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Endotoxin exposure, serum vitamin D, asthma and wheeze outcomes

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ABSTRACT

Background: Endotoxin has been shown to induce neutrophilic asthma and wheeze after binding toll-like receptor 4 to produce pro-inflammatory cytokines. Animal models have demonstrated that vitamin D might inhibit lipopolysaccharide-induced cytokines. However, whether endotoxin exposure and serum vitamin D deficiency interact to affect asthma and wheeze in humans has never been investigated in an epidemiological study.

Methods: Joint associations of house dust endotoxin and vitamin D with asthma and wheeze were examined using logistic regression adjusted for covariates in 5924 US participants of the National Health and Nutrition Examination Survey (NHANES). Interactions were assessed on the multiplicative as well as additive scale using the relative excess risk, the attributable portion due to additive interaction, and the synergy index.

Results: The median endotoxin concentration was 19.1 EU/mg. Prevalence of vitamin D inadequacy (20 −30 ng/ml) and deficiency (<20 ng/ml) were respectively 42.9 and 33.4%. The combination of high endotoxin and low vitamin D was associated with current asthma (OR: 1.56, 95% CI: 1.09, 2.23), wheeze in the past 12 months (OR: 1.72, 95% CI: 1.10, 3.71), recurrent wheeze (OR: 1.97, 95% CI: 1.00, 4.00), asthma diagnosis or recurrent wheeze (OR: 1.88, 95% CI: 1.33, 2.66), and current asthma or recurrent wheeze (OR:1.81, 95% CI: 1.23, 2.68) when compared to low endotoxin and normal vitamin D. The interactions between the exposures were not significant on the multiplicative or additive scale for any of the outcomes.

Conclusions: Combination of high endotoxin exposure and low vitamin D increases the odds of asthma and wheeze, but the exposures do not interact or modify each other's effect in the NHANES cohort.

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1. Introduction

Endotoxin is a lipopolysaccharide constituent of gram-negative bacteria cell walls and is ubiquitous in the environment as part of dust and ambient air [1]. Known predictors of higher endotoxin in homes include lower family income, younger age occupants, carpeting, pets, cockroaches or the presence of a smoker in the household [2–4]. Endotoxin has been proposed to cause asthma and asthma-like symptoms in both occupational and domestic settings because of its ability to induce T-helper (Th)-1 response with production of interferon (IFN)-γ and neutrophilic inflammation [3,5]. Paradoxically, early life exposure to endotoxin has been suggested to prevent later development of immunoglobulin (Ig) E mediated asthma and allergy by promoting Th-1 type immune development and inducing immune-modulatory effects [6].

Lately, vitamin D has also been of remarkable interest in asthma research because of growing reports of a potential relationship between vitamin D deficiency and asthma symptoms [7]. Sources of vitamin D include diet and sun exposure to ultraviolet B (UVB) light which converts 7-dehydrocholestrol in the skin into pre-vitamin D isomerized into vitamin D and later converted into 25-OH Vitamin D (25-OH-D) in the liver [8]. This vitamin has been shown to have immunoregulatory properties that could prevent asthma by modifying the effect of Th1, Th2 and regulatory T cells as well as improve asthma control by inhibiting Th17 lymphocytes linked to asthma severity and low steroid responsiveness [9,10]. Hypovitaminosis D is widespread in both developing countries where prevalences range between 30 and 90% and developed nations [11,12]. For example, in Europe, recent data suggest that serum

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vitamin D was below 20 ng/ml in 28.2–44.4% of Austrians, 40% or more of French, 50% or more of Germans and among 67–92% of Northern Europeans (Denmark, Finland, Ireland and Poland) [12]. In the US, according to 2001–2006 National Health and Nutrition Examination Survey (NHANES) data, 33% of the population have serum vitamin D levels below 20 ng/mL and 77% have levels below 30 ng/mL [13,14].

Despite the ubiquity of endotoxin in our environment and the high prevalence of low serum vitamin D, no epidemiological study has examined whether these two exposures interact to affect asthma and wheeze, though each of them has been found independently associated with at least one of these conditions. In a previous report using the NHANES, we found that endotoxin was independently associated with wheeze and that the relationship between endotoxin and asthma and wheeze was influenced by allergen-specific sensitization status as well as some environmental exposures [4]. Using the same study population, Keet et al. observed that lower serum vitamin D levels were positively associated with wheeze, asthma as well as IgE and noted that the relationship between vitamin D and wheeze was modified by age and atopic status [15]. The interaction between vitamin D and endotoxin with regard to asthma and wheeze has only been studied in animal models, suggesting a potentially synergistic effect in inducing these outcomes. It is established that extracellular monomeric endotoxin lymphocyte antigen 96 (LY96) complexes bind to Toll-like receptor (TLR)-4 triggering intracellular signal transduction cascades resulting in production of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, causing airway neutrophilic inflammation [16,17]. Both endotoxin induced cytokines have been found to be inhibited by serum vitamin D levels at or above 30 ng/ml exerting an anti-inflammatory action [18]. Moreover, it was demonstrated that vitamin D could upregulate mitogen-activated protein (MAP) kinase phosphatase-1 (MPK-1) expression by monocytes/macrophages and thus impede lipopolysaccharide induced phosphorylation of p38, a critical regulator of pro-inflammatory cytokines [19]. Therefore, in the present study, we aimed to test the hypothesis of a potential interactive effect of house dust endotoxin exposure and serum vitamin D on asthma and wheeze outcomes in a large epidemiological study representative of the US population.

2. Methods

2.1. Data source and study design

We used data from the NHANES conducted from 2005 to 2006 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and augmented by the National Institute for Environmental Health Sciences (NIEHS) to include endotoxin exposure assessment. The NHANES is an ongoing cross-sectional survey of the US non-institutionalized civilian population selected using a complex multistage sampling design to derive a representative sample of the US population. A total of 6185 NHANES participants had data on house dust endotoxin and serum vitamin D. After exclusion of 261 participants with missing poverty income ratio data, the final sample included 5924 subjects. NHANES protocols were approved by the institutional review boards of the NCHS and CDC and informed consent was obtained from all participants. Details on study design and procedures can be found in the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

2.2. Endotoxin measurement

Combined bed and bedroom floor dust samples were collected at each participant's home using a Sanitaire™ Model 3683 vacuum cleaner and a Mitest™ Dust Collector (Indoor Biotechnologies, Inc., Charlottesville, VA). One-square yard surfaces on beds and the adjacent floors were each vacuumed for 2 min. These composite dust samples were analyzed for endotoxin at our University of Iowa laboratory using a kinetic chromogenic *Limulus* amebocyte lysate assay with expansive quality assurance measures as previously described [4]. Sieved dust was extracted with sterile pyrogen-free water plus 0.05% Tween-20™. Control standard endotoxin (*E. coli* 055:B5) was used to develop 12-point standard curves and samples were assayed at four dilutions increasing four-fold from 1:400 to 1:25,600. Endotoxin concentrations were reported in endotoxin units per sieved dust weight (EU/mg of dust). The lower limit of detection was 0.000488 EU/mg.

2.3. Serum vitamin D

25-hydroxy vitamin D (25-OH-D) was measured using the DiaSorin assay, a two-step procedure. It consisted of extracting 25-OH-D and other hydroxylated metabolites from serum with acetonitrile and assaying the treated sample with an equilibrium RIA procedure based on an antibody specific to 25-OH-D. The sample, antibody, and tracer were incubated for 90 min at 20–25 °C. Separation was accomplished after a 20-min incubation at 20–25 °C with another antibody-precipitating complex. A NSB buffer was subsequently added after and before centrifugation to help decrease non-specific binding. More detailed information about this procedure is available at http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/vid_d.pdf.

The Institute of Medicine defines vitamin D deficiency as serum 25-OH-D levels <20 ng/ml [20]. In addition, the Endocrine Society Practice Guideline defines vitamin D as inadequate at serum 25-OH-D levels between 20 and 30 ng/ml [8]. Consequently, we categorized serum vitamin D as normal (≥30 ng/ml), inadequate (20–30 ng/ml), or deficient (<20 ng/ml) and defined low serum vitamin D as inadequate or deficient (<30 ng/ml).

2.4. Asthma and wheeze

The prevalence of asthma and wheeze were assessed by responses to the following questions [1]: “Has a doctor or other health professional ever told you that you/Sample Person [SP] had/have/has asthma?” (Asthma diagnosis) [2], “Do you/Does SP still have asthma?” (Current asthma) [3], “In the past 12 months, have you/has SP had any wheezing or whistling in chest?” (Wheeze in past 12 months) [4], “In the past 12 months, how many attacks of wheezing or whistling have you/has SP had?” Past asthma was defined as the presence of asthma diagnosis and the absence of current asthma.

2.5. Covariates and sensitization

Data on age, gender, race/ethnicity, family income, presence of a smoker in the household, number of people in the household, number of years lived in the house, pet avoidance because of allergies, as well as presence of mildew, cockroaches, and pets in the homes were collected using questionnaires. Poverty income ratio (PIR) was estimated using guidelines and adjustment for family size, year and state. Physical activity was evaluated by questions related to daily activities, leisure time activities, and sedentary activities (and metabolic-equivalent task (MET) scores were calculated. Participants' weight and height were measured in a mobile

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