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Low vitamin D serum level is inversely associated with eczema in children and adolescents in Germany

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Abstract

Background: Recent studies have yielded heterogeneous results regarding the relationship between vitamin D and atopic conditions. The aim of this study was to investigate the association between serum vitamin D level and the prevalence of eczema in German children and adolescents.

Methods: Data were drawn for children aged 1–17 from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), a nationwide cross-sectional representative survey. 25-hydroxyvitamin D (25(OH)D) serum concentration was measured in 9838 individuals with eczema and categorized into quartiles. We investigated the association of vitamin D level and eczema by means of logistic regression models.

Results: Weighted prevalence of eczema was 13.5% (95% confidence interval (CI) 12.6–14.4%). Mean vitamin D level was significantly higher in those with eczema compared with those without ($P < 0.0001$). Logistic regression revealed an inverse association between low levels of vitamin D and eczema (multivariate OR for quartile 1 vs quartile 2: 0.76 (95% CI 0.61–0.94)).

Conclusions: This study suggests that low serum vitamin D level is inversely associated with eczema in German children and adolescents. Prospective studies are required to confirm this result, to discuss a potential opportunity for prevention of eczema.

Representing the most common skin condition in infancy, eczema is a major public health problem in industrialized countries (1, 2). The term eczema is used according to the nomenclature paper of the World Allergy Organization and stands for what was previously (and by many authors still is) named 'atopic dermatitis' or 'atopic eczema' (3). Eczema causes negative effects on the quality of life of affected children and their families and creates a great financial burden to society (4).

Recently, the intake of vitamin D during infancy has been proposed to play a role for eczema as it was found to be more prevalent in children with higher vitamin D3 intake in a prospective birth cohort study (5).

Vitamin D3 (calcitriol) plays an important role in human calcium homeostasis and has a role in modulating cell proliferation and differentiation in a variety of cell types (6). Its predominant circulating form, 25(OH)D, reflects the individual

vitamin D content. In newborns and children, the oral supplementation of vitamin D has been successfully introduced worldwide to prevent nutritional rickets (7). However, in contrast to vitamin D deficiency, little is known so far about the complex effects of high serum vitamin D levels (8).

The aim of this study is to investigate the association between serum vitamin D level and the prevalence of eczema in German children and adolescents, using data from the German National Health Interview and Examination Survey for Children and Adolescents (KiGGS) (9).

Material and methods

Design and study population

KiGGS is the first representative survey of children and adolescents aged 0–17 with main residence in Germany and

was conducted from May 2003 to May 2006 (9). The study was approved by the Charité Berlin Ethics Committee and the Federal Office for the Protection of Data. Based on a two-stage sampling design stratified by federal state and community size, an age-stratified sample was randomly selected from local population registries. With a response rate of 66.6%, 17 641 children and adolescents participated in the study.

Data collection

Data were collected by means of an age-adapted standardized self-administered questionnaire to be completed by parents/caregivers, parallel questionnaires for children from age 11, physical examination, and tests as well as a computer-assisted personal interview (CAPI) with parents/caregivers conducted by trained physicians. If parents/caregivers gave their consent, a blood sample from nonfasting subjects was obtained and immediately processed and separated. Blood samples from children younger than 1 year of age were generally not obtained (10).

Laboratory assay

To determine the vitamin D status in subjects, serum 25(OH)D was measured. Due to a change in method from an enzyme immunoassay to a chemiluminescence immunoassay (DiaSorin), valid measurements were only completed for a total of 10 015 children and adolescents. Inter- and intra-assay coefficients of variation were 11.7% and 9.9%. The lower detection limit of the assay was 5 nM. No significant divergences between participants in the two different laboratory measurement methods were found for any of the main study characteristics (10). Therefore, data from all participants with valid measurements using either method were included for analysis.

Exposure and confounding variables

The main exposure variable (25(OH)D [nM]) was classified into quartiles yielding the following cutoff points: quartile (Q) 1: ≤ 29.20 nM; Q 2: >29.20 and ≤ 42.30 nM (reference group); Q 3: >42.30 and ≤ 61.20 nM; Q 4: >61.20 and ≤ 215.00 nM. The season of medical examination documented in the history file was used to classify sunny season (May until October) or darker season with less sunlight (November until April).

Potentially confounding variables were chosen on the basis of documented associations with both eczema and vitamin D (8, 11). Data on age, gender, socioeconomic status (SES), and migrant status were taken from the self-administered questionnaires. Age was categorized into three age groups (1–2 years (infant age), 3–6 years (kindergarten age), and 7–17 years (school age)). Using information on parental income, occupational status, and education, SES was classified into low, medium, and high according to the Winkler Index (12). The participant was defined being a migrant if he/she immigrated from another country or if at least one of the parents was not

born in Germany and/or had no German citizenship (13). According to the classification proposed by Kromeyer-Hauschild, obesity was defined as a BMI >97 th percentile (14).

Outcome variable

Data on the outcome variable 'ever physician-diagnosed eczema' were obtained from the CAPI.

Statistical analyses

All data were analyzed using SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). Only children with a definite 'yes' or 'no' to the question on ever physician-diagnosed eczema were included. A *P*-value of ≤ 0.05 was considered significant based on two-sided tests. Ordinary proc means in SAS was used to compute mean vitamin D values with standard deviations (SD). Nonparametric tests (Wilcoxon two-sample test or Kruskal–Wallis test) were employed to compare mean serum vitamin D between groups, using proc npar1way in SAS. To test the difference between weighted eczema prevalence across vitamin D quartiles, the Rao–Scott chi-square test was employed.

Multivariable logistic regression was performed. A binary logistic regression model was fitted with 'ever physician-diagnosed eczema' as dependent variable. The variable 'vitamin D category' was entered into this model as primary independent variable. Age group, gender, season of examination, social status, migrant status, and obesity were entered into the model to adjust for confounding.

Frequency and regression analyses applied weights to correct for sampling design, deviations between the actual study sample and German population statistics, and discrepancies due to the reduced sample size of individuals with valid 25 (OH)D measurements. To take the cluster structure of the two-stage sample into account, the SAS procedures proc surveyfreq and proc surveylogistic were used.

Results

A total of 9838 children and adolescents with data on main exposure (vitamin D) and outcome (eczema) were eligible for analysis. The overall mean vitamin D serum level was 47.5 nM.

Mean serum 25(OH)D values of potential vitamin D-associated parameters are shown in Table 1.

Children in the youngest age group showed the highest mean vitamin D serum level, whereas serum concentration diminished continuously in the middle- and oldest age group.

Participants who were medically examined during summertime had significant higher mean serum vitamin D than participants with examination during wintertime. Migrants had a significant lower mean vitamin D than nonmigrants. The same was found for obese children compared with nonobese children. Mean 25(OH)D increased with social status and had the maximum in children of high social status. No significant difference in mean vitamin D level was found between boys and girls.

Table 1 Mean serum 25(OH)D by age, gender, season, migrant status, social status, and obesity

	N (unweighted)	25(OH)D [nM] Mean (SD)	P-value
Age group			
Infant age	765	63.2 (31.1)	<0.001
Kindergarten age	2092	49.6 (26.1)	
School age	6981	45.2 (24.9)	
Female gender	4826	47.3 (26.2)	0.1643
Male gender	5012	47.8 (26.1)	
Medical examination during summer	4797	58.5	<.0001
Medical examination during winter	5041	37.2	
Migrant	1411	38.1	<.0001
Nonmigrant	8399	49.1	
Social status			
Low	2662	45.0	<.0001
Medium	4519	48.5	
High	2448	49.8	
Obese	545	41.3	<.0001
Not obese	8489	46.6	

Table 2 Results from multivariable logistic regression with eczema as dependent variable

Exposure	OR* (95% CI)	OR† (95% CI)
25(OH)D category 1 vs 2	0.71 (0.58–0.87)	0.76 (0.61–0.94)
25(OH)D category 3 vs 2	1.03 (0.85–1.23)	0.99 (0.81–1.21)
25(OH)D category 4 vs 2	1.05 (0.87–1.26)	1.03 (0.84–1.27)

*raw [*N* = 9838].

†Adjusted for gender, age group, medical examination during summer, migrant status, social status, and obesity [*N* = 8822].

category 1 (quartile 1): ≤29.20 nM; category 2 (quartile 2): >29.20 and ≤42.30 nM (reference group); category 3 (quartile 3): >42.30 and ≤61.20 nM; category 4 (quartile 4): >61.20 and ≤215.00 nM.

The weighted eczema prevalence was found to be 13.5% (95% CI: 12.6–14.4%) in the total sample. Those with eczema had significantly higher mean vitamin D serum level compared with those without eczema (mean vitamin D = 50.6 nM, *n* = 1363 vs 47.1 nM, *n* = 8475, *P* < 0.0001).

Weighted eczema prevalence increased with 25(OH)D category, yielding a prevalence of 10.5% in the first quartile, 14.2% in the second quartile, 14.6% in the third quartile, and 14.8%, in the fourth quartile (*P* < 0.0001). Table 2 displays results from multivariate logistic regression. Low serum vitamin D level showed a significant inverse association with eczema prevalence (multivariate OR for Q1 vs Q2: 0.76 (0.61–0.94)). Higher levels of serum vitamin D were not significantly related to eczema. Estimates changed only marginally from raw to adjusted analyses.

Discussion

Investigating the association between serum vitamin D level and the prevalence of eczema in German children and

adolescents, a significantly reduced odds of eczema was found for the lowest vitamin D serum quartile in comparison with the reference quartile in multivariate analysis.

To our knowledge, this is the first study to look at vitamin D status and the prevalence of eczema in a representative German pediatric population. Consideration of weights, determination of vitamin D status directly by 25(OH)D serum level measurement, and the two-stage sampling design contribute to a high external validity of the findings. Another strength is the accurate assessment of potentially confounding variables. A nonresponse analysis conducted for KiGGS suggested a slight middle-class bias, but hardly any differences for the health-related variables between responders and nonresponders were found (9).

The study is limited by its cross-sectional design, which does neither permit to give an indication of the sequence of events nor to infer causality, that is, whether vitamin D status had an influence before, after, or during the onset of eczema. Besides, the outcome variable 'ever physician-diagnosed eczema' is determined only indirectly by parental report and thus susceptible to information bias. Selected characteristics of the answering proxy respondent such as age, gender, or relationship to the child might influence responses to chronic conditions in health surveys involving children (15). Our analysis did not include information on nutrient intake of vitamin D. In KiGGS, nutrient intake was assessed using a food frequency questionnaire that was not developed with respect to specific information on foods containing vitamin D or calcium and is therefore a relatively imprecise instrument for our analysis. Hintzpeter et al. (16) constructed a vitamin D intake index using data from the KiGGS study, but did not show an association with 25(OH)D concentration in multivariate analysis. Our study population did not include children below age one. 25(OH)D serum level in this age group will probably have been higher as one could expect a higher proportion of children taking vitamin D supplements. The finding that the youngest children had the highest vitamin D serum levels can be explained by the fact that vitamin D supplementation in infants is recommended until the second early summer when UV exposure becomes more intense (hence one to one and a half years, depending on date of birth) (17).

So far, there are only few studies investigating the effect of vitamin D on eczema. Bäck et al. (5) observed that higher intake of vitamin D3 during the first year of life was correlated with increased risk of eczema at age 6. Gale et al. (18) demonstrated that increased maternal 25(OH)D levels predisposed infants at 9 months of age to eczema. A study performed in Italy demonstrated an inverse association between vitamin D level and the clinical severity of eczema in children (19). There is a marked paucity of data looking at the association between eczema prevalence and vitamin D in adults. Oren et al. (20) published a study in which an increased risk of AD was observed among individuals with vitamin D deficiency, which is in contrast to our results. The findings by Oren et al., however, are limited in scope as the study was performed in obese individuals. These controversial results could be explained by the hypothesis of Benson et al. (21)

who propose a bimodal relationship between vitamin D and allergic skin diseases. Hyppönen et al.(22) suggest a threshold effect with both low and high 25(OH)D levels associated with elevated IgE concentrations.

In eczema, a Th2-driven immune response downregulates and inhibits important innate immune mechanisms such as skin barrier function and secretion of antimicrobial peptides (23). The vitamin hypothesis suggests that the prophylaxis of rickets with vitamin D has the apparent side effect of suppressing Th1 development (24), as vitamin D supplementation was shown to alter early Th1 lymphocyte development towards Th2 preponderance (25, 26). However, there is a paucity of data indicating what vitamin D levels are optimal for the prevention or management of allergic disorders. Levels of vitamin D necessary for the prevention of rickets are likely not the same as those needed to prevent or modify allergic diseases.

There are a number of biological and environmental factors that influence vitamin D status. Besides the cutaneous synthesis under ultraviolet radiation, dietary intake of vitamin D and vitamin D supplementation play a major role especially in children and adolescents. There are some difficulties in estimating dietary vitamin D as certain foods naturally contain vitamin D and others are fortified with vitamin D in some countries (27). As the endocrine vitamin D system is directly linked to cutaneous vitamin D3 conversion, it remains to be explored either whether the eczematous skin produces more vitamin D3 or whether higher vitamin D levels directly or indirectly promote eczematous skin lesions. Children with eczema may have used natural sunlight or UV phototherapy as a treatment to suppress skin inflammation which could have increased their serum 25-OH-vitamin D concentration. This might be one explanation why we found low levels to be inversely related to eczema. Genetics may also play an important role. A study was performed using five different population samples, two children's cohorts, and three adult cross-sectional samples, investigating the relationship between serum 25-OH-vitamin D and filaggrin (FLG) mutations (28). Significantly higher concentrations of serum 25-OH-vitamin D were found in carriers of FLG mutations with homogeneity across the studies. As FLG mutations are a strong known risk factor for eczema, this could explain why low concentrations of

serum 25-OH-vitamin D were inversely associated with eczema in our study.

Conclusion

This study contributes to the ever increasing interest in vitamin D effects on allergy, suggesting that low serum vitamin D level is inversely associated with eczema in German children and adolescents. If this would be a standalone study, it would be too early to suggest interventional studies. However, given the bulk of studies so far (a PubMed search of 'vitamin d AND allergy' gives 690 hits, search date: 26 March 2013), it is certainly timely to do intervention studies to explore a potential opportunity for prevention or treatment of allergic disease. Such studies are already underway.

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Author contributions

All authors participated in designing the study and devising a protocol for data analysis. Irene Heimbeck and Christian Apfelbacher carried out the statistical analyses, interpreted the data, and prepared the manuscript. Christian Apfelbacher and Matthias Wjst supervised the work, provided references, contributed to the interpretation of the data, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Conflicts of interest

None.

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