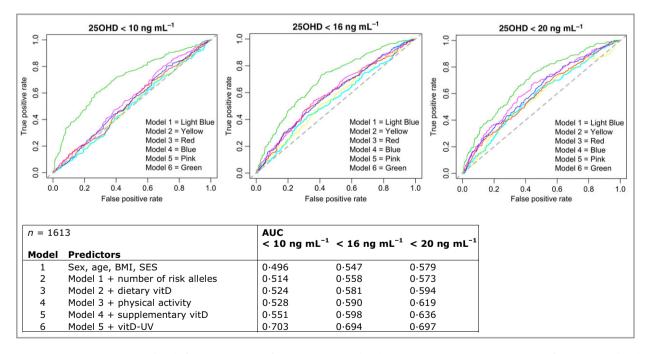

n = 1613	AUC		
Model **Predictors**	**< 10 ng mL^{-1}**	**< 16 ng mL^{-1}**	**< 20 ng mL^{-1}**
1 Sex, age, BMI, SES	0·496	0·547	0·579
2 Model 1 + number of risk alleles	0·514	0·558	0·573
3 Model 2 + dietary vitD	0·524	0·581	0·594
4 Model 3 + physical activity	0·528	0·590	0·619
5 Model 4 + supplementary vitD	0·551	0·598	0·636
6 Model 5 + vitD-UV	0·703	0·694	0·697

Fig 4. Receiver operator curves (ROC) for the prediction of plasma vitamin D (vitD) with cumulative and weighted dose of ultraviolet B (UVB) radiation that can induce vitamin D (vitD) synthesis (CW-vitD-UVB) exposure estimate using random forest method. Six models were fitted to predict plasma 25-hydroxyvitamin D (25OHD) with < 10 ng mL^{-1}, 16 ng mL^{-1} and 25 ng mL^{-1}; the predictors and area under the curve (AUC) results are listed. In total, 667 (34·0%) participants were severely deficient (25OHD < 10 ng mL^{-1}), 583 (29·7%) were at high risk of deficiency (25OHD 10–16 ng mL^{-1}) and 311 (15·8%) at low risk of deficiency (16–20 ng mL^{-1}); only 403 (20·5%) were vitD sufficient (25OHD > 20 ng mL^{-1}). BMI, body mass index; SES, socioeconomic status.

cloudiness.[18] Earlier estimates have been based on surveys of hours of sunshine,[7] full UV spectrum expressed as the erythemal dose, measured at a single geographic location or a small number of locations,[2,3] or fixed ozone and cloud cover.[23]

As a result of the gradual accumulation of vitD during summer months and gradual diminution of reserves in the months when solar radiation is low, a 'lag of seasons' is observed for 25OHD concentration. We found that in Scotland peak vitD-UVB occurs in June, while peak 25OHD occurs 1–2 months later, as has been observed previously.[24] We developed a simple method to calculate exposure for each individual: a cumulative and weighted ambient UVB exposure that accounts for gradual accumulation and diminution and allows estimation of vitD status at a particular point in time (for example, date of blood sample).

We showed a very strong association between measured 25OHD concentration and cumulative and weighted ambient UVB exposure at the place of residence, at wavelengths relevant for vitD production (CW-vitD-UVB). Although predictive ability of the final model with all relevant covariates was not complete, a dramatic improvement in the AUC was observed after addition of CW-vitD-UVB estimate. This suggests that ambient UVB is major determinant of vitD deficiency, even in a high-latitude region.[25,26] The association is particularly strong in summer and autumn (when UVB dose is high) and in individuals younger than 50 years of age, which is consistent with previous research.[27]

We observed significant regional variations in vitD-UVB exposure within Scotland, controlling for temporal and seasonal differences. This highlights that variation exists even in a relatively small northerly country without great differences in latitude as a result of local conditions, accentuating that precise local measurements should be favoured over crude macroestimates of UVB exposure. The regional variation in vitD-UVB within a small area has not been previously reported. During the summer months there was a high daily variability in CW-vitD-UVB between the different postcodes within Scotland, which decreased dramatically as level of UVB fell during the rest of the year. This suggests that geographical differences are likely to be even greater in lower latitude regions where UVB exposures are overall higher.

Many studies have previously shown a positive relationship between supplementation and circulating vitD levels.[28] In this study, the association with 25OHD levels was the strongest in winter and spring (when UVB dose is very low or following months of diminution), and this finding emphasizes the role of vitD supplementation in winter months. Interestingly, supplementation was not associated with vitD status in younger participants (aged < 50 years). Dietary intake had a minimal effect on vitD status, which was expected because it is now widely accepted that food sources of vitD are scarce.[15,29] The relationship between genetic factors and 25OHD was similar to what has been reported previously.[16]

It is important to emphasize that the proportion of variance explained is not a measure of the effect.[30] PVE is strongly determined by the variation of the exposure in the population:

in a population living an outdoor-oriented lifestyle and residing in a region where sunshine UVB is abundant, the majority of variation in 25OHD may be due to genetic factors or skin tone, and not UVB (because it is uniformly abundant). However, UVB radiation would still be the primary cause of vitD production. We found that UVB explained 11% of variance in 25OHD in this population overall, but it explained almost no variation in 25OHD in winter. It is reasonable to assume that the proportion of variance explained by UVB could be greater in regions where the annual oscillations in UVB radiation dose are greater.

With the exception of a few studies, accurate individual measures of ambient UVB have been largely underexploited in research. We suggest that the routinely collected data on UVB exposure can be used to approximate vitD status when 25OHD levels are not measured or a blood sample is not available. Existing past UVB dose recordings allow investigation of the relationship between UVB estimate as a proxy of vitD and outcomes retrospectively in existing cohorts at virtually no cost. Alternatively, UVB exposure data can be used to adjust 25OHD measurement for date of sampling, or they can be used in conjunction with 25OHD to predict the average yearly 25OHD of each individual.[31] Furthermore, randomized control trials (RCTs) on the effects of vitD intakes on health outcomes can suffer from confounding by high exposure to naturally occurring vitD-UVB. Skin-synthesized vitD can dominate 25OHD concentration and mask any impact of vitD supplementation on circulating level and/or study outcomes. We suggest that ambient UVB should be added as a covariate in the analysis; analogously, ignoring 'personal' vitD supplement use among participants in vitD RCTs has been shown previously to affect the findings.[32] Finally, UVB exposure can be used as an instrument for instrumental variable analysis and provide some insights into causality.[2,33]

The principal major strength of this study is the use of an all-encompassing UVB estimate from daily satellite measurements, restricted to wavelengths relevant for vitD production, and adjusted for regional terrain and atmospheric conditions (cloudiness and ozone).[34,35] To our knowledge, this study used the highest geographical resolution of the exposure to date with respect to the place of residence, and was the first study that correlated accurate individualized ambient vitD-UVB exposure and 25OHD levels. The study comprised a large number of participants that are homogeneous regarding skin type (all participants were white and of Scottish descent).

Information on personal characteristics and behaviours were largely unknown in this cohort, for example 'sun holidays' or sunscreen use, or time spent outside. However, sunlight exposure questionnaires were shown to provide poor estimates of vitD status.[7,9] The additional benefit of adjusting the vitD-UVB estimate for these factors is currently unknown. However, this means that the vitD-UVB exposure used here is not confounded by personal behaviours. Because of the narrow range of both UVB dose (high latitude) and supplements (conservative intake recommendations)[36,37] at low doses, we were not able to examine these exposures at higher levels. As observed

vitD-UVB data have only been available since July 2005, daily UVB dose had to be estimated for each day of the year from the available data. As a consequence, the random measurement error in our UVB estimate could bias our results towards the null (i.e. attenuate effect size)[38] and more accurate measurements are likely to yield even stronger associations and better predictors in the future.

There is a significant seasonal and geographical variation in ambient vitD-UVB exposures in Scotland, despite it being a relatively small country with no large differences in latitude. The cumulative and weighted ambient vitD-UVB exposure estimate was a good predictor of vitD status. The TEMIS database of ambient VitD-UVB exposures can be useful for epidemiological research aimed at examining relationships between UVB/vitD and health outcomes.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Schematic illustration of the difference between cumulative and cumulative and weighted exposure estimates.

Figure S2. Plasma 25-hydroxyvitamin D according to month of sampling in the Scottish Colorectal Cancer Study cohort; proportion of subjects that are vitamin D sufficient or at low risk of deficiency; average daily ultraviolet B (UVB) dose; and individual cumulative and weighted ambient vitamin D–UVB estimate.

Figure S3. Plasma 25-hydroxyvitamin D in relation to cumulative and weighted vitamin D–ultraviolet B stratification for supplement use.

Figure S4. Variable importance plot for random forest model predicting 25-hydroxyvitamin D.

Table S1. Number of participants sampled in each calendar month.

Table S2. Cumulative monthly ambient ultraviolet B (UVB) dose at wavelengths that can induce vitamin D synthesis (vitD-UVB), for selected regions in Scotland (averaged over 2005–10).

Table S3. Association between monthly ambient ultraviolet B (UVB) dose at wavelengths that can induce vitamin D synthesis (vitD-UVB) and region, month and year of measurement.

Appendix S1. Calculation of ambient ultraviolet B exposure per individual, using Tropospheric Emission Monitoring Internet Service data.