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# Race Differences in the Association between Multivitamin Exposure and Wheezing in Preterm Infants

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## Abstract

**Objective—**We aimed to determine whether vitamin D exposure, as estimated by use of multivitamins, is positively or negatively associated with recurrent wheezing in infants born preterm.

**Study Design—**This prospective cohort study enrolled 300 infants, born at 28 $^{0/7}$– 34 $^{6/7}$ weeks gestational age, and conducted follow-up at 3, 6, 9, and 12 months adjusted age.

**Results—**55.9% of black and 36.6% of non-black infants experienced recurrent wheezing. Adjusted odds ratios for the association between multivitamin exposure at 3 months and recurrent wheezing were 2.15 (95% CI: 0.97, 4.75) for black and 0.43 (95% CI: 0.19, 0.96) for non-black infants with an interaction by race (p=0.003). In lag-effect models, odds ratios were 2.69 (95% CI: 1.41, 5.14) for black and 0.50 (95% CI: 0.27, 0.92) for non-black infants.

**Conclusions—**Differences by race were seen in associations between multivitamins and wheezing; population heterogeneity should be considered when evaluating vitamin supplementation.

## Introduction

Wheezing in infancy is a major long-term morbidity of prematurity. Although most studies have focused on the outcomes of very low birth weight (VLBW) infants, particularly those with bronchopulmonary dysplasia (BPD), increased wheezing, asthma, respiratory infections, and healthcare utilization are also seen in larger premature infants without BPD.[1, 2] In larger preterm infants without overt neonatal lung injury, early exposures may



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perturb the development of the lung, airway, or immune system and lead to recurrent wheezing later in life.[3]

One such candidate exposure with the potential to impact lung and immune development is vitamin D. Long known to regulate calcium and phosphorous homeostasis, vitamin D is also a hormone implicated in a wide range of physiological processes and disease states, particularly those with an inflammatory or immune component. Polymorphisms in the vitamin D receptor (VDR) and vitamin D deficiency both have been associated with numerous disease states, including asthma.[4–7] While the impact of vitamin D on the immune system is controversial, some authors have claimed that the beneficial effects of stimulating the vitamin D pathway include decreased inflammation and enhanced defense against pathogens.[8–11] However, the VDR also plays a key role in the induction of lung inflammation.[12] Furthermore, exposure of the immature immune system to vitamin D may skew T-cells towards a more allergic TH-2 cytokine expression profile.[13–18] Vitamin D also has the potential to alter lung and airway development; in bronchial smooth muscle cells the vitamin D pathway plays a role in the up-regulation of genes involved in morphogenesis, cell growth, and survival, as well as structural proteins.[19] Therefore, vitamin D supplementation has the theoretic potential to positively or negatively impact pulmonary and immune health. Furthermore, preterm infants, with developmentally immature pulmonary and immune systems that have already been perturbed by preterm birth, may be particularly vulnerable to any positive and negative effects of vitamin D. There is a paucity of data on optimal vitamin D supplementation for preterm infants ≥28 wks GA, especially after discharge from the NICU, with most recommendations focusing on short-term outcomes in term or acutely ill VLBW infants. In addition, a growing body of literature suggests racial differences in the vitamin D pathway.[20–23] The Gastrointestinal Risk Factors for Wheezing in Premature Infants (GRWPI) study aimed to determine the association between vitamin D supplementation and wheezing in the first year of life in preterm infants without BPD, and to explore differences by race.

## Patients and Methods

A prospective cohort of 300 premature infants admitted to Rainbow Babies and Children's hospital from 2006 to 2011 was studied. Enrollment and baseline data collection occurred prior to initial discharge to home. Follow-up by telephone interview of the children's guardians was done at 3, 6, 9, and 12 months of age adjusted for prematurity. This study was approved by the University Hospitals Institutional Review Board, and parents provided written informed consent.

### Performance Site

Rainbow Babies and Children's Hospital is located in Cleveland, OH, at latitude 41 degrees North.

### Study Population

Inclusion criteria included gestational age of $28\ ^{0/7}$– $34\ ^{6/7}$ weeks at birth, and having been weaned off supplemental oxygen by 28 days of age (subsequent oxygen administration for

<72 hrs due to a procedure or intercurrent illness was allowed). Exclusion criteria included mild, moderate, or severe BPD (oxygen requirement >28 days), grade III or IV intraventricular hemorrhage, periventricular leukomalacia, post-hemorrhagic hydrocephalus requiring a shunt, chromosomal abnormality, pulmonary or airway malformations, complex congenital heart disease, gastrointestinal malformations or atresias requiring surgery, significant neurologic abnormalities, history of Bell's stage II–III necrotizing enterocolitis, and documented wheezing during initial neonatal hospitalization. Only infants of English-speaking parents were enrolled.

## Determination and Definition of Variables

Baseline data were abstracted from the inpatient medical record and by parent interview. A baseline questionnaire including family history and further demographic information was also administered to the parents while the infants were inpatients. Infants were considered to have a family history of asthma if a parent or sibling had been diagnosed with asthma. Infant race was based on self-reported maternal race.

The prescription of vitamins at the time of discharge was abstracted from the medical record. At follow-up, parents were asked to report if their child had taken any vitamins since the time of last contact, and then were asked to identify the type and brand. The most commonly reported form of vitamin D supplementation was in a standard pediatric multivitamin containing 400 IU/dose of cholecalciferol. Follow-up questionnaires also asked parents to report whether their child had respiratory symptoms at any time since the last contact.

The question about wheezing used to determine the outcome asked about "wheezing or whistling in the chest" since the last interview and the wording was based on several questionnaires validated in older children and shown to perform well in this population.[24–26] If parents reported wheezing, they were asked to estimate the number of separate episodes of wheezing that occurred. The primary study outcome, recurrent wheezing, was defined as either multiple episodes of wheezing reported during one interview, or single episodes of wheezing reported at multiple interviews. In the primary analysis, an infant who missed at least one but not all visits after baseline, but did not have recurrent wheezing based on the visits where they were seen, was assumed to have no recurrent wheezing. Secondary outcomes, such as oral steroid use and inhaled or nebulized medication use over the 12 month period, were defined similarly.

At each interview, parents were asked to report if their child had any respiratory infection (including a cold, bronchiolitis, or pneumonia), had been prescribed a medication by inhaler or nebulizer for a respiratory problem, had taken an oral steroid for a respiratory problem, or had emergency room visits or hospitalizations for a respiratory problem. An emergency room visit for a breathing problem was defined as an emergency visit that did not result in a hospitalization. Infants were considered to be exclusively formula-fed after discharge from the initial neonatal hospitalization if the parent never reported giving breast milk at any follow-up interview.

### Sample Size Justification

Assuming a two-sided significance level of 0.05, a 50% prevalence of multivitamin exposure at 3 months, and a 25% incidence of recurrent wheezing in the non-exposed group, a sample size of 300 was selected to detect an odds ratio of 2 for recurrent wheezing comparing those with to those without multivitamin exposure at 3 months with 80% power.

### Statistical Analysis

Medians and interquartile ranges were used to describe continuous data while frequencies and percentages were used to describe count data. Two-sample t-tests, Wilcoxon Mann-Whitney tests and Pearson chi-squared tests were used to compare continuous, ordinal and categorical variables respectively at baseline between black and non-black infants.

To investigate the association between multivitamin use at 3 months and the population averaged odds of recurrent wheezing (or other binary respiratory outcomes), a Generalized Estimating Equations (GEE) approach based on an unstructured working correlation structure was used to account for correlation among outcomes from infants within the same family. A robust variance-covariance estimate was also used to account for any model misspecification. To avoid over-fitting models, covariates were selected *a priori* based on biological knowledge and included characteristics determined at enrollment: gestational age at birth, race, family history of wheezing, and exclusive formula feeding at baseline. Because most participants were identified as either black or African American or white or Caucasian, participants were grouped as either black or non-black for all analyses. The study was not powered to detect interactions by race, but due to racial differences in the vitamin D pathway reported in the literature, a pre-specified analysis of interaction between multivitamin use and race was planned.

Similar models were also used to investigate potential time-lag effects of multivitamin use at earlier time points on the odds of wheezing reported at all subsequent time points. SAS Version 9.2 was used for all analyses.

## Results

Of the 300 infants enrolled in the study, 292 infants were seen on at least one follow-up visit after baseline. Of these 292 infants, 3 subjects were missing family history of asthma, resulting in an analytic sample of 289 infants. The percentage of the 289 infants that were followed-up at the 3, 6, 9, and 12 month visits were 96.2%, 95.8%, 92.7%, and 93.4% respectively. A comparison of black and non-black infants at baseline showed that black infants had lower birth weight, younger gestational age, lower maternal age, a higher proportion on public insurance, and a higher proportion of exclusive formula feeding at discharge. (table 1)

Vitamin supplementation in this cohort was overwhelmingly in the form of a multivitamin containing 400 IU/dose of cholecalciferol. Zero to two families at each time-point reported giving a vitamin that only contained vitamin D which also contained 400 IU/dose of cholecalciferol. The overall pattern of vitamin use was one of slow attrition, with rates dropping at each follow-up visit (table 2). Few families reported non-use at an earlier time-

point and then subsequent use, specifically, 3.0% at 6 months, 4.5% at 9 months, and 8.0% at the 12 month follow-up.

Overall, rates for wheezing, medication use, and healthcare utilization reported at each time-point were high, particularly among the black infants (table 2, figure 2). Recurrent wheezing was identified in 45.7% of the cohort (55.9% of black and 36.6% of non-black infants). An association between parental report of interval vitamin exposure at 3 months was associated with recurrent wheezing, with a strong interaction by race (table 3). Non-black vitamin exposed infants experienced less recurrent wheezing than non-black vitamin exposed infants while black vitamin exposed infants experienced more recurrent wheezing than their unexposed counterparts. Similar patterns were seen for respiratory medication use (table 3).

A secondary analysis excluding 13 infants who did not have follow-up at 12 months but were assumed to have no recurrent wheezing in the primary analysis showed no meaningful change in the estimated odds ratios. Multivitamin exposure reported at 3 months was associated with a significant increase in recurrent wheezing in black infants [OR 2.52 (95% CI 1.08, 5.88)], and a significant decrease in non-black infants [OR 0.42 (95% CI 0.19, 0.94)], with a significant interaction by race (p=0.001).

Lag effects between vitamin exposure and subsequent wheeze were also modeled. The association between interval vitamin use reported at the 3 month follow-up and subsequent interval wheezing reported at the 6, 9 or 12 month time-points showed a significant increase in wheezing in vitamin-exposed black infants [OR 2.69 (95% CI 1.41, 5.14)] and decrease in wheezing in non-black vitamin exposed infants [OR 0.50 (95% CI 0.27, 0.92)], with a significant interaction by race (p<0.001). Alternatively, the association between interval vitamin exposure reported at 3 or 6 months and subsequent wheezing at 9 or 12 months showed a significant increase in wheezing in black vitamin exposed infants [OR 3.09 (95% CI 1.56, 6.12) but a non-significant decrease in wheezing in white infants [OR 0.62 (95% CI 0.31, 1.22)], with the interaction by race also remaining significant (p<0.001).

## Discussion

Consistent with other studies in moderately preterm and late preterm infants, this cohort of relatively healthy neonates with a minimal initial requirement for oxygen and respiratory support nevertheless experienced high rates of pulmonary morbidity in the first year of life. This study demonstrated an association between early multivitamin exposure and recurrent wheezing in the first year of life, with a strong interaction by race. Black infants supplemented with multivitamins early in life experienced increased wheezing, whereas non-black supplemented infants experienced decreased wheezing. While our hypothesis was related to vitamin D supplementation, effects of other vitamins cannot be excluded because the primary form of vitamin D supplementation was in the form of a multivitamin containing 400 IU/dose of cholecalciferol. Nevertheless, due to known racial differences in the vitamin D pathway and its effects on immune and pulmonary development and inflammation, vitamin D remains a likely candidate to explain the associations that were seen.

Long known to regulate calcium and phosphorous homeostasis, vitamin D is also a hormone implicated in a wide range of physiological processes and disease states, particularly those with an inflammatory or immune component. While the impact of vitamin D on the immune system is controversial, some authors have claimed that the beneficial effects of stimulating the vitamin D pathway include decreased inflammation and enhanced defense against pathogens;[8–11] However, there are also theoretical reasons that vitamin D exposure could increase wheezing in immature patients; exposure of the immature immune system to vitamin D may skew T-cells towards a more allergic TH-2 cytokine expression profile.[13–18] Vitamin D also has the potential to alter lung and airway development.[19] Preterm infants, with developmentally immature pulmonary and immune systems, may be particularly vulnerable to any positive and negative effects of vitamin D. Because most of the participants were exposed to multivitamins, and not exclusively cholecalciferol or ergocalciferol, we cannot be certain that the association is with vitamin D and not another component of multivitamins. However, given the strong theoretical connection between the vitamin D and wheezing illnesses, as well as the growing body of literature showing racial differences in the vitamin D pathway, it is highly likely to be the associated vitamin.

The apparent benefit of supplementation in the non-black infants is consistent with a growing body of evidence that low levels of 25(OH)D3 are associated with disease states in older children and adults. Vitamin D is thought to have anti-inflammatory properties, and is hydroxylated to its active form, $1,25(OH)_2$ D3, in T-cells, B-cells, and macrophages.[8, 15] There is also evidence that vitamin D deficiency is associated with non-infectious wheezing illnesses in children.[27 5] Among American inner city youth, the prevalence of vitamin D deficiency is higher in children with asthma than in those without asthma.[28] Several studies have also found an association between low vitamin D levels or rickets with acute lower respiratory infections in children, including RSV.[9, 29–32] However, there are also potential mechanisms by which vitamin D supplementation may increase wheezing, as suggested by the findings in the non-black infants in this cohort. Exposing the immature immune system to vitamin D may predispose infants to asthma and allergy later in life. In vitro studies and mouse models suggest that vitamins may skew T cells towards either a less allergic T-helper 1 (vitamins $B_6$, E, and C) or a more allergic T-helper 2 (vitamins D and A) phenotypes.[13, 14, 16, 17, 33–37] There may be a critical developmental window for such an effect.[3] If this is the case, premature infants could be more or less vulnerable than term infants. Milner et al. (2004) found that black infants exposed to multivitamins in the first 6 months of life had a higher risk of asthma in early childhood, and that formula-fed vitamin-exposed infants of all races experience more food allergies.[21] Vitamin D supplementation at 3 years of age was not associated with asthma, suggesting that a critical window for exposure exists in early infancy, a time of rapid pulmonary and immunologic maturational changes.[3] The study by Milner et al. assessed a cohort not yet impacted by the 2003 recommendations for a minimum of 200 IU of vitamin D from formula or vitamin supplements. The authors hypothesized that vitamin D or A exposure in infancy were potentially skewing T-cells towards a more allergic T-helper-2 (Th2) cytokine profile. Vitamin D exposure in infancy was also associated with allergy and asthma among Finnish young adults.[38] These data suggest that infants' developing immune systems may be

vulnerable to immunomodulation, and the preterm immune system may have the potential to be even more vulnerable to the immunomodulatory effects of vitamin D.

Racial differences in the relationship between vitamin D status and health have been previously reported. Powe et al. (2013) showed that black patients had lower levels of both 25(OH)D levels and vitamin D binding protein than white patients, leading to similar levels of bioavailable vitamin.[22] Recently, 25(OH)D levels have been shown to be correlated with cardiovascular disease in white but not black adults.[23] In black diabetic adults, 25(OH)D levels are positively correlated with calcified atherosclerotic plaque.[39] Among postmenopausal women, black women have less bone turnover than white women despite lower 25(OH)D levels and higher PTH levels.[20] The previously mentioned study by Milner et al. found that black, but not white, infants supplemented with multivitamins in the first 6 months of life had an increased risk of asthma at age 3 years.[21] Finally, among white mothers, both low and very high serum levels of vitamin D are associated with having a small for gestational age infant (a U-shaped relationship), whereas for black mothers there is no association between maternal serum vitamin D levels and having a small infant.[40]

This study has several limitations. In this cohort study, we cannot show that the strong associations between multivitamin use and recurrent wheezing, as well as the interactions between multivitamin use and race, are causal. While the vitamin D literature is strongly suggestive of potential mechanisms, this cannot be definitively determined by an observational study or one in which the primary form of vitamin D supplementation was in the form of a multivitamin. This study also did not attempt to correlate serum vitamin levels to respiratory status. Vitamin use could be a marker for family beliefs about health status. However, the lag effects model and pattern of declining vitamin use also suggests that vitamin use preceded wheezing in most cases, making it less likely that families chose whether or not to give their child vitamins as a result of respiratory status. A further characteristic of all cohort studies is the inability to adjust for unknown confounders. It is difficult to imagine, however, a confounding variable accounting for such disparate apparent opposite effects by race. Finally, it is worth noting that the population of infants studied was highly formula exposed, and therefore was receiving significant dietary vitamin D from milk, as well as from vitamin supplementation. Thus, the results of this study cannot and should not be generalized to exclusively breastfeeding infants.

In conclusion, this study has found a striking interaction by race in the association between exposure to multivitamin preparations and recurrent wheezing. Vitamin exposure in black infants was associated with more recurrent wheezing but less recurrent wheezing in non-black infants. Vitamin D is postulated to be a potential causative agent. The results serve as an important reminder that, despite numerous theoretical benefits and harms, the effects of vitamin D on the immature and developing pulmonary and immune systems must be better understood to identify dosing that will maximize long-term health in the preterm population. Effects of any intervention in other populations, including *in utero* fetuses and older pediatric patients, cannot necessarily be extrapolated to premature infants. Furthermore, finding an optimal dosing strategy for vitamin preparations in black preterm infants is particularly important due to the increased rates of both prematurity and prematurity-associated wheezing in black children, and the signal of potential harm from this study.

Nevertheless, black infants are certainly at risk for rickets, and require vitamin D supplementation in some form. We speculate that the therapeutic window for vitamin D supplementation is shifted or narrower in black compared to non-black infants. A randomized clinical trial of two different vitamin D dosing strategies in black infants born preterm is currently underway (NCT01601847).

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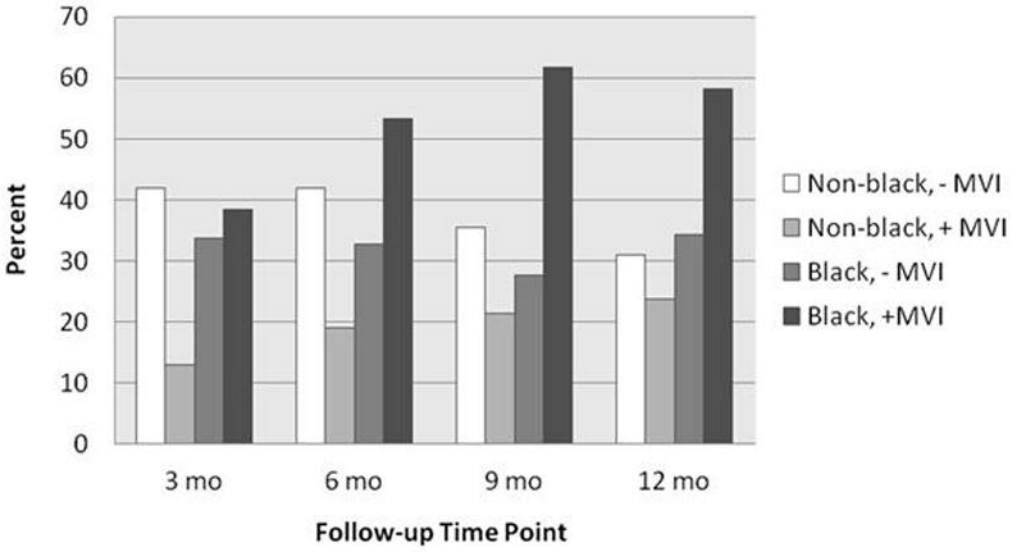


**Figure 1. Rates of interval wheezing reported at each follow-up time-point**
by race and reported multivitamin (MVI) use between hospital discharge and 3 months adjusted age.

## Table 1

Demographics.

| Characteristic | All Infants | Black (N=136) | Non-Black (N=153) | p-value |
|---|---|---|---|---|
| | Median(IQR) or N (%) | Median(IQR) or N (%) | Median(IQR) or N (%) | |
| Race | | | | |
| Black | 136 (47.1%) | | | |
| White | 144 (49.8%) | NA | NA | NA |
| Asian | 9 (3.1%) | | | |
| Family history of asthma | 114 (39.4 %) | 61 (44.9 %) | 53 (34.6 %) | 0.09[1] |
| Birth weight (grams) | 1760(1450,2080) | 1645(1376,1970) | 1879(1520,2280) | <0.001[2] |
| Gestational age (weeks) | 32.6(31.0,33.9) | 31.8(30.3,33.3) | 33.0(31.6,34.0) | <0.001[2] |
| Maternal age (years) | 26.0(22.0,32.0) | 24.0(20.0,29.0) | 29.0(24.0,33.0) | <0.001[2] |
| Total days on oxygen | 0.0(0.0,1.0) | 0.0(0.0,1.0) | 0.0(0.0,2.0) | 0.21[3] |
| Mother's education | | | | |
| Less than high school | 45 (15.6%) | 27 (19.9%) | 18 (11.8%) | |
| High school | 66 (22.8%) | 40 (29.4%) | 26 (17.0%) | 0.001[1] |
| Above high school | 178 (61.6%) | 69 (50.7%) | 109 (71.2%) | |
| Number of smokers in the household | | | | |
| 0 | 186 (64.4%) | 80 (58.8%) | 106 (69.3%) | |
| 1 | 73 (25.3%) | 44 (32.4%) | 29 (19.0%) | |
| 2 | 23 (8.0%) | 9 (6.6%) | 14 (9.1%) | 0.15[3] |
| 3 | 5 (1.7%) | 2 (1.5%) | 3 (2.0%) | |
| 4 | 2 (0.7%) | 1 (0.7%) | 1 (0.7%) | |
| Where baby will live | | | | |
| Rent | 123 (42.6%) | 80 (58.8%) | 43 (28.1%) | |
| Own | 123 (42.6%) | 25 (18.4%) | 98 (64.1%) | <0.001[1] |
| Family or Friends | 43 (14.9%) | 31 (22.8%) | 12 (7.8%) | |
| Number of people living in home | | | | |
| 2 | 9 (3.1%) | 8 (5.9%) | 1 (0.6%) | |
| 3 | 73 (25.3%) | 29 (21.3%) | 44 (28.8%) | |
| 4 | 84 (29.1%) | 33 (24.3%) | 51 (33.3%) | 0.24[3] |
| 5 | 61 (21.1%) | 35 (25.7%) | 26 (17.0%) | |
| 6 | 39 (13.5%) | 15 (11.0%) | 24 (15.7%) | |
| 7 or above | 23 (8.0%) | 16 (11.8%) | 7 (4.6%) | |
| Number of children under 5 living in home | | | | |

| Characteristic | All Infants | Black (N=136) | Non-Black (N=153) | p-value |
|---|---|---|---|---|
| | Median(IQR) or N (%) | Median(IQR) or N (%) | Median(IQR) or N (%) | |
| 1 | 130 (45.0%) | 70 (51.5%) | 60 (39.2%) | |
| 2 | 108 (37.4%) | 43 (31.6%) | 65 (42.5%) | 0.07[3] |
| 3 | 41 (14.2%) | 21 (15.4%) | 20 (13.1%) | |
| 4 | 10 (3.5%) | 2 (1.5%) | 8 (5.2%) | |
| Palivizumab dose during initial hospitalization[4] | 105 (36.3 %) | 50 (36.8%) | 55 (35.9%) | 0.90[1] |
| Palivizumab referral made[4] | 157 (54.3 %) | 76 (55.9%) | 81 (52.9%) | 0.64[1] |
| Number of pets in the household | | | | |
| 0 | 163 (56.4%) | 106 (77.9%) | 57 (37.2%) | |
| 1 | 67 (23.2%) | 19 (14.0%) | 48 (31.4%) | <0.001[3] |
| 2 | 35 (12.1%) | 6 (4.4%) | 29 (19.0%) | |
| 3 or above | 24 (8.3%) | 5 (3.7%) | 19 (12.4%) | |
| Cat in the household | 49 (17.0%) | 4 (2.9%) | 45 (29.4%) | <0.001[1] |
| Dog in the household | 87 (30.1%) | 21 (15.4%) | 66 (43.1%) | <0.001[1] |
| Bird in the household | 2 (0.7%) | 2 (1.5%) | 0 (0.0%) | NA |
| Reptile in the household | 3 (1.0%) | 2 (1.5%) | 1 (0.7%) | NA |
| Other pet in the household | 19 (6.6%) | 7 (5.1%) | 12 (7.8%) | 0.48[1] |
| Will live on a farm | 5 (1.7%) | 0 (0.0%) | 5 (3.3%) | NA |
| Child in daycare | 72 (28.1%) | 41 (34.5%) | 31 (22.6%) | 0.038[1] |
| Child is/will be enrolled in Healthy Start | 124 (51.5%) | 89 (80.2%) | 35 (26.9%) | <0.001[1] |
| Family is/will be enrolled in WIC | 180 (62.9 %) | 126 (94.7%) | 54 (35.3%) | <0.001[1] |
| Health insurance of the baby | | | | |
| No insurance | 2 (0.69%) | 2 (1.47%) | 0 (0%) | |
| Private insurance | 113 (39.1%) | 15 (11.0%) | 98 (64.1%) | <0.001[1] |
| Public insurance (SCHIP or Medicaid) | 174 (60.2%) | 119 (87.5%) | 55 (36.0%) | |
| Vitamin-D containing vitamin prescribed at discharge | 176 (60.6 %) | 82 (60.3%) | 93 (60.8%) | 0.99[1] |
| Exclusively formula feed at discharge | 81 (28.0 %) | 53 (39.0%) | 28 (18.3%) | <0.001[1] |
| Exclusive formula feeding after discharge from hospital | 214 (74.0%) | 116 (85.3%) | 98 (64.1%) | <0.001[1] |

[1] Comparison based on Pearson chi-squared test.

[2]Comparison based on two-sample t-test.

[3]Comparison based on Wilcoxon Mann-Whitney test.

[4]At the time of discharge from their initial neonatal hospitalization, patients who qualified for palivizumab prophylaxis for respiratory syncytial virus (RSV) were referred for monthly outpatient injections during the RSV season. Infants discharged during the RSV season receive the first dose prior to discharge.

**Table 2**

Percentage of vitamin use and respiratory symptoms by follow-up time.

| | Black | | | | Non-Black | | | |
|---|---|---|---|---|---|---|---|---|
| | **3 months** | **6 months** | **9 months** | **12 months** | **3 months** | **6 months** | **9 months** | **12 months** |
| **Multivitamin use** | 65/131 (60.3%) | 40/125 (32.0%) | 36/123 (29.3%) | 53/120 (29.2%) | 85/147 (57.8%) | 51/151 (33.8%) | 36/145 (24.8%) | 34/150 (22.7%) |
| **Exclusive formula feeding** | 113/131 (86.3%) | 117/126 (92.9%) | 118/123 (95.9%) | 119/120 (99.2%) | 95/147 (64.6%) | 111/151 (73.5%) | 125/146 (85.6%) | 138/150 (92.0%) |
| **Any wheezing** | 47/130 (36.2%) | 55/126 (43.7%) | 53/123 (43.1%) | 55/120 (45.8%) | 37/146 (25.3%) | 43/151 (28.5%) | 39/145 (26.9%) | 41/150 (27.3%) |
| **More than one episode of wheezing** | 27/130 (20.8%) | 31/126 (24.6%) | 31/122 (25.4%) | 29/120 (24.2%) | 21/146 (14.4%) | 23/151 (15.2%) | 18/145 (12.4%) | 22/150 (14.7%) |
| **Respiratory infection** | 64/131 (48.9%) | 72/126 (57.1%) | 76/123 (61.8%) | 79/119 (66.4%) | 45/147 (30.6%) | 76/151 (50.3%) | 81/146 (55.5%) | 79/150 (52.7%) |
| **Diagnosed with RSV** | 5/131 (3.8%) | 6/125 (4.8%) | 5/122 (4.1%) | 1/119 (0.8%) | 7/146 (4.8%) | 7/150 (4.7%) | 2/146 (1.4%) | 8/150 (5.3%) |
| **Seen in ER for breathing problem** | 24/131 (18.3%) | 19/126 (15.1%) | 14/123 (11.4%) | 23/120 (19.2%) | 7/146 (4.8%) | 11/151 (7.3%) | 8/146 (5.5%) | 8/150 (5.3%) |
| **Hospitalized for breathing problem** | (7.6%) | (7.1%) | (8.2%) | (2.5%) | (8.2%) | (4.6%) | (2.1%) | (3.3%) |
| **Oral steroid for respiratory indication** | 3/130 (2.3%) | 8/126 (6.3%) | 9/122 (7.4%) | 16/120 (13.3%) | 7/146 (4.8%) | 9/151 (6.0%) | 8/146 (5.5%) | 7/150 (4.7%) |
| **Inhaled or nebulized medication for respiratory problem** | 7/131 (5.3%) | 23/126 (18.3%) | 36/123 (29.3%) | 39/120 (32.5%) | 10/147 (6.8%) | 21/151 (13.9%) | 21/146 (14.4%) | 21/150 (14.0%) |

Percentage at each visit reflects parental report of interval use of behavior or symptoms at any time since the last interview. Listed as ratio of number reported to total followed (percentage reported).

## Table 3

Association between exposure to vitamin-D containing vitamins and measures of pulmonary health by race.

| Outcome | Race | OR (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|
| **Recurrent wheezing** | Black | 2.15 (0.97, 4.75) | 0.06 | 0.003 |
| | Non-Black | 0.43 (0.19, 0.96) | 0.04 | |
| **Inhaled or nebulized medication use** | Black | 1.99 (0.88, 4.54) | 0.10 | 0.06 |
| | Non-Black | 0.68 (0.29, 1.60) | 0.38 | |
| **Oral steroid use** | Black | 2.50 (0.86, 7.31) | 0.09 | 0.03 |
| | Non-Black | 0.51 (0.18, 1.47) | 0.21 | |