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Age- and Atopy-Dependent Effects of Vitamin D on Wheeze and Asthma

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To the Editor

The role of vitamin D in a myriad of physiologic processes has recently become a focus of controversy. Growing evidence suggests a role for vitamin D in the regulation of IgE and development of allergic sensitization, as well as in lung development, incident asthma and asthma exacerbation, although the studies are not all consistent (1–3). Despite these data, the Institute of Medicine recently reviewed the literature about vitamin D and concluded that there were insufficient data to recommend supplementation with vitamin D for prevention of non-bone related diseases(4). Here, we use nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to assess the relationship between vitamin D levels and respiratory outcomes.

Study participants included 6857 US subjects 6 years of age and older who participated in NHANES 2005–2006 as discussed in the supplementary methods. The relationships between serum vitamin D and wheeze, history of asthma, and asthma exacerbation were

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assessed by logistic regression in analyses that accounted for the complex survey methods and were adjusted for age, sex, race/ethnicity, house-hold income and BMI z-score. Analyses were performed with STATA 11.0/SE (Statacorp, College Station, TX) and R 2.12.2 (R Foundation, Vienna, Austria).

Serum vitamin D levels were inversely associated with both current wheeze and asthma in adjusted analyses. (Table I and Table EII) Each 10 ng/mL decrease in vitamin D was associated with a 26% greater odds (OR: 1.26 [95% CI: 1.09–1.46]) of current wheeze and an 8% greater odds of asthma (1.08 [1.01–1.16]). Among those with asthma, lower vitamin D levels were associated with increased odds of both emergency room visit and exacerbation in the past year (OR for each 10 ng/mL decrease in vitamin D: 1.53[1.01–2.32] and 1.38[1.06–1.80], respectively). Results relating to asthma are described in more detail in the supplementary results.

The association between lower vitamin D and wheeze was similar for asthmatics and non-asthmatics ($p=0.37$ for interaction term). The higher odds of current wheeze associated with lower vitamin D levels was driven by a strong inverse relationship between vitamin D level and current wheeze in older subjects ($p=0.007$ for interaction term). (Table I, Figure 1) This was not due to a stronger relationship between vitamin D and wheeze in patients who reported COPD (OR [95% CI] per 10ng/mL vitamin D: 1.23 [1.02–1.55] for those with COPD and 1.32 [1.13–1.55] for those without COPD). Nor was the vitamin D effect among older subjects on current wheeze due to smoking: the relationship between vitamin D and wheeze was similar in current, former, and never smokers (OR [95% CI]: 1.28 [1.04–1.57]; 1.35 [1.03–1.81]; and 1.24 [0.88–1.74] respectively for every 10ng/mL decrease in vitamin D).

In addition to age, there was a suggestion that the relationship between vitamin D and current wheeze was also modified by atopy and total IgE level, with a stronger relationship found in non-atopics and among those with lower IgE levels ($p=0.096$ and 0.08 for the interaction between vitamin D level and atopy and total IgE, respectively). (Table 1) Moreover, the relationship between vitamin D and wheeze was not mediated by either atopy or total IgE (Table EIV).

In this broadly representative sample of the US population, lower serum vitamin D levels were associated with increased risk of current wheeze, and this relationship varied by age,, suggesting an age-dependent relationship between vitamin D and wheeze that has not previously been reported. In addition, while vitamin D deficiency is known to be associated with higher total IgE levels in this population(5), the vitamin D-wheeze relationship found here was independent of total IgE and atopy, implying that vitamin D protects against wheeze by a mechanism other than the down-regulation of IgE. Indeed, we found that wheeze may be more strongly associated with vitamin D in non-atopic subjects and those with lower total IgE levels. Taken together, our findings highlight the complexity of the relationships between vitamin D and respiratory and allergic diseases, suggesting that vitamin D likely modifies respiratory disease risk through multiple mechanisms which manifest as pleiotropic and age-dependent effects.

There are several potential mechanisms to explain the relationship between vitamin D and wheeze, and why vitamin D deficiency may be a stronger risk factor for wheeze in those without atopy and in older people. The first is that low vitamin D is a risk factor particularly for respiratory infection. Data from both animal models and humans support this hypothesis. Vitamin D directly and indirectly induces production of antimicrobial proteins, and has other antimicrobial effects (2, 6). In humans, relative vitamin D deficiency has been associated with recent respiratory tract infection, viral infection accompanying wheeze, and, in small

interventional studies, vitamin D supplementation provided some protection against respiratory infection prospectively(2, 7). Alternatively, or additionally, vitamin D may protect against inflammatory reactions to environmental pollutants, and may be broadly important in regulating chronic inflammation in the lung(3). Finally, accumulating evidence suggests a role for vitamin D in lung development; vitamin D deficiency in early life may lead to permanent susceptibility to poorer respiratory outcomes that are not related to atopy(8). Each of these causes of wheeze could be more important in older people and non-atopics; wheeze in younger people may be more likely to be related to allergy than it is in older people. However, because the mechanistic rationale is not entirely clear, this novel finding should be replicated before definitive conclusions can be made.

Ultimately, cross-sectional studies such as this one are only a first step in understanding causal relationships between vitamin D and respiratory outcomes. Because data are collected simultaneously on all variables, it is not possible to determine temporal relationships between exposure and outcome. In addition, because vitamin D is closely related to both diet and outdoor activity, and may be related to socio-economic status in ways not fully accounted for by the adjustments here, there is potential for unmeasured and residual confounding to complicate the relationships that were evaluated. With those caveats in mind, the strength of this study is that it is of a nationally representative sample of the US population and the findings extend our current understanding of the role of vitamin D in respiratory and allergic diseases.

In sum, our findings point to a strong protective effect of vitamin D against wheeze and asthma exacerbation in a nationally representative study population, supporting the notion that vitamin D status may influence the risk of respiratory disease. In light of the known association between vitamin D and IgE, our findings that the vitamin D-wheeze relationship was strongest for non-atopics and older subjects suggest that vitamin D may modify the risk of allergic and respiratory disease through multiple mechanisms. Taken together, these findings underscore the importance of conducting prospective studies, including clinical trials, to understand better the role of vitamin D in incident asthma and wheeze.

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Abbreviations/Acronyms

IgE	Immunoglobulin E
NHANES	National Health and Nutrition Examination Survey
COPD	Chronic Obstructive Pulmonary Disease
OR	Odds Ratio
NCHS	National Center for Health Statistics

CDC Centers for Disease Control
BMI Body Mass Index

References

1. Searing DA, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunol Allergy Clin North Am*. Aug; 30(3):397–409. [PubMed: 20670821]
2. Taylor CE, Camargo CA Jr. Impact of micronutrients on respiratory infections. *Nutr Rev* May. 69(5):259–69.
3. Sandhu MS, Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol*. 2010 Sep; 105(3):191–9. quiz 200–2, 17. [PubMed: 20800785]
4. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin d from the institute of medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011 Jan; 96(1):53–8. [PubMed: 21118827]
5. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: Results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. May; 127(5):1195–202. [PubMed: 21329969]
6. Herr C, Greulich T, Koczulla RA, Meyer S, Zakharkina T, Branscheidt M, et al. The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. *Respir Res*. 12:31. [PubMed: 21418564]
7. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol*. May; 127(5):1294–6. [PubMed: 21315433]
8. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D Deficiency Causes Deficits in Lung Function and Alters Lung Structure. *Am J Respir Crit Care Med*. Feb 4.

Figure 1. 3-Dimensional representation of the predicted probability of wheeze by vitamin D level and age given by logistic regression

Predicted probabilities of wheeze at a given age and vitamin D level are specified for Caucasian females of mean income and BMI z score. Age is in years and vitamin D in ng/mL.

Table 1

Recent wheeze by vitamin D status and group.

		Wheeze in Past Year					
Category of Vitamin D	Unstratified Model	≥ 50 years old		Atopic		History of Asthma	
		No (5049)	Yes (1808)	No (3530)	Yes (3327)	No (5959)	Yes (998)
OR (95% CI)	≥30ng/mL	1 by definition					
	20–30ng/mL	1.21 (0.85–1.73)	1.28 (0.80–2.06)	1.09 (0.74–1.61)	1.37 (1.00–1.86)	1.23 (0.81–1.87)	1.16 (0.70–1.92)
	<20 ng/mL	1.25 (0.78–2.00)	2.48 (1.46–4.23)	1.80 (1.19–2.75)	1.41 (1.09–1.83)	1.70 (1.12–2.59)	1.57 (0.99–2.49)
	P value for Trend	0.34	0.002	0.008	0.02	0.01	0.05
	10 ng/mL decrease in Vit D	1.10 (0.92–1.31)	1.65 (1.30–2.10)	1.34 (1.11–1.62)	1.17 (1.03–1.32)	1.25 (1.04–1.51)	1.32 (1.13–1.54)
P value for interaction		0.007		0.097		0.37	

All analyses adjusted for age, gender, race/ethnicity, income, and BMI z score. **Bold** indicates statistically significant odds ratios. OR: Odds Ratio, Vit D: Vitamin D