Influence of external, intrinsic and individual behaviour variables on serum 25(OH)D in a German survey

Katja Richter [a,*], Susanne Breitner [a], Ann R. Webb [b], Cornelia Huth [a,c], Barbara Thorand [a], Richard Kift [b], Jakob Linseisen [a], Angela Schuh [d], Jürgen Kratzsch [e], Andreas Mielck [f], Stephan Weidinger [g], Annette Peters [a], Alexandra Schneider [a], KORA Study Group [1]

[a] *Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany*
[b] *School of Earth Atmospheric and Environmental Sciences, University of Manchester, Manchester, UK*
[c] *German Center for Diabetes Research (DZD), Neuherberg, Germany*
[d] *Public Health and Health Services Research, Ludwig-Maximilians-Universität München, Germany*
[e] *Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Leipzig, Germany*
[f] *Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, Neuherberg, Germany*
[g] *Department of Dermatology, Allergology, and Venereology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany*

1. Introduction

Vitamin D belongs to a group of hormones involved in calcium metabolism and bone mineralization. The principal source of vitamin D is from cutaneous synthesis after exposure to solar ultraviolet radiation (UVB), with smaller contributions coming from diet and supplementation. The best indicator of vitamin D status is considered to be the concentration of serum 25-hydroxyvitamin D (25(OH)D) in the blood [1–5].

Vitamin D is fat soluble and any excess can be stored for use when needed such as when ambient levels of UV are too low for cutaneous synthesis, as occurs from late autumn to early spring in middle and higher latitudes. This seasonal variation in UVB leads to an annual cycle in 25(OH)D concentrations with the maximum occurring in late summer and a corresponding minimum at the end of the winter. If optimal 25(OH)D concentrations are obtained during the summer months then long-term insufficiency (i.e. $\leqslant$50 nmol L^{-1}) or even hypovitaminosis D, defined here as 25(OH)D concentrations below 25 nmol L^{-1} [6–9] could be avoided [5]. This is important since vitamin D insufficiency has been implicated in a number of chronic diseases, such as cancer, osteoporosis, diabetes, various autoimmune disorders and incident cardiovascular disease events [10–12].

* Corresponding author.
E-mail address: katja.richter@helmholtz-muenchen.de (K. Richter).

[1] The KORA-Study Group consists of A. Peters (speaker), J. Heinrich, R. Holle, R. Leidl, C. Meisinger, K. Strauch, and their co-workers, who are responsible for the design and conduct of the KORA studies.

There are a variety of factors that influence personal cutaneous vitamin D synthesis, and these can be grouped into three categories: (i) external, (ii) intrinsic and (iii) behavioural [5]. Among the external factors, solar geometry (e.g. solar zenith angle, season), location (e.g. latitude, altitude, exposure geometry, local albedo, etc.) and atmospheric conditions (cloud coverage, ozone, etc.) affect the ambient UV level. Intrinsic attributes that may influence vitamin D synthesis include gender, age, health, skin type (i.e. pigmentation) and body weight. Personal behaviour that can influence the serum 25(OH)D concentration comprises times spent outdoors, use of sun protection, clothes, holiday destinations, diet, and vitamin D supplementation. Variations in personal behaviour can result in very large differences in UVB exposure, and hence cutaneous vitamin D synthesis [13], but despite their importance these factors are the most difficult to quantify and require further research.

Vitamin D insufficiency has been shown to be prevalent in many countries [7,14–16], including Germany which has levels of insufficiency of between 40% and 45% [17–19]. Causal factors for insufficiency have been investigated in a range of studies in different countries e.g. sun exposure [20,21], age, body mass index (BMI) [22,23], gender [23,24], pigmentation [25], latitude [24], season [22] and use of sun protection such as sunscreens [26].

There have been very few studies which directly examined potential causes of the widespread vitamin D insufficiency in the German population [14,18,19,27], and these have had little or no investigation of personal behaviour and its effect on vitamin D. Therefore, the objective of the present study was to use a population-based dataset to identify which external, intrinsic or behavioural variables had the greatest influence on the serum 25(OH)D concentrations of the population.

2. Materials and methods

2.1. Data description

All analyses used data from the Cooperative Health Research in the Region of Augsburg (KORA) F4 survey (conducted from October 2006 to May 2008 with $N = 3080$ participants between 32 and 81 years old [28,29]), a follow-up of the population-based representative KORA S4 survey (conducted from October 1999 to April 2001 with 4261 participants [30]). All participants in the surveys had German nationality and lived in the city of Augsburg (Bavaria, Southern Germany) or in the two adjacent counties. The demographic and socioeconomic characteristics of this mixed urban and rural area can be considered as representative of the mature average central European population [28] as the KORA F4 survey did not include people younger than 32 years.

Serum 25(OH)D concentration was measured once in samples of from 3061 of the KORA F4 participants. For the quantitative determination of 25-hydroxyvitamin D, LIAISON 25 OH Vitamin D TOTAL Assay was applied using chemiluminescent immunoassay (CLIA) technology (DiaSorin Inc., Stillwater, USA) traceable to company standard [31]. The inter-assay coefficients of variation (CV) were 8.7% and 9.1% for target values of 37 nmol L^{-1} and 119 nmol L^{-1}, respectively."

For statistical analysis a set of variables was defined with each having a standard set of answers. In the table of Appendix 1 all these variables (i.e. questions or measurements) and categories (i.e. possible answers) that were selected from the KORA F4 database or transformed for the current study are listed.

To study the annual variation of serum 25(OH)D concentrations the variable "season" was used and 25(OH)D samples were grouped according to the meteorological season in which they were taken: winter (December to February), spring (March to May), summer (June to August) or autumn (September to November). As well as season, another external-ambient variable used was residence, i.e. where people were living: either in the city of Augsburg, Bavaria (=urban) or in small adjacent communities, such as Eurasburg or very small cities, such as Gersthofen, close to Augsburg (=rural). Body mass index (BMI) was chosen according to WHO criteria [32]. Pigmentation was based on the Fitzpatrick skin classification [33], but only five from six types were present (there were no participants of skin type VI). The question of health state was general and not based on certain criteria. Socioeconomic status (SES) was assessed by an index often used in German studies, combining educational achievement, occupational status and household income [34]. Finally, specific questions about individual behaviour related to UV exposure were asked (see Appendix 1).

Unfortunately serum 25(OH)D concentrations were not measured during the KORA S4. However, some changes in behaviour (e.g. related to UV exposure) between the surveys could be evaluated. Therefore, variables that were also obtained in S4 are marked with a star (*) in the table of Appendix 1.

2.2. Statistical methods

The basic statistics were derived and ANOVA methods used to determine whether differences between means were significant.

In order to evaluate vitamin D deficiency, a logistic regression was applied to the variables. Serum 25(OH)D concentration was transformed into a binary variable: with the threshold of 25 nmol L^{-1} [6–9] quasi corresponding to the 25% quartile (Q1, at 23.11 nmol L^{-1}) of the dataset being chosen to define vitamin D deficiency versus non-deficiency. In the model, age, holiday weeks, h outdoors summer and h outdoors winter were treated as metric variables and all others as categorical variables. Stepwise option was applied to select which variables significantly correlated to serum 25(OH)D concentrations. The result was then tested with forward and backward selection options.

All statistical analyses were performed using the Statistical Analysis System (SAS) software version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Seasonal 25(OH)D

In the following section the mean 25(OH)D values were obtained for each of the defined seasons as cutaneous synthesis of vitamin D is very dependent on the available UVB, which in turn depends upon the season of the year. Therefore, in Fig. 1 the participants' serum 25(OH)D concentration are described at first for each season of blood samples and for each month.

Seasonal 25(OH)D concentrations (Fig. 1, left) showed the expected pattern: the highest median value of 47.4 nmol L^{-1} value was reached in summer, followed by autumn with 38.9 nmol L^{-1} and spring with 31.2 nmol L^{-1}. The lowest values were found in winter with a median of 28.2 nmol L^{-1}. The 25% – quartile (Q1) and 75% – quartile (Q3) followed the same pattern. There are only about half as many summer season samples as in the other seasons. Regarding the monthly distribution (Fig. 1, right), the highest mean value was reached in September, closely followed by August. Seasonal statistics are further presented in Table 2.

3.2. 25(OH) D classifications

Serum 25(OH)D values of the F4 participants were assigned to one of five classifications, commonly used, for instance by Joshi et al. [6]. The threshold for optimal 25(OH)D concentration of >75 nmol L^{-1} has been discussed by Vieth [35]. The definition of insufficiency (<50 nmol L^{-1}) was taken from Malabanan et al.

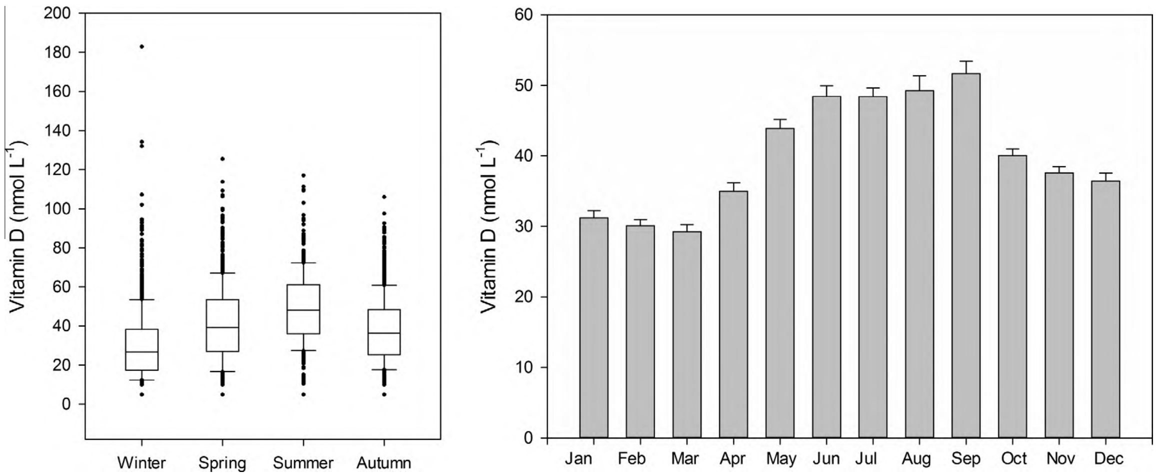

Fig. 1. 25(OH)D concentrations of the selected F4 participants depending on the season of blood withdrawal (1 – December to February, 2 – March to May, 3 – June to August, 4 – September to November). Box plots are drawn in the standard way: size of box characterizes the interquartile range (IQR, i.e. Q3–Q1 or 75th–25th percentiles), horizontal line within the box represents the median, whiskers correspond to 1.5 × IQR and outliers are signed with "*" (left). 25(OH)D concentrations per month with standard error of the mean (right).

[36,37]. The limit of 25 nmol L^{-1} for deficiency was firstly defined by Parfitt et al. [8] and the threshold of severe deficiency (<15 nmol L^{-1}) was used by Lee et al. [38].

An overview of the results is given in Table 1, where mean serum 25(OH)D values for the whole survey are presented alongside the results split into the four seasons.

Looking at the whole survey over the study period about half the individuals sampled were in class 3 meaning they were 25(OH)D insufficient, with only a few (∼4%) reaching optimal serum 25(OH)D concentrations in class 5 (Table 1).

In every season most of participants were 25(OH)D insufficient (class 3) with the highest proportion in this class occurring in autumn. The proportion of participants with sufficient serum 25(OH)D concentrations (class 4) increased from 13% in winter to 38% in summer samples, whilst the number of deficient participants (class 1) decreased from 14% of winter to only 2% of the summer blood samples.

3.3. Mean serum 25-hydroxyvitamin D for study variables

3.3.1. External – ambient

Generally, differences in serum 25(OH)D concentrations between participants living in urban and rural regions were small (Table 2) but statistically significant (i.e., $p < 0.05$) for 25(OH)D measured in summer, autumn and for the whole year. Participants living in Augsburg had slightly lower mean serum 25(OH)D concentrations than people living in rural regions. Maximum (mean) serum 25(OH)D value was reached by rural residents in the summer season (∼51 nmol L^{-1}), and the minimum value was obtained by urban residents in winter (∼31 nmol L^{-1}).

Serum 25(OH)D concentration over the seasons have been discussed above

3.3.2. Intrinsic – personal

An overview of serum 25(OH)D concentrations with respect to intrinsic – personal variables is given in Table 3, including different age classes, male and female participants, BMI classes, Fitzpatrick skin types, general health state and socioeconomic status per season.

25(OH)D concentrations show a decrease with age, although a substantial decrease in all seasons is only observed for the highest age group. The highest mean value (∼51 nmol L^{-1}) was reached by age class I (32–44 years) in summer and lowest by age class IV (75–81 years) in winter (∼28 nmol L^{-1}). Differences in serum 25(OH)D concentrations between the age classes were statistically significant for 25(OH)D measured during summer, autumn and the whole year ($p < 0.05$).

The mean 25(OH)D of the female participants was slightly lower than for the male participants throughout the year. The highest 25(OH)D concentration was reached by male (∼51 nmol L^{-1}) and female (∼46 nmol L^{-1}) participants in the summer season and the lowest by both male and female participants in winter (∼32 nmol L^{-1}). Gender-related differences in 25(OH)D concentrations were only significant for summer and the whole year ($p < 0.05$).

25(OH)D values decreased significantly ($p \leqslant 0.01$) with increasing BMI in all seasons over the whole year. The highest mean serum 25(OH)D value (∼53 nmol L^{-1}) was reached in summer in BMI class I and the lowest value (∼27 nmol L^{-1}) was reached in winter in BMI class III.

The mean serum 25(OH)D values were also determined for the skin types based on the Fitzpatrick classification [33]. The skin types ranged from very fair (type I) to very dark (type VI), depending on the skin's concentrations of melanin and reaction to sunlight [39]. Interestingly, mean serum 25(OH)D increased significantly

Table 1
Vitamin D classes defined by 25(OH)D concentration thresholds [6], 25(OH)D mean values over all seasons and standard deviation (SD), total number (*N*) of participants and number of participants per season (and in percent of each season) of blood samples (*N* = 3061) for each vitamin D class from the F4 measurements.

Class	Vitamin D status	Threshold (nmol L^{-1})	Mean (SD) (nmol L^{-1})	*N*	Winter	Spring	Summer	Autumn
1	Severe deficiency	<15	11.3 (0.7)	294	128 (14%)	117 (13%)	9 (2%)	40 (5%)
2	Deficiency	15–<25	20.4 (0.7)	614	274 (29%)	185 (21%)	26 (6%)	129 (16%)
3	Insufficiency	25–<50	37.0 (1.7)	1427	394 (42%)	401 (46%)	194 (47%)	438 (53%)
4	Sufficiency	50–<75	59.5 (0.6)	600	124 (13%)	134 (15%)	159 (38%)	183 (22%)
5	Optimum	⩾75	89.2 (2.8)	126	23 (2%)	37 (4%)	28 (7%)	38 (5%)

Table 2
External-ambient factors: mean (and standard deviation, SD) values of serum 25(OH)D concentrations in ($nmol\ L^{-1}$) for season and residence (urban/rural) for the whole year (mean of seasons) and per season.

Variables	All Mean (SD) ($nmol\ L^{-1}$)	*N*	Winter Mean (SD) ($nmol\ L^{-1}$)	*N*	Spring Mean (SD) ($nmol\ L^{-1}$)	*N*	Summer Mean (SD) ($nmol\ L^{-1}$)	*N*	Autumn Mean (SD) ($nmol\ L^{-1}$)	*N*
Season	39.1 (7.3)	3061	32.0 (17.7)	943	35.2 (20.3)	874	48.5 (17.6)	416	40.8 (18.1)	828
Residence										
Urban	37.4 (5.9)	1377	30.9 (17.7)	447	34.9 (19.9)	360	44.7 (17.6)	158	39.3 (17.9)	412
Rural	40.4 (8.0)	1684	32.9 (17.7)	496	35.4 (20.6)	514	**50.9**[a](17.3)	258	42.3(18.1)	416

[a] Values above the threshold of sufficient levels (i.e., class 4–5 with ⩾50 $nmol\ L^{-1}$) are indicated in bold.

Table 3
Intrinsic-personal factors: mean (and standard deviation, SD) values of serum 25(OH)D concentrations in ($nmol\ L^{-1}$) for age classes, gender, BMI classes, Fitzpatrick skin types (Fitz), general health state (Health) and socioeconomic status (SES) for the whole year (mean of seasons) and per season.

Variables	All Mean (SD) ($nmol\ L^{-1}$)	*N*	Winter Mean (SD) ($nmol\ L^{-1}$)	*N*	Spring Mean (SD) ($nmol\ L^{-1}$)	*N*	Summer Mean (SD) ($nmol\ L^{-1}$)	*N*	Autumn Mean(SD) ($nmol\ L^{-1}$])	*N*
Age										
I	40.4 (8.4)	775	31.5 (18.6)	220	36.8 (20.6)	268	**50.9**[a] (18.0)	92	42.4 (20.2)	195
II	39.5 (7.6)	1331	32.7 (17.5)	437	34.6 (20.2)	354	49.6 (18.0)	175	41.1 (17.0)	365
III	39.5 (7.5)	654	32.6 (17.1)	207	35.0 (20.7)	171	49.5 (17.5)	97	41.1 (18.0)	179
IV	33.8 (4.8)	301	27.7 (17.8)	79	32.9 (19.6)	81	39.1 (13.1)	52	35.4 (16.8)	89
Gender										
Male	40.1 (8.2)	1479	32.4 (16.9)	466	35.4 (20.4)	421	**51.0** (18.7)	203	41.8 (18.1)	389
Female	38.2 (6.4)	1582	31.6 (18.5)	477	35.0 (20.3)	453	46.2 (16.3)	213	39.9 (18.1)	439
BMI										
I	42.3 (8.4)	964	34.7 (18.3)	272	36.7 (22.6)	271	**53.2** (18.5)	134	44.6 (19.2)	287
II	39.9 (6.8)	1274	33.4 (17.8)	401	36.3 (19.8)	374	48.8 (17.0)	171	41.1 (17.2)	328
III	34.1 (6.4)	808	27.2 (15.8)	263	31.7 (17.9)	227	42.4 (15.9)	108	35.2 (16.4)	210
Fitz										
I	33.5 (7.7)	118	*24.2* (17.4)	27	30.4 (18.6)	37	41.5 (17.3)	33	37.9 (20.8)	21
II	38.0 (8.2)	1435	30.3 (17.0)	446	33.6 (19.7)	379	48.9 (17.3)	206	39.3 (16.9)	404
III	41.2 (6.8)	1369	34.1 (18.2)	437	38.1 (20.8)	388	**50.0** (17.7)	161	42.7 (19.2)	383
IV	46.0 (13.3)	25	37.8 (20.7)	11	42.3 (31.9)	9	**65.8** (1.9)	2	38.2 (23.4)	3
V	25.1 (20.1)	3	–	–	*10.7*[b] (–)	1	–	–	39.6 (1.9)	2
Health										
I	43.9 (12.9)	75	27.9 (14.3)	22	40.1 (19.7)	24	**57.8** (21.9)	10	49.9 (22.4)	19
II	42.8 (9.8)	607	35.6 (19.5)	185	34.3 (18.1)	169	**55.2** (16.9)	85	46.0 (19.6)	168
III	38.7 (6.7)	1890	31.8 (17.3)	580	35.8 (21.1)	533	47.6 (16.3)	261	39.8 (17.3)	516
IV	35.7 (5.9)	432	28.6 (16.8)	141	34.8 (20.3)	128	43.0 (20.7)	54	36.5 (16.5)	109
V	30.1 (6.7)	42	28.9 (19.6)	8	*23.1* (13.0)	16	29.1 (13.3)	4	39.3 (21.1)	14
SES										
I	35.8 (7.5)	673	27.8 (15.6)	193	31.3 (17.2)	210	43.7 (17.7)	97	40.4 (18.9)	173
II	39.3 (8.1)	597	31.5 (17.2)	181	36.2 (20.8)	190	**50.5** (15.8)	76	39.0 (17.2)	150
III	40.4 (7.3)	701	33.3 (17.9)	229	38.8 (21.0)	192	**50.6** (20.4)	84	39.0 (17.0)	196
IV	40.7 (7.7)	592	34.9 (19.5)	182	34.3 (20.0)	152	**50.7** (18.3)	79	42.8 (18.0)	179
V	39.7 (7.1)	490	32.2 (17.8)	155	35.6 (22.9)	129	48.0 (14.7)	78	43.1 (19.4)	128

[a] Values above the threshold of sufficient levels (i.e., class 4–5 with ⩾50 $nmol\ L^{-1}$) are indicated in bold.
[b] Values below the deficiency level (i.e., class 1–2 with <25 $nmol\ L^{-1}$) are marked in italic.

($p < 0.05$) from skin type I to skin type III for blood samples from all seasons. This trend continued into skin types IV and V, but due to the small sample size this has to be interpreted with care. The lowest mean values occurred in the winter season for skin type I (24 $nmol\ L^{-1}$) and the highest values for skin type III and IV (~50 and 66 $nmol\ L^{-1}$) in summer.

In terms of the self-assessed state of health question, lowest mean values were reached in the "bad" health state (V) with ~23 $nmol\ L^{-1}$ in spring. The highest values (~58 and 55 $nmol\ L^{-1}$) were seen in the summer season for the "great" (I) and "very good" (II) health states. The differences in serum 25(OH)D concentrations were significant ($p < 0.05$) between these classes for the whole year and all seasons except for spring.

Differences in 25(OH)D concentrations between the different SES were small but statistically significant ($p < 0.05$) in all seasons (except winter) and for the whole year. We saw that 25(OH)D concentrations increased from status I to status IV (except for spring) with changes between status IV and V showing no preferential trend. However, winter does not show a consistent increase with status. The lowest value can be found in status I (~28 $nmol\ L^{-1}$) in winter and highest in status II–IV (~51 $nmol\ L^{-1}$) in summer.

3.3.3. Individual behaviour

As part of study participants were questioned about their sun exposure and protection routines. In Table 4 the mean serum concentrations of participants using or not using sunscreen products, of weeks per year spent in a sunny region, of participants who have spent (or have not spent) some time in a sunny location during the six weeks before the blood samples, who have taken (or not taken) vitamin D supplements in form of pills or cod liver oil during the six weeks before the blood samples as well as hours per day spent outdoors in summer or winter, respectively, are presented (see Appendix 1 for explanations of the classes).

Participants who never used sunscreen exhibited significantly ($p < 0.005$) lower 25(OH)D values than users of sunscreen. Highest mean serum 25(OH)D were found in sunscreen users in summer

Table 4
Individual behaviour: mean (and standard deviation, SD) values of serum 25(OH)D in (nmol L^{-1}) for using or not using sunscreen products (UPF), of weeks per year spent in a sunny region (holiday weeks), of times spent – or not – in a sunny location during the six weeks before the blood samples (recent holiday), of vitamin D supplements intake (or not) in form of pills or cod liver oil during the six weeks before the blood samples (vitamin) and of hours per day spent outdoors in summer (h outdoors summer) or winter (h outdoors winter), respectively, for the whole year (mean of seasons) and per season.

Variables	All Mean (SD)	*N*	Winter Mean (SD)	*N*	Spring Mean (SD)	*N*	Summer Mean (SD)	*N*	Autumn Mean (SD)	*N*
UPF										
Yes	41.3 (7.8)	1913	33.6 (18.1)	561	37.4 (20.2)	565	**51.6**[a] (17.6)	253	42.6 (18.1)	534
No	35.5 (6.5)	1143	29.5 (16.9)	380	31.3 (20.0)	307	43.7 (16.7)	163	37.6 (17.8)	293
Holiday weeks										
I	34.7 (7.5)	1192	27.1 (16.2)	344	30.8 (21.0)	346	44.3 (17.3)	176	36.5 (16.9)	326
II	41.5 (7.5)	1732	34.1 (17.7)	551	37.6 (19.1)	497	**51.2** (17.4)	218	43.1 (18.1)	466
III	48.5 (7.1)	87	42.1 (20.1)	33	43.6 (24.6)	21	**57.6** (17.9)	14	**50.6** (18.8)	19
IV	48.6 (3.3)	50	43.9 (15.9)	15	**50.8** (15.4)	10	**51.0** (12.9)	8	48.7 (23.5)	17
Recent holiday										
Yes	49.0 (7.0)	379	40.7 (15.6)	71	46.2 (22.7)	100	**56.6** (18.9)	73	**52.5** (19.7)	135
No	37.6 (6.8)	2677	31.2 (17.7)	870	33.8 (19.6)	772	46.8 (16.9)	343	38.5 (16.8)	692
Vitamin										
Yes	47.5 (2.8)	116	43.8 (35.9)	34	48.1 (32.3)	31	**50.7** (14.8)	17	47.5 (16.2)	34
No	38.9 (7.5)	2905	31.5 (17.2)	899	34.9 (19.6)	836	48.6 (17.8)	392	40.5 (18.2)	778
h outdoors summer										
I	35.5 (5.8)	839	29.0 (17.6)	238	33.5 (21.8)	257	42.6 (17.6)	124	37.4 (18.0)	220
II	39.3 (7.4)	1501	32.6 (17.9)	471	34.8 (19.3)	419	49.2 (16.5)	193	40.5 (17.4)	418
III	42.3 (8.2)	553	33.5 (18.1)	176	38.0 (20.9)	151	**52.1** (16.4)	74	45.5 (18.7)	152
IV	45.4 (12.1)	168	34.3 (14.0)	58	39.4 (18.3)	47	**62.2** (19.8)	25	45.5 (19.3)	38
h outdoors winter										
I	38.2 (6.5)	6	30.7 (–)	1	42.2 (41.4)	4	–	0	41.6 (7.8)	1
II	37.9 (6.7)	2325	31.4 (17.9)	704	34.4 (20.1)	669	46.6 (17.2)	317	39.4 (17.7)	635
III	43.0 (8.9)	709	33.8 (17.3)	228	38.4 (20.4)	196	**54.2** (17.7)	97	45.6 (18.8)	188
IV	43.1 (20.8)	12	30.0 (14.4)	6	34.9 (7.4)	2	**74.1** (6.0)	2	33.3 (19.9)	2

[a] Values above the threshold of sufficient levels (i.e., class 4–5 with ⩾50 nmol L^{-1}) are indicated in bold.

season with ~52 nmol L^{-1}. The lowest value, however, was obtained by non-users in the winter season (~30 nmol L^{-1}).

In terms of weeks per year spent in a sunny region, a significant trend of increasing 25(OH)D concentrations for increasing number of weeks spent in sunny regions was found. The overall highest value (~58 nmol L^{-1}) was measured during summer in participants who spent up to 10 weeks per year in a sunny country (III). The lowest value (~27 nmol L^{-1}) was measured during winter in an individual who did not spend any week in sunny regions (I).

The mean 25(OH)D values of participants who had spent some time in a sunny region during the six weeks before the blood samples showed significantly higher 25(OH)D values ($p < 0.0001$) compared to the other participants in all seasons. The highest value (~57 nmol L^{-1}) was obtained in summer, and the lowest in winter (~31 nmol L^{-1}).

The mean of the group who took vitamin supplements was always higher than that of the group without supplements. The difference was highly significant ($p < 0.001$) in all but the summer and autumn months. Highest values were reached by the supplemented group in summer (~51 nmol L^{-1}) and lowest for participants who did not take any vitamin D in winter (~32 nmol L^{-1}).

Generally, 25(OH)D concentrations increased from 0–2 h (I) to >8 h (IV) spent outside in summer. During winter the hours spent outside had less effect, despite the surprising fact that of the total survey very few participants were staying outside in the winter season for only 0–2 h (I, $N = 1$) compared to the summer season ($N = 238$). The highest values (~62 nmol L^{-1}) were obtained by participants who recorded spending over eight hours per day outdoors in summer and also had their blood samples taken during the summer season. A higher mean value was obtained for class IV in winter with 74 nmol L^{-1}, but with only two participants this cannot be interpreted statistically. The lowest values (~30 nmol L^{-1}) were found for class I in summer and winter and also for participants who spent more than eight hours per day outdoors in winter, further underlining the point that winter exposure to sunlight has minimal influence on vitamin D status. Differences in 25(OH)D concentrations related to hours spent outside in summer and winter were statistically significant for the whole year, summer and autumn (with $p < 0.0005$).

3.4. 25(OH)D modelling

In order to investigate which external, personal and behavioural variables really affect 25(OH)D concentrations, logistic regression in a multivariable approach was used.

The most significant variables from the range of possible predictors are listed in Table 5.

A gender-specific regression model was tested as well, which gave the same results in the selection of predictors for female participants as for the whole survey. For male participants, the same determinants were selected except for vitamin and UPF. However, as there was a lower number of men taking vitamin supplements and using sunscreen products than women (2% versus 6% and 44% versus 56%, respectively) this is not surprising. Based on the similarity of results, we ceased gender-specific analyses.

Stepwise, forward and backward procedures resulted in the selection of the same variables to explain 25(OH)D concentrations. Finally, ten predictors were selected by the regression model. Using Kendall's tau correlation coefficient (k), we evaluated whether there were dependencies between the selected variables (using only categorical variables). Intercorrelations were low with a maximal $k = -0.33$ (UPF and holiday weeks) and $k = 0.25$ (age with health state and UPF). The table with Kendall's tau coefficient between all variables is provided in Appendix 2.

In Table 5, the odds ratios (OR) for having low 25(OH)D concentrations (defined as <25 nmol L^{-1}) in relation to these variables is shown. The reference of the categorical variables is always presented by the category for which vitamin D deficiency was

Table 5
Multivariable adjusted odds ratios for 25(OH)D < 25 nmol L^{-1} for seasons, residence (rural/urban), BMI (I–III), Fitz (I–IV), SES (I–V), UPF (yes – using; no – not using sunscreen products), holiday weeks (metric), recent holiday (yes-during last six weeks stay in a sunny region, no – no stay in a sunny region), Vitamin (yes – taken or no – not taken) and h outdoors summer (metric), persons at risk and percentage of persons from the category, confidence intervals of the ORs.

Predictors	Persons at risk (% of category)	Odds ratios	Confidence intervals
(i) External – ambient			
Season			
Summer	35 (8%)	1.0	Ref.[a]
Autumn	169 (20%)	3.4	2.2–5.2
Spring	302 (35%)	7.1	4.7–10.7
Winter	402 (43%)	10.2	6.8–15.3
Residence			
Rural	459 (27%)	1.0	Ref.[a]
Urban	449 (33%)	1.4	1.1–1.6
(ii) Intrinsic – personal			
BMI			
I	257 (27%)	1.0	Ref.[a]
II	343 (27%)	1.0	0.8–1.2
III	301 (37%)	1.5	1.2–1.8
Fitz			
I	48 (41%)	1.0	Ref.*
II	442 (31%)	0.6	0.4–0.9
III	365 (27%)	0.5	0.3–0.8
IV	8 (32%)	0.7	0.2–1.9
V	1 (66%)	1.1	0.1–16.4
SES			
V	140 (29%)	1.0	Ref.[a]
IV	149 (25%)	0.8	0.6–1.0
III	192 (27%)	0.8	0.6–1.0
II	182 (30%)	0.8	0.6–1.1
I	244 (36%)	1.1	0.8–1.5
(iii) Individual behaviour/decisions			
UPF			
Yes	426 (37%)	1.0	Ref.[a]
No	480 (25%)	0.7	0.6–0.8
Holiday weeks	–	0.8	0.8 – 0.9
Recent holiday			
Yes	44 (12%)	1.0	Ref.[a]
No	862 (32%)	2.3	1.6 – 3.4
Vitamin			
Yes	19 (16%)	1.0	Ref.[a]
No	875 (30%)	2.7	1.6–4.6
h outdoors summer	–	0.9	0.8–0.9

[a] Ref.: reference category.

expected to be less frequent, i.e. summer season, rural residence, lowest BMI class, Fitzpatrick I, SES V, Health I, recently been in holidays, vitamin D intake and no use of sunscreen. Odds ratios were then calculated for the other categories.

For the continuous variables (holiday weeks, h outdoors summer), ORs were calculated for an increase of one unit, i.e. one week or one hour, respectively.

In total, 908 of the 3061 participants suffered from vitamin D deficiency (Table 1). Compared to the reference (summer) there was a highly significant increase in the odds of being vitamin D deficient with odds ratios of 3.4, 7.1 and even 10.2 for people who had their blood sample withdrawn in autumn, spring, and winter, respectively. From people with blood sample withdrawn in summer there was only a low percentage deficient (8%) in contrast to winter blood samples (43%). For people living in urban environments the risk of hypovitaminosis increased significantly by 40% compared to people living in more rural regions. Regarding BMI, the odds for persons with BMI class III (i.e., BMI > 30 kg m^{-2}) increased by 40% compared to normal weight persons. Having skin that tanned and burned less (i.e. skin type II, III and IV) decreased the risk of vitamin D deficiency with odds 0.6, 0.5 and 0.7, though not significantly. This is also reflected by the number of people concerned: from the category of people with skin type I there were 41% deficient whereas from the skin type III category only 27% suffered from hypovitaminosis. Lower socioeconomic status also seems to decrease vitamin D deficiency of 20% (SES II–IV), but not significantly. Only the lowest status significantly increased the risk of vitamin D deficiency by 10%. The use of sunscreen decreased the odds by 30%. For each week per year more spent in a sunny region, e.g. for holiday, the odds of hypovitaminosis decreased by 20% and for each hour per day more spent outside in summer it diminished by 10%.

Individuals who did not spend time in a sunny region during the last six weeks had 2.3 times higher odds and people who took no vitamin D supplements had 2.7 higher odds of vitamin D deficiency.

To illustrate the influence of the most important variables on a deficient vitamin D status, Fig. 2 presents the odds as percentage effect (0% corresponds to the reference category). The figure clearly shows the dominant influence of winter season on low 25(OH)D concentrations and the significant influence of external factors on vitamin D production. The effect of individual behaviour is clearly seen with some lifestyle choices having a significant positive effect (i.e., times spent in the sun either in weeks per year or during the last six weeks or in hours per day as well as additional vitamin D intakes). Intrinsic variables are found to be of less importance, except for the largest BMI class. Note, however, that the vast majority of participants were of skin types II and III, with only 3 people who were not white Caucasian (i.e., had skin type V).

The low weight of age given by our model may be caused by the older sample used (>32 years).

No quantitative analyses were possible with data from the KORA S4 study due to missing measurements of serum 25(OH)D concentrations. However, the following changes in the variables measured in both studies can be found: the median BMI value increased from 26.6 kg m^{-2} (S4) to 27.0 kg m^{-2} (F4). Secondly, in the case of sun protection (UPF), the use of sunscreen has significantly decreased from 77% (S4) to 64% (F4). The weeks per year spent in sunny regions (holiday weeks) decreased from a median 2.0 weeks (S4) to 1.7 weeks (F4).

4. Discussion

4.1. Mean serum 25-hydroxyvitamin D status

For 25(OH)D measurements over the whole study (Table 1), only 24% of the study participants reached sufficient concentrations. This corresponds to the maximum values found by studies using data from German National Examination Surveys [19,27,40], with a prevalence of vitamin D insufficiency of 40–45% and a deficiency of 15–30% in the general population, i.e. up to 75% did not reach sufficient serum 25(OH)D concentrations.

Serum 25(OH)D concentrations for each season followed the annual changes in the availability of UVB radiation: from summer blood samples 55% of the participants were below sufficient concentrations and for winter blood samples this number increased to 84% (Table 1). This means, however, that even in summer more than half the population is deficient or insufficient.

The widespread vitamin D insufficiency and deficiency were explained as being due to the latitude of Germany resulting in a lack of cutaneous vitamin D production in the winter season. Moreover, dietary vitamin D intakes are low [19]. Another reason for widespread insufficiency in Germany may be sun avoidance due to health campaigns promoting sun protection measures to prevent skin cancer [41].

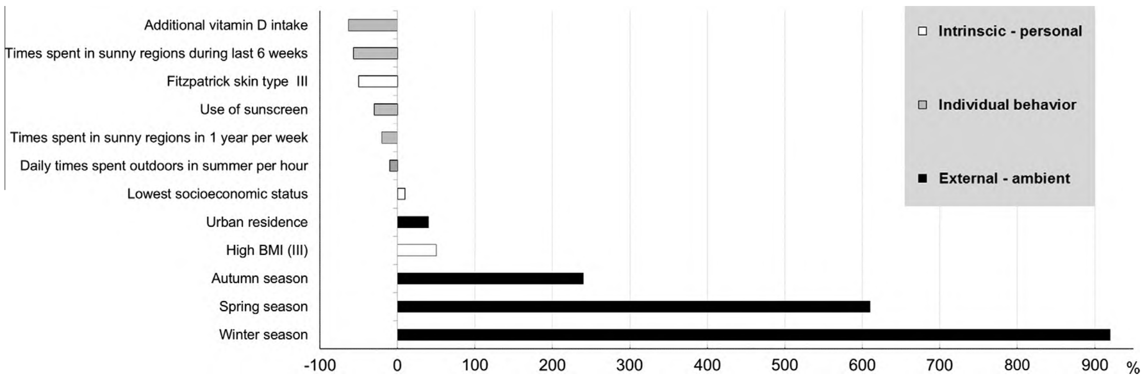

Fig. 2. Percent effect on deficient 25(OH)D status (<25 nmol L^{-1}) for the analysed variables.

4.2. Residence

Differences between the 25(OH)D concentrations for residents of the city of Augsburg and people living in rural areas around Augsburg were small but significant, with mean concentrations being lower in the city. It can only be speculated that this difference in 25(OH)D concentrations between urban and rural residents would probably increase if people living in larger cities had been involved in the study. Dependence of the 25(OH)D concentrations on place of residence was also analysed by Glass et al. [25]. In contrast to our results, this study found that living in an urban or rural location in the UK had no influence on serum 25(OH)D; although other studies [42–44], have seen that values of 25(OH)D were higher in rural communities compared to those living in an urban environment.

One reason for this may be due to the urban life style providing for fewer activities outdoors in both work and leisure time [45]. In fact, considering all people staying 6–8 h and more than 8 h outdoors in summer, 60% of them were of rural and only 40% of urban residence. The urban environment also has lower levels of ambient UV due to shadowing by buildings as well as stronger attenuation of the incoming UV radiation by aerosols or ozone from local air pollution, compared to the generally clearer rural atmosphere [46].

4.3. Age and gender

The higher prevalence of vitamin D insufficiency in older participants, especially those >75 years (Table 3), has also been seen in other studies [7,19,47,48]. This may be explained by the decreasing capacity of the skin to make vitamin D via cutaneous synthesis [49] and perhaps the fact that the old wear more clothes when outdoors. Studies in Nordic countries have found higher values of 25(OH)D in the older population due to vitamin D rich food (oily fish) or vitamin supplements [23]. There is, however, not (yet) any similar move to increase vitamin D in the older German population.

Regarding gender-differences in the 25(OH)D concentrations, studies are inconsistent: some confirmed our findings [21,50] of higher 25(OH)D concentrations for men, whereas other found higher values for women [24]. Nevertheless, gender specific differences were small and other factors seem to be more important in regards to individual 25(OH)D concentrations.

4.4. Body mass index

The results of the BMI analyses were similar to other studies: there is a decrease in 25(OH)D concentrations with high BMI [22,23,51,52]. This is an established fact and several explanations have been suggested, amongst others reduced exposure to UV radiation [53], a higher distribution volume for 25(OH)D concentrations or the fact that it is a fat soluble vitamin and may be locked up in the excess fat [52].

4.5. Fitzpatrick skin type

It was hypothesized that fairer skin types, i.e. skin types 1–2 [33], would exhibit higher 25(OH)D values than darker pigmented persons (skin types 3–5). This may be the case from a worldwide perspective [24]. However, for people living under the same environmental conditions, this may not always hold true, as shown with our data, though it should be noted that the comparison was only made amongst Caucasian individuals as there were too few skin type V individuals to be statistically representative. Similar results were found for Caucasian females in the UK [25] with lower serum 25(OH)D concentrations measured in fair skin types compared to darker skin types. This was explained by the different behaviour of fair-skinned people in the sun, in particular advice on preventing skin cancer which advocates sun avoidance. Therefore, fair skinned people may avoid direct sun exposure (at lunch time) and/or use clothes to protect themselves from the sun. There may also be genetic differences in vitamin D metabolism in fair skin types [25]. The important point to note is that mean 25(OH)D values throughout the year were mostly below the sufficiency levels in all skin types.

4.6. General health state

No other studies have shown an association between the general subjective state of health and 25(OH)D concentrations. In the study of Kimlin et al. [54], for instance, the variable ‘perceived general health’ did not influence 25(OH)D concentrations. Nevertheless, many disorders have been linked to vitamin D insufficiency or hypovitaminosis D, such as different types of cancer, osteoporosis, osteomalacia, fractures, diabetes, heart disease and other chronic illnesses [15]. Moreover, people who suffer from a range of medical disorders may spend less time outside than healthy people. In fact, 11% of participants from Health class I spend more than 8 h outdoors in summer in comparison to only 5% of Health class V. For the lowest number of hours spent outdoors (0–2 h), the difference is even more pronounced: 21% from Health class I versus 43% from Health class V participants. So it seems reasonable that the amount of serum 25(OH)D may correlate also with the participants subjective well-being, as observed.

4.7. Socioeconomic status

Socioeconomic status has been analysed in some studies in relation to serum 25(OH)D concentrations [7,25,55]. Whereas in some cases [25] social status was not associated with 25(OH)D concentrations, other studies have found the prevalence of hypovitaminosis (by the authors defined as 25(OH)D < 37.5 nmol L^{-1} [7,25,55]) to be 12% higher in women from low income groups than from higher income groups in Bangladesh. But lack of consistency in the way 'socioeconomic status' is defined, as well as other intrinsic and extrinsic factors, makes comparison of results difficult. Data in the study from Glass et al. [25], for instance, were derived from regional variables (post codes). Therefore, no comparable study exists for regions presenting similar economic characteristics as Germany.

The fact that the SES differences in our study are most prominent in summer implies that sun exposure is the dominant difference of social status, at least regarding the holiday behaviour. Indeed, from all people staying more than 10 weeks per year in a sunny holiday location, 26% are from the upper SES class in comparison to only 14% of the lowest economic class. While for participants not going on holidays 33% are of lower social class versus only 8% of the upper class. Correlation between the two variables is therefore positive with $k = 0.24$.

4.8. Use of sunscreen

One would expect lower instead of higher 25(OH)D values in people using sunscreen products, but contrary results were also found in other studies [13,26,56,57]. Situations where people apply sunscreen were examined [58]. The authors found that the use of sunscreen was highly correlated with risk behaviour, i.e. people who intend to sunbath also use sunscreen. This may also explain the high 25(OH)D concentrations found in the summer season from sunscreen users. Several studies analysing application and protection of sunscreen found that people do not apply sunscreen in the required concentration, or do not equally distribute the cream on the exposed skin which leads to inadequate protection from UV-radiation [26]. This is, however, advantageous with regard to cutaneous synthesis of vitamin D [58,59].

4.9. Sun exposure

Since vitamin D is produced by UVB radiation and can be stored in fat cells [5], a clear positive relationship between weeks per year spent in sunny regions (holiday weeks, Table 4), during last six weeks in sunny region (recent holiday), hours spent outside in particular in summer (h outdoors summer) and mean serum 25(OH)D was found as expected. Due to the very low UV level in Germany in winter time, staying outside does not effectively increase 25(OH)D concentrations. A few minutes outside in summer at midday is much more effective at raising serum 25(OH)D concentration than many hours outside in winter.

Our results were confirmed by other studies [48,60]. Van der Wielen et al. [48], for instance, whilst analysing 25(OH)D concentrations of elderly people in Europe, found that spending less than one hour on outdoor activities resulted in a 12% lower 25(OH)D concentration. However, other studies could not find significant correlations between (diary – reported) times spent outdoors and 25(OH)D concentrations [61,62]. This was explained by a number of uncertainty factors, such as variations of ambient UVB (which depends on season, time of day and weather conditions) as well as personal factors (e.g. clothing, behaviour, genetic variations). Moreover, these studies emphasized the difficulty of predicting 25(OH)D values using self-reported sunlight exposure questionnaires.

In all cases 25(OH)D values were lowest in winter, i.e. from December to February. With the onset of spring, i.e. from March to May, the concentrations rose and reached the maximum in summer (i.e. from June to August). In autumn (September to November), the 25(OH)D concentrations decreased below the levels of summer as ambient UV declines due to the lower solar altitude. This indicates that the dominant process of vitamin D production is cutaneous synthesis on exposure to solar UVB as shown in Fig. 2.

4.10. Modelling 25(OH)D

According to our results, the most significant factors for hypovitaminosis D – defined as mean 25(OH)D below 25 nmol L^{-1} – were seasons (winter, spring and autumn) and living in an urban environment from the external-ambient category (i), then BMI ($\geqslant$30 kg m^{-2}) from the intrinsic-personal category (ii). Conversely, individual behaviour (iii) such as a stay in a sunny region during the last six weeks, vitamin D intake, use of sunscreen, weeks per year in sunny (holiday) places and hours per day spent outdoors in summer improved the 25(OH)D concentrations.

Obviously, the categories (i) and (iii) contain the most influential factors with regard to cutaneous vitamin D synthesis. In particular the variable "season" showed very high ORs. The model included also skin type and socioeconomic status variables, but their influence was not significant (except for the lowest SES). The variables h outdoors winter, age, gender and health status were not included by the model building procedures.

For a translation of these results into recommendations to improve vitamin D status, some variables must be regarded with care, in particular Fitzpatrick skin type (Caucasian only analysed) and sunscreen: more pigmentation and the use of sun blocking creams limit UV penetration into the skin and therefore lower the cutaneous production of vitamin D. However, due to individual behaviour – as discussed above – these factors may lead to enhanced 25(OH)D serum concentrations.

In other studies, similar variables have been selected, such as season, vitamin D intake and BMI (males only) [27] and skin type [25]. In contrast to our results, age and gender [27] have been determined to be important variables.

As summarized by the review study of Mithal et al. [7] from a global point of view, the most important determinants for hypovitaminosis D were older age, being female, higher latitude, winter season, darker skin pigmentation, degree of sunlight exposure, dietary habits and absence of vitamin D intake.

The results of different studies are of course influenced amongst others by the specific characteristics of the population sample, the geographic location and the model selection procedures, rendering comparisons difficult. According to a cross-sectional Australian study [54], behavioural factors contributed more than ambient-external factors to serum 25(OH)D concentrations in the population. A major factor in this difference is the higher UV radiation level in Australian latitudes compared to Germany. Therefore, more studies must be carried out with regard to the vitamin D research topic for different regions in the world. This is not only important for validation of results but for the understanding of the specific weight of influencing factors in different environments.

Regarding the results of the KORA S4 study, changes in these three variables (BMI, UPF, holiday weeks) from 1999/2001 to 2006/2008 suggest an increase in risk of vitamin D deficiency in the general population.

4.11. Strengths and limitations of the study

The strength of this study is the large ($N = 3061$) and representative (although older >32 years of age) population sample with an equal gender distribution. This is similar in size to the representative German National Health Interview and Examination Survey [27]. In other studies sample size has often been far lower, e.g. 47 volunteers in Cargill et al. [61], 483 adults in Bischof et al. [22], or 1414 participants in the study of Glass et al. [25]. Moreover, a greater range of data was collected including personal factors such as body weight and socioeconomic status or behavioural factors such as times spent outdoors and holiday habits. All with potential to influence the 25(OH)D concentrations of the individuals in the study; in other studies the focus has been on a more limited range of factors, such as BMI and age [22,52].

One limitation is that the serum 25(OH)D was only measured once per participant with samples being spread over the whole study period of 20 month, and due to seasonal changes the data has had to be analysed at the seasonal level. If 25(OH)D concentrations had been measured in each of the four seasons, the analyses could have been based on seasonal thresholds [63]. This may be more appropriate than using one threshold for the whole year and will be examined in a future study.

Besides, the lab method for the quantification of 25(OH)D concentrations has some limitations: DiaSorin Liaison may slightly underestimate the serum concentrations as observed for instance by de Konig et al. [64] who found that patients were more likely to be determined as vitamin D inadequate or deficient by DiaSorin Liaison (36%) versus an LC-MS/MS method (9%). This would not influence the relative risks in our study, but may indicate that a greater number of the population are in the deficient category than would be the case if an alternative analysis had been used.

5. Conclusion: vitamin D insufficiency in the German population

As shown by this and other studies [17,27], insufficiency and even hypovitaminosis D is widespread in the German population. This is mainly the result of ambient factors combined with individual behaviour.

According to research by Webb et al. [65], a relatively simple method to mitigate this problem would be by exposure to sunlight of about 1/3 skin area (equivalent to wearing modest shorts/skirt and T-shirt) during lunchtime hours for short periods of between 9 and 18 min per day in middle latitudes such as Manchester, UK. However, it must be kept in mind that these times are only valid for ideal conditions (cloud free sky, Caucasian skin types), and do not take into account different skin types, locations, varying ambient conditions, sunscreen or clothing, etc. [66,67]. To estimate the effect of some of the latter, a web-based model estimating time of required exposure to obtain UV-induced vitamin D-effective doses is provided in Webb and Engelsen [67].

Obviously, the most effective, cheapest and simplest way to satisfy vitamin D needs for the white Caucasian German population, through cutaneous production, without significantly increasing the risk of UV-induced skin cancer, would be short and frequent skin exposures to the sun [65]. For those unwilling or unable to gain such regular sun exposure, or certain 'risk groups' such as older people, pregnant and breastfeeding women and young infants, there is a clear need for guidance on oral intake of vitamin D through diet or supplementation. Since vitamin D insufficiency is so widespread, recommendations to this effect would be welcome from governmental or public health bodies.

Acknowledgments

The KORA research platform (KORA, Cooperative Health Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jphotobiol.2014.07.018.

References

[1] M.F. Holick, J.A. MacLaughlin, M.B. Clark, S.A. Holick, J.T. Potts Jr., R.R. Anderson, I.H. Blank, J.A. Parrish, P. Elias, Photosynthesis of previtamin D3 in human skin and the physiologic consequences, Science 210 (1980) 203–205.
[2] M.F. Holick, J.A. MacLaughlin, S.H. Doppelt, Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator, Science 211 (1981) 590–593.
[3] B. Lehmann, The vitamin D3 pathway in human skin and its role for regulation of biological processes, Photochem. Photobiol. 81 (2005) 1246–1251.
[4] J.A. MacLaughlin, R.R. Anderson, M.F. Holick, Spectral character of sunlight modulates photosynthesis of previtamin D3 and its photoisomers in human skin, Science 216 (1982) 1001–1003.
[5] A.R. Webb, Who, what, where and when—influences on cutaneous vitamin D synthesis, Prog. Biophys. Mol. Biol. 92 (2006) 17–25.
[6] D. Joshi, J.R. Center, J.A. Eisman, Vitamin D deficiency in adults, Aust. Prescriber 33 (2010) 103–106.
[7] A. Mithal, D.A. Wahl, J.P. Bonjour, P. Burckhardt, B. Dawson-Hughes, J.A. Eisman, G. El-Hajj Fuleihan, R.G. Josse, P. Lips, J. Morales-Torres, Global vitamin D status and determinants of hypovitaminosis D, Osteoporos. Int. 20 (2009) 1807–1820.
[8] A.M. Parfitt, J.C. Gallagher, R.P. Heaney, C.C. Johnston, R. Neer, G.D. Whedon, Vitamin D and bone disease in the elderly, Am. J. Clin. Nutr. 36 (1982) 1014–1031.
[9] R. Vieth, Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety, Am. J. Clin. Nutr. 69 (1999) 842–856.
[10] M.F. Holick, T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences, Am. J. Clin. Nutr. 87 (2008) 1080S–1086S.
[11] C.J. Lavie, J.H. Lee, R.V. Milani, Vitamin D and cardiovascular diseasewill it live up to its hype?, J Am. Coll. Cardiol. 58 (2011) 1547–1556.
[12] K. Vähävihu, Heliotherapy and narrow-band UVB improve vitamin D balance: studies in healthy subjects a nd in patients with atopic dermatitis and psoriasis, in: Faculty of Medicine University of Tampere, Tampere, Finland, 2010, pp. 96.
[13] C.A. McCarty, Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires?, Am J. Clin. Nutr. 87 (2008) 1097S–1101S.
[14] B. Hintzpeter, C. Scheidt-Nave, M.J. Muller, L. Schenk, G.B. Mensink, Higher prevalence of vitamin D deficiency is associated with immigrant background among children and adolescents in Germany, J. Nutr. 138 (2008) 1482–1490.
[15] M.F. Holick, The vitamin D deficiency pandemic: a forgotten hormone important for health, Public Health Rev. 32 (2010) 267–283.
[16] P. Lips, Worldwide status of vitamin D nutrition, J. Steroid Biochem. Mol. Biol. 121 (2010) 297–300.
[17] L. Perna, U. Haug, B. Schottker, H. Muller, E. Raum, E.H. Jansen, H. Brenner, Public health implications of standardized 25-hydroxyvitamin D levels: a decrease in the prevalence of vitamin D deficiency among older women in Germany, Prev. Med. 55 (2012) 228–232.
[18] J.D. Ringe, C. Kipshoven, Vitamin D-insufficiency: an estimate of the situation in Germany, Derm. – Endocrinol. 4 (2012) 72–80.
[19] A. Zittermann, The estimated benefits of vitamin D for Germany, Mol. Nutr. Food Res. 54 (2010) 1164–1171.
[20] E. Azizi, F. Pavlotsky, A. Kudish, P. Flint, A. Solomon, Y. Lerman, B. Oberman, S. Sadetzki, Serum levels of 25-hydroxy-vitamin D3 among sun-protected outdoor workers in Israel, Photochem. Photobiol. 88 (2012) 1507–1512.
[21] A.R. Webb, R. Kift, M.T. Durkin, S.J. O'Brien, A. Vail, J.L. Berry, L.E. Rhodes, The role of sunlight exposure in determining the vitamin D status of the U.K. white adult population, Br. J. Dermatol. 163 (2010) 1050–1055.
[22] M.G. Bischof, G. Heinze, H. Vierhapper, Vitamin D status and its relation to age and body mass index, Horm. Res. 66 (2006) 211–215.
[23] Z. Lagunova, A.C. Porojnicu, F. Lindberg, S. Hexeberg, J. Moan, The dependency of vitamin D status on body mass index, gender, age and season, Anticancer Res. 29 (2009) 3713–3720.
[24] T. Hagenau, R. Vest, T.N. Gissel, C.S. Poulsen, M. Erlandsen, L. Mosekilde, P. Vestergaard, Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis, Osteoporos. Int. 20 (2009) 133–140.
[25] D. Glass, M. Lens, R. Swaminathan, T.D. Spector, V. Bataille, Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK, PLoS ONE 4 (2009) e6477.
[26] M. Norval, H.C. Wulf, Does chronic sunscreen use reduce vitamin D production to insufficient levels?, Br J. Dermatol. 161 (2009) 732–736.
[27] B. Hintzpeter, G.B. Mensink, W. Thierfelder, M.J. Muller, C. Scheidt-Nave, Vitamin D status and health correlates among German adults, Eur. J. Clin. Nutr. 62 (2008) 1079–1089.
[28] K. Lukaschek, J. Baumert, J. Kruse, R.T. Emeny, M.E. Lacruz, C. Huth, B. Thorand, R. Holle, W. Rathmann, C. Meisinger, K.H. Ladwig, Relationship between

posttraumatic stress disorder and type 2 diabetes in a population-based cross-sectional study with 2970 participants, J. Psychosom. Res. 74 (2013) 340–345.
[29] D. Stockl, A. Doring, A. Peters, B. Thorand, M. Heier, C. Huth, H. Stockl, W. Rathmann, B. Kowall, C. Meisinger, Age at menarche is associated with prediabetes and diabetes in women (aged 32–81 years) from the general population: the KORA F4 Study, Diabetologia 55 (2012) 681–688.
[30] R. Holle, M. Happich, H. Lowel, H.E. Wichmann, KORA – a research platform for population based health research, Gesundheitswesen 67 (Suppl. 1) (2005) S19–25.
[31] J.P. Thyssen, B. Thuesen, C. Huth, M. Standl, C.G. Carson, J. Heinrich, U. Kramer, J. Kratzsch, N.D. Berg, T. Menne, J.D. Johansen, B.C. Carlsen, S. Schwab, B. Thorand, M. Munk, H. Wallaschofski, L. Heickendorff, M. Meldgaard, P.B. Szecsi, S. Stender, K. Bonnelykke, S. Weidinger, H. Bisgaard, A. Linneberg, Skin barrier abnormality caused by filaggrin (FLG) mutations is associated with increased serum 25-hydroxyvitamin D concentrations, J. Allergy Clin. Immunol. 130 (2012) 1204–1207. e1202.
[32] WHO, BMI Classification, in: W.H. Organisation (Ed.), 2012.
[33] S. Sachdeva, Fitzpatrick skin typing: applications in dermatology, Indian J. Dermatol. Venereol. Leprol. 75 (2009) 93–96.
[34] U. Helmert, S. Shea, Social inequalities and health status in western Germany, Public Health 108 (1994) 341–356.
[35] R. Vieth, Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol L^{-1} (30 ng/ml), Best Pract. Res. Clin. Endocrinol. Metab. 25 (2011) 681–691.
[36] P. Lips, T. Duong, A. Oleksik, D. Black, S. Cummings, D. Cox, T. Nickelsen, A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial, J. Clin. Endocrinol. Metab. 86 (2001) 1212–1221.
[37] A. Malabanan, I.E. Veronikis, M.F. Holick, Redefining vitamin D insufficiency, Lancet 351 (1998) 805–806.
[38] P. Lee, J.R. Greenfield, M.J. Seibel, J.A. Eisman, J.R. Center, Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index, Am. J. Med. 122 (2009) 1056–1060.
[39] H. Lu, C. Edwards, S. Gaskell, A. Pearse, R. Marks, Melanin content and distribution in the surface corneocyte with skin phototypes, Br. J. Dermatol. 135 (1996) 263–267.
[40] A. Zittermann, R. von Helden, W. Grant, C. Kipshoven, J.D. Ringe, An estimate of the survival benefit of improving vitamin D status in the adult german population, Derm. – Endocrinol. 1 (2009) 300–306.
[41] J. Reichrath, B. Nurnberg, Cutaneous vitamin D synthesis versus skin cancer development: the Janus faces of solar UV-radiation, Derm. – Endocrinol. 1 (2009) 253–261.
[42] C.V. Harinarayan, T. Ramalakshmi, U.V. Prasad, D. Sudhakar, P.V. Srinivasarao, K.V. Sarma, E.G. Kumar, High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians, Am. J. Clin. Nutr. 85 (2007) 1062–1067.
[43] C. Heere, C.M. Skeaff, L. Waqatakirewa, P. Vatucawaqa, A.N. Khan, T.J. Green, Serum 25-hydroxyvitamin D concentration of Indigenous-Fijian and Fijian-Indian women, Asia Pac. J. Clin. Nutr. 19 (2010) 43–48.
[44] B.K. Lee, S. Park, Y. Kim, Age- and gender-specific associations between low serum 25-hydroxyvitamin D level and type 2 diabetes in the Korean general population: analysis of 2008–2009 Korean national health and nutrition examination survey data, Asia Pac. J. Clin. Nutr. 21 (2012) 536–546.
[45] M.H. Gannage-Yared, A. Tohme, G. Halaby, Hypovitaminosis D: a major worldwide public health problem, Presse Med. 30 (2001) 653–658.
[46] D.H. Manicourt, J.P. Devogelaer, Urban tropospheric ozone increases the prevalence of vitamin D deficiency among Belgian postmenopausal women with outdoor activities during summer, J. Clin. Endocrinol. Metab. 93 (2008) 3893–3899.
[47] J.M. Quesada, I. Jans, P. Benito, J.A. Jimenez, R. Bouillon, Vitamin D status of elderly people in Spain, Age Ageing 18 (1989) 392–397.
[48] R.P. van der Wielen, M.R. Lowik, H. van den Berg, L.C. de Groot, J. Haller, O. Moreiras, W.A. van Staveren, Serum vitamin D concentrations among elderly people in Europe, Lancet 346 (1995) 207–210.
[49] J. MacLaughlin, M.F. Holick, Aging decreases the capacity of human skin to produce vitamin D3, J. Clin. Invest. 76 (1985) 1536–1538.
[50] M.J. Bolland, A.B. Grey, R.W. Ames, A.M. Horne, B.H. Mason, D.J. Wattie, G.D. Gamble, R. Bouillon, I.R. Reid, Age-, gender-, and weight-related effects on levels of 25-hydroxyvitamin D are not mediated by vitamin D binding protein, Clin. Endocrinol. (Oxf.) 67 (2007) 259–264.
[51] M. Kull Jr., R. Kallikorm, A. Tamm, M. Lember, Seasonal variance of 25-(OH) vitamin D in the general population of Estonia, a Northern European country, BMC Public Health 9 (2009) 22.
[52] S. Konradsen, H. Ag, F. Lindberg, S. Hexeberg, R. Jorde, Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index, Eur. J. Nutr. 47 (2008) 87–91.
[53] J.E. Compston, S. Vedi, J.E. Ledger, A. Webb, J.C. Gazet, T.R. Pilkington, Vitamin D status and bone histomorphometry in gross obesity, Am. J. Clin. Nutr. 34 (1981) 2359–2363.
[54] M.G. Kimlin, R.M. Lucas, S.L. Harrison, I. van der Mei, B.K. Armstrong, D.C. Whiteman, A. Kricker, M. Nowak, A.M. Brodie, J. Sun, The contributions of solar ultraviolet radiation exposure and other determinants to serum 25-hydroxyvitamin D concentrations in Australian adults: the AusD Study, Am. J. Epidemiol. 179 (2014) 864–874.
[55] M.Z. Islam, C. Lamberg-Allardt, M. Karkkainen, T. Outila, Q. Salamatullah, A.A. Shamim, Vitamin D deficiency: a concern in premenopausal Bangladeshi women of two socio-economic groups in rural and urban region, Eur. J. Clin. Nutr. 56 (2002) 51–56.
[56] J. Farrerons, M. Barnadas, J. Rodriguez, A. Renau, B. Yoldi, A. Lopez-Navidad, J. Moragas, Clinically prescribed sunscreen (sun protection factor 15) does not decrease serum vitamin D concentration sufficiently either to induce changes in parathyroid function or in metabolic markers, Br. J. Dermatol. 139 (1998) 422–427.
[57] R. Marks, P.A. Foley, D. Jolley, K.R. Knight, J. Harrison, S.C. Thompson, The effect of regular sunscreen use on vitamin D levels in an Australian population. Results of a randomized controlled trial, Arch. Dermatol. 131 (1995) 415–421.
[58] E. Thieden, P.A. Philipsen, J. Sandby-Moller, H.C. Wulf, Sunscreen use related to UV exposure, age, sex, and occupation based on personal dosimeter readings and sun-exposure behavior diaries, Arch. Dermatol. 141 (2005) 967–973.
[59] N. Bech-Thomsen, H.C. Wulf, Sunbathers' application of sunscreen is probably inadequate to obtain the sun protection factor assigned to the preparation, Photodermatol. Photoimmunol. Photomed. 9 (1992) 242–244.
[60] J.H. Kim, S.J. Moon, Time spent outdoors and seasonal variation in serum concentrations of 25-hydroxyvitamin D in Korean women, Int. J. Food Sci. Nutr. 51 (2000) 439–451.
[61] J. Cargill, R.M. Lucas, P. Gies, K. King, A. Swaminathan, M.W. Allen, E. Banks, Validation of brief questionnaire measures of sun exposure and skin pigmentation against detailed and objective measures including vitamin d status, Photochem. Photobiol. 89 (2013) 219–226.
[62] D.M. Freedman, E.K. Cahoon, P. Rajaraman, J.M. Major, M.M. Doody, B.H. Alexander, R.W. Hoffbeck, M.G. Kimlin, B.I. Graubard, M.S. Linet, Sunlight and other determinants of circulating 25-hydroxyvitamin D Levels in black and white participants in a nationwide US study, Am. J. Epidemiol. 177 (2013) 180–192.
[63] I.H. de Boer, G. Levin, C. Robinson-Cohen, M.L. Biggs, A.N. Hoofnagle, D.S. Siscovick, B. Kestenbaum, Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study, Ann. Intern. Med. 156 (2012) 627–634.
[64] L. de Koning, M.R. Al-Turkmani, A.H. Berg, A. Shkreta, T. Law, M.D. Kellogg, Variation in clinical vitamin D status by DiaSorin Liaison and LC-MS/MS in the presence of elevated 25-OH vitamin D2, Clin. Chim. Acta 415 (2013) 54–58.
[65] A.R. Webb, R. Kift, J.L. Berry, L.E. Rhodes, The vitamin D debate: translating controlled experiments into reality for human sun exposure times, Photochem. Photobiol. 87 (2011) 741–745.
[66] O. Engelsen, The relationship between ultraviolet radiation exposure and vitamin D status, Nutrients 2 (2010) 482–495.
[67] A.R. Webb, O. Engelsen, Calculated ultraviolet exposure levels for a healthy vitamin D status, Photochem. Photobiol. 82 (2006) 1697–1703.