Prevalence of Asthma and Allergies and Risk of Relapse in Childhood Nephrotic Syndrome: Insight into Nephrotic Syndrome Cohort

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Objective To determine the lifetime prevalence of allergies in childhood nephrotic syndrome, the seasonality of presentation and relapses, and the impact of allergies on subsequent relapses.

Study design In a longitudinal cohort of children with nephrotic syndrome (ages 1-18 years), assessment for allergic diseases was conducted using the validated and modified version of the International Study of Asthma and Allergies in Childhood questionnaire at enrollment. Outcomes included frequently relapsing nephrotic syndrome, relapse rates, and the relapse-free duration after initial steroid therapy.

Results Among 277 participants, the majority were male (65%) with a median age of 3.7 years (IQR 2.8-5.8) at presentation. A total of 64% reported lifetime allergies with 20% having asthma, 33% wheezing, 27% eczema, and 24% rhinitis. Over 3.3 years of follow-up, presence of asthma and allergies was not associated with frequently relapsing nephrotic syndrome (OR 1.20; 95% CI 0.60, 2.40), higher relapse rates (relative risk 0.95; 95% CI 0.71, 1.27), or risk of first relapse (hazard ratio 1.10; 95% CI 0.83, 1.47) compared with those with no history of allergic diseases. There was also no seasonal variation evident at initial presentation or frequency of relapses.

Conclusions Two-thirds of children with nephrotic syndrome at presentation have allergic symptoms and asthma; however, neither are associated with an increased frequency of relapses. *(J Pediatr 2019;208:251-7)*.

Several lines of evidence suggest that the link between allergies and nephrotic syndrome onset or relapse is related to an individual's immune system response.[1] Clinical symptoms such as wheezing and itchy rash, asthma, rhinitis, hay fever, and eczema are commonly described in children with nephrotic syndrome.[1] The reported frequency of asthma and allergic conditions in nephrotic syndrome ranges from as low as 10% to as high as 50%.[1-10] The reported prevalence of allergies is variable due to cross-sectional study design with small study populations, and inconsistent definitions of allergies.[2-9,11-14] Despite the prevalence of allergies, the use of antiallergen medications (eg, disodium cromoglycate or sodium nivimedone) among 10 children with nephrotic syndrome in a randomized clinical trial was unsuccessful in preventing relapses as all children relapsed within 11 weeks of stopping steroid treatment.[11]

It is unclear why approximately 20% of children respond after a single course of prednisone whereas others have repeated relapses requiring various treatment regimens with steroid sparing agents.[15] Allergies are often ascribed as triggers for relapses, but treatment for allergies with dietary restrictions, skin desensitization, or mast cell stabilizers has demonstrated little benefit in preventing relapsing disease.[1] Immune dysfunction, or dysregulation, of T-lymphocytes is suspected as the pathogenesis of nephrotic syndrome because of the success with immunosuppression in inducing remission.[16-18] Additional supportive evidence includes the development of nephrotic syndrome in children after a severe allergic reaction to various stings and poisons. Yet, triggers for relapsing episodes of nephrotic syndrome are less clear.

Previous studies in childhood nephrotic syndrome have not explored the longitudinal association of asthma and allergies with clinical outcomes. Children are often not followed for an extended period or varying definitions are used to describe clinical outcomes.[3-6] There are anecdotal reports of seasonal allergies as a trigger for relapsing disease.[1,3,5,6] The primary aim of this study is to determine the lifetime prevalence of asthma and allergies among children with nephrotic syndrome using a validated assessment, seasonality of presentation,

IL	Interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
T_h2	T helper 2

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and relapses and also to determine whether prevalent asthma and allergies are associated with adverse outcomes of relapsing disease.

Methods

Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics study is a disease-based observational cohort study[19] with 294 participants diagnosed from January 2005 to October 2015 and followed through May 2016 from the Hospital for Sick Children (SickKids) in Toronto, Canada and local community hospitals in the Greater Toronto Area. Children were eligible if diagnosed with nephrotic syndrome from ages 1 to 18 years, able to provide informed consent (or had a parent/guardian provide informed consent on their behalf), and willing to complete questionnaires at baseline and annually. Participants were recruited between from February 2011 to December 2015. Participants were excluded if they had congenital nephrotic syndrome, disease with multiple organ involvement, or conditions causing secondary nephrotic syndrome (such as systemic lupus erythematosus or vasculitis). In addition, children with initial steroid resistance were excluded from all analyses (n = 17) leaving a remainder of 277 for the final study. We describe the prevalence of asthma and allergies at presentation and longitudinal analysis at follow-up in children with steroid-sensitive nephrotic syndrome. The Research Ethics Board of the Hospital for Sick Children approved the Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics study (ClinicalTrials: NCT01605266).

Data Collection

At enrollment, participants and/or parents completed baseline questionnaires, which included sociodemographic information and self-reported asthma and allergies based on the modified version of The International Study of Asthma and Allergies in Childhood (ISAAC)[20] questionnaire to assess for lifetime asthma and allergies and also symptoms of allergies within the 12 months before onset of nephrotic syndrome. ISAAC questionnaires are considered the international standard for defining allergies since 1995 and can be used to compare estimates with the general population.[21] We used the ISAAC questionnaire to collect data on presence of allergic symptoms and conditions of disease. Questionnaires were administered by research staff, and additional clinical data on longitudinal outcomes were obtained from electronic patient records using standardized data collection forms. All data were validated through double data entry.

Asthma and Allergies

Participants reported both a lifetime history of wheezing, asthma, rhinitis, hay fever, itchy rash, and/or eczema, and whether these conditions were present during the 12 months before diagnosis with nephrotic syndrome. Lifetime history of allergies was defined as ever having wheezing, asthma, rhinitis, hay fever, itchy rash, or eczema. Moreover, wheezing is a common condition ascribed to young children. Additional analyses excluded wheezing to account for possible over diagnosis in young children as wheezing occurs with bronchiolitis, gastric esophageal reflux, or obstructive sleep apnea.[22,23]

Outcomes

All children were treated with a standard clinical protocol for nephrotic syndrome typically consisting of a 6-week course followed by a 10-week taper (maximum cumulative dose: ~3200 mg over 16 weeks) similar to International Study of Kidney Disease in Children (maximum cumulative dose: ~2960 mg over 8 weeks) and Kidney Disease: Improving Global Outcomes (maximum cumulative dose: ~3020 mg over 12 weeks) guidelines.[15,24,25] Frequently relapsing nephrotic syndrome was defined as having at least 2 relapses in the first 6 months or ≥4 relapses during any 12-month period after diagnosis. The relapse rate is the number of relapses per year for the duration of individual follow-up, and the time to first relapse (relapse-free period) is the length of time, in days, from the date of diagnosis to the first relapse. Furthermore, the calendar timing of disease onset and all relapses during follow-up were used to assess possible evidence of seasonal variation.

Additional Covariates

Sex, age at diagnosis, ethnicity (ie, European, South Asian [eg, India, Bangladesh, Pakistan], East/Southeast Asian [eg, China, Philippines, Tibet, Vietnam], and other),[15] child's immigration status, family income, and caregiver education are included, obtained by self-report by child or parent depending on the age of the child. Immigration status was determined based on the child's birthplace. Income level was defined as the combined family income in the past 12 months, and dichotomized using the low income cutoff, defined by Statistics Canada of approximately $35 000, similar to the poverty designation in the US.[26] The education level of the primary caregiver was also dichotomized based on completion of high school education and higher with at least 12 years of schooling.

Statistical Analyses

Distributions of values were examined for outliers and for normality. Descriptive statistics are provided for prevalence of asthma and allergies. Differences among children with and without a history of asthma and allergies were determined using χ^2 or rank-sum for characteristics as appropriate. We determined the occurrences of disease presentation and relapses by calendar months descriptively using a histogram.

Using logistic regression, we determined the odds of frequently relapsing nephrotic syndrome at 12 months. Applying negative binomial regression, we estimated whether relapse rates differed by lifetime exposure of asthma and allergies (presented as a rate ratio). Median relapse-free period after diagnosis were calculated using Kaplan-Meier analysis.

Table I. Characteristics of children with nephrotic syndrome by self-reported asthma and allergies

	No asthma/allergic conditions (n = 100)	Asthma/allergic conditions (n = 177)	Total (n = 277)
	n (%) or median (IQR)		
Demographic factors			
Age at diagnosis (y)	3.48 (2.53, 5.07)	3.79 (2.81, 5.91)	3.67 (2.77, 5.83)
Male	69 (69.0)	110 (62.2)	179 (64.6)
Born outside Canada*	17 (17.4)	25 (14.2)	42 (15.3)
Annual income above $35 000†	61 (72.6)	115 (75.2)	176 (74.3)
Caregiver education ≥12 y‡	89 (90.8)	164 (93.2)	253 (92.3)
Ethnicity			
European	23 (23.0)	43 (24.3)	66 (23.8)
South Asian	44 (44.0)	70 (39.6)	114 (41.2)
East/Southeast Asian	4 (4.0)	16 (9.0)	20 (7.2)
Other§	29 (29.0)	48 (27.1)	77 (27.8)
Clinical course			
Distribution of disease onset			
January-March	29 (29.0)	44 (24.9)	73 (26.4)
April-June	23 (23.0)	42 (23.7)	65 (23.5)
July-September	27 (27.0)	43 (24.3)	70 (25.3)
October-December	21 (21.0)	48 (27.1)	69 (24.9)
Complete remission after initial course	26 (26.0)	37 (20.9)	63 (22.7)
Frequently relapsing at 12 mo (FRNS12)	14 (14.0)	29 (16.4)	43 (15.5)
Relapse rate among those with FRNS12	2.11 (1.69, 3.02)	2.29 (1.80, 3.18)	2.29 (1.71, 3.18)
Biopsy performed	26 (26.0)	38 (21.5)	64 (23.1)
Received steroid sparing agents	48 (48.0)	86 (48.6)	134 (48.4)
Cyclophosphamide	40 (83.3)	68 (79.1)	108 (80.6)
Complete remission after treatment	10 (25.0)	22 (32.4)	32 (29.6)
Calcineurin inhibitor¶	5 (10.4)	12 (14.0)	17 (12.7)
Other**	3 (6.3)	6 (6.9)	9 (6.7)
Total relapses (n)	4 (0, 8)	4 (1, 6)	4 (1, 7)
Clinical follow-up time (y)	3.90 (1.94, 5.88)	3.05 (1.64, 5.04)	3.30 (1.82, 5.28)
Relapses per y	1.27 (0.20, 2.19)	1.10 (0.30, 1.89)	1.18 (0.27, 1.94)
Required inpatient admission during follow-up	56 (56.0)	104 (58.8)	160 (57.8)

P value ≤ .05 using χ^2-test or Wilcoxon rank-sum test.
*Subject born outside of Canada, (n = 274).
†Proportion living above the Canadian low-income cut-off of $35 000 per year (gross), (n = 237).
‡Proportion with at least 12 years of education (n = 274).
§Includes individuals classified as West Central Asian/Middle Eastern (n = 9), West Indian/Caribbean and African (n = 19), Latin/Central/South American and Aboriginal (n < 5), multiethnic (n = 44), and unknown (n < 5).
¶Calcineurin inhibitors include cyclosporine and tacrolimus. Complete remission rates not provided due to small sample size.
**Other includes myfortic, mycophenolate mofetil, and levamisole. Complete remission rates not provided due to small sample size.

Using Cox proportional hazard models, we analyzed relative hazard for asthma and allergies to risk of first relapse. All models were adjusted for age at diagnosis, sex, immigration status, and ethnicity. Sensitivity analyses included stratification among children diagnosed ≤5 years of age vs children diagnosed >5 years of age to determine whether there was an age effect. Statistical significance was defined as a *P* value of ≤ .05. All analyses were performed using STATA/SE-14 (StataCorp, College Station, Texas).

Results

The study population was predominantly male (65%) and had a median age at diagnosis of 3.7 years (IQR 2.8-5.8). The majority of families were above the low-income cut-off, although a substantial number (n = 40) did not wish to report income level. The cohort was diverse with children from South Asian (41%), European (24%), and East/Southeast Asian (7%) ancestry (Table I). The median follow-up time was 3.3 years (IQR 1.8-5.3).

Prevalence of Asthma and Allergies

The estimated lifetime prevalence of asthma and allergies was 64% at presentation of nephrotic syndrome. The median number of allergic conditions was 1, with 82% of children reporting at most 2 conditions. There were no differences in sex, immigration, ethnicity, or caregiver education status by presence of asthma and allergies. Children diagnosed with nephrotic syndrome at an older age were more likely to report having an allergic condition (*P* = .05).

Wheezing was the most commonly reported symptom affecting 33% (n = 92) and hay fever was least prevalent at 6% (n = 17; Figure 1, A). With wheezing excluded from the analysis, the estimated overall prevalence of atopy only drops from 64% to 58%.

In the year prior to onset of nephrotic syndrome, 41% of children reported 1 of 3 allergic conditions (wheezing, rhinitis, or itchy rash) with 20% having wheezing, 17% rhinitis, and 16% an itchy rash (Figure 1, B). The prevalence of allergies 12 months prior to disease onset also did not differ by sociodemographic factors (data not shown). There was also no seasonal variation found in the

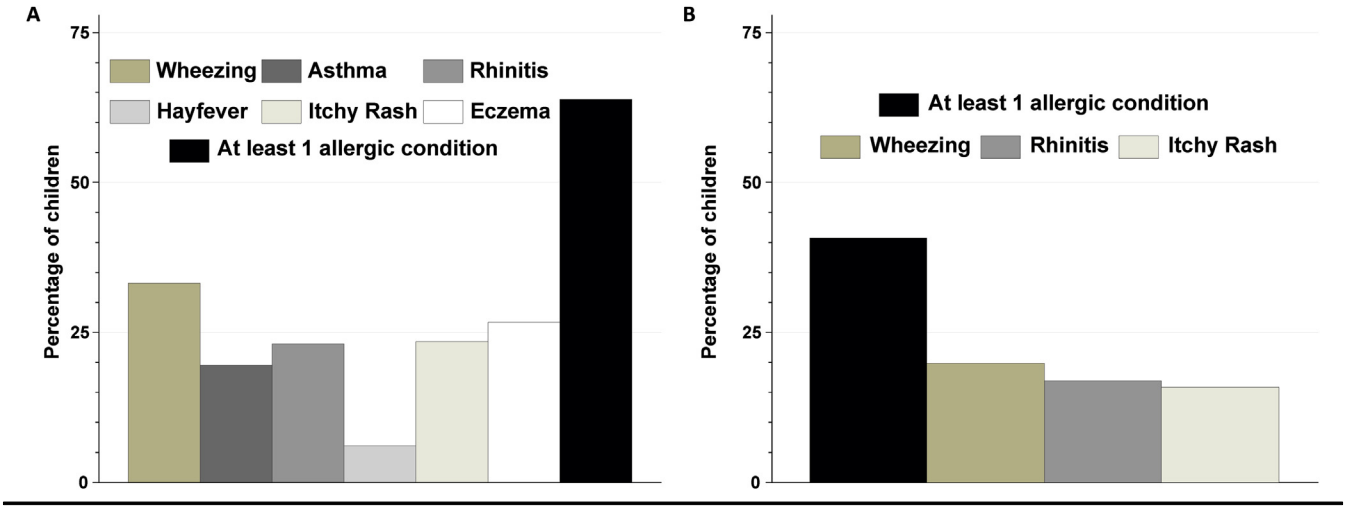

Figure 1. Prevalence of asthma and allergic conditions among children with nephrotic syndrome (2005-2016). **A,** Lifetime prevalence of asthma and allergic conditions; **B,** Prevalence of specific allergic conditions 12 months prior to onset of nephrotic syndrome.

timing of disease onset or relapses among the 277 children (Figure 2).

Asthma and Allergies Association with Clinical Outcomes

Presence of lifetime allergies did not influence outcomes. There was also no difference among those who never relapsed and went into complete remission after their initial treatment (Table I). Among those with a history of lifetime allergies, only 16% (n = 29) developed frequently relapsing nephrotic syndrome 12 months after disease onset. History of lifetime allergies did not result in a significant association with frequently relapsing disease at 12 months even after adjustment for age at diagnosis, sex, ethnicity, and immigration status (Table II; OR 1.20, 95% CI 0.60, 2.40).

The overall median relapse rate per year was 1.18 (IQR 0.27, 1.94) relapses per year. There was no statistical difference in the relapse rates between those with reported allergies (1.10; IQR 0.30, 1.89) and those without allergies (1.27; IQR 0.20, 2.19; rate ratio 0.95; 95% CI 0.71, 1.27). There was also no difference in the initial relapse-free period between those with allergies (median 190 days) and without allergies (median 181 days; hazard ratio 1.11; 95% CI 0.83, 1.47). Adjustment of household size and income did not alter the association of allergies and relapse-free period.

Furthermore, upon removal of wheezing as an allergic condition, the association between allergies and outcomes

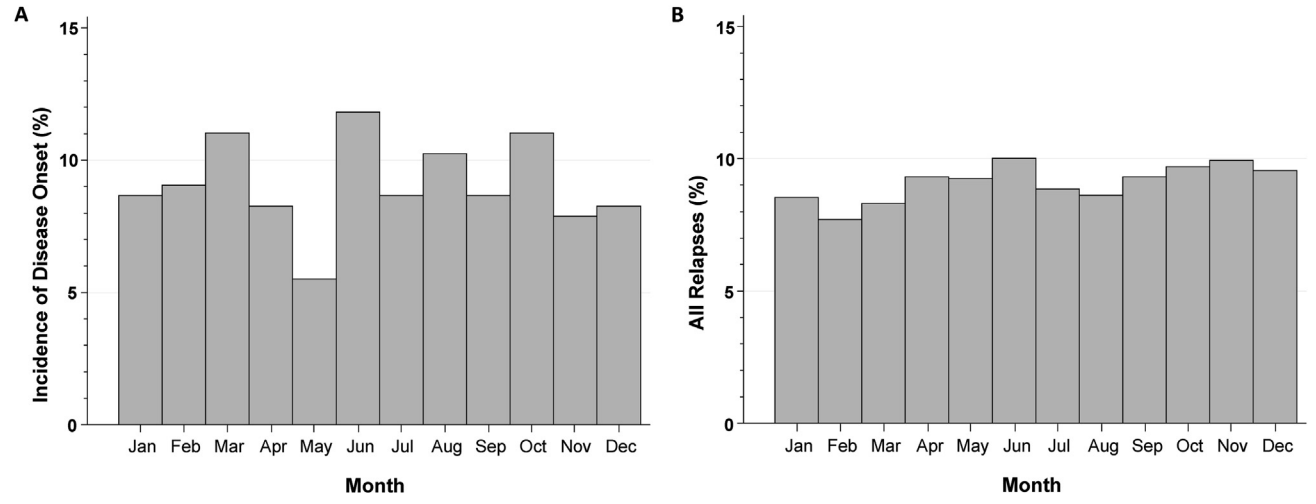

Figure 2. Distribution of diagnosis and relapses by calendar month among 277 children with nephrotic syndrome. **A,** Distribution of the timing of disease onset by months per calendar year; **B,** Distribution of all relapses by months per calendar year for all children in longitudinal follow-up.

Table II. Association of lifetime asthma and allergies with clinical outcomes of nephrotic syndrome

	No asthma/allergic conditions (n = 100)	Asthma/allergic conditions (n = 177)
Frequently relapsing nephrotic syndrome at 12 mo		
OR	Reference	1.20
95% CI	-	[0.60, 2.40]
P value	-	.60
aOR*	Reference	1.29
95% CI	-	[0.63, 2.63]
P value	-	.48
Relapse rate		
Relative risk	Reference	0.95
95% CI	-	[0.71, 1.27]
P value	-	.74
Adjusted relative risk*	Reference	.97
95% CI	-	[0.72, 1.30]
P value	-	.82
Time to first relapse		
Hazard ratio	Reference	1.11
95% CI	-	[0.83, 1.47]
P value	-	.49
Adjusted hazard ratio*	Reference	1.20
95% CI	-	[0.89, 1.61]
P value	-	.23

*Adjusted for age at diagnosis, sex, immigration status, and ethnicity.

in nephrotic syndrome was not attenuated (**Table III**; available at www.jpeds.com). In addition, there was no statistical difference in frequently relapsing nephrotic syndrome, relapse rate, and time to first relapse among those who reported allergies in the 12 months prior to nephrotic syndrome onset (data not shown). Similarly, stratification of age at diagnosis showed no statistical difference between nephrotic syndrome outcomes and prevalent asthma and allergies (**Table IV**; available at www.jpeds.com).

Discussion

Two-thirds of children with nephrotic syndrome have asthma and allergies, with wheezing as the most commonly reported condition. Despite the high prevalence of lifetime allergies and history of allergies 12 months prior to diagnosis of nephrotic syndrome, there is a consistent null association with various measures of relapsing disease including initial relapse-free period, relapse rates, and frequently relapsing disease. Furthermore, analysis excluding wheezing demonstrates similar results. In addition, there is no seasonality with either the presentation of nephrotic syndrome or timing of relapses despite the high proportion with asthma and allergies. The lack of association with allergies and asthma with increased risk of relapses suggest that once the disease is established, other potential triggers may lead to disease variability.

The cause of childhood nephrotic syndrome is still unknown, however, the combination of asthma, allergies, and nephrotic syndrome at disease presentation underscores the action of immune dysregulation. There may be a common immune mechanism leading to the high prevalence of coexistent disease. Prior mechanistic studies indicate a possible T-cell mediated disease through T helper 2 (T_h2) directed immune response, which leads to both allergic diseases and nephrotic syndrome. In a population-based cohort among children, the incidence of nephrotic syndrome is 3.36-fold greater in those with asthma than without.[27] Asthma as one of the most common allergic diseases in childhood is another T_h2-mediated disease. Various T_h2 associated cytokines, interleukin (IL)-4, and IL-13, are also elevated in relapsing nephrotic syndrome. IL-4 and IL-13 regulate IgE or light chains of immunoglobulin production, both products of B-cells, which stimulates a cytokine cascade culminating in the development of atopy.[27] In a cross-sectional analyses of 79 children with relapsing nephrotic syndrome, a polymorphism in the IL-12B promoter region, encoding IL-12 (a T_h2 process), is associated with steroid dependence.[28] In addition, podocytes play a key role in maintaining the structural integrity of the glomerular filtration barrier by preventing proteinuria.[29] Podocytes express IL-13 receptors (CD80), and CD80 induction by T-cell co-stimulation leads to possible actin rearrangement of podocyte structure and damage to filtration barrier resulting in proteinuria.[30] Urinary levels of CD80 increase during nephrotic syndrome relapse, and decrease during remission further supporting this hypothesis. Increased permeability of the glomerular capillary wall may occur due to T-cell activation and release of cytokines.

With the high frequency of allergies and asthma, it had been hypothesized that typical triggers for relapses include seasonally related atopic diseases. We did not observe any seasonal variation in either the incidence of nephrotic syndrome nor timing of relapses. A possible explanation for the lack of association with longitudinal outcomes is confounded by treatment of nephrotic syndrome with steroids, predominantly prednisone, which is the common treatment for both diseases.[1] To address possible confounding, we also studied the relapse-free period after initial therapy, and still found no association with either lifetime allergies with or without wheezing. What is not known for those not on either steroids or steroid sparing agents, if allergic events trigger further relapses.

Studies in the general population using the ISAAC questionnaire demonstrate differences in prevalence of symptoms of atopic diseases among children worldwide with the highest in Costa Rica (37.6%) and lowest in Indonesia (2.8%).[31] In our study population, we report a higher prevalence than reported in children worldwide that ranges from 10% to 50%.[1-10,32] In comparison with a study from a similar catchment in Toronto, we report a higher prevalence of 19.6% with asthma than a 16.1% prevalence of asthma among 5619 grade school children.[33] In addition, our study population mostly has a family income well above poverty line supporting reports of higher prevalence of asthma and allergies in higher income countries.[20] Interestingly, factors known to impact allergic disease burden in urban settings such as low income, younger ages, and recent immigration do not differ by atopic disease status in our cohort implying other causative factors playing a role in prevalence of asthma and allergies. These results suggest that asthma and allergy

mediated disease and nephrotic syndrome occurring concurrently is not due to chance or patient selection and provides the empirical evidence suggesting a common pathway leading to the disease.[33]

The strengths of this study are the use of a standardized and validated measure to assess allergic diseases in a well-characterized cohort with detailed and standardized clinical outcomes over time. Our diverse study population with longitudinal outcomes also enhances generalizability. To determine a more comprehensive environmental and serologic evaluation of allergies was not possible. Prior studies in nephrotic syndrome have demonstrated that IgE levels, a serologic measure for sensitization,[34] do not differ by steroid response.[35] Although, total serum IgE levels are not a reliable indicator of allergic disease alone, it is also possible that IgE and other proteins (up to 200 000 kDa) could be lost with massive proteinuria in nephrotic syndrome.[34,35] Additional limitations of the study includes the potential recall bias on the prevalence of atopy, a limitation when using the validated ISAAC self-report questionnaires. We have confirmed prior studies demonstrating a higher incidence of allergic rhinitis compared with other conditions such as asthma and atopic dermatitis and have extended the findings with longitudinal outcomes.[36,37] We were limited in assessing the type of allergy correlated with nephrotic syndrome outcomes due to power. The increased prevalence could also be due to recall bias of wheezing related to upper respiratory infections, yet, after exclusion of wheezing, results were similar. In addition, we did not capture the presence of allergic flares coexistent with each relapse, but not all children go on to have relapsing disease. Even among those with prevalent asthma or allergies, there was 21% that never relapsed again after the initial course of therapy. Lastly, we did not assess over the counter medications, such as antihistamines nor do we ask specifically about immunotherapy. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table III. Association of lifetime asthma and allergies with clinical outcomes of nephrotic syndrome (excluding wheezing as an allergic condition)

	No asthma/allergic conditions (n = 115)	Asthma/allergic conditions (n = 162)
Frequently relapsing nephrotic syndrome at 12 mo		
OR	Reference	1.39
95% CI	-	[0.71, 2.74]
P value	-	.34
aOR*	Reference	1.48
95% CI	-	[0.73, 2.98]
P value	-	.27
Relapse rate		
Relative risk	Reference	1.02
95% CI	-	[0.77, 1.36]
P value	-	.87
Adjusted relative risk*	Reference	1.03
95% CI	-	[0.77, 1.38]
P value	-	.85
Time to first relapse		
Hazard ratio	Reference	1.14
95% CI	-	[0.86, 1.50]
P value	-	.36
Adjusted hazard ratio*	Reference	1.22
95% CI	-	[0.92, 1.64]
P value	-	.17

*Adjusted for age at diagnosis, sex, immigration status, and ethnicity.

Table IV. Association of lifetime asthma and allergies with clinical outcomes of nephrotic syndrome stratified by age at diagnosis

	Diagnosed ≤5 y of age		Diagnosed >5 y of age	
	No asthma/allergic conditions (n = 75)	Asthma/allergic conditions (n = 115)	No asthma/allergic conditions (n = 25)	Asthma/allergic conditions (n = 62)
Frequently relapsing nephrotic syndrome at 12 mo				
OR	Reference	1.15	Reference	*
95% CI	–	[0.55, 2.40]	–	
P value	–	.71	–	
aOR†	Reference	1.12	Reference	*
95% CI	–	[0.53, 2.34]	–	
P value	–	.77	–	
Relapse rate				
Relative risk	Reference	.97	Reference	1.05
95% CI	–	[0.69, 1.35]	–	[0.57, 1.91]
P value	–	.84	–	.88
Adjusted relative risk†	Reference	0.96	Reference	1.14
95% CI	–	[0.68, 1.34]	–	[0.58, 2.23]
P value	–	.79	–	.71
Time to first relapse				
Hazard ratio	Reference	1.16	Reference	1.24
95% CI	–	[0.83, 1.60]	–	[0.67, 2.27]
P value	–	.39	–	.50
Adjusted hazard ratio†	Reference	1.11	Reference	1.52
95% CI	–	[0.80, 1.54]	–	[0.80, 2.89]
P value	–	.54	–	.20

*Omitted because of collinearity. All patients with frequently relapsing nephrotic syndrome at 12 months (n = 5) had asthma/allergic conditions.
†Adjusted for sex, immigration status, and ethnicity.