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Early Infant Multivitamin Supplementation Is Associated With Increased Risk for Food Allergy and Asthma

Joshua D. Milner, MD*; Daniel M. Stein, MHS‡; Robert McCarter, ScD§; and Rachel Y. Moon, MD||

ABSTRACT. Objective. Dietary vitamins have potent immunomodulating effects in vitro. Individual vitamins have been shown to skew T cells toward either T-helper 1 or T-helper 2 phenotypic classes, suggesting that they may participate in inflammatory or allergic disease. With the exception of antioxidant protection, there has been little study on the effect of early vitamin supplementation on the subsequent risk for asthma and allergic disease. The objective of this study was to determine whether early vitamin supplementation during infancy affects the risk for asthma and allergic disease during early childhood.

Methods. Cohort data were analyzed from the National Center for Health Statistics 1988 National Maternal-Infant Health Survey, which followed pregnant women and their newborns, and the 1991 Longitudinal Follow-up of the same patients, which measured health and disease outcomes. Patients were stratified by race and breastfeeding status. Factors that are known to be associated with alteration of risk for asthma or food allergies were identified using univariate logistic regression. Those factors were then analyzed in multivariate logistic regression models. Early vitamin supplementation was defined as vitamin use within the first 6 months.

Results. There were >8000 total patients in the study. The overall incidence of asthma was 10.5% and of food allergy was 4.9%. In univariate analysis, male gender, smoker in the household, child care, prematurity (<37 weeks), being black, no history of breastfeeding, lower income, and lower education were associated with higher risk for asthma. Child care, higher levels of education, income, and history of breastfeeding were associated with a higher risk for food allergies. In multivariate logistic analyses, a history of vitamin use within the first 6 months of life was associated with a higher risk for asthma in black infants (odds ratio [OR]: 1.27; 95% confidence interval [CI]: 1.04–1.56). Early vitamin use was also associated with a higher risk for food allergies in the exclusively formula-fed population (OR: 1.63; 95% CI: 1.21–2.20). Vitamin use at 3 years of age was associated with increased risk for food allergies but not asthma in both breastfed (OR: 1.62; 95% CI: 1.19–2.21) and exclusively formula-fed infants (OR: 1.39; 95% CI: 1.03–1.88).

Conclusions. Early vitamin supplementation is associated with increased risk for asthma in black children and food allergies in exclusively formula-fed children. Additional study is warranted to examine which components most strongly contribute to this risk. Pediatrics 2004;114:27–32; multivitamins, asthma, allergy, infants.

ABBREVIATIONS. Th, T-helper; NMIHS, National Maternal and Infant Health Survey; LF, longitudinal follow-up study; OR, odds ratio; CI, confidence interval.

Changes in dietary practice are among the many environmental exposures posited to explain the increase observed in asthmatic and allergic disease in recent years. Formula feeding and early food exposures predispose to increased risk for asthma and allergy.1,2 Although the milk protein component of formula has been associated with increased risk for allergy and asthma, other factors may also be involved. One such factor could be multivitamin supplementation. In addition to the vast vitamin supplementation of common foods and beverages, including infant formula, multivitamin use in infants and toddlers is very common, with >50% of all toddlers taking some sort of vitamin.3 The recent American Academy of Pediatrics recommendations for vitamin D supplementation in all breastfed infants4 are likely to result in an additional increase in early multivitamin usage. It will be important to determine if such usage could have any deleterious effects.

T-helper subsets (Th1 and Th2) define discrete cytokine production phenotypes for T-helper cells that serve antagonistic functions in the development and maintenance of the normal immune response.5 Pathologic Th1 phenotypes are associated with multiple sclerosis, juvenile rheumatoid arthritis, and type 1 diabetes, whereas pathologic Th2 responses are associated with systemic lupus erythematosus, allergy, and asthma. In vitro, a variety of vitamins have been shown to skew T cells toward Th1 (vitamins B6, E, and C) or Th2 (vitamins D and A) phenotypes.6–8 In mice, vitamin D has been shown to prevent experimental autoimmune encephalomyelitis,9,10 the mouse model of multiple sclerosis, in a Th2-dependent manner. Via a similar mechanism, vitamin D has also been shown to prevent diabetes in
Epidemiologic data likewise demonstrate that vitamin D intake is associated with protection from type 1 diabetes. Some have hypothesized that dietary vitamin A and/or D may play a role in development of allergy and asthma because the pathogenesis of both is associated with Th2 cytokines.

A number of studies have looked at associations between asthma and vitamins, particularly focusing on the dietary status at the time of diagnosis and concentrating on the potential antioxidant properties of vitamins that could confer protection from asthma. However, early infant exposure to immunomodulatory compounds may have a more pronounced effect in infants than in other populations, as the first few months of life seem to be a particularly immunologically impressionable period of time. As an example, short periods of breastfeeding in the first few months of life may confer long-term protection from asthma.

This study therefore aimed to examine the effects of infant exposure to potential immunomodulating vitamins on the subsequent risk for food allergy and asthma. The 1988 National Maternal and Infant Health Survey (NMIHS) collected perinatal, maternal, and child data on >8000 mothers who gave birth in 1988. A follow-up survey, the Longitudinal Follow-up (LF), was conducted in 1991 and focused on assessing participant health and disease status through early childhood. We used the NMIHS and LF cohort to study the effect of infant multivitamin supplementation on the subsequent risk for asthma and other allergic diseases. We hypothesized that early infant exposure to multivitamins may alter the risk for allergic and asthmatic disease via immunomodulation by individual components of the multivitamins. For part of the analysis, patients were stratified by race, because black breastfed infants, because of concerns for rickets, have historically been the main group for whom early multivitamin supplementation was recommended, and by breastfeeding status because parents who have fed their infants formula rarely have been told to supplement their child’s diet.

**METHODS**

**Patients**

Data were acquired from the NMIHS of 1988 and linked to the LF of 1991, which included nearly 90% of initial respondents in the NMIHS. Blacks, individuals with low socioeconomic status, and premature infants were intentionally overrepresented in the survey sample. All data were collected as self-reported by the individual surveyed (see Appendix). We included in analyses all live-born infants who were in the follow-up assessment at 3 years. Multivitamin supplementation was reported monthly in the NMIHS. The primary analyses were performed using patients who were supplemented at any point before 6 months of age and also included an evaluation of those who were reported to have received supplementation at any time before 3 months of age. The report was in the form of a written questionnaire, with parents indicating during which month(s) of their child’s life their child took vitamins at least 3 days a week. Vitamin usage from the LF was defined as supplementation in the month before the survey. Outcome measures of asthma and food allergy were based on parental report of physician diagnosis of asthma or food allergies at the time of the LF during a verbal interview.

**Statistical Methods**

Statistical analysis was performed using STATA (version 7.0; STATA, College Station, TX) software package. Analysis of variance (for measurement data) or contingency table analysis (for discrete data) was conducted to identify risk factors for asthma and allergy in the survey population. Multiple logistic regression analyses were used to estimate the odds ratio (OR) for the association between multivitamin supplementation and food allergies or asthma. These analyses included risk factors and possible interactions. Statistical significance, at the 2-tailed <.05 level, was based on t tests and χ² tests.

**RESULTS**

**Patient Demographics (Table 1)**

Blacks composed 51.2% of the survey population, and 50.2% of participating families had a household income of <$20,000. Nearly one quarter (23.6%) of respondents were premature (born before 37 weeks’ gestation); 26.2% of black infants and 20.9% of nonblack infants were premature. Nonblack, nonwhite children composed only 3% of the survey population and did not significantly affect the results. Of the 8285 respondents to the LF, 214 (2.6%) were excluded from the asthma analysis because of missing outcome data, and 212 (2.6%) were excluded from the food allergy analysis for the same reason. For the multivariate analysis, 712 (8.6%) patients were excluded from the asthma analysis because of missing covariate data, and 711 (8.6%) patients were excluded from the food allergy analysis. The excluded asthma subjects had lower rates of vitamin usage (31% vs 42%; P = .016) and higher rates of asthma (13% vs 10%; P < .001), whereas the excluded food allergy subjects had lower rates of both vitamin use (31% vs 42%; P < .001) and food allergy (3.5% vs 5.0%; P = .073). However, when included in the multivariate model despite missing information, these differences did not significantly affect the association (data not shown).

**Vitamin Usage**

As reported by patients’ caregivers, vitamin supplementation before 6 months of age occurred more frequently in children who were born to families with a higher annual income and higher level of maternal education (P < .001; Table 2). As expected, it was also more common in premature infants (52% vs 38%; P < .001) and breastfed infants (49% vs 38%;

**TABLE 1. Study Population Demographics (N = 8285)**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>31</td>
</tr>
<tr>
<td>White</td>
<td>46</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>&lt;37 weeks’ gestation</td>
<td>24</td>
</tr>
<tr>
<td>Mothers who completed high school</td>
<td>59</td>
</tr>
<tr>
<td>Household income &lt;$20 000</td>
<td>50</td>
</tr>
<tr>
<td>Ever breastfed</td>
<td>40</td>
</tr>
<tr>
<td>Enrolled in child care</td>
<td>27</td>
</tr>
<tr>
<td>Multivitamin supplementation</td>
<td></td>
</tr>
<tr>
<td>Before 3 mo of age</td>
<td>32</td>
</tr>
<tr>
<td>Before 6 mo of age</td>
<td>41</td>
</tr>
<tr>
<td>At 3 y of age</td>
<td>42</td>
</tr>
</tbody>
</table>
TABLE 2. Percentage Who Supplement With Multivitamins 
(N = 8285)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker in house?</td>
<td>40</td>
<td>42</td>
<td>.139</td>
</tr>
<tr>
<td>High school diploma?</td>
<td>43</td>
<td>35</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Annual income &gt;$20,000?</td>
<td>46</td>
<td>37</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Child care attendance?</td>
<td>44</td>
<td>41</td>
<td>.022</td>
</tr>
<tr>
<td>Breastfed ever?</td>
<td>49</td>
<td>38</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Black?</td>
<td>37</td>
<td>46</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Gestational age &lt;37 wk?</td>
<td>52</td>
<td>38</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Supplement at 3 y of age?</td>
<td>50</td>
<td>35</td>
<td>.&lt;.001</td>
</tr>
</tbody>
</table>

Values represent percentages of those responding positively or negatively to the demographic question asked.

P < .001). Parents who gave their child multivitamin supplements during infancy, as compared with those who did not, were more likely to give supplements at 3 years of age (50% vs 35%; P < .001). Of the patients who reported giving vitamins at least 3 times a week for at least 1 month within the first 6 months of life, nearly 70% reported giving vitamins for at least 3 of those months, suggesting that vitamin supplementation was fairly consistent (data not shown).

Asthma

Asthma was reported by parents to have been diagnosed by a medical professional in 851 (10.5%) of total respondents. Results of univariate analysis of risk factors for asthma are summarized in Table 3. Multivitamin supplementation before 3 or 6 months of age did not significantly alter the risk for asthma in the unadjusted model, whereas there was a mildly protective effect in those who received supplementation at 3 years of age. Household smoking and child care attendance were associated with increased risk for asthma (P < .001 for each). In addition, a number of important risk modifiers for asthma seen in the univariate analysis were also risk modifiers for taking multivitamins. They included income and education, race, gender, breastfeeding status, and the degree of prematurity (P < .001 for each).

Using multivariate logistic regression models of the association between multivitamin and asthma, it was necessary to stratify our analysis by race because of statistically significant interactions between being black and multivitamin usage. Another reason for stratification was that, at the time of this survey, breastfed black infants were the only members of the healthy general population for whom multivitamin supplementation was specifically recommended by many practitioners. After adjusting for the covariates in the univariate analysis mentioned above, including the degree of prematurity, we found an association between infant multivitamin supplementation within the first 6 months of life and an increased risk of developing asthma by 3 years of age among black children (OR: 1.27; 95% confidence interval [CI]: 1.04–1.56; P = .022) but not in nonblack children (OR: 0.91; 95% CI: 0.70–1.18; P = .479). There was no such association between multivitamin supplementation at 3 years and the risk of developing asthma (Table 4).

Food Allergies

Food allergies were reported to have been diagnosed by a medical professional in 396 (4.9%) of total respondents by 3 years of age. Table 5 summarizes the results of univariate analysis for risk factors for food allergy. In this population, prematurity, regardless of degree, was associated with a reduced risk of food allergy. Multivitamin supplementation before both 3 and 6 months of age and at 3 years of age were also associated with an increased risk for food allergies (Table 5).

Patients were stratified by breastfeeding status in multivariate logistic regression models because of statistically significant interactions between breastfeeding status and multivitamin usage and because generally only breastfed infants were advised to supplement with multivitamins. In addition, the regression model took into account the significant variables from the univariate analysis on food allergies. Among formula-fed infants, vitamin supplementation within 3 (OR: 1.75; 95% CI: 1.29–2.38; P = .001) and 6 (OR: 1.63; 95% CI: 1.21–2.20; P = .001) months of age was associated with increased risk of developing food allergies by 3 years of age (Table 6). Analysis of children who received supplementation with multivitamins at 3 years of age showed an association between supplementation and food allergies among both children who had been breastfed (OR: 1.62; 95% CI: 1.19–2.21; P = .002) and those who had not (OR: 1.39; 95% CI: 1.03–1.88; P = .031).

DISCUSSION

This study demonstrates an association between early infant multivitamin intake and asthma among black infants and an association between early infant multivitamin intake and food allergies in formula-fed infants. It also demonstrates an association between later multivitamin supplementation (at 3 years of age) and an increased risk of food allergies in all infants.
infants. Although the associations are not causal, they nonetheless merit additional study.

Unlike previous studies, which focused on associations between concurrent nutritional status and asthma or allergy or followed adults primarily, this study followed a cohort of infants from birth to age 3, measuring multivitamin supplementation before any diagnosis of asthma or food allergy. The basis for our proposed mechanism for this observation comes primarily from in vitro and animal data, which have shown that a variety of vitamins commonly found in multivitamins can cause naïve T cells to differentiate toward the extremes of the Th1 and Th2 phenotypes, physiologic states that may increase the odds of an allergic response when encountering certain antigens. As a potential example of this phenomenon, one recent study showed decreased maternal vitamin E intake during pregnancy to be correlated with increased proliferative response to allergens in cord blood. The authors posited that this either may be attributable to the lack of antioxidant properties of vitamin E or may be a marker for the absence of other immunomodulatory nutritional agents. However, an alternative explanation for their findings on the basis of our hypothesis would be that vitamin E protects T cells from an extreme Th2 phenotype during development via Th1 deviation.

There are several potential implications for these findings, should a causal relationship for this association be found. Recommendations for vitamin supplementation and the actual multivitamin formulation may need to be changed to reduce the risk for allergy and asthma. For instance, should the racial differences observed in asthma risk continue to persist in future studies or if parents of infants who are formula-fed continue to wish to supplement despite no specific recommendations (which, according to the NMIHS, is a surprisingly sizable population), a reformulated multivitamin with lower levels of Th2-inducing vitamins and perhaps higher levels of Th1-inducing vitamins could be used to reduce the risk of asthma or food allergies. Of course, any such alterations also would have to satisfy the child's basic nutritional requirements.

Furthermore, this finding may indicate that indeed there are very early environmental exposures that can affect the risk for subsequent development of allergic disease. There is some debate as to when the critical windows of exposure to exogenous stimuli open and close in dictating the risk for allergic disease. These data may indicate that early infancy is one such window and that vitamin supplementation may be a potent exogenous stimulus.

Formula-fed infants seem to have the highest associated risk for developing food allergy when supplementing with multivitamins. This may be attributable to population selection, predisposition to hypersensitivity from formula, or a dose response, given that formula contains significantly higher amounts of a number of vitamins, particularly vitamin D, than breast milk.

Our study found a stronger association between multivitamin intake and asthma in black infants. A potential explanation for the findings on the basis of our hypothesis would be that vitamin E protects T cells from an extreme Th2 phenotype during development via Th1 deviation.

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Our study found a stronger association between multivitamin intake and asthma in black infants. A number of factors could explain this racial difference. First, physicians may be more likely to diagnose...
asthma in blacks because of physician–parent communication issues, physician biases, and cultural norms for labeling children with diagnoses. There may be similar biases in diagnosing food allergies. As an example of such bias, nonimmunologic cow milk intolerance is more common in adolescent and adult black populations than in European populations, and it is often mislabeled as a food allergy by both practitioners and patients. There may also be biological explanations. Differences in susceptibility may be attributable to differential responses of T cells to vitamins, which in turn may be the result of a genetic predisposition or attributable to differences in environmental exposures, such as diet or urban/rural settings. Vitamin D levels are also generally lower in individuals with darker skin, and if vitamin D exposure plays a part in this observation, then supplementation could cause a more substantial observed risk effect.

It is also unclear whether the differences in risk associations seen between supplementing before 3 months versus before 6 months reflects a dose-response or a critical window for exposure to the elements that increases risk. Although the risk for asthma was greater in those who began supplementing before 6 months of life (which would include both those who began supplementing before 3 months of age and those who began supplementing between 3 and 6 months of age), the risk for food allergies was greater for those who began supplementing before 3 months of age.

There are several limitations to this study. First, the diagnoses of food allergies and asthma were made by 3 years of age. Cases of asthma and food allergies that would develop subsequently therefore are missed. Furthermore, no uniform standard was used by physicians to diagnose asthma or food allergies, and diagnosis reporting relied on parental self-report of physician diagnosis. In a study based on the survey used here, parental and physician reports of asthma diagnoses correlated only about half the time. However, this may have reflected the accuracy of the physician-reported diagnosis as well. Only International Classification of Diseases, Ninth Revision codes were used, and the code for asthma is identical to reactive airways disease and other diagnoses that do not necessarily convey a diagnosis of asthma. It should also be mentioned that in this patient population, parental reports of food allergies did not correlate with the presence of early formula intolerance—which is often confused with food allergy (data not shown).

Second, the patients and practices in this survey are now 15 years of age. There are likely differences in recommendations, common practices, and environmental exposures between then and now, and care should be taken when generalizing these findings.

Third, parents with children who have significant disease may be more likely to provide multivitamin supplements for their children. Alternatively, parents who tend to supplement may also be more likely to overdialgnose their children. However, the survey documented parental report of physician diagnosis. In addition, the parents were asked about supplementation before the child was 1 year of age, likely before any diagnosis of asthma or food allergy. Physician visits were not any more frequent in the supplemented group than in the nonsupplemented group, suggesting that frequent physician visits as a result of a particular diagnoses did not lead to an increase in recommendations for vitamin supplementation (data not shown). Finally, we expect that such a bias would have been seen in both black and white patients; however, this was not so.

Finally, in contrast to the early infant multivitamin supplementation data, more care should be taken in interpreting the multivitamin intake data from 3 years of age. Although month-to-month confirmation of multivitamin supplementation demonstrated steady use in the NMIHS, the LF asks only whether the child was given vitamins in the month before the survey at 3 years. Nonetheless, if true, then the increased associated risk for food allergies in patients who received supplementation at 3 years of age may reflect a physiologic phenomenon or may be reflective of the above-mentioned issue of parents’ being more likely to supplement children with current diagnoses. For all multivitamin supplementation histories, we do not have any indication, beyond monthly confirmations, of the dose and frequency of supplementation. This could potentially affect our findings.

In conclusion, this study demonstrates an association between infant multivitamin usage and the development of food allergies in exclusively formula-fed infants, between infant multivitamin usage and asthma in black infants, and between childhood multivitamin usage and the development of food allergies in all children. A number of issues require additional study. The racial difference observed should be explored to determine whether it is a true reflection of a physiologic phenomenon or merely reflective of detected confounding or bias. If it is physiologic, then it may help shed light on the underlying mechanism for this observation. Prospective studies with more accurate accounting of the type, timing, and dosing of multivitamin supplementation, as well as longer follow-up with validated methods of diagnosing allergy and asthma, are necessary to establish the strength of this association. Most important, determination of a causal association is essential, as well as determination of the elements of the multivitamins most responsible. While this article was being reviewed, Matheu et al demonstrated that injecting mice with calcitriol (1,25-Dihydroxycholecalciferol or 1,25-[OH]2-D3) during allergic sensitization increased formation of total and antigen-specific immunoglobulin E, while administration later during rechallenge inhibited pulmonary eosinophilia in a murine allergic disease model. This provides potential laboratory evidence to correlate with some of this clinical findings of this study.

The recent American Academy of Pediatrics recommendations to supplement all breastfed infants with vitamin D could provide us with the opportunity to track rates of allergies and asthma in closely followed populations before and after establishment
of the new recommendations. The recommendations also present potential risks, because as a result of the recommendation, many more individuals will be more likely to supplement their infants, exposing them to far higher doses of multivitamins. This study suggests that higher doses of multivitamins may not always be benign.

APPENDIX

Pertinent questions asked of mothers in the NMIHS (all questions asked of mothers on a mailed written form at one time):

- “During which months was your infant given vitamin/mineral drops at least 3 days a week?”
  (respondent can check off months 1–6 as well as “this past month” or can check a box marked “if you never gave vitamin/mineral drops 3 days a week”)
- We divided these into 3 groups: 1) if they never gave any drops, 2) if they reported having given drops in any of the months 0 to 3, and 3) if they reported giving any drops in any of the months (only 0–6 included).

Pertinent questions asked of mothers in the LF (all questions were asked in verbal interview with mothers):

- “Now, I’m going to read you a list of health problems that some children have. Please tell me whether you have ever been told by a doctor, nurse, or other health care provider that (child) has any of these problems.”
- Asthma? Yes/No
- Food allergy? Yes/No

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