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Associations of self-reported allergic diseases and musculoskeletal problems in children

A US population-based study

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ABSTRACT

Background: Previous studies have found increased rates of musculoskeletal problems in adults with allergic disease, but whether this association holds true for children is unknown.

Objective: To investigate the association of bone, joint, and muscle problems in children with a history of allergic disease.

Methods: Data were obtained from the 2007 Child and Adolescent Health Measurement Initiative. Univariable and multivariable logistic regression models accounting for the sampling design were used to evaluate associations of bone, joint, and muscle problems with allergic diseases, such as asthma, hay fever, food allergies, and eczema. Associations were summarized with odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The survey included 91,642 individuals aged 0 to 17 years. Multivariable modeling found statistically significant associations between the number of allergic diseases and bone, joint, and muscle problems (1 allergic disease: adjusted OR, 1.28; 95% CI, 1.04–1.56; $P = .02$; 2 allergic diseases: adjusted OR, 2.55; 95% CI, 1.92–3.39; $P < .001$; 3 allergic diseases: adjusted OR, 2.70; 95% CI, 1.88–3.86; $P < .001$; and 4 allergic diseases: adjusted OR, 4.35; 95% CI, 2.46–7.69; $P < .001$). Severe eczema (but not mild eczema) was associated with bone, joint, and muscle problems (adjusted OR, 2.81; 95% CI, 1.64–4.81; $P < .001$) and with bone problems (adjusted OR, 6.08; 95% CI, 1.94–19.12; $P = .002$).

Conclusion: Self-reported allergic diseases in children were associated with bone, joint, and muscle problems, and associations strengthened with allergic disease severity and number of allergic diseases. Severe eczema may be associated with bone problems in children. Bone, joint, and muscle problems must be considered in children with severe allergic disease, and prospective studies are necessary to define this association.

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Introduction

Allergic disease, including food allergy, asthma, hay fever, and eczema, are prevalent in US children (aged <18 years),^{1,2} with prevalence rates of 10% to 12.5% in the US pediatric population in

the past decade.^{2–4} Recent population-based studies have reported that children and adults with allergic disease have increased rates of other nonallergy medical problems, such as sleep disruptions,⁵ injury requiring medical attention,⁶ psychological and behavioral disorders,⁶ and epilepsy.⁷ Specifically in children, eczema has been associated with anemia,⁸ obesity,^{9–11} low bone mineral density (BMD),¹² juvenile idiopathic arthritis, autoimmune diseases, and Henoch-Schönlein purpura.^{13–15}

A recent prospective study of 34,500 adults (aged 18–85 years) from the 2012 National Health Interview survey found that adults with eczema had a higher incidence of fractures and other bone or

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joint problems compared with those without eczema.¹⁶ However, sparse data directly address the association between allergic conditions and musculoskeletal problems within the pediatric population. We hypothesized that children with allergic disease would have a higher prevalence of musculoskeletal disease. Thus, using a nationally representative children's health survey, we aimed to determine whether pediatric patients with a history of allergic disease (ie, eczema, hay fever, food allergy, and asthma) had a higher prevalence of coexisting bone, joint, or muscle problems.

Methods

Study Design and Subject Identification

Data were obtained from the Child and Adolescent Health Measurement Initiative.¹⁷ This survey of 91,642 households was designed to estimate the prevalence of health issues in childhood (aged 0–17 years), with approximately 1,800 interviews (range, 1,725–1,932) collected per state. Results were weighted to represent the population of noninstitutionalized children in each state. The National Center for Health Statistics conducted the study using the State and Local Area Integrated Telephone Survey program in Cantonese, English, Korean, Mandarin, Spanish, and Vietnamese. After verbal consent was obtained, 1 child from the family was randomly selected as the subject of the interview process. Specific questions were asked for children in early childhood (aged 0–5 years) and middle childhood and adolescence (aged 6–17 years), with additional questions asked for children of all ages. This study was exempt from institutional review board evaluation.

Parents or guardians were specifically asked if the patient ever had or currently had eczema, asthma, food allergy, or hay fever. If the patient had a history of allergic disease, parents were asked whether it was mild, moderate, or severe.⁷ This line of questioning was also used for bone, joint, or muscle problems.

Features Analyzed

The features evaluated were as follows: age of patient in years; sex; race/ethnicity; poverty level of the household (based on US Department of Health and Human Services guidelines); visited a health care professional for preventive services in the past 12 months; metropolitan statistical area (in states meeting the 500,000 threshold); injured or required medical attention in the past 12 months (available only for patients aged 0–5 years); body mass index (BMI) (available only for patients aged 10–17 years and reported by telephone interview); eczema or skin allergy in the past 12 months; severity of eczema; any history of asthma; current asthma; severity of current asthma; hay fever or respiratory allergy in the past 12 months; severity of hay fever or respiratory allergy; food or digestive allergy in the past 12 months; severity of food or digestive allergy; number of allergic diseases; any history of bone, joint, or muscle problems; current bone, joint, or muscle problems; severity of current bone, joint, or muscle problems; current problems involving bones; current problems involving joints; and current problems involving muscles.

Two sets of multivariable models were considered. The first multivariable model included the covariates of age group, sex, race/ethnicity, poverty level of the household, and visited a health care professional for preventive services in the past 12 months. The second multivariable model included the covariates of sex, race/ethnicity, poverty level of the household, visited a health care professional for preventive services in the past 12 months, and BMI (evaluated only for the subset of patients aged 10–17 years). For example, the odds ratio (OR) for eczema in the first multivariable model was 1.46 ($P < .001$), indicating that eczema was significantly associated with a history of bone, joint, or muscle problems, even after adjusting for age group, sex, race/ethnicity, poverty level of

the household, and visited a health care professional for preventive services in the past 12 months. Data for poverty level were not modified. The covariate metropolitan statistical area was not included in either multivariable model because substantial data were missing. The covariate injured or required medical attention in the past 12 months was not included in either multivariable model because this covariate was available only for patients aged 0 to 5 years.

Statistical Analysis

Mean ages, 95% confidence intervals (CIs) for the mean ages, and percentages for the other features studied were calculated after accounting for the sampling using SAS procedures SURVEYMEANS and SURVEYFREQ and using variable *state* as the stratum identifier, variable *idnumr* as the primary sampling unit, and variable *nschwt* as the sampling weight. Associations of the covariates of interest with bone, joint, or muscle problems were evaluated using logistic regression with SAS procedure SURVEYLOGISTIC and summarized with ORs and 95% CIs. All tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

The mean age of the 91,642 patients studied was 8.6 years (95% CI, 8.5–8.7 years). The remaining features studied are summarized in Table 1.

Univariable and multivariable associations of eczema, severity of eczema, history of asthma, current asthma, severity of current asthma, hay fever, severity of hay fever, food allergy, severity of food allergy, number of allergic diseases, and 1 or more allergic diseases with a history of bone, joint, or muscle problems were evaluated. Multivariable associations are summarized in Table 2. Multivariable associations with current bone, joint, or muscle problems are summarized in Table 3.

Univariable analysis of patients with severe bone, joint, or muscle problems found significant associations with severe eczema (OR, 5.07; 95% CI, 1.48–17.41; $P = .01$) and severe hay fever (OR, 3.11; 95% CI, 1.13–8.59; $P = .03$). No significant associations were identified among severe bone, joint, or muscle problems and asthma, food allergy, or number of allergic diseases. Multivariable analysis found that severe bone, joint, or muscle problems were not significantly associated with any specific allergic disease or number of allergic diseases. The proportional odds assumption associated with ordinal logistic regression for the end point of severity of current problems (mild vs moderate vs severe) was not appropriate for any of the features studied. Therefore, mild and moderate were combined and compared with severe for the analyses.

Univariable associations with current bone problems were notable for a significant association with severe eczema (OR, 4.40; 95% CI, 1.36–14.27; $P = .01$) and severe asthma (OR, 5.07; 95% CI, 1.47–17.43; $P = .01$). No statistically significant associations were identified between bone problems and hay fever, food allergy, or number of allergic diseases with univariable modeling. Multivariable analysis found a significant association between severe eczema and bone problems (OR, 6.08; 95% CI, 1.94–19.12; $P = .002$); however, in children aged 10 to 17 years, this association was not significant when adjusted (model 2) for BMI (OR, 2.48; 95% CI, 0.67–9.26; $P = .18$). Bone problems were not significantly associated with asthma, hay fever, food allergy, or number of allergic diseases.

Univariable associations with current joint problems were notable for a significant association with a history of asthma (OR, 1.96; 95% CI, 1.15–3.33; $P = .01$), hay fever (OR, 1.89; 95% CI, 1.16–3.11; $P = .01$), and 1 or more allergic diseases (OR, 1.69; 95% CI, 1.03–2.77; $P = .04$). No significant associations were identified between current joint problems and eczema, asthma, hay fever, or

Table 1
Summary of Patient Characteristics (N = 91,642)^a

Characteristic	No. (%) of patients
Age group, y	
0–5	27,566 (33)
6–9	18,179 (22)
10–17	45,897 (45)
Sex (n = 91,532)	
Female	43,997 (49)
Male	47,535 (51)
Race/ethnicity (n = 90,096)	
Hispanic, any race	11,523 (20)
White, non-Hispanic	61,377 (56)
Black, non-Hispanic	8,873 (14)
Multiracial, non-Hispanic	4,329 (4)
Other, non-Hispanic	3,994 (5)
Poverty level of the household	
<100% FPL	10,971 (19)
100%–199% FPL	15,591 (21)
200%–399% FPL	30,792 (31)
≥400% FPL	34,288 (29)
Visited a health care professional (n = 90,816)	79,667 (88)
Metropolitan statistical area (n = 63,157)	49,374 (85)
Required medical attention (n = 27,543) ^b	2,856 (10)
Body mass index (n = 44,101) ^c	
Weight	
Underweight	2,186 (5)
Healthy weight	29,121 (63)
Overweight	6,754 (15)
Obese	6,040 (16)
Eczema (n = 91,543)	11,330 (12)
Severity of eczema (n = 11,305)	
Mild	7,824 (67)
Moderate	2,845 (26)
Severe	636 (7)
History of asthma (n = 91,525)	12,025 (14)
Current asthma (n = 91,404)	7,925 (9)
Severity of current asthma (n = 7,908)	
Mild	5,761 (71)
Moderate	1,807 (23)
Severe	340 (6)
Hay fever (n = 91,455)	16,460 (16)
Severity of hay fever (n = 16,405)	
Mild	11,486 (68)
Moderate	4,331 (28)
Severe	588 (4)
Food allergy (n = 91,502)	4,657 (5)
Severity of food allergy (n = 4,618)	
Mild	2,333 (50)
Moderate	1,340 (30)
Severe	945 (20)
No. of self-reported allergic disorders (n = 91,162)	
0	60,199 (67)
1	20,945 (22)
2	7,305 (7)
3	2,209 (2)
4	504 (1)
No. of self-reported allergic disorders (n = 91,162)	
0	60,199 (67)
≥1	30,963 (33)
History of bone, joint, and muscle problems (n = 91,553)	3,001 (3)
Current bone, joint, and muscle problems (n = 91,541)	2,105 (2)
Severity of current bone, joint, and muscle problems (n = 2,084)	
Mild	979 (46)
Moderate	823 (40)
Severe	282 (14)
Current bone problems (n = 1,993)	945 (47)
Current joint problems (n = 1,993)	748 (39)
Current muscle problems (n = 1,993)	844 (39)

Abbreviation: FPL, federal poverty level.

^aSample sizes for features with missing data or for subsets of interest are indicated in parentheses. Percentages were calculated after accounting for the sampling.^bOnly available for patients 0 to 5 years old.^cOnly available for patients 10 to 17 years old.

food allergy in univariable modeling. Multivariable models 1 and 2 (model 2 adjusted for BMI) found associations between current joint problems and a history of asthma (OR, 1.87; 95% CI, 1.15–3.05; $P = .01$ and OR, 2.30; 95% CI, 1.34–3.97; $P = .003$, respectively). The presence of 1 or more allergic diseases also was significantly associated with current joint problems in multivariable models 1 and 2 (OR, 1.57; 95% CI, 1.02–2.42; $P = .04$ and OR, 1.75; 95% CI, 1.03–2.97; $P = .04$, respectively).

In the univariable analysis, current muscle problems were significantly associated with a history of eczema (OR, 2.24; 95% CI, 1.43–3.49; $P < .001$). No other significant associations were noted between muscle problems and other allergic diseases or number of allergic diseases in univariable models. Multivariable models 1 and 2 found associations between current muscle problems and a history of eczema (OR, 2.16; 95% CI, 1.36–3.44; $P = .001$ and OR, 2.33; 95% CI, 1.28–4.22; $P = .005$, respectively). No other significant associations were observed between muscle problems and other allergic diseases or number of allergic diseases in a multivariable setting.

Discussion

Allergic diseases as an aggregate were associated with bone, joint, or muscle problems, and the associations were strengthened by allergic disease severity and by the presence of multiple allergic diseases.

Eczema

In our cohort, a history of eczema was associated with bone, joint, or muscle problems. This association strengthened with increasing severity of eczema (ie, only severe eczema was associated with bone problems in the first multivariable analysis). However, for patients aged 10 to 17 years, there was no statistically significant association when the multivariable analysis adjusted for BMI.

An increasing body of literature describes bone problems in adults with eczema, particularly fracture and bone or joint injury.¹⁶ Similarly, eczema in adults is associated with decreased BMD, osteoporosis, and increased risk of bone fractures.¹⁸ Although these trends are less clear in children, a study of 3,049 children and adolescents (aged 8–19 years) reported decreased BMD in children with atopic dermatitis.¹² However, this finding has not been reported consistently, and prior studies have not accounted for BMI.^{12,19}

Asthma

Children with asthma were more likely to have current or previous bone, joint, or muscle problems. However, separate multivariable associations between asthma and severe bone, joint, or muscle, bone-only, or muscle-only problems were not statistically significant. Although a history of asthma was associated with joint problems, the association did not hold in children with current asthma. Although our study did not find a specific association with bone problems, a population-based study using data from the Rochester Epidemiology Project found increased risk of limb rather than axial skeleton fractures in children with asthma.²⁰ Although the increased fracture risk may be attributable to corticosteroid use, some authors have attributed the risk to the disease process of asthma and its severity rather than use of corticosteroids.²¹ They speculated that children with asthma had increased rates of fracture because asthma was associated with obesity and decreased physical activity; however, this association was not directly

Table 2

Multivariable Associations of Self-reported Allergic Disorders With a History of Bone, Joint, or Muscle Problems

Feature ^a	Multivariable model 1 ^b		Multivariable model 2 ^c	
	OR (95% CI)	P value	OR (95% CI)	P value
Eczema (n = 89,070:43,067)	1.46 (1.20–1.78)	<.001	1.31 (1.02–1.69)	.04
Severity of eczema (n = 11,025:4,386)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.30 (0.90–1.88)	.17	1.35 (0.87–2.11)	.18
Severe	2.81 (1.64–4.81)	<.001	3.24 (1.57–6.70)	.002
History of asthma (n = 89,053:43,072)	1.91 (1.53–2.39)	<.001	2.02 (1.55–2.65)	<.001
Current asthma (n = 88,934:43,017)	1.85 (1.42–2.42)	<.001	1.89 (1.37–2.62)	<.001
Severity of current asthma (n = 7,656:4,322)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.47 (0.91–2.36)	.11	1.47 (0.92–2.35)	.11
Severe	2.39 (1.27–4.51)	.007	1.54 (0.72–3.29)	.27
Hay fever (n = 88,997:43,045)	1.94 (1.60–2.35)	<.001	1.86 (1.46–2.37)	<.001
Severity of hay fever (n = 16,067:9,213)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.83 (1.26–2.64)	.002	2.00 (1.31–3.05)	.001
Severe	2.14 (1.28–3.57)	.004	1.91 (1.03–3.54)	.04
Food allergy (n = 89,035:43,057)	2.24 (1.73–2.90)	<.001	2.19 (1.53–3.14)	<.001
Severity of food allergy (n = 4,502:1,901)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.88 (1.15–3.08)	.01	1.86 (1.01–3.41)	.046
Severe	2.48 (1.36–4.54)	.003	2.85 (1.37–5.90)	.005
No. of self-reported allergic disorders (n = 88,725:42,945)				
0	1.0 [Reference]	NA	1.0 [Reference]	NA
1	1.28 (1.04–1.56)	.02	1.22 (0.94–1.58)	.13
2	2.55 (1.92–3.39)	<.001	2.57 (1.78–3.72)	<.001
3	2.70 (1.88–3.86)	<.001	2.33 (1.43–3.80)	<.001
4	4.35 (2.46–7.69)	<.001	5.30 (2.60–10.81)	<.001
≥1	1.70 (1.41–2.05)	<.001	1.66 (1.31–2.11)	<.001

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aSample sizes for multivariable models are indicated in parentheses (model 1:model 2).^bMultivariable model 1 included the covariates of age group, sex, race/ethnicity, poverty level of the household, and visited a health care professional for preventive services in the past 12 months.^cMultivariable model 2 included the covariates of sex, race/ethnicity, poverty level of the household, visited a health care professional for preventive services in the past 12 months, and body mass index for the subset of patients 10 to 17 years old.

evaluated in their study.²¹ Quick et al²² reported that children with asthma have slender long bones with thicker cortices than children without asthma when assessed by peripheral quantitative computed tomography. This finding generated the hypothesis that the increased fracture risk could be associated with changes in cortical bone geometry in the asthmatic population. However, these data did not control for BMI, physical activity, or use of corticosteroids.

Other Allergic Diseases

Few studies have investigated the association of musculoskeletal problems with childhood hay fever or food allergies. In our cohort, hay fever and food allergies were associated with current or previous bone, joint, or muscle problems. Hay fever was associated with joint problems; however, the association did not strengthen with disease severity. Hay fever and food allergies are often associated with other allergic processes, such as asthma and eczema, which may be confounding variables.

Musculoskeletal Problems

Common musculoskeletal conditions in children include trauma or sports injuries, pain syndromes, skeletal deformity, rheumatic conditions, neuromuscular conditions, and neoplasms.²³ Our data revealed a total prevalence rate of 3.4% for bone, joint, or muscle problems, with older children (aged 10–17 years) being affected more frequently. Prevalence rates were not significantly different by sex, race/ethnicity, or household income levels; however, affected children aged 0 to 5 years were more likely to have required medical attention during the past year.

Prior studies reported that greater than 6% of all visits to outpatient pediatric clinics are attributable to musculoskeletal pain²⁴ and approximately one-third of pediatric medical problems are associated with the musculoskeletal system.²⁵ Data from the 2012 National Health Interview Survey indicated that for patients aged 0 to 17 years 10.9% of reported health conditions affected the musculoskeletal system; prevalence increased to 22.6% in children aged 13 to 17 years.²⁶ In 2012, 19 million pediatric health care visits were prompted by musculoskeletal concerns.^{23,27}

In our cohort, children with allergic diseases were more likely to have musculoskeletal problems than children without allergic diseases, and these associations were strengthened by allergic disease severity. Determining which specific populations have a higher risk of musculoskeletal disease may help focus preventive measures or potential interventions to improve patient health. Potential but untested interventions for patients with allergic diseases could include increased screening for musculoskeletal disorders, improved dietary intake, and increased weightbearing activities.

Potential Confounding Factors

Several important confounding factors in this analysis should be considered. Obesity has been associated with atopic dermatitis and asthma; thus, obesity may be a confounding variable for bone, joint, or muscle problems.^{9–11,28} Musculoskeletal pain is common, especially in the knee and hip joints, in obese children.²⁹ In our data, the association of severe eczema and bone problems did not remain significant after adjusting for BMI in children aged 10 to 17 years. However, BMI was only partially controlled for in our

Table 3

Multivariable Associations of Self-reported Allergic Disorders With Current Bone, Joint, or Muscle Problems

Feature ^a	Multivariable model 1 ^b		Multivariable model 2 ^c	
	OR (95% CI)	P value	OR (95% CI)	P value
Eczema (n = 89,059:43,058)	1.65 (1.32–2.07)	<.001	1.54 (1.15–2.05)	.004
Severity of eczema (n = 11,022:4,383)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.69 (1.10–2.57)	.01	1.72 (1.04–2.83)	.03
Severe	3.91 (2.18–7.01)	<.001	4.48 (2.03–9.92)	<.001
History of asthma (n = 89,042:43,063)	2.25 (1.74–2.91)	<.001	2.41 (1.77–3.28)	<.001
Current asthma (n = 88,923:43,008)	2.50 (1.85–3.36)	<.001	2.57 (1.79–3.68)	<.001
Severity of current asthma (n = 7,655:4,321)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	1.51 (0.90–2.55)	.12	1.55 (0.93–2.58)	.10
Severe	2.59 (1.34–5.02)	.005	1.59 (0.69–3.62)	.27
Hay fever (n = 88,987:43,036)	2.22 (1.77–2.78)	<.001	2.25 (1.70–2.98)	<.001
Severity of hay fever (n = 16,065:9,211)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	2.27 (1.47–3.51)	<.001	2.40 (1.48–3.87)	<.001
Severe	2.65 (1.50–4.70)	<.001	2.20 (1.10–4.43)	.03
Food allergy (n = 89,024:43,048)	2.77 (2.08–3.70)	<.001	3.01 (2.05–4.43)	<.001
Severity of food allergy (n = 4,502:1,901)				
Mild	1.0 [Reference]	NA	1.0 [Reference]	NA
Moderate	2.05 (1.21–3.48)	.008	2.07 (1.10–3.91)	.03
Severe	3.01 (1.54–5.86)	.001	3.10 (1.43–6.70)	.004
No. of self-reported allergic disorders (n = 88,715:42,936)				
0	1.0 [Reference]	NA	1.0 [Reference]	NA
1	1.38 (1.08–1.75)	.009	1.37 (1.02–1.86)	.04
2	3.13 (2.24–4.37)	<.001	3.38 (2.22–5.15)	<.001
3	3.57 (2.40–5.30)	<.001	3.26 (1.90–5.60)	<.001
4	5.69 (3.05–10.63)	<.001	7.36 (3.39–15.95)	<.001
≥1	1.99 (1.61–2.46)	<.001	2.04 (1.55–2.69)	<.001

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aSample sizes for multivariable models are indicated in parentheses (model 1:model 2).^bMultivariable model 1 included the covariates of age group, sex, race/ethnicity, poverty level of household, and visited a health care professional for preventive services in the past 12 months.^cMultivariable model 2 included the covariates of sex, race/ethnicity, poverty level of household, visited a health care professional for preventive services in the past 12 months, and body mass index for the subset of patients 10 to 17 years old.

multivariable analysis because height and weight data were available only for a subset of patients (aged 10–17 years). In addition, BMI was not accounted for in an adult study that found a positive association between atopic dermatitis and bone fractures.¹⁶ However, adjusting for obesity did not change the significance of having bone, joint, or muscle problems as a whole, suggesting that although obesity may have a modifying or confounding role in the association between eczema and bone problems, allergic diseases may still be a contributing factor in the development of musculoskeletal problems. Furthermore, children with allergic disease may be less physically active, which may also contribute to the association of musculoskeletal problems. Using the same database as the current study, Strom and Silverberg³⁰ noted a higher risk of sedentary behavior in children with severe allergic diseases. Children with allergic diseases may have sleep disturbance,^{31,32} exercise-induced asthma exacerbation,³³ and exacerbation of dermatitis with increased heat and sweat; these all may contribute to deconditioning and sedentary behavior.³⁴

Garg and Silverberg⁶ reviewed the same population, specifically children 0 to 5 years of age, and described a positive association between allergic diseases and injury. The association was believed to be multifactorial and possibly influenced by psychiatric and behavioral problems. Sleep disturbance has also been associated with allergic disease and may contribute to injury.³¹ Increased rates of injuries have also been reported in child athletes with chronic lack of sleep.³²

Prior studies have reported associations between atopic dermatitis and conditions such as juvenile idiopathic arthritis and Henoch-Schönlein purpura.^{13,14} Although our data are not granular enough to further investigate these associations, future research

may be directed toward evaluating autoimmune phenomena in patients with allergic diseases to explore the association between T_H1- and T_H2-dominant diseases.

Children and adults with eczema have been noted to have increased health care use.^{35,36} However, in our cohort, individuals with bone, joint, or muscle problems were not more likely to have visited a health care professional for routine care during the past year. Associations of bone, joint, or muscle problems and allergic diseases remained after accounting for health care use in the multivariable analysis.

Corticosteroids may be prescribed to patients with allergic disease; the association between corticosteroid use and low BMD has been previously investigated. In adults with asthma, a clear inverse association exists between inhaled corticosteroid use and BMD.³⁷ Data are conflicting regarding BMD in children with asthma who require inhaled corticosteroids.^{38–40} However, a recent review of the literature and meta-analysis failed to find any association between prolonged use of inhaled corticosteroids and decreased BMD or bone fracture in children.⁴¹ Alternatively, children with allergic diseases may require systemic glucocorticoid treatment, and systemic glucocorticoid-induced osteoporosis is known to be the most common type of iatrogenic and secondary osteoporosis.⁴² In one study, the prevalence of vertebral fractures in children receiving long-term systemic corticosteroids was 6% after 1 year of treatment,⁴³ and the relative risk of fracture may be higher than 30% compared with the general pediatric population.⁴⁴ Corticosteroids may also limit growth in children.⁴² In eczema, use of topical corticosteroids does not affect BMD in adults with atopic dermatitis in a 2-year follow-up study.⁴⁵

Strengths and Limitations

This study is strengthened by the large number of participants included in the population-based survey, which captured prevalence data on allergic diseases and other comorbidities. The population studied was a representative sample from the United States. Multivariable analyses were conducted to control for many potential confounders. Finally, dose responses were noted for many of the associations between bone, joint, or muscle problems and allergic disease; we noted that associations with bone, joint, or muscle problems strengthened with severity of individual allergic diseases and with the number of allergic diseases per individual.

Limitations of this study include the possibility of survey and recall bias, which may falsely exaggerate associations between bone, joint, or muscle problems and allergic diseases. There is potential for misclassification bias because self-reporting may exaggerate disease prevalence. However, use of self- and parent-reported data has been validated in other studies that used a mild, moderate, or severe scale for both eczema and asthma.^{46,47} bone, joint, or muscle problems were not defined in the survey; therefore, it is impossible to comment on specific bone, joint, or muscle problems, such as bone fracture, bone or joint injury, and low BMD. In addition, data regarding specific risk factors for bone, joint, or muscle problems (eg, corticosteroid use, psychosocial and behavioral factors) were not available. BMI and injury data were available for only a subset of the population. The cross-sectional design of the study precluded determination of causality. Finally, more recent versions of the National Survey of Children's Health are available; however, they do not evaluate both bone, joint, or muscle problems and allergic diseases.⁴⁸

Conclusion

Bone, joint, or muscle problems were associated with self-reported allergic diseases in children, and associations were strengthened in a dose-dependent manner with regard to allergic disease severity and number of allergic diseases. These findings should prompt further research to determine the specific types of bone, joint, or muscle problems associated with this population and to examine directionality of the association between allergic disease and bone, joint, or muscle problems. Additional research efforts should be taken to explore the contribution of comorbid disorders, physical deconditioning, and other biologically plausible explanations for the epidemiologic observations. Further characterization of these associations may have implications for screening and interventions in this population.

References

- [1] Zhong W, Finnie DM, Shah ND, et al. Effect of multiple chronic diseases on health care expenditures in childhood. *J Prim Care Community Health*. 2015;6:2–9.
- [2] Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief*. 2013;121:1–8.
- [3] Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis*. 2014;25:107–114.
- [4] Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. 2011;131:67–73.
- [5] Koinis-Mitchell D, Craig T, Esteban CA, Klein RB. Sleep and allergic disease: a summary of the literature and future directions for research. *J Allergy Clin Immunol*. 2012;130:1275–1281.
- [6] Garg N, Silverberg JI. Association between childhood allergic disease, psychological comorbidity, and injury requiring medical attention. *Ann Allergy Asthma Immunol*. 2014;112:525–532.
- [7] Silverberg JI, Joks R, Durkin HG. Allergic disease is associated with epilepsy in childhood: a US population-based study [published correction in *Allergy*. 2014;69(10):1428]. *Allergy*. 2014;69:95–103.
- [8] Drury KE, Schaeffer M, Silverberg JI. Association between atopic disease and anemia in US children. *JAMA Pediatr*. 2016;170:29–34.
- [9] Silverberg JI, Becker L, Kwasny M, Menter A, Cordoro KM, Paller AS. Central obesity and high blood pressure in pediatric patients with atopic dermatitis. *JAMA Dermatol*. 2015;151:144–152.
- [10] Silverberg JI, Silverberg NB, Lee-Wong M. Association between atopic dermatitis and obesity in adulthood. *Br J Dermatol*. 2012;166:498–504.
- [11] Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. *J Am Acad Dermatol*. 2015;72:606–616.e4.
- [12] Silverberg JI. Association between childhood atopic dermatitis, malnutrition, and low bone mineral density: a US population-based study. *Pediatr Allergy Immunol*. 2015;26:54–61.
- [13] Lin CH, Lin CL, Shen TC, Wei CC. Epidemiology and risk of juvenile idiopathic arthritis among children with allergic diseases: a nationwide population-based study. *Pediatr Rheumatol Online J*. 2016;14:15.
- [14] Wei CC, Lin CL, Shen TC, Li TC, Chen AC. Atopic dermatitis and association of risk for Henoch-Schönlein purpura (IgA vasculitis) and renal involvement among children: results from a population-based cohort study in Taiwan. *Medicine (Baltimore)*. 2016;95:e2586.
- [15] Wei CC, Lin CL, Shen TC, Tsai JD. Atopic dermatitis and association of risk for primary immune thrombocytopenia and autoimmune diseases among children: a nationwide population-based cohort study. *Medicine (Baltimore)*. 2016;95:e4226.
- [16] Garg N, Silverberg JI. Association between eczema and increased fracture and bone or joint injury in adults: a US population-based study. *JAMA Dermatol*. 2015;151:33–41.
- [17] The Child & Adolescent Health Measurement Initiative (CAHMI) [Internet]. DRC Indicator Dataset: 2007 National Survey of Children's Health; Data Resource Center for Child & Adolescent Health. <http://www.childhealthdata.org>. Accessed June 10, 2016.
- [18] Garg NK, Silverberg JI. Eczema is associated with osteoporosis and fractures in adults: a US population-based study. *J Allergy Clin Immunol*. 2015;135:1085–1087.e2.
- [19] van Velsen SG, Knol MJ, van Eijk RL, et al. Bone mineral density in children with moderate to severe atopic dermatitis. *J Am Acad Dermatol*. 2010;63:824–831.
- [20] Melton LJ 3rd, Patel A, Achenbach SJ, Ober AL, Yunginger JW. Long-term fracture risk among children with asthma: a population-based study. *J Bone Miner Res*. 2005;20:564–570.
- [21] van Staa TP, Bishop N, Leufkens HG, Cooper C. Are inhaled corticosteroids associated with an increased risk of fracture in children? *Osteoporos Int*. 2004;15:785–791.
- [22] Quick JL, Ward KA, Adams JE, Mughal MZ. Cortical bone geometry in asthmatic children. *Arch Dis Child*. 2006;91:346–348.
- [23] The Burden of Musculoskeletal Diseases in the United States (BMUS). 3rd ed. c2014. Rosemont, IL: US Bone and Joint Initiative. <http://www.boneandjointburden.org>. Accessed January 22, 2016.
- [24] de Inocencio J. Musculoskeletal pain in primary pediatric care: analysis of 1000 consecutive general pediatric clinic visits. *Pediatrics*. 1998;102:E63.
- [25] Schwend RM, Geiger J. Outpatient pediatric orthopedics: common and important conditions. *Pediatr Clin North Am*. 1998;45:943–971.
- [26] National Health Interview Survey (NHIS). 2012 Data release [Internet]. c2012. Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/nhis/nhis_2012_data_release.htm. Accessed June 10, 2016.
- [27] HCUP databases [Internet]. Healthcare Cost and Utilization Project (HCUP). February c2016. Rockville (MD): Agency for Healthcare Research and Quality. Available from: www.hcup-us.ahrq.gov/kidoverview.jsp.
- [28] Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med*. 1998;152:1197–1200.
- [29] Stovitz SD, Pardee PE, Vazquez G, Duval S, Schwimmer JB. Musculoskeletal pain in obese children and adolescents. *Acta Paediatr*. 2008;97:489–493.
- [30] Strom MA, Silverberg JI. Associations of physical activity and sedentary behavior with atopic disease in United States children. *J Pediatr*. 2016;174:247–253.e3.
- [31] Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health: the HUNT-2 study. *J Psychosom Res*. 2009;67:109–116.
- [32] Milewski MD, Skaggs DL, Bishop GA, et al. Chronic lack of sleep is associated with increased sports injuries in adolescent athletes. *J Pediatr Orthop*. 2014;34:129–133.
- [33] Randolph C. Pediatric exercise-induced bronchoconstriction: contemporary developments in epidemiology, pathogenesis, presentation, diagnosis, and therapy. *Curr Allergy Asthma Rep*. 2013;13:662–671.
- [34] Williams JR, Burr ML, Williams HC. Factors influencing atopic dermatitis—a questionnaire survey of schoolchildren's perceptions. *Br J Dermatol*. 2004;150:1154–1161.
- [35] Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol*. 2013;24:476–486.
- [36] Strom MA, Silverberg JI. Utilization of preventive health care in adults and children with eczema. *Am J Prev Med*. 2016;50:e33–e44.
- [37] Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet*. 2000;355:1399–1403.
- [38] Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med*. 1998;157:178–183.
- [39] Boot AM, de Jongste JC, Verberne AA, Pols HA, de Muinck Keizer-Schrama SM. Bone mineral density and bone metabolism of prepubertal children with asthma after long-term treatment with inhaled corticosteroids. *Pediatr Pulmonol*. 1997;24:379–384.

- [40] Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC; CAMP Research Group. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the Childhood Asthma Management Program (CAMP) study. *Pediatrics*. 2008;122:e53–e61.
- [41] Loke YK, Gilbert D, Thavarajah M, Blanco P, Wilson AM. Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis. *BMJ Open*. 2015;5:e008554.
- [42] Buehring B, Viswanathan R, Binkley N, Busse W. Glucocorticoid-induced osteoporosis: an update on effects and management. *J Allergy Clin Immunol*. 2013;132:1019–1030.
- [43] Rodd C, Lang B, Ramsay T, et al; Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. *Arthritis Care Res (Hoboken)*. 2012; 64:122–131.
- [44] van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res*. 2003;18:913–918.
- [45] van Velsen SG, Haeck IM, Knol MJ, Lam MG, Bruijnzeel-Koomen CA. Two-year assessment of effect of topical corticosteroids on bone mineral density in adults with moderate to severe atopic dermatitis. *J Am Acad Dermatol*. 2012; 66:691–693.
- [46] Rausch ME, Weisberg S, Vardhana P, Tortoriello DV. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int J Obes (Lond)*. 2008;32:451–463.
- [47] Housman TS, Patel MJ, Camacho F, Feldman SR, Fleischer AB Jr, Balkrishnan R. Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *Br J Dermatol*. 2002;147:1192–1198.
- [48] The Child & Adolescent Health Measurement Initiative (CAHMI) [Internet]. DRC Indicator Dataset: 2011/12 National Survey of Children's Health; Data Resource Center for Child & Adolescent Health. <http://www.childhealthdata.org>. Accessed November 30, 2016.