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An estimate of the survival benefit of improving vitamin D status in the adult german population

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Background: Inadequate vitamin D status is a worldwide problem. Evidence is accumulating that individuals with low vitamin D status have excess mortality rates. We calculated to which extent annual mortality rates can be reduced in the German population by optimizing vitamin D status.

Results: Mean serum concentrations of 25-hydroxyvitamin D in the DEVID study cohort were 41 nmol/l (SD: 22 nmol/l). More than 90% of individuals had 25-hydroxyvitamin D concentrations below the threshold that was associated with lowest mortality risk in the two aforementioned trials (75 nmol/l). According to conservative estimations, at least 2.2% of all deaths or 18,300 lives annually can be saved by achieving 25(OH)D concentrations of at least 75 nmol/l in the entire adult German population. Available data provide evidence for an exponential increase in total mortality with deficient 25-hydroxyvitamin D concentrations.

Methods: Our calculations are based on (1) an annual mortality rate of 1.34% in the adult German population as provided by the Statistical Yearbook, (2) the actual vitamin D status in German adults with a high mortality risk as assessed in 1,343 individuals from 264 general practitioners in different German regions (DEVID study), and (3) data from two very large prospective cohorts (Dobnig et al. 2008; Melamed et al. 2008) about the excess mortality in individuals with inadequate vitamin D status.

Conclusion: Improving vitamin D status in a population with inadequate vitamin D status might be an effective strategy to reduce annual mortality rates.

Introduction

Vitamin D is well known for its effects on calcium and bone metabolism. Vitamin D deficiency results in rickets in infants and small children and in osteomalacia and osteoporosis in adults. However, recent advances in the understanding of vitamin D have revolutionized our view of this old nutritional factor and suggested that it has much wider effects on the body than ever believed before.[1] Once in the circulation, vitamin D is metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D [25(OH)D] and by a renal 1α-hydroxylase into the vitamin D hormone 1,25-dihydroxyvitamin D (calcitriol). The vitamin D receptor (VDR) is nearly ubiquitously expressed, and almost all cells respond to calcitriol exposure; about 3% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system.[2] Consequently, vitamin D influences many physiological processes, including muscle function, cardiovascular homeostasis, nervous function, cellular integrity, and the immune response.[3]

In the adult European and North American population, vitamin D insufficiency [serum 25(OH)D <50 nmol/l] and even deficiency [25(OH)D <25 nmol/l] is still very prevalent.[3,4] Only a minority of individuals worldwide has 25(OH)D concentrations above 75 nmol/l,[5] a concentration that is considered to be the lower target level for adequate vitamin D status.[6] Major reasons for this situation are insufficient skin exposure to solar ultraviolet B radiation together with inadequate oral vitamin D intake.

There is accumulating evidence that vitamin D deficiency/insufficiency might contribute to the etiology of various chronic diseases such as cardiovascular disease, specific types of cancer, multiple sclerosis, and type 1 diabetes.[3,4] Recent studies demonstrated that poor vitamin D status is independently associated with excess cancer mortality[7] and poor outcome in congestive heart failure individuals.[8] In addition, poor vitamin D status is associated with excess all-cause mortality in individuals with end-stage renal disease.[9] In 2007, Autier and Gandini[10] published a meta-analysis of randomized controlled trials on vitamin D and total mortality that were not primarily designed to assess mortality. The authors concluded that vitamin D supplementation is linked to lower all-cause mortality in middle-aged and elderly individuals with low serum concentrations of 25(OH)D than in unsupplemented subjects. Risk reduction was 7% during a mean follow-up of 5.7 years.

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Table 1. Characteristics of the DEVID study cohort in comparison to different other large study cohorts

Parameter	DEVID[a]	GNHIES study[13b]	LURIC study[11b]	NHANES III study[12b]
Individuals included	1,343	4,030	3,258	13,331
Age, yr	59	18–79[c]	64	45
Women, %	54	56	30	55
25(OH)D, nmol/l	41	45	43	63
PTH, pg/ml	45	30.0	29.3	No data
Serum phosphate, mg/dl	4.58	No data	3.5	No data
Diseases (%)				
Hypertension, yes	62	45	73	25
Cardiovascular disease, yes	33	12	No data	8
Diabetes mellitus,yes	18	5	32	7
Insulin dependent diabetes yes	4	1	No data	No data
Non insulin dependent diabetes, yes	14	4	No data	No data
Medications (%)				
ACE-Inhibitors, yes	15	No data	53	No data
Cholesterol lowering medications, yes	15	No data	47	3
Aspirin, yes	10	No data	72	No data
Anticoagulants, yes	8	No data	No data	No data
Supplements (%)				
Calcium , yes	4	16	No data	No data
Vitamin D, yes	3	3	No data	27
Season of blood drawing	winter, spring	all seasons	all seasons	all seasons

According to the presentation in the original articles biochemical parameters in table are given as [a]mean or [b]median, [c]range.

During recent years, two very large prospective cohort studies have investigated the association between vitamin D status and all-cause mortality in the adult European and North American population.[11,12] They also came to the conclusion that vitamin D deficiency is associated with excess mortality (see below). Thus, results support the meta-analysis by Autier and Gandini.[10] Improving vitamin D status might therefore be a promising public health strategy for increasing survival.

The aforementioned relationship of vitamin D with mortality led us to estimate from the available literature to which extent annual mortality rates in adult Germans could be reduced by optimizing vitamin D status.

Results

Vitamin D status of the DEVID study cohort was similar compared to the LURIC study cohort and the GNHIES study cohort. As presented in **Table 1**, not all parameters that have been assessed in the other studies were assessed in the DEVID study sample and vice versa. However, it is obvious that the participants of the DEVID study were less severely ill than the LURIC study cohort and more severely ill than the GNIES study cohort.

Table 2 illustrates the total number of deaths in the adult German population and the percentage of individuals who died in each age group. As expected, data demonstrates an exponential increase in mortality with older age. In total, 385,940 males and 435,687 females died in Germany in 2006. Thus, the total annual mortality rate in the adult German population was 1.34% if the calculation is restricted to individuals who were 25 years and older.

In the DEVID study, only 55 individuals were aged between 20 and 25 years. Therefore, we excluded this age group from further data analysis. Thirty individuals of the DEVID study of whom no 25(OH)D concentrations were available were also excluded. Thus, we were able to evaluate results of 1,255 individuals 25 years and older. Mean 25(OH)D concentrations in the entire study cohort was 41 nmol/l (SD: 22.0 nmol/l). There was a decrease in 25(OH)D concentrations with increasing age. The percentage of individuals with deficient 25(OH)D concentrations was nearly twice as high in individuals 75 years and older compared to younger individuals. In all age groups, approximately 50% of individuals had insufficient 25(OH)D concentrations. Only a minority of individuals had 25(OH)D concentrations above 75 nmol/l in all age groups and this percentage markedly decreased in individuals 75 and older compared to younger individuals.

Table 3 presents the hazard ratio and the excess annual mortality rates according to the 1st, 2nd and 3rd 25(OH)D quartiles in the LURIC study. Moreover, **Table 3** illustrates the percentage of individuals in the DEVID study which belong to the 1st, 2nd, 3rd and 4th quartile of the LURIC study. The unadjusted and fully adjusted model by the LURIC study for all-cause mortality and the percentage of individuals from the DEVID study in each quartile were then used to estimate the number and percentage of lives that can be saved if all German individuals would be in the 4th quartile of the LURIC study

Table 2. Mortality in the adult german population (19) and 25-hydroxyvitamin D levels in subjects of the DEVID study

	25–45	45–65	65–75	75 and older	Total
German population					
Number of subjects (x1,000)	22,897	22,022	11,316	5,203	61,438
Percent of adult population[1]	37	36	18	9	100
Number of deaths	20,763	113,336	167,711	508,408	821,627
Percent of age group	0.091	0.515	1.482	9.771	1.34
DEVID-study					
Number of subjects	292	428	264	274	1 258
Percent of study cohort[2]	23	33	21	21	98
25(OH)D (nmol/l)	42 ± 22	42 ± 23	41 ± 20	35 ± 20	41 ± 22
25(OH)D levels <25 nmol/l (%)	22	24	20	38	25
25(OH)D levels 25–50 nmol/l (%)	50	49	55	47	50
25(OH)D levels 50–75 nmol/l (%)	20	17	19	11	17
25(OH)D levels >75 nmol/l (%)	8	10	6	4	7

[1]based on subjects 25 years and older; [2]based on subjects 25 years and older.

Table 3. Hazard ratios for all-cause mortality according to 25-hydroxyvitamin D quartile in the LURIC study[11]

	1st quartile	2nd quartile	3rd quartile	4th quartile
LURIC-study				
25(OH)D (nmol/l)	<26.0	26.0–36.25	36.3–58.75	≥58.75
Deaths during follow-up, No. (%)	307 (36.9)	185 (23.1)	142 (17.6)	103 (12.8)
Unadjusted model	3.33	1.88	1.39	1.0
Multivariable adjusted model	2.08	1.53	1.24	1.0
Excess mortality per year, unadjusted model (%)	30.3	11.4	5.1	0
Excess mortality per year (adjusted model)	14.0	6.9	3.1	0
DEVID-study				
Percent of study cohort[2]	28	25	30	18
Estimated number of deaths in the German Population				
Estimated deaths per LURIC quartile, unadjusted model No.	382,599	192,524	174,169	72,845
Estimated lives saved according to the unadjusted model, No. (%)	115,928 (14.1)	21,948 (2.7)	8,883 (1.1)	0
Estimated deaths per LURIC quartile, adjusted model No.	314,705	206,328	204,606	95,933
Estimated lives saved according to multivariable model, No. (%)	44,059 (5.4)	14,237 (1.7)	6,343 (0.8)	0

[1]based on subjects 25 years and older; [2]based on subjects 25 years and older.

[median 25(OH)D level 71 nmol]. Data demonstrate that between 7.9% or 65,000 deaths (adjusted model) and 17.9% or 147,000 deaths (unadjusted model) could be prevented each year. **Table 4** illustrates results if the calculation is based on the data of the NHANES III study. According to these data, between 2.2% or 18,300 deaths (adjusted model) and 7.8% or 64,000 deaths (unadjusted model) could be prevented each year if all individuals would be in the 4th quartile of the NHANES III study (>81 nmol/l).

Figure 1 illustrates that there is an exponential increase in total mortality with decreasing 25(OH)D concentrations, if the median 25(OH)D data of each quartile in the LURIC and the NHANES III studies are plotted against unadjusted annualized mortality rates of the respective quartile. According to these unadjusted data it seems that very low annual mortality rates are achievable if 25(OH)D concentrations are above 100 nmol/l, whereas individuals with insufficient and especially with deficient 25(OH)D concentrations seem to have an excess mortality risk.

Discussion

The present calculations indicate that improving vitamin D status in the adult German population might be an effective strategy to reduce annual mortality rates. Such a strategy should at least save 18,300 lives or 2.2% of all deaths in adult Germans annually. The figure is probably higher and may be up to 17.9% or 147,000 lives that can be saved. Thus, the number of adult Germans needed to treat would range between 500 and 5,000 persons to save one life annually.

Table 4. Hazard ratios for all-cause mortality according to 25-hydroxyvitamin D quartile in the NHANES III study[12]

	1st quartile	2nd quartile	3rd quartile	4th quartile
NHANES-study				
25(OH)D (nmol/l)	<44.5	44.5–60.75	60.8–80.25	≥80.25
Unadjusted model	1.78	1.52	1.26	1.0
Multivariable adjusted model	1.26	1.06	0.93	1.0
Excess mortality per year, unadjusted model (%)	9.0	6.0	3.0	0
Excess mortality per year (adjusted model)	3.0	0.69	-0.80	0
DEVID-study				
Percent of study cohort[2]	68	16	9	6
Estimated number of deaths in the German Population				
Estimated deaths per HNANES quartile, unadjusted model, No.	608,827	121,970	58,768	32,097
Estimated lives saved according to the unadjusted model, No. (%)	54,795 (6.7)	7,318 (0.9)	1,763 (0.2)	0
Estimated deaths per NHANES quartile, adjusted model, No.	598,638	118,150	60,252	44,614
Estimated lives saved according to multivariable model, No. (%)	17,959 (2.2)	815 (0.1)	-482 (-0.1)	0

[1]based on subjects 25 years and older; [2]based on subjects 25 years and older.

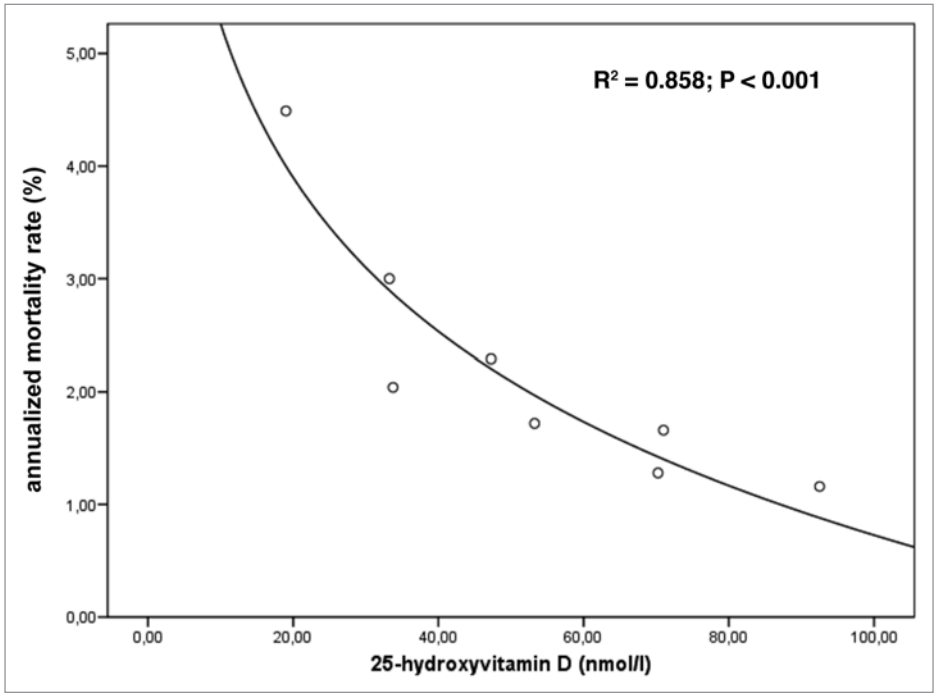

Figure 1. Association of 25-hydroxyvitamin D concentrations with annual mortality rates according to 25-hydroxyvitamin D quartiles (median concentrations) of previously published data in adults.[11,12]

Our assumption of an excess mortality in individuals with deficient 25(OH)D concentrations, which is the basis for our estimate, is in line with the fact that vitamin D is important for cellular and vascular integrity.[3,16] In case of vitamin D deficiency/insufficiency, renal synthesis of the vitamin D hormone calcitriol becomes substrate dependent, i.e., dependent on the circulating 25(OH)D concentration.[17] Evidence is now accumulating that deficiency 25(OH)D concentrations are linked to excess morbidity and mortality.[3,4,18] Interestingly, the high prevalence of deaths in adults with poor vitamin D status fit well together with the high mortality rates associated with rickets. In times when rickets was highly prevalent in Europe, e.g., in 1900, mortality under the age of 5 years was about 250/1,000 life-born children, than dropped to 50 around 1950, and is now about five.[19] In 1909, among infants 18 months or less who had died, histophathological evidence of rickets was found in 96% at autopsy,[20] highlighting the strong association of rickets with infant mortality. Experimental studies support data in humans. Studies in mice demonstrate that a complete or partial lack of vitamin D action ($VDR^{-/-}$ mice and $CYP27B1^{-/-}$) results in premature aging. VDR mutant mice have growth retardation, osteoporosis, kyphosis, skin thickening and wrinkling, alopecia,

ectopic calcification, progressive loss of hearing and balance as well as a short lifespan.[21]

The 25(OH)D data from the DEVID study (mean value: 41 nmol/l) we presented here are comparable with 25(OH)D concentrations obtained in adults who participated in the representative GNHIES study (median value: 45 nmol/l).[13] Therefore, results of 25(OH)D concentrations in the DEVID study seems to be generalizeable for the German population. This assumption is also supported be the fact that even in young female German students, mean winter values of 25(OH)D were only 33 nmol/l[22] and thus not higher than mean 25(OH)D concentrations in the DEVID study. There is evidence that vitamin D status has further decreased in developed countries during the last 15 years[23] and that especially persons in Germany with immigrant background have a high prevalence of vitamin D deficiency.[24] These results may indicate a further increase in vitamin D-related mortality in Germany in future.

In the very large Women's Health Initiative study[25] the hazard ratio for total mortality was 0.91 (95% confidence interval: 0.83–1.01) in postmenopausal women randomized to calcium and vitamin D compared to the placebo group during an average follow-up of 7 years. However, vitamin D supplementation was only 10 μg per day, and thus very low. Autier and Gandini[10] have recently performed a meta-analysis of randomised controlled trials in osteoporotic individuals and could demonstrate that vitamin D supplementation is linked to lower total mortality in middle-aged and elderly individuals with low 25(OH)D concentrations compared with un-supplemented individuals. Risk reduction was 7% during a mean follow-up of 5.7 years, which is equivalent to an annual risk reduction of 1.23%, and thus very similar to the nonsignificant results observed in the Women's Health Initiative study (1.29% per year). It is noteworthy that the data of the WHI study also entered the meta-analysis by Autier and Gandini[10] and, because of its large size, contributed to a large extent to the results of that meta-analysis. Although the meta-analysis by Autier and Gandini[10] is in general agreement with our calculations, the survival benefit was lower in their analysis compared to the lowest annual risk reduction estimated by us (2.2%). However, in the vast majority of the randomised trials which entered that earlier meta-analysis daily vitamin D supplementation ranged between 10 μg and 20 μg only. These dosages are far below the daily recommended amount of 40–50 μg by vitamin D researchers.[26] Therefore, the meta-analysis by Autier and Gandini[10] may underestimate the true effect of adequate vitamin D supplementation on all cause mortality. It has recently been demonstrated in an Irish study in free-living adults aged 64 years and over[27] that in order to achieve a serum 25(OH)D level of at least 80 nmol/l in almost all individuals a daily dose of approximately 40 μg is required. Therefore, one can reliably assume that the annual risk reduction in all-cause mortality in German adults would be higher than calculated by Autier and Gandini[10] and would be in the range estimated by us. An improvement of vitamin D status can not only be achieved by daily vitamin D supplementation, but also by monthly administration of an oral vitamin D bolus,[28] or by food fortification with vitamin D.[29-31] It has been assumed that the cost-saving effects of measures to improve vitamin D status on vitamin D-related morbidity and mortality are approximately 19 times higher than the resulting costs of those measures.[32]

The LURIC participants may have been sicker than the general population. In addition the mean age range in the LURIC study cohort was considerably higher than in the DEVID and NHANES III study cohorts (**Table 1**). This is a possible reason why the death estimates using mortality data from the LURIC study were higher than those using data from the NHANES III study. However, it is also noteworthy that in the NHANES III study the lowest 25(OH)D quartile was almost identical with the 2nd lowest quartile of the LURIC study. Although lower 25(OH)D concentrations in the LURIC study compared with the NHANES III study can possibly be attributed age differences, there is also evidence from representative data that vitamin D status is generally lower in German adults than in white US adults.[13,33] The calculations which are based on the NHANES III data do not take into account the enhanced mortality risk of very low 25(OH)D concentrations. Note that **Figure 1** indicates an exponential increase in mortality risk with declining 25(OH)D concentrations. Therefore, our lowest estimate of annual risk reduction (2.2%) may under-estimate the true number of individuals that can be saved in Germany by improving vitamin D status. This suggestion is in line with a recent subgroup analysis of 3,408 NHANES III participants aged 65 and older.[34] Compared with individuals with 25(OH)D levels of 100 nmol/L or higher, the adjusted mortality risk for individuals with levels less than 25.0 nmol/L was 83% higher and for levels of 25.0 to 49.9 nmol/L was 47% higher. Interestingly, deficient 25(OH)D concentrations are also associated with an exponential increase in serum parathyroid hormone concentrations and are accompanied by a decline in circulating concentrations of the vitamin D hormone calcitriol.[17] Both alterations seem to contribute to the high mortality risk in vitamin D deficient individuals.[35,36]

In an earlier Dutch investigation in 1,260 independent, community-dwelling persons aged >65 years,[37] category of 25(OH)D level was not significantly associated with mortality in a multivariable adjusted model. The unadjusted mortality was however approximately 2.3 times higher in the lowest category compared with the highest category. Whereas the DEVID study, the NHANES III study, and the LURIC study were all performed with 25(OH)D assays provided by DiaSorin (Stillwater, MN USA), the Dutch study was performed with an assay supplied by Nichols (Nichols Institute, San Clemente, CA USA). It has been demonstrated that the Nichols assay can either under-estimate or over-estimate true 25(OH)D concentrations, depending on the vitamin D form that is predominantly circulating in the blood.[38] Therefore, it cannot be ruled out that results in the Dutch study were affected by assay imprecision. In a recently published study in 614 older Dutch men and women,[39] where 25(OH)D concentrations were measured by the DiaSorin assay, the unadjusted and multivariable adjusted hazard ratios for total mortality were 2.24 (1.28–3.92; p = 0.005) and 1.97 (1.08–3.58; p = 0.027), respectively, for individuals in the lowest 25(OH) quartile (mean: 30.6 nmol/l; SD 6.9 nmol/l) compared to other individuals.

Our study has some limitations. Of course, our investigation can only be a rough estimate of the survival benefit of improving

vitamin D status in the German adult population. Nevertheless, calculations are based on reliable data and give an indication to which extent lives can be saved if the lower target vitamin D level of approximately 75 nmol/l is achieved. Since 25(OH)D concentrations below the detection limit of the assay were considered 15 nmol/l, 25(OH)D concentrations may have been over-estimated by the DEVID study. This may especially be true in individuals 75 years and older, because the percentage of individuals with deficient 25(OH)D was highest in this age group. Therefore, especially elderly people belong to the group which may benefit most from an improvement in vitamin D status. The decline in 25(OH)D concentrations with increasing age (**Table 1**) and the exponential increase in excess mortality with deficient 25(OH)D (**Fig. 1**) are in general agreement with the exponential increase in mortality risk in advanced age (**Table 1**). Nevertheless, it is unlikely that vitamin D deficiency alone can explain excess mortality in advanced age. Vitamin D may be one factor among others that contribute to total mortality. In other words, vitamin D may modulate mortality risk, but other risk factors for mortality also have to be present. Some may argue that the survival benefit may have been over-estimated, since we only measured 25(OH)D concentrations in winter and spring and not in summer, when values are generally higher. However, there are not only seasonal variations in 25(OH)D concentrations but also inverse seasonal fluctuations in all cause mortality in countries located at geographic latitudes of 30°–50° North or South.[40] The inverse seasonal changes in both, vitamin D status and all cause mortality strengthen our hypothesis of a true relationship between the two factors. In addition, seasonal variations in 25(OH)D concentrations are only modest in those individuals in western Europe who have the highest annual mortality rates, e.g., older men and women.[38] Some may additionally argue that the use of unadjusted data in order to calculate the survival benefit may over-estimate the true beneficial effect. However, the opposite would be true if we would have used only fully adjusted data. Note that in the LURIC and NHANES III studies[11,12] adjustments were made for various factors such as physical activity, age, body mass index and smoking status. These factors are important predictors not only for mortality but also for serum 25OHD concentrations. It does not make sense to adjust for parameters that influence both, 25OHD concentrations and all cause mortality, if one wants to elucidate the relationship between 25OHD concentrations and mortality risk.[14] Therefore, one can reasonably assume that annual risk reduction may lie between the lowest and the highest values of our estimates. Finally, the selection criteria of the DEVID study (attending an outpatient visit with a general practitioner) is a possible limitation, since the cohort is not representative for the entire German population. However, due to their relatively high mortality rates, this cohort should be the target group for improving vitamin D status. Despite the presumed benefits of improving vitamin D status, large randomised controlled trials with adequate amounts of vitamin D have to clarify to which extent exactly an improvement in vitamin D status can reduce mortality rates in Germany. Moreover, it should be investigated whether primary, secondary and/or tertiary prevention is most effective. Ecological studies on cancer outcome already support the assumption that use of vitamin D should have beneficial effects on mortality.[41]

In conclusion, our calculations indicate that an absolute risk reduction in annual mortality rates of at least 2.2% may be possible, if all German adults would achieve a 25(OH)D level above a value of 75 nmol/l. Thus, improving vitamin D status in an adult population with inadequate vitamin D status might be an effective strategy to reduce annual mortality rates and increase lifespan.

Materials and Methods

We used data of the DEVID (De Vitamin in Deutschland) study in order to estimate vitamin D status in the adult German population. The DEVID study is an investigation performed in 1,343 adult individuals who had an outpatient visit with their general practitioner. The study was initiated to estimate the percentage of adult Germans with insufficient and deficient vitamin D status. Blood samples were collected in an unselected cohort of individuals from 264 general practitioners in different German regions (geographic latitude: 47°16'N to 55°04'N) between February 26 and May 25, 2007. 25(OH)D and parathyroid hormone concentrations were measured using the LIAISON electrochemiluminescence immunoassay (ECLIA) (DiaSorin Inc., Stillwater, MN USA). Detection limit of the 25(OH)D assay was 17.5 nmol/l. All values below the detection limit were considered 15 nmol/l. Serum phosphate was analyzed by routine laboratory method. Diagnoses and medications were assessed by questionnaire. The age of the study participants ranged from 20 to 99 years. All individuals gave written informed consent to the study procedures, which were approved by the ethics committee of the Aerztekammer Nordrhein, Düsseldorf, Germany. Since the DEVID study did not include a follow-up to assess mortality rates, we used two recently published very large prospective studies (**Table 1**) to perform the calculations of 25(OH)D concentrations with all-cause mortality. The LURIC (Ludwigshafen risk and Cardiovascular Health) study[11] is a prospective cohort study performed in southwest Germany in 3,258 consecutive male and female individuals scheduled for coronary angiography at a single tertiary center. Individuals were recruited between July 1, 1997 and January 14, 2000, and were followed-up for a period of 7.7 years. Melamed et al.[12] published data from the Third National Health and Nutrition Examination Survey (NHANES III) in 13,331 nationally representative US adults 20 years or older. Laboratory values were collected during 1988 through 1994 and individuals were followed for mortality through 2000.

We chose the NHANES III study,[12] because it is the only population-based study that investigated adult mortality according to 25(OH)D concentrations. We selected the LURIC study,[11] although this study is not representative for the general German population in Germany. However, it is the only German study which examined adult mortality according to 25(OH)D concentrations. Therefore, we also compared our data with results from the German National Health Interview and Examination Survey (GNHIES) study cohort,[13] the latter being a representative study

in the entire adult German population. Unfortunately, however, the GNHIES study did not assess mortality. We have chosen the DEVID study sample to calculate mortality in Germany because is a nationwide sample of individuals who have a visit with their general practitioner. The participants of the DEVID study might have a higher mortality risk compared with the GNHIES study and a lower mortality risk compared with the LURIC study. Based on the NHANES III and LURIC study results, we were able to calculate excess annual mortality rates in individuals with inadequate 25-hydroxyvitamin D concentrations from the DEVID study. We calculated these mortality rates using the multivariable adjusted data but also using the unadjusted data of these earlier studies. We followed this strategy, because multivariable adjustment may lead to an underestimation of true vitamin D-related mortality rates.[14] We then used the Statistical Yearbook for the Federal Republic of Germany[15] to assess annual numbers of death in the German population. The 2008 issue provides numbers of death for the year 2006. Data were used to calculate annual mortality rates for the entire adult (25 years and older) German population. Based on the annual mortality rates for the adult German population, the actual vitamin D status in German adults, and data about the excess mortality in individuals with inadequate vitamin D status, we were able to calculate the survival benefit of improving vitamin D status in the adult German population. The survival benefit is given as percent per year and as total numbers of lives saved per year.

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