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Vitamin D status and health correlates among German adults

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Objective: To analyze vitamin D status based on serum 25-hydroxyvitamin D (25OHD) measurements, its determinants and health correlates in a representative sample of German adults.
Subjects: A total of 1763 men and 2267 women, 18- to 79-year old, who participated in the representative German National Health Interview and Examination Survey 1998 and the integrated German Nutrition Survey.
Results: The median vitamin D intake from both diet and supplements did not meet the recommended level of 5 mg/day, in either men (2.8 mg/day) or women (2.3 mg/day). Altogether 80.9% of men and 88.5% of women had vitamin D intakes below this level. Moderate (12.5–25 nmol/l serum 25OHD levels) and mild (25–50 nmol/l) vitamin D deficiency was prevalent in the adult population in Germany, even in younger age groups. Overall, 57% of men and 58% of women had vitamin D levels below 50 nmol/l. Among 65- to 79-year-old women, the proportion amounted to 75%, even during the sunnier half of the year. In sexspecific multiple linear regression models, independent determinants of serum 25OHD levels consistently included season, vitamin D intake from both diet and supplements, physical activity and living in a partnership. In addition, age and current menopausal hormone use contributed to the model among women, as opposed to time of day of blood sampling and body mass index (marginally) among men. Significantly lower serum 25OHD levels were observed in women with hypertension, cardiovascular diseases and noninsulin-treated diabetes mellitus as well as in men with insulin-treated diabetes mellitus compared with nonaffected participants. Conclusions: Vitamin D deficiency is a public health issue in Germany. We identified a number of determinants with potential for primary prevention of vitamin D deficiency. Risk and benefits of preventive actions need to be examined in further studies.

Introduction

Vitamin D plays a vital role in maintenance of calcium homeostasis. Currently, in Europe and North America, rickets and osteomalacia, the clinical outcomes of a severe vitamin D deficiency, are rarely observed (Lips, 2004). Milder states of vitamin D deficiency are more common and may contribute to the risk of fragility fractures in the elderly on the basis of secondary hyperparathyroidism and high bone turnover (Avenell et al., 2005) as well as muscle weakness and an increased propensity to falls (Bischoff-Ferrari et al., 2004). Beyond these musculoskeletal effects, long-standing suboptimal vitamin D states as defined by serum 25-hydroxyvitamin D (25OHD) levels below 50nmol/l may contribute to the pathogenesis of chronic conditions involving the immune system and low-grade inflammation, such as multiple sclerosis, type 1 and 2 diabetes, cardiovascular diseases and specific types of cancer (Chiu et al., 2004; Holick, 2004b; Zittermann et al., 2005; Christakos et al., 2006; Garland et al., 2006; Vieth and Kimball, 2006). A recent study suggests that lower serum 25OHD levels are also associated with a greater risk of future nursing home admission and possibly with mortality in older persons (Visser et al., 2006). It is well known that vitamin D status shows a marked seasonal variation as ultraviolet-B radiation is not strong enough during winter time to assure sufficient dermal synthesis of vitamin D. Vitamin D deficiency states appear to be prevalent in populations of different latitudes and ethnic backgrounds (Mc Kenna, 1992; Ovesen et al., 2003; Hashemipour et al., 2004; Heaney, 2004; Meyer et al., 2004; Raiten and Picciano, 2004; Gannage-Yared et al., 2005; Hanley and Davision, 2005; Lucas et al., 2005; Meddeb et al., 2005; Park and Johnson, 2005; Whiting and Calvo, 2005). Specific risk factors of vitamin D deficiency mediated by lack of sunshine exposure include residence at high latitudes and in large cities, high skin pigmentation, cultural dress code or immobility (Semba et al., 2000; Hashemipour et al., 2004; Meyer et al., 2004; Meyer, 2004; Gannage-Yared et al., 2005). Insufficient dietary compensation (Calvo et al., 2005), and diseases interfering with vitamin D and calcium absorption (Lips, 2004) have a role as well. Previous studies among the adult population in Germany showed that the average dietary vitamin D intake does not meet the recommended level (Mensink et al., 2002; DGE, 2004). However, information regarding vitamin D status and potential health correlates in Germany is scarce. Data available so far relate to vitamin D deficiency among residents of older people's homes (Mc Kenna, 1992) and to the association between serum 25OHD levels and bone mineral density or bone metabolism in a small regional sample of older

adults (Scharla et al., 1996; Woitge et al., 1998). The present study aimed to assess the prevalence of vitamin D deficiency and replete states in a representative sample of the German noninstitutionalized adult population and to examine some independent determinants of vitamin D status as well as the cross-sectional relationship between serum 25OHD levels and several common chronic conditions previously related to vitamin D deficiency.

Subjects and methods

Subjects

The representative German National Health Interview and Examination Survey 1998 (GNHIES) was conducted from October 1997 to March 1999. The population sample included 7124 men and women, aged 18–79 years, reflecting the noninstitutionalized adult population in Germany. Participants were selected by a random sampling method based on a two-staged clustered design, stratified by age, community size and federal state. The response rate was 61.4% (Bellach et al., 1998; Thefeld et al., 1999). The sampling procedure has been previously described in detail (Mensink and Beitz, 2004). The present analysis is based on a random subsample of 2267 women and 1763 men who also participated in an extended dietary assessment, the German Nutrition Survey 1998. As budget and time restrictions precluded to include all persons who responded to the main survey, participants were recruited consecutively according to interviewer availability without any systematic selection. As an exception, we attempted to cover the largest possible proportion of women of childbearing age assuring a sufficient number of participants for the allied folic acid study. To correct for this disproportionality as well as for discrepancies due to nonresponse and noncoverage between the net sample and the situation of the German population according to age, gender, community size and residence in West or East Germany in 1998, a weighting factor was computed (Mensink and Beitz, 2004). Surveys were approved by the federal data protection office. Respondents were informed in detail about the study objectives, interview and examination procedures as well as pseudonymized record-keeping and data analyses. All participants provided written informed consent before the interview and examination.

Data collection

Participants filled in a questionnaire on health and lifestyle issues, among them leisure-time physical activity, income, education and profession. A computer-assisted personal interview (CAPI) was conducted by specifically trained physicians to obtain a detailed medical history and information on any medication used within 7 days before the interview. To assess the lifetime diagnosis of particular health problems, including various cardiovascular conditions as well as diabetes mellitus, participants were asked ‘Has a doctor ever told you that you have one or more of the following diseases?’. Diabetes mellitus was further differentiated
as noninsulin-treated and insulin-treated diabetes mellitus. Standardized measures of blood pressure, height and weight as well as blood samples were taken as part of a medical examination. Blood pressure was measured by a physician 3 times after at least 3min rest, using a mercury sphygmomanometer (Erkameter 3000, Erka, Bad Jölz, Germany). Mean systolic and diastolic blood pressure was calculated from the second and the third measurements.

Laboratory analyses

The participants were asked to fast for at least 3 h, whereupon venous blood samples were drawn for biochemical analyses. Blood samples were immediately processed and separated. Whole blood and the larger part of serum were immediately used for analysis of hematologic parameters and blood chemistry. Extra serum was aliquoted and stored at _401C. Total serum calcium was measured by cresolphthalein complexon method (Merck, Darmstadt, Germany) on a Mega-Analyzer. Calcium levels were corrected for serum
albumin (Rustad et al., 2004). The best indicator of vitamin D status is serum 25OHD. Serum 25OHD levels and serum intact parathyroid hormone levels (iPTH) were both measured from June to September 2005 in the Epidemiological Research Laboratory of the Robert Koch-Institute, using LIAISON chemiluminescence immunoassay (CLIA) (DiaSorin Inc., Stillwater, MN, USA). Inter- and intraassay coefficients of variation for serum 25OHD were 11.7 and 9.9% and for serum iPTH 7.2 and 3.7%, respectively. The lower detection limits of the assays were 5 nmol/l for serum 25OHD and 0.106 pmol/L for serum iPTH.

Dietary assessment
Trained nutritionists interviewed the participants about their dietary habits in the past 4 weeks before the examination, using the computerized modified dietary history instrument DISHES 98 (Dietary Interview Software for Health Examination
Studies) with documented validity (Mensink et al., 2001). Special tableware and drawings of food portions helped to facilitate the estimations of portion sizes. The individual nutrient intake from the information on food consumption was calculated using the German Food Consumption Table, Version 2.3 (Dehne et al., 1999). As part of the dietary interview, the participants were asked about their use of vitamin B complex, C, E, folic acid, multivitamin and mineral supplements during the last year. This included the frequency of intake as well as the corresponding brand names of the supplements. Besides, there was the possibility to provide open-ended information about the use of other vitamins, for example vitamin D. Based on the brand names, the quantities of supplement ingredients were calculated, using an updated supplement composition database, developed by the GSF – National Research Centre for Environment and Health (Beitz et al., 2002).

Operationalization of variables
Vitamin D status was categorized into groups, according to Lips as serum 25OHD levels o12.5 nmol/l, 12.5–25 nmol/l, 25–50 nmol/l and 450 nmol/l, indicating severe, moderate and mild vitamin D deficiency as well as the desirable safe reference limit, respectively (Lips, 2004). For each individual, daily intakes of vitamin D (in mg/day) and calcium (in mg/day) from both diet and supplements were calculated from dietary assessment data. In addition, supplement use of vitamin D and calcium was indicated by dichotomous variables (yes vs no). Estimates of resting energy expenditure (REE) were computed from new standard equations based on height, weight, age and sex, according to specific body mass index (BMI) groups derived from German individuals (Müller et al., 2004). Energy intake (EI, in MJ/day) from diet was calculated and the ratio between EI and REE (EI/REE) was assessed to examine the potential influence of EI on vitamin D status. For some analyses, the study group was classified into age groups of 18–34, 35–64 and 65–79 years. Information on current month of examination was categorized according to calendar seasons: spring (March–May), summer (June–August), autumn (September–November) and winter (December–February). Time of day of blood sampling was categorized as morning (0800–1300), noon/afternoon (1300– 1800) and evening (1800–2200). Information on physical activity was defined using the question ‘How often do you engage in sports?’ as inactive (no engagement in sports), moderately active (1–2 h/week) and active (X2 h/week). However, survey questions on physical activity were not designed to permit any further differentiation between indoor and outdoor physical activity. BMI was calculated by dividing weight (in kg) by squared height (in meters). BMI measures were categorized in four groups: underweight (o20 kg/m2), normal weight (20 to o25 kg/m2), overweight (25 to o30 kg/m2) and obese (X30 kg/m2). In addition, information on social and professional status was included in the analyses as the dichotomous variables ‘outdoor working’ as well as ‘married or living with a partner’. A lifetime diagnosis of any cardiovascular disease was based on reported lifetime diagnosis of any one or more of the following conditions: previous yocardial infarction or stroke, angina, cerebral ischemia, congestive heart failure and intermittent claudication of the leg. Hypertension was defined as X90mmHg diastolic or X140mmHg systolic blood pressures according to Joint National Committtee criteria for stage 1 and 2 hypertension (Chobanian et al., 2003). In addition, participants with current antihypertensive medication were labeled as hypertensives irrespective of blood pressure measurements. With respect to other medication use, current uses of ‘antiepileptic therapy’ as well as ‘menopausal hormone therapy’ among women were considered in the analyses as potential confounders due to their known effect on calcium and bone metabolism.

Statistical analyses
All statistical analyses were performed using the SAS-software package Version 9.1. (SAS Institute Inc., Carry, NC, USA). They were performed sex specifically, and a P-value of p0.05 was considered statistically significant based on two-sided tests. No adjustment for multiple testing was applied. The weighting factor was used for all analyses. The distribution of serum 25OHD levels was skewed and required logarithmical transformation for the multiple linear regression models. Values for seasonal variation were given as individual data points for serum 25OHD levels and serum iPTH levels.
Both curves were fitted using a periodic function: F (month)¼ax1þbx2þC, where x1¼cos(month*p/6) and x2¼sin(month*p/6). These variations were similar for both sexes and were therefore not shown separately. Unadjusted associations between serum 25OHD levels and explanatory variables were first tested using w-square statistics, simple linear regression and Pearson’s as well as Spearman’s correlation analyses, suitable for the nature and distribution of the variables. Differences in serum 25OHD levels between BMI groups were tested using the Kruskal–Wallis test. In addition, a multiple linear regression model with log serum 25OHD levels as the dependent variable was constructed to

identify the importance of determinants. For this purpose, we excluded participants with antiepileptic therapy (n¼31) to make sure that the observed association was not biased by this prevailing treatment. Antiepileptic drugs are inducers of the cytochrome P450 system in the liver, promoting the metabolism of 25OHD to less biologically active analogs (Kulak et al., 2004; Mintzer et al., 2006). We calculated prevalence rates across sex-specific quartiles of serum 25OHD levels to examine the association between serum 25OHD levels and hypertension as well as a lifetime diagnosis of diabetes mellitus and cardiovascular disease. The association between serum 25OHD levels and these conditions was further examined in multiple logistic regression analysis. Separate models were fitted for the various dependent variables including serum 25OHD levels as a continuous variable as well as the following covariates: age (continuous), calendar season and time of day of blood sampling (ordinate variables). Reported odds ratios, 95% confidence intervals and P-values relate to increase in serum 25OHD levels per 10 nmol/l.

Results

Characteristics of the study population are summarized in Table 1 for men and women separately. Median serum 25OHD levels were 45.2 nmol/l for men and 44.7 nmol/l for women. We observed that median vitamin D intake from both diet and supplements did not meet the recommended level, in either men (2.81 mg/day) or women (2.31 mg/day). Overall, 80.9% of men and 88.5% of women had vitamin D intakes below the recommended 5 mg/day (data not shown). Median calcium intake of both men (1181 mg/day) and women (1082 mg/day) reached the recommended 1000 mg/day. A small amount of 1.5% of men and 3.8% of women used vitamin D supplements, whereas 12.1% of men and 19.3% of women reported use of calcium supplements. There was no age gradient in Vitamin D supplement use but a smaller amount in summer compared to winter (data not shown). Seasonal variation in serum 25OHD levels is demonstrated in Figure 1a. There were disparities throughout the year in vitamin D status with the highest median observed in summer (56.6 nmol/l in June) and the lowest at the end of winter (33.2 nmol/l in March). Furthermore, the largest variability occurred during winter while a smaller variability was seen in summer. Seasonal declines in serum 25OHD levels were closely mirrored by increases in serum iPTH levels (Figure 1b). Sex- and age-specific prevalence rates of vitamin D status for the sunnier (May–October) and sun-deprived (November–April) half of the year are shown in Table 2. In the total sample, 56.8% of men and 57.8% of women showed serum 25OHD levels of 50nmol/l and below. Vitamin D deficiency and replete states were strongly related to season with the highest prevalence of replete states during sunnier months compared to sun-deprived months. From May to October replete vitamin D states were generally more prevalent in men than in women, whereas the reverse was true from November to April except for the highest age group. There was a strong age dependency of vitamin D status in women but not in men. Even from May–October, nearly 75% of the 65- to 79-year-old women had serum 25OHD levels below 50nmol/l. We found several significant associations between vitamin D status and potential determinants (as shown in Table 1) in bivariate analyses. Calcium intake from both diet and supplements as well as EI/REE was not significantly correlated with serum 25OHD levels. EI/REE was strongly and inversely correlated with BMI. In both sexes, serum 25OHD levels varied significantly between different BMI groups with the lowest levels in both low and high BMI, indicating a curvilinear, U-shaped association. Box plots of serum 25OHD levels by BMI groups for men and women, respectively, showed this relationship (Figure 2a and b). In full multiple linear regression models, season, vitamin D intake, married or living with a partner and being physically active were significantly and positively associated with serum 25OHD levels in both sexes (Table 3). In addition, age and current menopausal hormone therapy were independent determinants of serum 25OHD levels in women, whereas time of day of blood sampling independently contributed to the model in men. BMI at the lower and upper end of the distribution (U-shaped relationship as reflected by the squared term) was marginally significant in men. Calcium intake did not contribute to the multiple models in either sex, estimates in Table 3 are therefore based on the models without calcium intake. Due to the strong correlation between BMI and EI/REE, the potential effect of EI/REE was examined in separate models replacing BMI by EI/REE. We observed no significant effect on serum 25OHD levels. Men with lower serum 25OHD levels were more likely to have insulin-treated diabetes mellitus. However, the number of observations was rather small (1.1% in men and 1.2% in women). Among women, hypertension and a reported lifetime diagnosis of cardiovascular disease and noninsulintreated diabetes mellitus were associated with lower serum 25OHD levels. Prevalence rates showed a significant stepwise increase from highest to lowest 25OHD quartiles (Table 4a). These associations persisted in multiple logistic models adjusted for age, season and time of day of blood sampling (Table 4b). In addition, the relationship between hypertension and serum 25OHD levels was also significant in men.

TABLE 1 Participant characteristics by gender [a]

Variable	Men (n=1763)	Women (n=2267)
Serum levels [b]		
25OHD (nmol/l)	45.2 (30.5-68.6)	44.7 (30.7-72.2)
iPTH (pmol/l)	3.5 (2.2-4.9)	2.9 (1.7-4.5)
Calcium, corr. (mmol/l)	2.14 (2.06-2.21)	2.18 (2.10-2.26)
Dietary intake (from diet and supplements)		
EI/REE (MJ/d) [c]	1.40 (1.13-1.73)	1.32 (1.10-1.60)
Vitamin D (µg/d)	2.81 (1.89-4.44)	2.31 (1.53-3.56)
Calcium (mg/d)	1181 (902-1535)	1082 (849-1379)
Supplement use (%)		
Vitamin D (yes)	1.5	3.8
Calcium (yes)	12.1	19.3
Age group (%)		
18-34 y	30.7	27.8
35-64 y	55.4	52.5
65-79 y	13.9	19.7
Season of examination (%)		
Spring (March-May)	33.6	32.3
Summer (June-August)	17.9	17.4
Autumn (September-November)	36.9	39.7
Winter (December-February)	11.6	10.6
Time of day of blood sampling (%) [b]		
Morning	30.5	49.6
Noon/afternoon	35.3	36.5
Evening	33.7	12.9
Leisure time physical activity (%) [b]		
Inactive	40.5	45.5
Moderately active (1-2 h/week)	33.7	38.0
Active (≥2 h/week)	25.4	16.1
Body mass index (%)		
<20 kg/m² (underweight)	1.9	6.4
20-25 kg/m² (normal weight)	30.9	40.5
25-30 kg/m² (overweight)	49.4	31.4
>30 kg/m² (obesity)	17.8	21.7
Social and professional status (%) [b]		
Married or living with a partner (yes)	76.7	71.1
Outdoor working (yes)	37.7	23.3
Medical history of diseases (%) [b]		
Hypertension (yes)	20.3	24.0
Cardiovascular disease (yes)	11.1	12.1
Insulin treated diabetes mellitus (yes)	1.1	1.2
Non-insulin treated diabetes mellitus (yes)	3.5	4.9
Medication use (%) [b]		
Antiepileptic therapy (yes)	0.7	0.8
Menopausal hormone therapy (yes)	-	11.9

[a] Data are presented as median and interquartile range (25th - 75th Percentile) or percentage as indicated.
[b] Marked variables show few missing values (therefore, the sum of these variables is not 100%).
[c] EI/REE: Energy intake/Resting energy expenditure.

Figure 1a Seasonal variation in 25OHD levels (nmol/l)

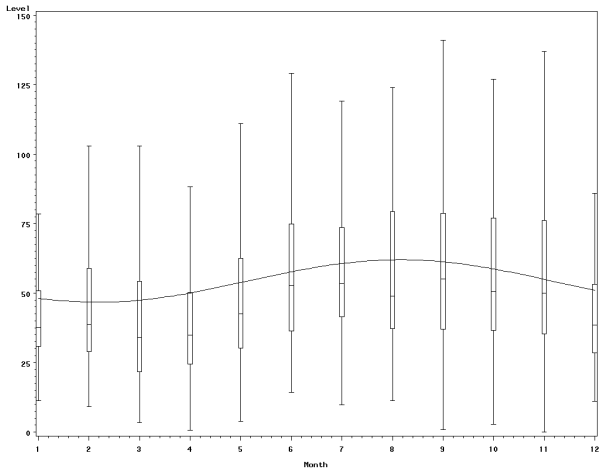


Figure 1b Seasonal variation in iPTH levels (pmol/l)

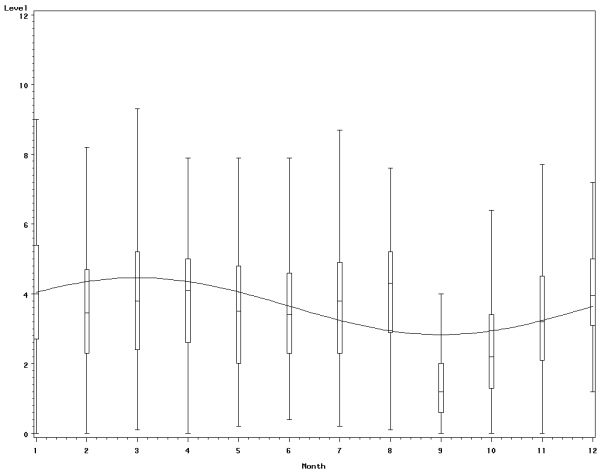


Figure 1 (a) Values for seasonal variation are given as individual data points for serum 25OHD levels. The curve is fitted using a periodic function: F (month)¼ax1þbx2þC, where x1¼cos (month p/6) and x2¼sin (month p/6), Po0.001. The median 25OHD levels were lower in winter than in summer. The lowest median was observed at the end of winter (March), the highest median in summer (June). (b) Values for seasonal variation are given as individual data points for serum iPTH levels. The curve is fitted using a periodic function: F (month)¼ax1þbx2þC, where x1¼cos (month p/6) and x2¼sin (month p/6), Po0.001. Serum iPTH levels showed an inverse seasonal variation in comparison with serum 25OHD levels, with lowest median values in September and October.

TABLE 2 Prevalence of vitamin D deficient and replete states by gender, season and age group [a]

Men	Severe deficiency (<12.5 nmol/l)	Moderate deficiency (12.5-25 nmol/l)	Mild deficiency (25-50 nmol/l)	Replete (>50 nmo/l)
Total (%)	2.2	13.4	41.2	43.2
May-October				
Age group (%)				
18-34 y	0.5	10.1	33.6	55.8
35-64 y	1.3	8.3	34.4	56.0
65-79 y	1.4	7.0	43.3	48.3
All ages (%)	1.1	8.7	35.4	54.8
November-April				
Age group (%)				
18-34 y	2.0	18.5	47.5	32.0
35-64 y	3.8	18.6	47.7	29.9
65-79 y	4.2	14.8	41.6	39.4
All ages (%)	3.3	18.1	46.8	31.8
Women	**Severe deficiency (<12.5 nmol/l)**	**Moderate deficiency (12.5-25 nmol/l)**	**Mild deficiency (25-50 nmol/l)**	**Replete (>50 nmol/l)**
Total (%)	1.9	15.1	40.8	42.2
May-October				
Age group (%)				
18-34 y	0.5	5.6	37.4	56.5
35-64 y	1.1	10.3	41.2	47.4
65-79 y	1.2	21.7	51.9	25.2
All ages (%)	0.9	11.5	42.4	45.2
November-April				
Age group (%)				
18-34 y	3.0	16.1	34.2	46.7
35-64 y	3.2	16.4	41.0	39.4
65-79 y	0.9	30.2	42.3	26.6
All ages (%)	2.7	18.8	39.3	39.2

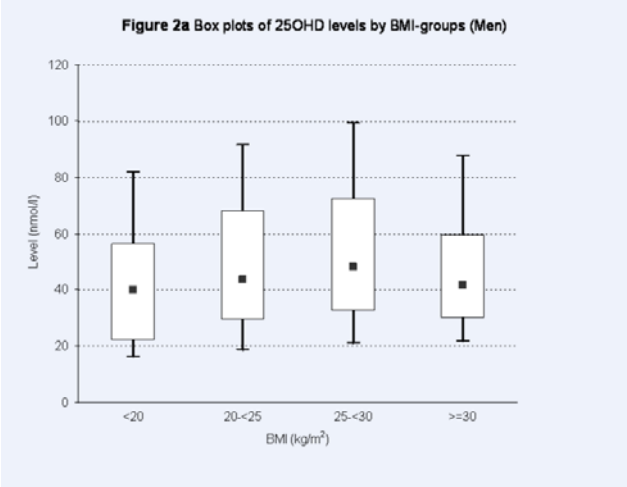
[a] Categories of serum 25OHD levels as described by Lips (Lips, 2004). The sum of each row is 100%.

Discussion

Prevalence of vitamin D deficiency and seasonal variation

We observed a high prevalence of vitamin D deficiency among German adults. Regardless of season, 15.6% of men and 17.0% of women had severe to moderate vitamin D deficiency (o25 nmol/l). Over half of the population (56.8% of men and 57.8% of women) generally had serum 25OHD levels below 50 nmol/l. Vitamin D-deficient states were most prevalent among women 65 years and older. Nearly 75% of women in this age group had serum 25OHD levels below 50 nmol/l, even during sunnier months. Nevertheless, vitamin D deficiency was prevalent among younger persons.

For example depending on seasonal changes 20.5% of men and 19.1% of women, 18 to 34-year old, showed severe to moderate vitamin D deficiency during sun-deprived months. To our knowledge, this is the first survey to examine the vitamin D status in a representative sample of the German noninstitutionalized adult population. As there is no consensus on an optimal vitamin D status (Lips, 2004; Dawson- Hughes et al., 2005; Aloia et al., 2006; Bischoff-Ferrari et al., 2006) and no standardization of vitamin D measurement (Lips et al., 1999; Binkley et al., 2004), comparison between different studies and results is rather difficult. However, our data are similar to results of other European studies concerning the prevalence of vitamin D deficiency from various countries in Europe (Burnand et al., 1992; Scharla et al., 1996; Chapuy et al., 1997;Woitge et al., 1998; Lamberg- Allardt et al., 2001; Kudlacek et al., 2003; Ovesen et al., 2003; MacFarlane et al., 2004; Meyer et al., 2004) and other continents (Sherman et al., 1990; Mc Kenna, 1992; Jacques et al., 1997; Looker et al., 2002; Rapuri et al., 2002; Hashemipour et al., 2004; Hanley and Davision, 2005),



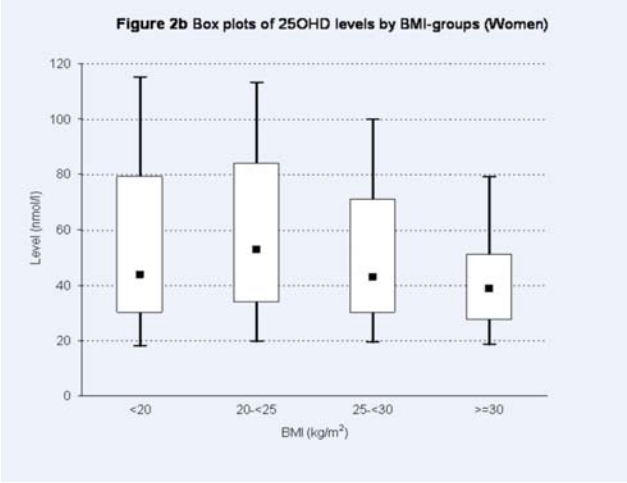


Figure 2 (a) The center in the box indicates the median. Boxes represent values within the twenty-fifth and seventy-fifth percentiles and lines represent values within the tenth and ninetieth percentiles. Serum 25OHD levels and BMI showed a curvilinear, U-shaped association with the lowest 25OHD levels observed in both low- and high-BMI groups (P¼0.0034). (b) The center in the box indicates the median. Boxes represent values within the twenty-fifth and seventy-fifth percentiles and lines represent values within the tenth and ninetieth percentiles. Serum 25OHD levels and BMI showed a curvilinear, U-shaped association with the lowest 25OHD levels observed in both low- and high-BMI groups (Po0.001).

including countries located at low latitudes (Levis et al., 2005; Lucas et al., 2005). Moreover, studies considerably vary with respect to the recruitment and the age range of the included sample, and only few studies have been based on nationally representative samples (Chapuy et al., 1997; Finch et al., 1998; Looker et al., 2002; Hirani and Primatesta, 2005). The median vitamin D intake from both diet and supplements did not meet the recommended level of 5 mg/ day, in either men or women. Altogether, 80.9% of men and 88.5% of women had vitamin D intakes below the recommended level. In comparison with studies from northern countries concerning elderly women (Andersen et al., 2005), median vitamin D intakes seem to be rather small. In accordance with previous reports from a number of regional cross-sectional studies (Scharla et al., 1996; Woitge et al., 1998; Rapuri et al., 2002; Bhattoa et al., 2004), we observed considerable seasonal changes in serum 25OHD levels, with lowest and highest median values among participants studied in late winter (March) and summer (June), respectively. Serum iPTH also showed the expected inverse seasonal variation, with lowest median values in September and October (Woitge et al., 1998; Rapuri et al., 2002). Lack of fit between seasonal variation predicted from models based on the individual iPTH measurements and the observed variation based on median values was evident between July and September. The rise in median iPTH from July to August is likely to be explained by a smaller number of study participants (since August is the typical holiday month in Germany, the fieldwork was paused for some weeks) and the coincidental relatively high proportion of elderly women participating between mid July and mid September. This may, at least in part, also explain why the variability in serum 25OHD levels was observed to be larger during winter than summer. However, there are also a number of biochemical explanations. First, it may be that people generally have a certain degree of sunlight exposure during summer, partly explaining the smaller variability. Second, a larger variability in outdoor activities during the sun-deprived season is likely, as some participants may have traveled to sunny districts or skiing regions within several weeks before the survey examination. Finally, an increase in supplement use during winter as observed in our study population is also possible. Determinants of vitamin D status Given the fact that vitamin D deficiency has been implicated in many disorders, it is of high public health relevance to identify risk groups. We therefore examined determinants of serum 25OHD levels. According to our observations, Jacques et al. (1997) found an inverse relationship between serum 25OHD levels and age among elderly women but not in men in the Framingham Heart Study.While there is evidence that cutaneous vitamin D biosynthesis (Holick et al., 1989) may become less efficient with advancing age, this would not explain the observed sex differences. Clinical as well as population-based studies have consistently found that obesity is associated with lower serum 25OHD levels (Jacques et al., 1997; Wortsman et al., 2000; Snijder et al., 2006). In contrast, there is only one population- based study conducted in the framework of the Health Survey for England 2000, that has reported a significant association between low BMI (o25 kg/m2) and vitamin D status (Hirani and Primatesta, 2005). In extension of these previous reports, we observed not only a high but also a low

TABLE 3 Independent determinants of log-serum 25OHD levels: multiple linear regression [a]

Men Variable	B	SE	stand.B	p value
Intercept	2.909	0.496	0.0	<0.001
Age (per year)	-0.001	0.001	-0.026	0.333
Body mass index (per kg/m²)	0.060	0.035	0.310	0.088
Body mass index squared	-0.001	0.001	-0.339	0.059
Leisure time physical activity (versus inactive)				
Moderately active (1-2 h/week)	0.058	0.041	0.037	0.154
Active (≥ 2 h/week)	0.227	0.045	0.135	<0.001
Season (versus autumn)				
Spring	-0.270	0.040	-0.175	<0.001
Summer	0.234	0.049	0.124	<0.001
Winter	-0.188	0.058	-0.081	0.001
Time of day of blood sampling (versus morning)				
Noon/Afternoon	0.007	0.044	0.005	0.865
Evening	-0.171	0.045	-0.111	<0.001
Vitamin D intake (per µg/d) [b]	0.018	0.006	0.076	0.002
Vitamin D supplement use	0.147	0.143	0.024	0.303
Outdoor working	0.063	0.036	0.042	0.077
Married or living with a partner	0.149	0.044	0.086	<0.001
R^2 = 0.109				

TABLE 4 a Prevalence (%) of chronic diseases according to quartiles of vitamin D levels [a]

Men

Quartiles p value	1	2	3	4
Hypertension 0.211	51.9	47.7	49.5	47.2
Cardiovascular disease 0.517	11.9	9.5	10.4	10.3
Insulin treated diabetes mellitus <0.001	3.0	0.3	0.8	0.4
Non-insulin treated diabetes mellitus 0.617	4.0	2.7	5.4	2.6

Women

Quartiles p value	1	2	3	4
Hypertension <0.001	50.1	48.1	40.9	30.1
Cardiovascular disease <0.001	16.7	13.1	9.4	5.6
Insulin treated diabetes mellitus 0.123	2.3	0.1	1.5	0.8
Non-insulin treated diabetes mellitus <0.001	6.5	6.5	4.4	1.5

[a] Tested using the Cochran-Mantel-Haenszel test for linear trend.

TABLE 4 b Relationship between serum 25OHD levels and chronic diseases (Odds Ratio and 95% Confidence Intervals) [a]

Men

	Odds Ratio	p value
Hypertension	0.97 (0.94-0.99)	0.036
Cardiovascular disease	0.95 (0.90-1.01)	0.080
Insulin treated diabetes mellitus	0.67 (0.53-0.86)	0.001
Non-insulin treated diabetes mellitus	0.97 (0.90-1.05)	0.471

Women

	Odds Ratio	p value
Hypertension	0.96 (0.93-0.99)	0.030
Cardiovascular disease	0.94 (0.89-0.99)	0.040
Insulin treated diabetes mellitus	0.89 (0.76-1.06)	0.205
Non-insulin treated diabetes mellitus	0.91 (0.83-1.00)	0.051

[a] From separate logistic models including serum 25OHD levels (per 10 nmol/l) as continuous variable, adjusted for age, season and time of day of blood sampling.

BMI to be associated with low serum 25OHD levels. A recent study suggests that decreased bioavailability due to its deposition in body fat is responsible for low serum 25OHD levels in obese subjects (Wortsman et al., 2000). It is also possible that obese as well as very lean persons may be less exposed to sunlight as they are less often outdoor or wear more covering clothing. Residual confounding of sunlight exposure is possible, since we had to rely on proxy variables to control for UV exposure. As underweight persons may be prone to vitamin D deficiency due to inadequate food consumption, we examined the association between serum 25OHD levels and the ratio of EI to REE (EI/REE) (Wortsman et al., 2000) as measure of adequate food consumption. It is often observed that EI/REE correlates strongly with BMI (Mensink et al., 2001). Low-energy reporting as determined by a low ratio of EI/REE is positively associated with BMI. In the regression model we included this ratio to analyze the impact of low-energy reporters. Since the influence was not relevant and EI/REE showed collinearity with BMI, it was not included in the presented models.

We did not observe a significant relationship between vitamin D supplement use and serum 25OHD levels in either gender. Andersen et al. (2005) reported that vitamin D supplement use was a significant determinant of serum 25 OHD levels in postmenopausal women living in northern Europe. Our study is a representative of nationwide survey including adults from 18 to 79 years of age. In this group, the observed proportion of vitamin D supplement users was very small compared to postmenopausal women in the previous study. We can, however, not exclude misclassification due to imprecise questions concerning vitamin D supplement use. Persons who are married or live with a partner are known to be generally healthier than singles (Joutsenniemi et al., 2006) and more active in their leisure time (Pettee et al., 2006). We therefore hypothesized that these groups may spend more time outdoors and have a more balanced diet than singles. While the observed significant and independent positive association between vitamin D status and living in a partnership does not prove any of the particular mechanisms, it is likely to serve as a proxy for differences in health-related behavior that was not captured by the constructs of ‘physical activity’ or ‘vitamin D intake’. To exclude possible effects of diurnal variation of serum 25OHD levels, we included time of day of blood sampling in our analyses. In men, but not in women, we found a significant relationship with serum 25OHD levels, increasing from morning to noon/afternoon and strongly declining until evening. The sex difference disappeared when we confined the analyses to younger women up to the age of 50 years, which may indicate an interrelationship with sex hormone metabolism. To our knowledge, this is the first observation of diurnal variation in serum 25-OHD. Diurnal rhythm of 1,25-dihydroxyvitamin D and other markers of bone mineral metabolism was shown previously (Greenspan et al., 1997; Rejnmark et al., 2002). Multiple regression models explained only a small fraction of the variance in vitamin D status. It is likely that this is largely attributable to difficulties in the estimation of sunlight exposure, as we had no information on time spent outdoors, traveling to sunny regions, clothing habits, use of

sunscreen or grade of skin pigmentation. We could also not consider genetic factors such as vitamin D receptor gene polymorphism (Zajickova et al., 2006).

Role of diseases

Due to the increasing number of studies implicating vitamin D deficiency in the pathogenesis of various chronic disorders, we also examined the cross-sectional relationship between serum 25OHD levels and chronic conditions. There is strong evidence for a role of hypovitaminosis D in type 1 diabetes mellitus. Hyppönen et al. (2001) found that children, studied at 1 year of age, who took a recommended dose of vitamin D during infancy, were only one-fifth likely to develop type 1 diabetes mellitus compared to those who received less than the recommended amount. We were not able to precisely distinguish between type 1 and type 2 diabetes mellitus. Based on medical history regarding the first onset of disease and insulin treatment, the vast majority of our diabetics can be assumed to have had type 2 diabetes mellitus. An association of vitamin D with type 2 diabetes is more controversial, and may be more pronounced in insulintreated type 2 diabetics (Scragg et al., 2004; Suzuki et al., 2006). This may explain why we observed a stronger association with insulin-treated than noninsulin-treated diabetes, at least among men. There is potential for misclassification bias due to undiagnosed diabetes, which would have weakened the association between serum 25OHD and noninsulin-treated diabetes mellitus. It is well possible that the observed sex differences result from a small number of insulin-treated diabetics as well as a higher proportion of undiagnosed disease among men than women (Scheidt-Nave et al., 1990; Rathmann et al., 2003). Recent reviews suggest that suboptimal vitamin D status may also play a role in the development of other chronic diseases including hypertension and cardiovascular diseases (Zittermann, 2003; Holick, 2004a, b). In adjusted models, hypertension was related to 25OHD in both sexes, whereas a significant association with cardiovascular disease was also restricted to women. At any rate, our study is cross sectional with the consequence that causality cannot be inferred. Only longitudinal studies are capable to identify disorders due to long-standing vitamin D deficiency.

Study limitations

Based on blood specimens and highly standardized interview methods including assessment of diet and supplement use, the German National Health Interview and Examination Survey provided a unique source of data to assess vitamin D status at the population level. Results were weighted with a factor adjusting for deviations in demographic characteristics between the study populations and official population statistics at the time of the survey. Therefore, the reported results can be extended to the noninstitutionalized adult population residing in Germany in 1998. Our study also has several major limitations. Mainly, a detailed history of sunlight exposure was not assessed at the time of the survey. Synthesis of vitamin D in the skin under UV exposure essentially contributes to maintain vitamin D supplies, and an effect of ultraviolet radiation on serum 25OHD concentrations can be expected within 4–8 weeks of exposure (Chel et al., 1998; Lucas et al., 2005). In the present study, season, outdoor working as well as leisure-time physical activity served as proxy measures of this effect. We can therefore not exclude misclassification with possible bias of effect estimates in the regression model. A further limitation may be the possible measurement errors in the dietary assessment. While it has been shown previously that dietary vitamin D in general only contributes in a small part to vitamin D status in comparison with UV radiation, the influence may increase in winter (Ovesen et al., 2003). Our survey explicitly excluded persons who were not fluently speaking German. Thus, persons with a migrant background, who are known to be at particularly high risk of vitamin D deficiency (Meyer et al., 2004), are underrepresented. The presence or absence of chronic disease was based on self-report (ever diagnosed by a physician), except for hypertension. Information on morbidity was obtained from various sources, including self-administered questionnaires prompting study participants with a list of conditions as well as detailed computer-assisted health interviews regarding a lifetime diagnosis by a physician, year of first onset, presence of the condition within the past 12 months or 4 weeks and current medication use. Using this information, a selfreported diagnosis of diabetes mellitus and several cardiovascular conditions have previously been found highly reliable and reasonably valid in German national health surveys (Bormann et al., 1990; Thefeld, 1999). Nevertheless, misclassification bias remains an issue, as persons who are yet undiagnosed as well as those who may have not participated due to advanced illness or hospitalization will be missed in health surveys.

Conclusions

Our results demonstrate that moderate and mild vitamin D deficiency affects a large proportion of the adult population in Germany, and is already prevalent in younger age groups. Specific risk groups include women 65 years of age and older, obese as well as very lean persons. Together with the observed demographic shift toward an elderly population in Germany, this is a serious public health problem. Attention should be paid to optimizing vitamin D status, in both young and elderly persons. Regular outdoor activities (while paying attention to the risk of skin cancer due to unprotected or prolonged sun exposure) should be considered as well as optimizing vitamin D intake, in particular during winter. To clarify in how far our observations have implications on health and health care responsibilities, in particular preventive actions, prospective observational and interventional studies are urgently needed.

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