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Vitamin D and health care costs: Results from two independent population-based cohort studies

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SUMMARY

Background & aims: Vitamin D deficiency is associated with higher morbidity. However, there is few data regarding the effect of vitamin D deficiency on health care costs. This study examined the cross-sectional and longitudinal associations between the serum 25-hydroxy vitamin D concentration (25OHD) and direct health care costs and hospitalization in two independent samples of the general population in North-Eastern Germany.

Methods: We studied 7217 healthy individuals from the 'Study of Health in Pomerania' (SHIP n = 3203) and the 'Study of Health in Pomerania-Trend' (SHIP-Trend n = 4014) who had valid 25OHD measurements and provided data on annual total costs, outpatient costs, hospital stays, and inpatient costs. The associations between 25OHD concentrations (modelled continuously using factional polynomials) and health care costs were examined using a generalized linear model with gamma distribution and a log link. Poisson regression models were used to estimate relative risks of hospitalization.

Results: In cross-sectional analysis of SHIP-Trend, non-linear associations between the 25OHD concentration and inpatient costs and hospitalization were detected: participants with 25OHD concentrations of 5, 10 and 15 ng/ml had 226.1%, 51.5% and 14.1%, respectively, higher inpatient costs than those with 25OHD concentrations of 20 ng/ml (overall p-value = 0.001) in multivariable models.

Conclusions: We found a relation between lower 25OHD concentrations and increased inpatient health care costs and hospitalization. Our results thus indicate an influence of vitamin D deficiency on health care costs in the general population.

1. Introduction

Vitamin D is essential for the development, growth and maintenance of musculoskeletal health [1,2]. Chronic vitamin D deficiency causes multiple bone diseases including rickets in children and osteomalacia in adults [1,2]. In addition to bone disease, vitamin D deficiency has been associated with a multitude of pathologic changes, including cardiac and vascular impairment as well as an impairment of immune and nervous functions [3–6]. Vitamin D deficiency may thus contribute to or serve as a marker for several diseases including cardiovascular disease, bacterial and viral infections, autoimmune disease and cancer [3–5,7,8].

The major determinants of the serum 25-hydroxy vitamin D concentration (25OHD), the best indicator of vitamin D status, are exposure of the skin to sunlight and dietary intake [1]. Yet, in regions above 45° north latitude, the ultraviolet radiation is not sufficient during winter months and the nutritional contribution to the 25OHD concentration is small [9]. Vitamin D deficiency is thus common in North-Europe and North-America [1,2]. In Germany, low 25OHD concentrations often occur during winter time and spring [10]. Among 6995 German men and women, 18–79 years of age, who participated in the 'German Health Interview and Examination Study for Adults 2010', nearly two out of three (61.6%)

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had 25OHD concentrations below 20 ng/ml, and nearly one out of three (30.2%) had 25OHD concentrations below 12 ng/ml [10].

Given the numerous diseases associated with vitamin D deficiency [3–5,7,8] and the high prevalence [1,2,10], we hypothesized that low 25OHD concentrations might be associated with increased health care costs. Indeed, a study of 866 US. veterans [11] found, that subjects with 25OHD concentrations below 20 ng/ml had more clinic visits and 39% higher health care costs compared with subjects who had 25OHD concentrations ≥20 ng/ml. In another study among older adults from the U.S. general population, low serum 25OHD concentrations were associated with a 3-fold higher risk of hospitalization with an infection [12]. Apart from the latter study that used data from the U.S. National Health and Nutrition Examination Survey (NHANES), few general population data regarding the association between vitamin D deficiency and health care costs is available. We used data from two independent general population studies conducted in northeast Germany to further examine the association between vitamin D and health care costs.

2. Methods

2.1. Study population

Data from two independent population-based cohort studies, the Study of Health in Pomerania (SHIP) and SHIP-Trend, were obtained. Both studies have been performed in the same region of North-East Germany. Details on study design, protocols and sampling methods have been reported elsewhere [13].

For the SHIP, a sample of 6265 residents in the target region, between 20 and 79 years of age, was drawn from local population registries and 4308 (2192 women) participated at the first examination (SHIP-0) between 1997 and 2001. A second examination cycle (SHIP-1) was conducted between 2002 and 2006 and comprised 3300 participants (1711 women). Between 2008 and 2012, a third examination cycle (SHIP-2) was conducted among 2333 participants (1235 women). 25OHD concentrations were measured in the SHIP-1 examination cycle, which was therefore defined as the baseline examination for the present analyses, SHIP-2 was defined as follow-up examination. We performed cross-sectional analyses using data from SHIP-1. Next, we associated baseline 25OHD concentrations with health care costs after five years using data from SHIP-2. For the cross-sectional analyses in SHIP-1, all subjects with self-reported vitamin D supplementation (Anatomical Therapeutic Chemical code A11CC, n = 25), extremely high concentrations of 25OHD (i.e., cases exceeding the 99th percentile of 25OHD concentration, n = 23), missing 25OHD concentration, or missing covariate data were excluded (n = 50). This resulted in a study population of 3203 subjects. For the longitudinal analyses, predicting health care costs and hospitalization at SHIP-2, a total of 2182 subjects were included.

For the second study, SHIP-Trend, a stratified sample of 10,000 (net sample size 8826) was drawn from the same geographical area and 4420 individuals aged 20–79 years (2275 women) participated (response 50.1%). Participation in SHIP was an exclusion criterion for SHIP-Trend. After exclusion of subjects with self-reported vitamin D supplementation (Anatomical Therapeutic Chemical code A11CC, n = 39), extremely high concentrations of 25OHD (i.e., cases exceeding the 99th percentile of 25OHD concentrations, n = 45), missing 25OHD concentration, or invalid covariate data (n = 328), 4014 SHIP-Trend participants were available for the present study. We used population-based data from SHIP-Trend to replicate the cross-sectional association between 25OHD concentrations and inpatient costs and hospitalization. Because outpatient costs cannot be derived from the survey interview of the SHIP-Trend study, we were not able to replicate the association between vitamin D and outpatient costs.

All investigations in SHIP and SHIP-Trend were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The study methods were approved by an institutional review board (ethics committee of the University of Greifswald).

2.2. Personal interview

All SHIP and SHIP-Trend participants provided socio-economic characteristics, lifestyle, medical histories, health care and medication use during computer-assisted personal interviews. As described in detail in Baumeister et al. [14], direct medical costs from a societal perspective were calculated based on a bottom-up micro-costing approach, where monetary values were assigned to all services consumed. SHIP-1 and SHIP-Trend participants were asked if and how often they had seen each of 18 different types of physicians and specialists over the last twelve months. Additionally, SHIP-1, SHIP-2, and SHIP-Trend participants were asked whether they had been hospitalized and for how many days in the last 12 months. Annual costs were estimated from the information on the number of visits to different types of outpatient care providers and inpatient days, the standardised unit costs for Germany provided by Bock et al. [15]. The Consumer Price Index for health care in Germany [15–17] was applied to inflate original costs to 2015 Euro.

An established Behavioural Model of Health Services Use was used to guide selection of covariates [18,19]. This model includes predisposing characteristics, enabling resources and perceived and evaluated need on a contextual and individual level. Individual-level predisposing characteristics include for example age, sex, race, marital status and education, which affect enabling factors. Enabling factors (e.g. income, type of insurance, social support, availability of care) are thought to affect access and amount of services use. Perceived need is self-evaluated suffering, symptoms and pain on the part of the patient seeking help or clinical disease severity. Education was defined as years of schooling completed. The monthly household income (in Euro) was divided by the square root of the number of household members according to the Luxembourg Income Study recommendation [20] to obtain an “equalized” value. Waist circumference (WC) was measured midway between the lower rib margin and the iliac crest.

2.3. Laboratory measurements

Venous blood samples were taken from the study participants between 08:30 a.m. and 07:30 p.m. in SHIP-1 and between 7:00 a.m. and 2:00 p.m. in SHIP-2 and SHIP-Trend with the majority of samples (56% in SHIP-1 and 93% in SHIP-2 and SHIP-Trend) being taken in the mornings before 12 a.m. Serum aliquots were stored at −80°. Serum 25OHD concentrations were determined as previously described [21] on the IDS-iSYS Multi-Discipline Automated Analyser (Immunodiagnostic Systems Limited, Frankfurt am Main, Germany). 25OHD concentrations had a range of 5.0–51.4 ng/ml in SHIP-1 and of 6.2–52.3 ng/ml in SHIP-Trend. The conversion factor for 25OHD concentrations from ng/ml to nmol/l is 2.496. Vitamin D status was categorised in deficient (25OHD<20 ng/ml) and sufficient (25OHD≥20 ng/ml) according to the recommendation of the German Nutrition Society [22] or as severely vitamin D deficient (25OHD concentration<10 ng/ml) for descriptive analyses (Table 1). 25OHD was modelled as a continuous exposure using fractional polynomials [23] variable for regression analyses (Tables 2–4) to allow for flexible modelling of non-linear relationships.

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Table 1
Characteristics of the study populations by vitamin D status.

Characteristics	Vitamin D status in SHIP-1			Vitamin D status in SHIP-Trend		
	Severe deficiency (n = 438)	Deficiency (n = 1514)	Sufficiency (n = 1251)	Severe deficiency (n = 142)	Deficiency (n = 1444)	Sufficiency (n = 2428)
Female, %	55.0	50.5	51.4	57.8	53.0	49.6
Age, years	57.0 (42.0–72.0)	55.0 (43.0–67.0)	53.0 (41.0–64.0)	49.0 (33.0–62.0)	54.0 (41.0–66.0)	52.0 (39.0–63.0)
School education, %						
≤10 years	46.1	42.7	36.0	27.5	26.0	20.8
10-11 years	39.5	44.4	48.6	43.0	48.8	53.8
≥12 years	14.4	12.9	15.4	29.6	25.1	25.4
Equivalent household income, €	1550 (1100–2050)	1550 (1100–2050)	2050 (1470–2550)	1098 (700–1550)	1100 (778–1550)	1450 (1025–1803)
Unemployed, %	9.8	7.7	7.5	16.2	11.3	9.2
Waist circumference, cm	95 (85–104)	95 (85–104)	89 (80–100)	88 (77–100)	92 (82–103)	90 (80–99.9)
Statutory insurance, %	97.5	96.6	95.9	92.3	94.8	92.9
Total annual health care costs, €*	328 (5.3)	291 (5.0)	254 (4.9)	–	–	–
Annual outpatient costs, €*	188 (2.7)	178 (2.8)	164 (2.8)	–	–	–
Hospitalization during the last 12 month, %	17.4	16.4	14.7	18.4	15.3	13.6
Annual inpatient costs of those with hospitalization during the last 12 months, €*	5049 (2.5)	3984 (2.4)	3836 (2.4)	4823 (2.3)	3695 (2.7)	3177 (2.6)

Entries are median (25^{th}–75th percentiles) or proportions if not indicated differently. * geometric mean (standard deviation). 25OHD, 25-hydroxy vitamin D. Vitamin D status: Severe deficiency 25OHD <10 ng/ml; Deficiency 25OHD 10 − <20 ng/ml; Sufficiency 25OHD ≥20 ng/ml.

Table 2
Cross-sectional associations of vitamin D and health care costs and hospitalization in SHIP-1.

25OHD (ng/ml)	Average total health care costs	Annual outpatient costs	Hospitalization	Inpatient costs
	% (95%–CI)	% (95%–CI)	RR (95%–CI)	% (95%–CI)
Model 1				
5	74.2 (2.4–196.2)	5.0 (−3.0 to 13.5)	0.99 (0.85–1.15)	333.0 (−3.0 to 1833.0)
10	20.3 (0.8–43.6)	3.3 (−2.0 to 8.8)	0.99 (0.90–1.10)	40.0 (9.0–82.0)
15	6.4 (0.3–12.8)	1.6 (−1.0 to 4.3)	1.00 (0.95–1.05)	11.0 (2.0–21.0)
20	Ref.	Ref.	Ref.	Ref.
25	−3.6 (−7.0 to −0.2)	−1.6 (−4.1 to 1.0)	1.00 (0.96–1.06)	−6.0 (−15.0 to −3.0)
30	−6.0 (−11.4 to −0.3)	−3.2 (−8.1 to 2.0)	1.01 (0.91–1.11)	−11.0 (−26.0 to 8.0)
Overall p-value[$]	0.041	0.229	0.869	0.031
Model 2				
5	74.6 (−14.1 to 254.8)	−1.1 (−8.4 to 6.8)	0.97 (0.84–1.13)	204.0 (−16.0 to 1001.0)
10	11.8 (−3.0 to 28.8)	−0.7 (−5.7 to 4.5)	0.98 (0.89–1.09)	27.0 (0–60.0)
15	2.9 (−0.8 to 6.8)	−0.4 (−2.9 to 2.2)	0.99 (0.94–1.04)	7.0 (0–14.0)
20	Ref.	Ref.	Ref.	Ref.
25	−1.3 (−3.0 to 0.4)	0.4 (−2.2 to 3.0)	1.01 (0.96–1.06)	−4.0 (−11.0 to 4.0)
30	−2.0 (−4.6 to 0.6)	0.8 (−4.3 to 6.0)	1.02 (0.92–1.13)	−7.0 (−21.0 to 11.0)
Overall p-value[$]	0.124	0.773	0.723	0.116

[$]Overall p-value of a joint Wald test for fractional polynomial transformations of 25OHD. 25OHD concentrations comprised a range of 5.0–51.4 ng/ml in SHIP-1. Point estimates for total, in- and outpatient costs as well as hospitalization at selected 25OHD concentrations (5, 10, 15, 20, 25, 30 ng/ml) in reference to a 25OHD concentration of 20 ng/ml are given. *$p < 0.05$. Ref, reference point; RR, Relative risk; CI, confidence interval; 25OHD, 25-hydroxy vitamin D. Model 1: adjustment for sex, age, month of blood sampling; Model 2: Model 1 + years of schooling, unemployment, equivalent household income, type of insurance (private vs. statuory), waist circumference.

2.4. Statistical analyses

Selected participant characteristics were compared across categories of vitamin D status using medians or geometric means for continuous covariates and percentage values for categorical covariates. The associations between 25OHD and average annual health care costs were examined using a generalized linear model (GLM) with gamma distribution and a log link, and e^{β} was interpreted as percent change of the outcome [24,25]. Poisson regression models with robust standard errors were used to model relative risks of hospitalization [26].

We used fractional polynomials to model 25OHD as a continuous covariate and to derive possible non-linear relationships of 25OHD with health care costs and hospitalization [23].

We reported e^{β} and RR with 95% confidence intervals for total, in- and outpatient costs and hospitalization at selected 25OHD concentrations (5, 6.2, 10, 15, 20, 25, 30 ng/ml) in comparison to the reference point of a 25OHD concentration of 20 ng/ml. The confidence intervals provide the information whether the estimate is significantly different from the reference point. Moreover, we plotted adjusted costs against 25OHD concentrations using a marginal effect plot [27].

The first model (model 1) adjusted for sex, age and month of examination. Month of examination (polynomial transformation) was added as covariate due to the seasonal variation of serum 25OHD concentration. Further covariates were selected according to the behavioural model [18], as described above. The full model (model 2) added years of schooling, unemployment, income, type of insurance (i.e. private vs. statutory) and waist circumference. We controlled for waist circumference because it raises costs and lowers 25OHD concentrations. Because we aimed to examine direct effects of vitamin D on health care costs, we did not adjust for comorbid conditions.

Vitamin D and cost variables at baseline were inversely related to loss of follow-up in a logistic model ($p < 0.01$) that also included socio-economic, behavioural and clinical predictors. Thus, we weighted regression models by the inverse probability (from the multivariable logistic model) of taking part at the follow-up

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Table 3
Cross-sectional associations of vitamin D and hospitalization and inpatient costs in SHIP-TREND.

25(OH)D (ng/ml)	Hospitalization	Inpatient costs
	RR (95%–CI)	% (95%–CI)
Model 1		
6.2	1.19 (1.05–1.35)	270.5 (−2.1 to 1302.6)
10	1.14 (1.04–1.24)	59.1 (5.7–139.3)
15	1.07 (1.02–1.12)	16.1 (5.1–28.2)
20	Ref.	Ref.
25	0.94 (0.90–0.98)	−11.8 (−16.8 to −6.4)
30	0.88 (0.80–0.96)	−23.5 (−33.3 to −12.2)
Overall p-value $	0.006	<0.001
Model 2		
6.2	1.18 (1.03–1.34)	226.1 (−6.3 to 1034.7)
10	1.13 (1.02–1.24)	51.5 (3.2–122.4)
15	1.06 (1.01–1.11)	14.1 (3.8–25.3)
20	Ref.	Ref.
25	0.94 (0.90–0.99)	−10.2 (−15.2 to −4.9)
30	0.89 (0.81–0.98)	−20.4 (−30.4 to −8.9)
Overall p-value $	0.014	0.001

$Overall p-value of a joint Wald test for fractional polynomial transformations of 25(OH)D. 25OHD concentrations comprised a range of 6.2–52.3 ng/ml in SHIP-Trend. Point estimates for inpatient costs as well as hospitalization at selected 25OHD concentrations (6.2, 10, 15, 20, 25, 30 ng/ml) in reference to a 25OHD concentration of 20 ng/ml are given. *p < 0.05. Ref, reference point; RR, Relative risk; CI, confidence interval; 25(OH)D, 25-hydroxy vitamin D. Model 1: adjustment for sex, age, month of blood sampling; Model 2: Model 1 + years of schooling, unemployment, equivalent household income, type of insurance (private vs. statuory), waist circumference.

examination. Stata 14.1 SE (Stata Corp.) was used for statistical analyses.

3. Results

3.1. Characteristics of the study populations

More than 60% of the baseline SHIP-1 study population and about 40% of the SHIP-Trend study population was vitamin D deficient or severely deficient (Table 1). Women dominated the severely vitamin D deficient group, whereas the sex proportion was nearly balanced in the other categories. The proportions of subjects with less than ten years of schooling were highest in severely vitamin D deficient men and women, as were the proportions of unemployed study participants. In addition, vitamin D deficient or severely deficient individuals had lower income than vitamin D sufficient subjects. Severely vitamin D deficient subjects had higher health care costs and were more likely to report hospitalizations than vitamin D sufficient subjects (Table 1).

3.2. Cross-sectional association of vitamin D status with health care costs and hospitalization

In SHIP-1, multivariable analyses revealed a curvilinear, inverse association of 25OHD concentrations with total average annual health care costs (Table 2). After adjustment for sex, age and month of blood sampling, study participants with 25OHD concentrations of 5, 10 and 15 ng/ml had 74.2%, 20.3% and 6.4%, respectively, higher total average health care costs than those with a 25OHD concentration of 20 ng/ml (overall p value = 0.041). After full adjustment, the non-linear association between 25OHD concentrations and total health care costs was attenuated and became statistically non-significant (overall p-value = 0.124). Similarly, a non-linear cross-sectional association was found with average annual inpatient costs. After full adjustment, the association became non-significant: compared to subjects with 25OHD concentrations of 20 ng/ml those with 5, 10 and 15 ng/ml had 204.0%, 27.0% and 7.0%, respectively, higher inpatient costs (overall p-value = 0.116). Similarly, baseline relations between 25OHD concentrations and average annual outpatient costs and hospitalization were not statistically significant.

We used independent population-based data from SHIP-Trend to replicate the relations of 25OHD concentrations with hospitalizations and inpatient costs (Table 3). A similar curvilinear association between vitamin D and hospital care utilization was found. After full adjustment, subjects with 25OHD concentrations of 6.2, 10 and 15 ng/ml had a relative risk of 1.18, 1.13 and 1.06 for hospitalization (overall p-value = 0.014), and 226.1%, 51.5% and 14.1%, respectively, higher inpatient costs (overall p-value = 0.001), than those with 25OHD concentrations of 20 ng/ml.

3.3. Association of vitamin D at baseline and health care costs and hospitalization at follow-up

Next, we studied the association between 25OHD concentrations, measured at baseline, with health care costs and hospitalization at the 5.7 year follow-up examination (Table 4). In a model

Table 4
Associations of baseline vitamin D status (SHIP-1) with health care costs and hospitalization at follow-up (SHIP-2).

25OHD (ng/ml)	Average total health care costs	Annual outpatient costs	Hospitalization	Inpatient costs
	% (95%–CI)	% (95%–CI)	RR (95%–CI)	% (95%–CI)
Model 1				
5	197.1 (−15.7 to 947.5)	5.1 (−5.6 to 17.0)	1.06 (0.88–1.26)	135.0 (−44.0 to 890.0)
10	28.2 (1.2–62.4)	3.4 (−3.7 to 11.0)	1.04 (0.92–1.17)	24.0 (−5.0 to 61.0)
15	8.3 (2.2–14.8)	1.7 (−1.9 to 5.4)	1.02 (0.96–1.08)	8.0 (1.0–15.0)
20	Ref.	Ref.	Ref.	Ref.
25	−6.6 (−11.0 to −1.9)	−1.6 (−5.1 to 1.9)	0.98 (0.93–1.04)	−8.0 (−14.0 to −1.0)
30	−13.5 (−23.6 to −2.2)	−3.3 (−9.9 to 3.9)	0.97 (0.86–1.09)	−17.0 (−30.0 to −1.0)
Overall p-value $	0.009	0.361	0.557	0.028
Model 2				
5	47.4 (−42.1 to 275.1)	−5.1 (−14.7 to 5.5)	0.94 (0.78–1.12)	53.0 (−60.0 to 489.0)
10	8.1 (−10.3 to 30.3)	−3.4 (−10.0 to 3.7)	0.96 (0.85–1.08)	13.0 (−12.0 to 46.0)
15	2.0 (−2.8 to 7.1)	−1.7 (−5.1 to 1.8)	0.98 (0.92–1.04)	5.0 (−2.0 to 13.0)
20	Ref.	Ref.	Ref.	Ref.
25	−0.9 (−3.1 to 1.3)	1.8 (−1.8 to 5.4)	1.02 (0.96–1.09)	−6.0 (−12.0 to 1.0)
30	−1.4 (−4.8 to 2.0)	3.6 (−3.5 to 11.2)	1.05 (0.93–1.18)	−13.0 (−28.0 to 4.0)
Overall p-value $	0.415	0.333	0.461	0.225

$Overall p-value of a joint Wald test for fractional polynomial transformations of 25OHD. 25OHD concentrations comprised a range of 5.0–51.3 ng/ml in SHIP-1. Point estimates for total, in- and outpatient costs as well as hospitalization at selected 25OHD concentrations (5, 10, 15, 20, 25, 30 ng/ml) in reference to a 25OHD concentration of 20 ng/ml are given. *p < 0.05. Ref, reference point; RR, Relative risk; CI, confidence interval; 25OHD, 25-hydroxy vitamin D. Model 1: adjustment for sex, age, month of blood sampling; Model 2: Model 1 + years of schooling, unemployment, equivalent household income, type of insurance (private vs. statuory), waist circumference.

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adjusted for sex, age and month of blood sampling, individuals with 25OHD concentrations of 5, 10 and 15 ng/ml had 197.1%, 28.2% and 8.3% (overall p-value = 0.009), respectively, higher total average follow-up costs than those with 25OHD concentrations of 20 ng/ml (Fig. 1). After full adjustment this association turned non-significant. In line with this finding, regression analyses showed no consistent relationship between baseline 25OHD concentrations and follow-up outpatient costs, hospitalization and inpatient costs after full adjustment.

Adjusted for sex, age, month of blood sampling, years of schooling, unemployment, equivalent household income, type of insurance (private vs. statuory), waist circumference.

4. Discussion

In our predominantly vitamin D deficient or insufficient population we observed a non-linear, inverse association between the 25OHD concentration and inpatient costs in cross-sectional sex, age and seasonal adjusted analyses, which, however, turned non-significant after further adjustment for education, unemployment, income, health insurance, and waist circumference. Low vitamin D concentrations were related to a higher risk of hospitalization and higher inpatient costs in a second independent population-based dataset. The association between lower 25OHD concentrations and health care costs after five years pointed into the same direction, and effect sizes were comparable but the statistical certainty was much lower.

The biologically active form of vitamin D, 1,25-dihydroxyvitamin D, is a potent steroid hormone, which exerts manifold actions throughout the body [29]. It binds to the vitamin D receptor, which is present in nearly every cell of the human body [2,29]. Thus, vitamin D not only acts on bone and the intestine to regulate calcium homoeostasis, but also on several other physiological systems, including the immune system and the cardiovascular system; and it affects the brain, pancreas, and the cell cycle [30]. A multitude of conditions and diseases were thus suggested to be related to vitamin D deficiency [3–5,7,8,30]. This in turn, led to the hypothesis, that vitamin D deficiency may be related to increased health care costs [30,31]. However, observational data regarding the association between vitamin D deficiency and health care costs in unselected, healthy subjects from community samples is sparse.

A range of studies among U.S. veterans [11,32–34] largely support the hypothesis of increased health care costs in vitamin D deficiency (25OHD<20 ng/ml). In one study of 15,340 veterans, vitamin D deficiency was related to increased out- and inpatient health care costs [33]. Similarly, among 886 veterans [11] the overall health care costs were 39% higher in vitamin D deficient compared to non-deficient (25OHD≥20 ng/ml) subjects and the 25OHD concentration was inversely correlated with total and inpatient costs but not with outpatient costs. In another study of 58 veterans with methicillin resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* infection, inpatient but not outpatient costs were higher in vitamin D deficient subjects compared to non-deficient subjects [34]. In contrast, in a study involving 125 veterans with inflammatory bowel disease, no association between vitamin D deficiency and health care costs was observed [32]. These veteran studies [11,32–34] included predominantly men (89–96% of the study population), comprised relatively old samples (mean age between 64 and 70 years), and two studies focussed on specific diseases or infections, thus limiting the generalizability of the results. Moreover, they reported inconsistent results. Three [11,33,34] out of four studies [11,32–34] demonstrated associations between vitamin D deficiency and inpatient costs, two studies [11,33] with total health care costs but only one study [33] with outpatient costs. Taken together, these four studies [11,32–34] suggest an association between vitamin D and inpatient costs, while the evidence for outpatient costs is not convincing. Our data is in line with these results. We confirmed non-linear, inverse associations of 25OHD concentrations and inpatient but not with outpatient costs. The observed association with inpatient costs was weakened by the sensitivity analyses, as the exclusion of extreme 25OHD values led to a reduction of statistical certainty in SHIP-1. However, in both cross-sectional, as well as in the longitudinal analyses, the association between 25OHD and inpatient costs points in the same direction, has comparable effect sizes, and in SHIP-Trend the results remained highly significant even after exclusion of extreme 25OHD values. In contrast, there was no association with outpatient costs neither in cross-sectional nor in longitudinal analyses. One explanation for the difference between out- and inpatient costs may lie in the disease patterns and severity associated with these costs. As previously reported, vitamin D is actively involved in the control of immune responses [4] and vitamin D deficient individuals compared to non-deficient individuals have higher rates of hospitalization with an infection [12]. Thus, in acute severe infections, a vitamin D deficiency may lead to increased rates of hospitalization and inpatient costs. Regarding total costs, we observed a suggestive, but not statistically significant (p = 0.124), non-linear inverse association with 25OHD concentrations, similar to the association observed with inpatient costs. Thus, our analyses, in part, support the hypothesis that a low vitamin D status might be associated with increased health care costs.

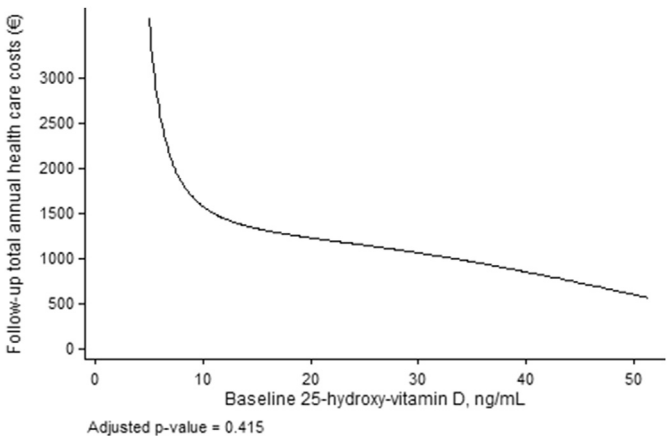

Fig. 1. Association between baseline 25OHD concentration and follow-up total annual health care costs.

In line with our data and the studies of U.S. veterans, more reports [12,35,36] demonstrated associations between 25OHD concentrations and inpatient costs. For example, among 1083 patients with hip or knee arthroplasty an inverse association between 25OHD concentrations and length of stay in an orthopaedic department was reported [36]. Patients with vitamin D deficiency (25OHD<20 ng/ml) had longer hospital stays than patients with higher vitamin D concentrations (25OHD>30 ng/ml) [36]. A similar result was obtained in 253 acute geriatric patients [35]. The average length of stay in the hospital increased by 3.1 days in patients with vitamin D deficiency (25OHD<20 ng/ml) compared to patients with higher 25OHD concentrations (25OHD≥20 ng/ml). A prospective study [12], that was based on data from 1713 Medicare beneficiaries, who participated in the 2001–2002 or 2003–2004 NHANES cycles, showed a longitudinal association between low vitamin D status (25OHD<15 ng/ml) and hospitalization in the following year. Elderly men and women (mean age above 69 years) with a low vitamin D status had a 3-fold higher risk of hospitalization with an infection than those with a higher vitamin D status (25OHD≥15 ng/

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ml), while associations between a low vitamin D status and hospitalization without an infection were suggestive but not statistically significant [12]. Our study confirmed associations between a low vitamin D status and hospitalization in two independent cross-sectional studies, but the longitudinal associations had a lower statistical certainty. A single 25OHD measurement may thus be a good marker for an individual's health status [37] and provide information on current health care costs. However, the ability of a single spot measurement of 25OHD to predict future health care costs in the general population is unknown. Although the cross-sectional and longitudinal analyses revealed similar effect estimates, the estimates for follow-up health care costs/hospitalization were not statistically significant. Possible reasons for this difference include reduced statistical power and selection bias. Additionally, our analyses were not stratified according to hospitalization with or without infection, as the respective data was not collected. Therefore, we cannot exclude prospective associations between vitamin D status and hospitalization in certain patient subgroups, especially with infections.

Strong evidence points to associations of vitamin D deficiency with a multitude of pathologic changes [3–6], which may translate into excess inpatient costs. In critically ill patients, for example, a high prevalence of vitamin D deficiency and associations with the outcome have been reported [as reviewed in [38]]. The observed associations may be related to the immunomodulatory role of vitamin D. In fact, it is known that vitamin D is central to the innate and adaptive immune system and thus in infection control [4,39]. Immune cells, including monocytes/macrophages, T-cells and B-cells express the vitamin D receptor and vitamin D metabolizing enzymes. 25OHD stimulates the response of monocytes/macrophages to bacterial infection via localized induction of the vitamin D receptor and 1α-hydroxylase [39]. Moreover, vitamin D enhances antimicrobial capacities of immune cells [4,39]. Vitamin D deficiency may thus result in a dysregulation of immune responses, while vitamin D supplementation may have a beneficial effect on immune function and may help to recover from acute illness, e.g. in intensive care patients [4,40].

Together with former studies [11,12,33–36], our cross-sectional and longitudinal data point towards an association of 25OHD concentrations and inpatient costs. This may have a practical implication, i.e. an increased monitoring of such patients, as they may be more vulnerable to severe disease than patients with normal or high vitamin D levels. However, our observational data does not allow to determine causality between the measures. Observational studies, as ours, are limited by confounding and selection effects, which may lead to and under- or overestimation of the observed association. We considered a large number of covariates and weighted the longitudinal data to account for selective loss of study participants between baseline and follow-up, still, it is necessary that our results are replicated in further studies to obtain conclusive evidence. Moreover reverse causality may apply. Indeed, it is highly debated whether vitamin D is a cause or a marker of ill health [37,41]. At the moment it is also unclear, whether certain patient groups, e.g. severely ill patients, benefit from vitamin D supplementation [42,43]. Thus, further studies are needed to determine whether vitamin D supplementation may contribute to a decrease in morbidity. Currently ongoing randomized controlled trials may help to answer this question [41] and define the clinical relevance of vitamin D also in respect to health care costs.

Our study has several limitations that need to be considered. First, blood sampling for 25OHD measurements was performed throughout the year and only once in all participants. It is arguable whether single-occasion measurements adequately illustrate the participant's vitamin D status, especially with regard to seasonal variation [44]. Yet, to minimize the influence of seasonal variation of 25OHD concentrations we considered month of blood sampling as covariate. Second, costs were estimated based on self-report. This approach has multiple limitations, including underreporting or incomplete assessment of services. Yet, the main results, reported as relative effects are less biased than absolute numbers. Third, although we weighted the longitudinal models we cannot completely rule out a selection bias, as those individuals who were lost to follow-up might have been among the most expensive at follow-up. Fourth, the follow-up time may have been too short to detect late effects. Fifth, our study population comprised a Caucasian population, representative for North Germany. We do not know if our findings are generalizable to other populations or ethnicities or regions with respect to latitude. In opposite to these limitations, our study also has considerable strengths. These include two independent study populations of intensively characterized adults from the general population. Further, the cross-sectional results regarding inpatient costs and hospitalization obtained in the SHIP cohort were strengthened by the replication in the SHIP-Trend cohort. Moreover, all examinations and laboratory measurements were performed by certified examiners following standardized protocols, assuring excellent quality of the cross-sectional and longitudinal data.

Taken together, our study argues for a relation between lower 25OHD concentrations and increased inpatient health care costs and hospitalization, while there was no association with outpatient costs. Thus, our results indicate an influence of vitamin D deficiency on health care costs in the general population that needs replication from different health care settings. Future studies might use linked claims data from health insurers to provide more direct measures of health care costs that might improve statistical precision.

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Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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