

Body Mass Index, Vitamin D Status, and Asthma Control Among Inner-City Children: A Feasibility Study

Phuong Vo, MD, MPH,¹ Carlos A. Camargo Jr., MD, DrPH,²
Melissa Prosper, BS, MPH,³ and Megan Bair-Merritt, MD, MSCE¹

Childhood obesity and asthma are major public health problems. Obesity appears to significantly increase risk of poor asthma control, with serum 25-hydroxyvitamin D (25OHD) deficiency being a potential, modifiable risk factor on this pathway. In this pilot study of 32 young children with asthma, who were recruited from a safety-net hospital, we examined the feasibility of assessing weekly reports of breathing problems from caregivers and the distributions of 25OHD and related biomarkers among the children. Most (83%) caregivers completed the entire 3 months of weekly surveys. Approximately half of the children had body mass index z -score ≥ 1.04 ; and one-third had 25OHD level < 20 ng/mL. Mean Test for Respiratory and Asthma Control in Kids scores indicated poor asthma control. Intensive longitudinal follow-up of vulnerable children is feasible.

Keywords: obesity, 25-hydroxyvitamin D, asthma, urban, minority, pediatrics

Introduction

CHILDHOOD OBESITY AND asthma are major public health problems, particularly among Hispanic, non-Hispanic black, and impoverished children.^{1,2} Several studies have reported the association between obesity and poor asthma control.^{3–6} Vitamin D deficiency, which is highly prevalent among obese, minority children,⁷ may play a modifiable role on the obesity-asthma control pathway.⁸

Vitamin D likely plays a role in at least 2 mechanisms related to asthma morbidity. It regulates the production of cathelicidin (LL-37), an antimicrobial peptide that promotes intracellular killing of bacteria and viruses,⁹ and may thus decrease risk of acute respiratory infections, a common trigger of asthma exacerbations in children.¹⁰ Vitamin D also increases glucocorticoid bioavailability in bronchial smooth muscle cells,¹¹ which improve responsiveness to inhaled corticosteroids. Serum 25-hydroxyvitamin D (25OHD) is commonly used to estimate vitamin D status. Most (88%) of 25OHD is bound to vitamin D-binding protein (DBP), while the remainder is bound to albumin; only 0.03% of 25OHD is available in its free form.¹² Bioavailable 25OHD includes free and albumin-bound 25OHD. It is unclear how these

different forms of 25OHD and its related biomarkers are distributed among children with asthma.

Before pursuing a large-scale randomized controlled trial to understand the role of vitamin D deficiency on the obesity-asthma control pathway, it is important (1) to determine how to accurately measure the children's breathing problems to assess their level of asthma control and (2) to explore the distribution of the different forms of 25OHD and its related biomarkers such as DBP, albumin, or LL-37 among children with asthma to later examine which form of 25OHD best predicts poor asthma control and whether its related biomarkers also play a role. Obtaining accurate measurement of asthma control is challenging; and caregivers often underestimate their children's level of asthma control due to recall bias.¹³ Hence, weekly follow-up might better measure the frequency of the children's breathing problems than relying on caregivers' reports at 3-month interval follow-up.^{14,15} It is unclear how receptive urban, low-income caregivers would be to weekly follow-up given that they may have multiple stressors that limit their ability to engage in this more intensive symptom reporting. Therefore, we conducted a pilot study to determine the following: (1) the feasibility of assessing weekly reports of breathing problems from vulnerable

¹Department of Pediatrics, Boston Medical Center, Boston, Massachusetts.

²Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts.

³Department of Community Health Sciences, Boston University School of Public Health, Boston, Massachusetts.

caregivers; and (2) the distributions of serum 25OHD and related biomarkers among children with asthma.

Methods and Materials

Study design and sample

Children aged 2 to 5.9 years were recruited from pediatric general and pulmonary clinics if they (1) had either a physician diagnosis of asthma or symptoms and medication use consistent with asthma in the previous 6 months (obtained by medical record review); and (2) were not on vitamin D supplementation. Because vitamin D status is affected by seasonality and because children with asthma tend to have more exacerbations during the fall/winter months,¹⁶ recruitment occurred over a 4-month period from November through March. The authors' Institutional Review Board approved the study.

Data collection

Recruitment and retention. We maintained a log of the number of eligible study participants, the number who agreed to participate, the number who declined to participate, and the number who completed the full study (baseline survey, blood draw, and follow-up). A brief survey on basic demographics and reasons for declining to participate was administered to those who elected not to participate.

Feasibility of weekly survey. By either telephone or email weekly, for 12 weeks from study enrollment, we asked the following to assess children's breathing problems: "Please reply yes or no to let us know whether your child had breathing problems (coughing during the day or night, wheezing, or shortness of breath) during the past week." If caregivers had concerns about their children's breathing problems, they were instructed to follow-up with their children's healthcare providers.

Caregivers indicated at enrollment whether they would like to be reached by telephone or email and the best time period to call them if by telephone. If no response after a 2-day interval, another attempt was made. All calls and emails were made by the research assistant (RA).

Height and weight measurement. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2) from weight and height measured at enrollment as part of the children's clinic visits. BMI z-scores were calculated using EPI Info Nutrition Module.¹⁷ BMI z-score of >1.64 represented >95 th percentile (obese); BMI z-score of ≤ 1.64 and ≥ 1.04 as the 85th to 95th percentile (overweight); BMI z-score of -1.64 to <1.04 as 5th to 85th percentile (normal weight).

25OHD and other biomarkers. The caregiver and the child were accompanied by the RA to the phlebotomy laboratory once the questionnaire on asthma control was completed at enrollment. Serum 25OHD was measured by using the Abbott Architect assay (Abbott, Waukegan, IL); DBP by the Human Gc-Globulin ELISA Kit (AssayPro, St. Charles, MO); albumin by Bromocresol Green Albumin Assay Kit (Sigma-Aldrich, St. Louis, MO); and LL-37 by Human LL-37 ELISA Kit (Hycult Biotech, Uden, The Netherlands).

According to the Institute of Medicine, a serum 25OHD level of at least 20 ng/mL adequately meets the requirement

for bone health, whereas the scientific evidence as to the optimal level to recommend for other health conditions was inconclusive.¹⁸ The published normal reference range for DBP levels is 300–600 $\mu\text{g}/\text{mL}$ ¹⁹ and albumin 3.5–5.5 g/dL.²⁰ Total 25OHD levels were reported to the caregivers; in cases where the levels were <20 ng/mL, caregivers were instructed to talk to their children's healthcare providers. Free and bioavailable 25OHD were calculated using a formula outlined by Powe et al.²¹

Asthma control. At enrollment and then at 3 and 6 months follow-up, caregivers completed a 15-item close-ended questionnaire, which included validated questions from the Test for Respiratory and Asthma Control in Kids (TRACK),²² which assesses asthma control in children younger than 5 years old. A TRACK score of 80 or less suggests that asthma is not well controlled. The questionnaire also included the child's atopy status (positive skin prick tests, presence of eczema), age, sex, self-reported race/ethnicity, smokers in the household, parental education, household income, and parental history of asthma or allergies.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

Demographics (n = 32)	n (%) or mean $\pm$ SD
Age (years), mean	3.8 $\pm$ 1.1
Sex	
Female	14 (44)
Male	18 (56)
Race/ethnicity	
Non-Hispanic white	8 (25)
Non-Hispanic black	15 (47)
Hispanic	7 (22)
Other	2 (6)
Parental education	
<High school	5 (16)
High school graduate	19 (59)
More than high school	8 (25)
Annual family income	
<\$30,000	21 (66)
\$30,000 to \$69,000	6 (19)
>\$69,000	1 (3)
Declined	4 (12)
Clinical factors (n = 32)	n (%) or mean $\pm$ SD
Child history of eczema	17 (56)
Smokers in the household	7 (23)
Parental asthma or allergies status	16 (50)
BMI z-score ≥ 1.04	15 (47)
Baseline TRACK score, mean	59 $\pm$ 26
Biomarkers (n = 28)	Median (IQR)
Total 25OHD (ng/mL)	23.9 (9.6–33.6)
Bioavailable 25OHD (ng/mL)	1.7 (0.6–2.7)
Free 25OHD (pg/mL)	4.3 (1.6–6.3)
D-binding protein ($\mu\text{g}/\text{mL}$)	434 (287–548)
Albumin (g/dL)	4.6 (4.2–5.0)
LL-37 (ng/mL)	46 (20–308)

BMI, body mass index; 25OHD, 25-hydroxyvitamin D; LL-37, cathelicidin; TRACK, Test for Respiratory and Asthma Control in Kids.

Statistical analyses

All statistical analyses were conducted by using STATA 12.1 (StataCorp, College Station, TX). Descriptive analyses (eg, frequencies and distributions) summarized the feasibility of recruitment and retention, the feasibility of the weekly survey, and the key study parameters. Chi-squared statistics were conducted to examine whether there were any socio-demographic differences in those that were eligible and consented versus those who were eligible and did not consent. Pearson correlation coefficient was used to examine the relationship between weekly breathing problems and TRACK question on breathing problems during the past 4 weeks at the 3-month follow-up survey. Although statistical power was limited, unadjusted analyses using chi-square, Kruskal–Wallis and Wilcoxon rank sum tests were conducted to explore possible associations between BMI and serum 25OHD and its related biomarkers and asthma control (ie, TRACK

scores as categorical variables—asthma controlled or not controlled).

Results

Recruitment and retention

Of the 49 children who met study criteria and were approached, 32 (65%) were enrolled. Other than annual family income, where more enrolled had an annual family income less than \$30,000 compared with nonenrolled (66% versus 36%, respectively; $P=0.03$), there were no significant differences in age, sex, race/ethnicity, or parental education between the enrolled and nonenrolled groups ($P>0.20$). Not having time was the most common reason caregivers declined participation (53%). Table 1 summarizes demographic characteristics of the study population. Study retention rate for the 6-month study was 81%.

TABLE 2. DEMOGRAPHIC CHARACTERISTICS, CLINICAL FACTORS, AND VITAMIN D-RELATED BIOMARKERS STRATIFIED BY BODY MASS INDEX Z-SCORE AND SERUM TOTAL 25-HYDROXYVITAMIN D

	BMI z-score			Total 25 OHD levels		
	-1.64 to <1.04 (n = 16)	≥1.04 (n = 14)	P	<20 ng/mL (n = 9)	≥20 ng/mL (n = 19)	P
Demographics						
Age (years)						
2 to 3.9	9 (56)	9 (64)	0.65	2 (22)	7 (39)	0.39
4 to 5.9	7 (44)	5 (36)		7 (78)	11 (61)	
Sex						
Female	5 (31)	8 (57)	0.15	4 (44)	7 (37)	0.70
Male	11 (69)	6 (43)		5 (56)	12 (63)	
Race/ethnicity						
Non-Hispanic white	3 (19)	5 (36)	0.45	3 (33)	4 (21)	0.72
Non-Hispanic black	8 (50)	6 (43)		4 (45)	9 (48)	
Hispanic	3 (19)	3 (21)		1 (11)	5 (26)	
Other	2 (12)	0 (0)		1 (11)	1 (5)	
Parental education						
<High school	2 (12)	3 (21)	0.74	1 (11)	4 (21)	0.75
High school graduate	10 (63)	7 (50)		6 (67)	10 (53)	
More than high school	4 (25)	4 (29)		2 (22)	5 (26)	
Annual family income						
<\$30,000	12 (75)	7 (50)	0.10	7 (78)	13 (68)	0.65
\$30,000 to \$69,000	3 (19)	3 (21)		2 (22)	3 (16)	
>\$69,000	1 (6)	0 (0)		0 (0)	1 (5)	
Declined	0 (0)	4 (29)		0 (0)	2 (11)	
Clinical factors						
Child history of eczema	10 (63)	7 (50)	0.49	8 (89)	7 (37)	0.01
Smokers in the household	2 (12)	6 (43)	0.06	4 (44)	4 (21)	0.20
Parental asthma or allergies status	7 (44)	7 (50)	0.73	4 (44)	8 (42)	0.91
BMI z-score						
-1.64 to <1.04	N/A	N/A		5 (56)	10 (59)	0.87
≥1.04	N/A	N/A		4 (44)	7 (41)	
Baseline TRACK score ^a						
≤80	11 (69)	10 (71)	0.87	8 (89)	12 (63)	0.16
>80	5 (31)	4 (29)		1 (11)	7 (37)	
Biomarkers						
D-binding protein (μg/mL), median (IQR)	441 (332–500)	427 (406–486)	0.62	412 (402–453)	446 (376–500)	0.64
Albumin (g/dL), median (IQR)	4.6 (4.4–4.7)	4.6 (4.5–4.8)	0.70	4.5 (4.4–4.7)	4.6 (4.4–4.6)	0.75
LL-37 (ng/mL), median (IQR)	47 (28–60)	45 (39–57)	0.74	45 (34–55)	46 (39–57)	0.90

Data are number (%) of children unless otherwise indicated.

^aTRACK score of 80 or less suggests that asthma is not well controlled.

BMI, body mass index; 25OHD, 25-hydroxyvitamin D; LL-37, cathelicidin; TRACK, Test for Respiratory and Asthma Control in Kids.

Feasibility of weekly survey

Most (83%) caregivers completed all 12 weeks of the weekly surveys focused on recent breathing problems. Ninety-percent of caregivers (28 of 31) preferred follow-up by telephone over email. No more than 2 attempts at contacting the caregivers were needed to be made each week. At the 3-month follow-up, caregivers' report of their children's breathing problems in the last 4 weeks positively correlated with their weekly reports ($r=0.72$, $P<0.01$).

BMI, 25OHD, and asthma control

Almost half (47%) of the children had BMI z -score ≥ 1.04 . One-third (32%) of the children had total 25OHD <20 ng/mL. The median serum total, bioavailable, and free 25OHD, DBP, albumin, and LL-37 levels are summarized in Table 1. Mean TRACK scores at enrollment, 3-, and 6-month follow-up were 59 ± 26 , 75 ± 29 , and 71 ± 28 , respectively, with a score of 80 or greater suggesting well-controlled asthma.

Although statistical power was limited in this pilot feasibility study, unadjusted analyses showed that among children with BMI z -score -1.64 to <1.04 compared to those with BMI z -score ≥ 1.04 at enrollment, there were no significant differences in asthma control based on TRACK scores at enrollment ($P=0.87$). Similarly, among children with total 25OHD <20 ng/mL compared to those with total 25OHD ≥ 20 ng/mL, there were no significant differences in asthma control based on TRACK scores at enrollment ($P=0.16$) (Table 2). Furthermore, enrollment levels of free and bioavailable 25OHD as well as the other vitamin D-related biomarkers were not significantly associated with asthma control (as measured by TRACK scores at enrollment) (all $P>0.05$).

Discussion

In this pilot study, we demonstrated the feasibility of conducting a study involving intensive longitudinal follow-up and biomarker measurement in a sample of urban, impoverished 2 to 5.9 years old children. Few studies to date have examined parental study retention in intensive longitudinal study with weekly surveys focused on their children. One intensive longitudinal study that collected weekly web-based surveys from 18- and 19-year-olds reported that minority and lower socioeconomic status respondents completed fewer weekly surveys compared with their white, higher income peers.²³ In contrast, parents in our study were able to provide intensive data for a period of 3 months.

In our sample, almost half of the children were overweight or obese and a third with inadequate total 25OHD level (<20 ng/mL); their mean TRACK scores indicated poor asthma control. With lower levels of total 25OHD, bioavailable and free 25OHD and LL-37 levels may also be altered. The bioavailable and free 25OHD and LL-37 levels in our sample were in the lower range, while DBP and albumin levels were in the normal range. Studies reporting free and bioavailable 25OHD levels among children are limited to those with chronic kidney diseases, insulin resistance, and critical care hospitalization.^{24–27} Among children with chronic kidney diseases where both levels were measured, free 25OHD ranged from 3.8 to 14.4 pg/mL and bioavailable 25OHD from 0.9 to 5.2 ng/mL^{26,27}; we provide important estimates in low-income, under-represented asthmatic children.

As a pilot study, our objective was to gather critical data to inform planning of a large-scale randomized controlled trial. As such, we had limited power to examine associations between obesity and asthma morbidity or the potential mediating role of vitamin D. Preliminary unadjusted analyses showed no significant association between BMI and asthma control, nor between multiple vitamin D-related biomarkers (total, bioavailable or free 25OHD; DBP, albumin, and LL-37) and asthma control. Larger, more generalizable studies are needed to address these important questions. We intend to seek support for such studies based, in part, on the success of this pilot study.

In conclusion, conducting a study with intensive longitudinal follow-up and biomarker measurement among a sample of urban, impoverished children is feasible. Large randomized controlled trials are needed to examine the role of vitamin D in the obesity and asthma control pathway. A better understanding of this pathway could have major impact on asthma control among high-risk children.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Phuong Vo, MD, MPH
Department of Pediatrics
Boston Medical Center
818 Harrison Avenue
Boston, MA 02118

E-mail: phuong.vo@bmc.org

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