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Original article

25-Hydroxyvitamin D concentrations, asthma and eczema in childhood: The generation R study

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SUMMARY

Background & aims: A role of vitamin D in the development of respiratory and allergic disease in children remains unclear. It may be likely that vitamin D has an effect on airway inflammation, but only few studies examined the effect in children. We aimed to examine whether serum 25-hydroxyvitamin D (25(OH) vitamin D) concentrations are associated with the fraction of exhaled nitric oxide (FeNO), airway interrupter resistance (Rint), physician diagnosed asthma ever, wheezing and eczema in a population-based cohort study in 6 year old children.

Methods: Serum 25(OH) vitamin D concentration was assessed in 3815 children. 25(OH) vitamin D concentrations ≥75 nmol/L were considered as sufficient, between 50 and 75 nmol/L as insufficient, and <50 nmol/L as deficient. FeNO and Rint were measured at the research center. Data on physician diagnosed asthma, wheezing, and eczema were obtained by parent-reported questionnaires.

Results: In comparison with sufficient 25(OH) vitamin D concentration, deficient concentrations were associated with elevated FeNO of ≥25 ppb (OR: 2.54; 95% CI: 1.34–4.80). In addition, deficient and insufficient 25(OH) vitamin D concentrations were associated with a lower Rint (Z-score: −1.26; 95% CI: −1.66 to −0.85) (ß: −0.75; 95% CI: −1.08 to −0.42), and increased risks of eczema (OR: 1.65; 95% CI: 1.13–2.41) (OR: 1.44; 95% CI: 1.06–1.95). Insufficient 25(OH) vitamin D concentration were associated with a decreased risk of physician diagnosed asthma ever (OR: 0.59; 95% CI: 0.38–0.94).

Conclusions: Our results indicate that lower 25(OH) vitamin D levels are associated with elevated FeNO levels, but lower Rint values. Lower 25(OH) vitamin D levels are also associated with a decreased risk for asthma diagnoses but an increased risk for eczema.

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1. Introduction

In the past decades the prevalence of allergic disease has increased and has therefore become a major public health problem [1]. The development of allergic disease might be influenced by exposures including diet and behavioral changes associated with a Western lifestyle [2]. Vitamin D may be another important environmental factor and the prevalence of vitamin D insufficiency has increased [3]. Potential extra-skeletal functions of vitamin D may play a role in the risk of asthma and allergic disease [4–9]. Sun exposure and dietary intake are the main source of vitamin D [7]. Changes in lifestyle, such as decreased exposure to sunlight, increased time spent indoors, and physical inactivity, are important determinants of vitamin D deficiency [6,10]. There is at present no universally accepted definition for optimal 25-hydroxyvitamin D (25(OH) vitamin D) concentrations [9]. The Institute of Medicine

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defined 25(OH) vitamin D concentration of <50 nmol/L as deficient [11]. However, the definition of vitamin D sufficiency by the Institute of Medicine is controversial since the recommendation was primarily based on the effects on bone health whereas it has been argued that extra-skeletal effects of vitamin D are as important [12]. Vitamin D has immunomodulatory effects [13]. The effect of vitamin D on immune function in relation to respiratory and allergic disease have been examined [13]. Epidemiological studies have shown inconsistent results. Different studies found low and high levels of vitamin D in children to be associated with and increased risk of asthma and allergy outcomes [14–18]. Other studies did not find an association [19,20]. For the prevention of respiratory and allergic disease in children a role of vitamin D remains unclear [13,21,22]. Higher vitamin D levels have been associated with lower level of biomarkers of inflammation [23] and oxidative stress [24] in children. Therefore, it may be likely that vitamin D has an influence on airway inflammation. However, only few studies examined the effect in children as by measuring the fraction of exhaled nitric oxide (FeNO), which is a biomarker of airway inflammation [25,26]. We aimed to examine the cross-sectional association between serum 25(OH) vitamin D concentrations and FeNO, Rint, physician diagnosed asthma ever, wheezing and eczema in a population-based cohort study in 6 year old children.

2. Subjects and methods

2.1. Participants and study design

These analyses were part of the Generation R study, which is a population-based prospective cohort study and has been described in detail previously [27]. All children were born from April 2002 through January 2006. The study was approved by the medical ethical review board of the Erasmus Medical Center, Rotterdam, the Netherlands. At the start of each phase of the study both parents were asked for written informed consent.

2.2. Asthma-related outcomes and eczema

Fractional exhaled nitric oxide (FeNO), which is a biomarker of eosinophilic airway inflammation, was measured at 6 years of age using the NIOX chemiluminescence analyzer during a visit to the research center. Airway resistance (interrupter resistance (Rint), MicroRint, Micromedical, Rochester, Kent, UK) was measured during tidal breathing, with occlusion of the airway at tidal peak expiratory flow. To calculate Z-scores median values for no less than 5 acceptable measurements were calculated. The Z-scores were adjusted for the device that was used and for the child's height. Lung function measurements were obtained following the European Respiratory Society and American Thoracic Society guidelines [28]. Parents were asked to temporarily cease medication for respiratory conditions in children without symptoms 24 h before the visit to the research center. Data on physician diagnosed asthma ever since birth was obtained by annual parent-reported questionnaires. Data on current wheezing was collected by parent-reported questionnaires at the age 6 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC) [29]. Also, data on current eczema was collected by parent-reported questionnaires at 6 years of age.

2.3. 25-Hydroxyvitamin D concentration

25(OH) vitamin D concentration was assessed in thawed venous serum samples at the Endocrine Laboratory of the VU University Medical Center in Amsterdam. Isotope dilution online solid phase extraction liquid chromatography-tandem mass spectrometry (ID-XLC-MS/MS) was used to measure serum 25(OH) vitamin D and has been described in detail previously [30]. Serum 25(OH) vitamin D was taken during a visit to the research center at 6 years of age and available in 4167 children. Serum 25(OH) vitamin D was not available for children who expressed anxiety for blood sampling, whose parents did not provide informed consent for blood sampling, and when blood sample was not possible for logistic reasons (i.e. time constraints). The median 25(OH) vitamin D concentration in the study population was 64 nmol/L, varying from 4 to 211. On the basis of previous studies in the pediatric population, serum 25(OH) vitamin D concentrations ≥75 nmol/L were considered as vitamin D sufficient, concentrations between 50 and 75 nmol/L were considered as vitamin D insufficient, and <50 nmol/L as deficient [15,25,30].

2.4. Covariates

Information on potential confounders including sex, gestational age, birth weight and mode of delivery were collected from obstetric records evaluated in mid-wife practices and hospital registries [27]. Further information on potential confounders was obtained using a combination of pre-and postnatal questionnaires completed by both parents. These questionnaires included information on ethnicity [31], maternal educational level, maternal marital status, household income per month (≤ €2200 and > €2200), folic acid intake during pregnancy, maternal alcohol use during pregnancy, maternal smoking during pregnancy, multiparity and parental history of atopy. Ethnicity of the child was categorized into Western (Dutch, American, European, and Oceanian) and non-Western (Moroccan, Turkish, Dutch Antillean, Surinamese, Asian, Indonesian, African and Cape Verdean). Data on breastfeeding were collected by questionnaires at 2, 6 and 12 months of age. Information on the presence of cow's milk allergy in the first year was obtained by questionnaire at the ages of 6 and 12 months. Questionnaires completed by the mother at age 12 months included information on vitamin D supplementation in the previous 6 months and questionnaires at the age of 12 and 24 months included information on day-care attendance in the first 2 years. Information on the time the child spent playing outside during daytime, walking or biking to school and the time spend watching television was assessed by parent-reported questionnaires at the age of 6 years. Also, data on respiratory tract infections in the previous year was obtained by questionnaire at the same time point. During a visit to the research center at the age of 6 years total body fat mass was measured using a Dual-energy X-ray absorptiometry (DXA) scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA), which analyzed fat, lean and bone mass of the total body using enCORE software v.13.6. We calculated age- and sex-specific z-scores for body fat percentage based on the total Generation R Study sample with body composition measurements available the age of 6 years.

2.5. Population for analyses

All children with 25(OH) vitamin D concentrations available (n = 4167) were included in the analyses. To prevent clustering, only one child per family within the Generation R cohort was included by random selection (n = 352). In total, 3815 children were available for statistical analyses (Supplementary Fig. 1).

2.6. Statistical methods

Student's t test and chi-squared analyses were performed to examine differences between groups in 25(OH) vitamin D

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