Association Between Atopic Disease and Anemia in US Children

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**IMPORTANCE** Atopic disease is associated with chronic inflammation, food allergen avoidance, and use of systemic immunosuppressant medications. All these factors have been shown to be associated with anemia.

**OBJECTIVE** To investigate whether atopic disease is associated with increased risk of childhood anemia.

**DESIGN, SETTING, AND PARTICIPANTS** A cross-sectional survey and laboratory assessment were conducted using data from the 1997-2013 US National Health Interview Survey (NHIS) that included 207,007 children and adolescents and the 1999-2012 National Health and Nutrition Examination Survey (NHANES) that included 30,673 children and adolescents. Analysis of the data was conducted between August 1, 2014, and August 28, 2015.

**EXPOSURES** Caregiver-reported history of eczema, asthma, hay fever, and/or food allergy.

**MAIN OUTCOMES AND MEASURES** Anemia was defined by caregiver report in the NHIS and by hemoglobin levels for age and sex in the NHANES.

**RESULTS** Data were collected on 207,007 children and adolescents from NHIS, representing all pediatric age, sex, racial/ethnic, household educational level, and income groups. The US prevalence was 9.5% (95% CI, 9.4%-9.7%) from all years of the NHIS for health care–diagnosed eczema, 12.8% (95% CI, 12.6%-13.0%) for asthma, 17.1% (95% CI, 16.9%-17.3%) for hay fever, 4.2% (95% CI, 4.1%-4.3%) for food allergy, and 1.1% (95% CI, 1.1%-1.2%) for anemia. In multivariable logistic regression models controlling for age, sex, race/ethnicity, annual household income, highest educational level in the family, insurance coverage, number of persons in the household, birthplace in the United States, and history of asthma, hay fever, and food allergy, anemia was associated with eczema in 14 of 17 studies, asthma in 11, hay fever in 12, and food allergy in 12. In multivariable analysis across the NHIS (with results reported as adjusted odds ratios [95% CIs]), children with any eczema (1.83; 1.58-2.13), asthma (1.31; 1.14-1.51), hay fever (1.57; 1.36-1.81), and food allergy (2.08; 1.71-2.52) had higher odds of anemia ($P < .001$ for all). In the NHANES, current history of asthma (1.33; 1.04-1.70; $P = .02$) and eczema (1.93; 1.04-3.59; $P = .04$) were associated with higher odds of anemia, particularly microcytic anemia (asthma: 1.61; 1.09-2.38; $P = .02$; eczema: 2.03; 1.20-3.46; $P = .009$) while history of hay fever was not associated with anemia (0.85; 0.62-1.17; $P = .33$).

**CONCLUSIONS AND RELEVANCE** The association between atopic disease and anemia was reproducible in multiple cohorts. Future studies are needed to identify the determinants of association between atopic disease and anemia.

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Methods

Study Sources
Deidentified data were assessed from the 1997-2013 US National Health Interview Survey (NHIS) child health surveys and the 1999-2012 National Health and Nutrition Examination Survey (NHANES). Analysis of the data was conducted between August 1, 2014, and August 28, 2015. Study characteristics are presented in eTable 1 in the Supplement. The NHIS and NHANES are prospectively collected household questionnaire-based studies. Households were selected through a stratified, randomized, multistage, probability-cluster design. Health interviews were conducted in the participant’s home in either English or Spanish. In the NHANES, blood collection was performed in mobile examination centers.

Using data from the US Census Bureau, sample weights were created for each study by their sponsors that used a multistage area probability sampling design to adjust for age, sex, race/ethnicity, household size, and educational level of the most educated household member. These sample weights allow for nationally representative prevalence estimates for each state’s population of noninstitutionalized children. The complex weighting is reflected in all prevalence estimates presented in this study. The sample designs and methods were consistent across all years of the NHIS and NHANES, respectively. Therefore, it was possible to include the sample weights in analyses across multiple years in addition to individual analyses. Weighted prevalence estimates are presented for analyses across multiple years. The study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board.

Caregiver- and Self-reported Measures
Caregiver-reported sociodemographics included age (year), sex, race/ethnicity (Hispanic, white, black, or other ethnicity), educational level (less than high school graduate, high school graduate or General Educational Development certificate, or beyond high school), annual household income (<100%, 100%-299%, 300%-399%, and ≥400% of the federal poverty level), birthplace in the United States (yes or no), and health insurance status (yes or no). Caregiver-reported history of smoking in the household (yes or no) was assessed for adults from the child’s household. The questions used in the study to assess for history of atopic disease and anemia in children (NHIS and NHANES) and parents (NHIS) are presented in eTable 2 in the Supplement.

Definition of Anemia by Laboratory Values
Participants provided blood samples, which were analyzed for hemoglobin level and mean corpuscular volume (21 674 samples from the NHANES 1999-2012). Anemia was determined using age- and sex-specific cutoffs for hemoglobin level as previously described. The type of anemia was determined by a combination of anemia and mean corpuscular volume (microcytic, <80 μm³; normocytic, 80-99.9 μm³; macrocytic, ≥100 μm³ [to convert mean corpuscular volume to femtoliters, multiply by 1.0)]. Further details about the blood sampling and analytics are described on the NHANES website.

Statistical Analysis
The frequency of missing values is presented in eTable 3 in the Supplement. There were low frequencies of missing values for history of atopic disease, anemia, and other covariates. Complete data analysis was performed for all variables; that is, participants with missing data were excluded, except for annual household income in the 1997-2013 NHIS, where 18.6% of respondents had missing values. Therefore, we used multiple imputation of missing household income levels that were generated by the National Center for Health Statistics. The sociodemographic composition of the complete case analysis cohort was nearly identical to that of the original NHIS cohort (eTable 4 in the Supplement).

All analyses used procedures that accounted for the surveys’ complex weighting factors. For caregiver-reported history of anemia, multivariable survey weighted binary logistic regression models were constructed for individual studies and analysis across all 17 years of the NHIS. Analysis for anemia (low hemoglobin level for age and sex) was performed across all years of the NHANES for asthma and hay fever, and in 2005-2006 for eczema. The dependent variable was anemia and the independent variable was history of atopic diseases (yes or no). In the NHIS, multivariable models included age, sex, race/ethnicity, family size and annual household income, highest educational level in the family, birthplace in the United States,
and insurance coverage as covariates. In the NHANES, multivariable models included age, sex, and race/ethnicity. Domain analysis was performed to yield appropriate estimates of variance. Crude and adjusted odds ratios (aORs) and 95% CIs were estimated. All data processing and statistical analyses were performed in SAS, version 9.4 (SAS Institute).

Results

Population Characteristics

Data were collected on 207,007 children and adolescents from NHIS, representing all pediatric age, sex, racial/ethnic, household education level, and income groups. The US prevalence was 9.5% (95% CI, 9.4%-9.7%) from all years of the NHIS for health care–diagnosed eczema, 12.8% (95% CI, 12.6%-13.0%) for asthma, 17.1% (95% CI, 16.9%-17.3%) for hay fever, 4.2% (95% CI, 4.1%-4.3%) for food allergy, and 1.1% (95% CI, 1.1%-1.2%) for anemia. Associations of each of these disorders with sociodemographic factors are presented in eTable 5 in the Supplement.

Association Between Caregiver-reported Atopic Disease and Anemia

In bivariate models of data from the NHIS, eczema was associated with significantly higher odds of anemia in 15 of 17 years and marginally significantly higher odds of anemia in 1 of 17 years (eTable 6 in the Supplement). In multivariable models controlling for age, sex, race/ethnicity, annual household income, highest educational level in the family, insurance coverage, number of persons in the household, and birthplace in the United States, the association between eczema and anemia remained significant in 14 of 17 studies (eTable 6 in the Supplement).

Similarly, using data from the NHIS, there was a significant association between asthma and anemia in 11 of 17 studies in bivariate models and 11 of 17 studies in multivariable models (eTable 7 in the Supplement). Likewise, there was a significant association between hay fever and anemia in 13 of 17 studies in bivariate models and 12 of 17 studies in multivariable models (eTable 8 in the Supplement). Finally, there was a significant association between food allergy and anemia in 14 of 17 studies in bivariate models and 12 of 17 studies in multivariable models (eTable 9 in the Supplement). For the years in which the associations did not remain significant, we constructed models that tested each covariate individually and found that none of them were confounders by themselves.

In multivariable analysis across the NHIS, children and adolescents with any eczema (aOR, 1.83; 95% CI, 1.58-2.13; p < .001), particularly intrinsic (aOR, 1.95; 95% CI, 1.57-2.41; P < .001) or extrinsic eczema (aOR, 2.69; 95% CI, 2.26-3.21; P < .001), asthma (aOR, 1.31; 95% CI, 1.14-1.51; P < .001), hay fever (aOR, 1.57; 95% CI, 1.36-1.81; P < .001), and food allergy (aOR, 2.08; 95% CI, 1.71-2.52; P < .001) had significantly higher odds of anemia compared with children without these disorders (Table 1).

The number of comorbid atopic disorders was also associated with anemia. That is, having a single atopic disorder was associated with modestly increased odds of anemia (aOR, 1.84; 95% CI, 1.60-2.11; P < .001) (Table 1). However, having all 4 atopic disorders was associated with demonstrably increased odds of anemia (aOR, 7.87; 95% CI, 5.17-12.00; P < .001).

Association Between Asthma and Microcytic Anemia

We analyzed data on objective laboratory measures for 30,673 children and adolescents from the 1999-2012 NHANES to confirm the association between atopic disease and anemia. Current history of asthma was associated with higher odds of anemia in multivariable models controlling for age, sex, and race/ethnicity (aOR, 1.33; 95% CI, 1.04-1.70; P = .02); however, hay fever was not associated with anemia overall (aOR, 0.85; 95% CI, 0.62-1.17; P = .33) (Table 2). In particular, asthma was associated with higher odds of microcytic anemia (aOR, 1.61; 95% CI, 1.09-2.38; P = .02) whereas hay fever was inversely associated with microcytic anemia (aOR, 0.60; 95% CI, 0.37-0.98; P = .04). Both asthma and hay fever were associated with lower odds of macrocytic anemia (aOR, <0.01; 95% CI, <0.01 to <0.01; P < .001) and not associated with normocytic anemia (asthma: aOR, 1.10; 95% CI, 0.82-1.49; P = .52; hay fever: aOR, 1.18; 95% CI, 0.83-1.68; P = .37). In the 2005-2006 NHANES, history of eczema was associated with anemia (aOR, 1.93; 95% CI, 1.04-3.59; P = .04), particularly microcytic anemia (aOR, 2.03; 95% CI, 1.20-3.46; P = .009), but not normocytic (aOR, 1.89; 95% CI, 0.75-4.78; P = .18) or macrocytic (aOR, <0.01; 95% CI, <0.01 to <0.01; P < .001) anemia.

Discussion

We analyzed data from 2 US population-based studies and found that history of caregiver-reported eczema, asthma, hay fever, and food allergy is associated with increased odds of anemia. The odds of anemia increased with the number of atopic disorders present. Childhood asthma and eczema were associated with higher odds of microcytic anemia as defined by laboratory assay test results in the NHANES. In contrast, hay fever was not associated with anemia overall but was inversely associated with microcytic anemia.

Atopic disease has been shown to be associated with several different comorbid conditions, many of which are known to increase the risk for anemia. The chronic inflammation present in atopic disease, use of systemic immunosuppressant medications, increased incidence of malnutrition15,21,22 and/or obesity,6-8 and increased use of alternative medicines23 are examples of such comorbidities. Nevertheless, there is a paucity of data examining the association between atopic disease and anemia. The present study demonstrates higher rates of anemia in atopic disease.

The precise mechanism of the association between atopic disease and anemia is unknown. The increased odds of microcytic anemia in children with asthma and eczema demonstrated in our study suggest that iron deficiency anemia and/or anemia of chronic disease (ACD) might be occurring. It is likely that the association between atopic disease and anemia is multifactorial. Regardless of the underlying mechanisms, awareness of the association between atopic disease and anemia is important. Physicians who care for children with atopic disease should be aware that fatigue may be related to unrecog-
Iron deficiency anemia might occur secondary to food avoidance and malnutrition. Previous studies have demonstrated that atopic disease is associated with malnutrition and anemia.

<table>
<thead>
<tr>
<th>Atopic Disease</th>
<th>No Anemia</th>
<th>% Prevalence (95% CI)</th>
<th>Anemia</th>
<th>% Prevalence (95% CI)</th>
<th>Crude OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any eczema</td>
<td>No</td>
<td>184/260 (99.0-99.1)</td>
<td>1993</td>
<td>1.0 (0.9-1.1)</td>
<td>1 [Reference]</td>
<td>.001</td>
<td>1.83 (1.58-2.13)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19/107 (97.3-97.6)</td>
<td>521</td>
<td>2.7 (2.4-2.9)</td>
<td>2.46 (2.16-2.79)</td>
<td>&lt;.001</td>
<td>2.69 (2.26-3.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type of eczema</td>
<td>None</td>
<td>184/260 (99.0-99.1)</td>
<td>1993</td>
<td>1.0 (0.9-1.1)</td>
<td>1 [Reference]</td>
<td>.001</td>
<td>1.95 (1.57-2.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intrinsic</td>
<td>9506 (97.7-98.4)</td>
<td>203</td>
<td>2.0 (1.6-2.3)</td>
<td>2.06 (1.67-2.54)</td>
<td>&lt;.001</td>
<td>2.43 (2.04-2.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Extrinsic</td>
<td>9601 (97.2-96.8)</td>
<td>318</td>
<td>2.8 (2.4-3.2)</td>
<td>2.72 (2.28-3.24)</td>
<td>&lt;.001</td>
<td>2.69 (2.26-3.21)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: NHIS, National Health Interview Survey; OR, odds ratio.
*Analyses were performed for all participants in the 1997-2013 NHIS. Binary survey logistic regression models were constructed with anemia as the binary dependent variable and history of eczema, asthma, hay fever, food allergy, and the number of atopic diseases as the binary independent variable. Multivariable models were constructed that included age, sex, race/ethnicity, annual household income, highest educational level in the family, insurance coverage, number of persons in the household, and birthplace in the United States. In addition, multivariable models of any eczema, asthma, hay fever, and food allergy included each of the other atopic disorders. Crude and adjusted ORs and 95% CIs were estimated.
I to 2 years and is the most common type of microcytic anemia in childhood.\textsuperscript{19} Iron deficiency can lead to fatigue, small-bowel dysfunction,\textsuperscript{28} growth retardation,\textsuperscript{29} and impaired cognitive development\textsuperscript{26,30-33} and has been linked to deficits in attention span, intelligence, sensory perception,\textsuperscript{28} and altered behavior and emotion.\textsuperscript{34} The restrictive diets followed by many patients with suspected food allergies or apparent exacerbation of skin or airway disease brought on by specific foods has been hypothesized to play a role in the malnutrition seen in patients with atopic disease. It has been established that diets devoid of milk products and other crucial foods can lead to malnutrition.\textsuperscript{7,21,22} In our study, history of food allergy was assessed by caregiver report that did not depend on a previous health care diagnosis of food allergy. Thus, it is possible that some or many of the children reported as having food allergies were not true food allergies. However, concerns or perceptions by parents that their child has a food allergy will likely result in empirical avoidance of the suspected food. This finding underscores the importance of properly evaluating and ruling out suspected food allergy in children rather than placing them on empirical avoidance diets that might contribute to anemia. Moreover, children and parents need to be cautioned about self-prescribing of strict diets that avoid the suspected food owing to concerns about the effect of such diets on the child’s risk for anemia and overall health.

On the other hand, the association between atopic disease and microcytic anemia may be owing to ACD. This possibility may explain why a higher number of atopic disorders was associated with increasing odds of anemia in the NHIS. Previous studies found that children with atopic dermatitis as well as asthma and hay fever (so-called extrinsic disease)\textsuperscript{35,36} and children with more severe atopic dermatitis\textsuperscript{37} are more likely to carry mutations of the \textit{Filaggrin} gene (OMIM 135940). Nevertheless, anemia was associated with eczema even in the absence of allergic disease (ie, intrinsic eczema). This finding suggests that chronic inflammation occurring in eczema may contribute to ACD. In the NHANES, asthma and eczema but not hay fever, were associated with anemia overall and microcytic anemia in particular. There may be a specific subset of patients with atopic disease who have increased risk of anemia, perhaps secondary to more severe disease and chronic inflammation. Unfortunately, ferritin, transferrin, and serum iron levels, as well as iron binding capacity, were not measured consistently across all years of the NHANES or all pediatric age groups. Thus, we were unable to assess for specific associations between asthma, iron deficiency anemia, and/or ACD. Future studies are needed to further investigate whether atopic disease is associated with iron deficiency anemia per se vs ACD or other types of anemia and the mechanisms of such associations. Moreover, further research appears warranted to investigate the association between mutations of the \textit{Filaggrin} gene, disease severity, systemic inflammation, and the risk of anemia in children with atopic disease.

This study has several strengths that include that the data are derived from 2 US population-based studies with large random sampled and diverse samples and complex survey weighting, which demonstrate reproducibility and external validity. These sample weights for each study allow for nationally representative prevalence estimates, suggesting that our findings are likely generalizable to the entire US population. The availability of hemoglobin levels and mean corpuscular volume in the NHANES allowed for objective confirmation of anemia occurring in patients with asthma and revealed that asthma is associated with microcytic anemia.

This study also has limitations. History of atopic disease was reported by caregivers and was not verified with diagnostic testing. A recent multicenter validation study found that caregiver-reported history of health care–diagnosed eczema has very good sensitivity, specificity, and positive and negative predictive values.\textsuperscript{38} Moreover, self- and caregiver-report of asthma have been validated and found to have strong correlation to clinical examination and diagnostic testing.\textsuperscript{39} The cross-sectional nature of the studies precludes any conclusions about the directionality of the associations. Although a large sample size was obtained overall, there were smaller sample sizes for some individual subset analyses, particularly those using the NHANES data. Markers of iron storage were not consistently measured, precluding conclusions about the type of anemia occurring in children with atopic disease. Finally, while we did control for race/ethnicity, we were unable to control for history of thalassemia or sickle cell trait, which might also contribute toward microcytic anemia. Given these limitations, future studies with even larger cohorts and/or case-control studies and expanded diagnostic testing are needed to verify these findings.

Conclusions

Atopic disease was associated with increased odds of caregiver-reported anemia in the majority of years of the NHIS and in analyses of all 17 years of the NHIS. Childhood asthma and eczema were associated with higher odds of anemia, particularly microcytic anemia as defined by laboratory assay test results, in the NHANES. Future studies are needed to verify the determinants of association between asthma, eczema, other atopic disease, and anemia.
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approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES