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Do human rhinovirus infections and food allergy modify grass pollen–induced asthma hospital admissions in children?

To the Editor:

Asthma prevalence in children has remained relatively constant in many Western countries, but hospital admissions for younger age groups have increased over time.[1] Although the role of outdoor aeroallergens as triggers for asthma exacerbations requiring hospitalization in children and adolescents is complex, there is evidence that increasing concentrations of grass pollen are associated with an increased risk of asthma exacerbations in children.[2] Human rhinovirus (HRV) infections are implicated in most of the serious asthma exacerbations in school-age children.[3] In previous research, HRV infections and aeroallergen exposure have usually been studied independently. To our knowledge, only 1 study has examined interactions between these 2 factors,[4] but lack of power prevented any meaningful interpretation.

Furthermore, although sensitization to aeroallergens is an important risk factor for the development of asthma in children,[5] little is known about the role of allergic sensitization to food and the risk of asthma admissions.[6] The aims of this study were to assess the effect of outdoor grass pollen levels on the incidence of asthma admissions in children and to assess whether the presence of HRV and allergic sensitization modified this effect.

Data from the Melbourne Air Pollen Children and Adolescent Health study (see this article's Methods section in the Online Repository at www.jacionline.org[E1]) were analyzed. A total of 644 children and adolescents aged between 2 and 17 years with a principal diagnosis of asthma were enrolled between September

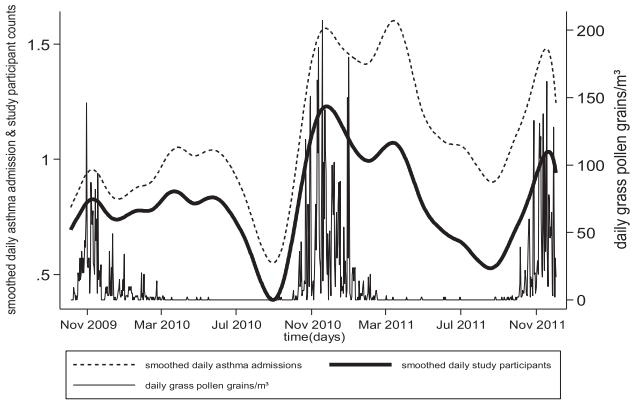

FIG 1. The total numbers of asthma admissions to the Royal Children's Hospital and participants enrolled in the Melbourne Air Pollen Children and Adolescent Health study (smoothed) and the seasonal distribution (in days) of ambient grass pollen during the study period.

TABLE I. Adjusted ORs for a per 50 grains/m^3 increase in grass pollen, stratified by HRV and sensitization to pollen and food

	All (N = 644)	Boys (N = 407; 63%)	Girls (N = 237; 37%)
Grass pollen	1.11 (1.00-1.22)*	1.22 (1.05-1.35)*	1.00 (0.84-1.21)
HRV infection status			
No HRV infection	1.04 (0.61-1.28)	1.11 (0.61-1.42)	0.89 (0.60-1.34)
HRV infection	1.22 (1.02-1.57)*	1.42 (1.11-1.64)*	0.58 (0.26-1.09)
Pollen sensitization			
Not sensitized to pollen	1.11 (0.61-1.28)	1.16 (0.61-1.42)	1.02 (0.77-1.36)
Sensitized to grass pollen	1.16 (1.02-1.28)*	1.22 (1.11-1.42)*	1.01 (0.77-1.32)
Food sensitization			
Not sensitized to food	1.11 (0.61-1.22)	1.22 (1.11-1.42)*	0.87 (0.71-1.05)
Sensitized to food	1.07 (0.83-1.39)	0.94 (0.68-1.30)	1.52 (1.03-2.24)*

Adjusted for age, HRV infection status (when not stratified by), pollutants, relative humidity, rainfall, and temperature. Adjusted models included only those variables that were significant at the 5% level. Values represent OR (95% CI).
*$P < .05$.

2009 and December 2011. The design was case-crossover. The *case day* was defined as the day of admission. The control period was the same day of the week as the case day in all weeks within the same month of the same year in which the case day occurred. At admission, respiratory viral infections and skin prick test response to common allergens were tested. Daily ambient concentrations of grass pollen and air pollutants and weather data were available during the study period.

Population-averaged conditional regression models with robust standard errors were used to investigate the association between grass pollen and asthma admissions.[E2] The primary exposure variable was daily concentrations of grass pollen fitted as a continuous variable. HRV infection status at admission, sex, and positive skin prick test result for allergens were considered as effect modifiers, and stratified analysis has been presented in tables. All models of the association between grass pollen and hospital admissions were adjusted for age, air pollutants, and weather variables. Potential confounders were retained if they changed the estimated associations between pollen exposure and the outcome by 10% or more, or were significant at the 5% level in adjusted models. Results are presented as odds ratios (ORs) with 95% CIs; these can be interpreted as an increment of 50 grains/m^3 in airborne grass pollen (defined as high pollen days). Analyses were performed using Stata, release 10.1 (StataCorp, College Station, Tex).

Of 644 participants in the Melbourne Air Pollen Children and Adolescent Health study, 407 (63%) were male and the median (range) age was 5.2 years (2-17 years). There were 249 patients (39%) admitted during the peak grass pollen season, which occurred between October and December in Melbourne, Australia (Fig 1). Of this group, 164 were male, similar in age to girls, and showed comparable infection rates with HRV and other viruses. Although the rate of sensitization to food was similar in boys and girls, the rate of sensitization to grass pollen differed, with 47% in boys and 37% in girls (see Table E1 in this article's Online Repository at www.jacionline.org).

Presence of grass pollen in the atmosphere was significantly associated with an increased risk of admission in an adjusted model (Table I; OR = 1.11; 95% CI, 1.003-1.22). High levels of airborne grass pollen were associated with increased admission in boys (OR = 1.22; 95% CI, 1.05-1.35) but not in girls (OR = 1.00; 95% CI, 0.84-1.21). When stratified by HRV infection status, daily exposure to 50 grains/m^3 of grass pollen or more increased admission only in boys with HRV infection (OR = 1.42; 95% CI, 1.11-1.64). Grass pollen exposure was associated with increased admission among girls who were sensitized only to food (OR = 1.52; 95% CI, 1.03-2.24).

It is known that boys have higher risks of asthma exacerbations requiring emergency treatment or admission, particularly before puberty.[7] Sex differences in lung physiology may partly contribute to early life increase in asthma admission for boys.[8] Hitherto, the risk of asthma exacerbations requiring hospitalization associated with pollen exposure and cosensitization to food and aeroallergens was largely unknown.

Our results indicate that the combination of grass pollen exposure and HRV infection increases asthma exacerbations in boys. The reasons need further exploration because these factors are presumably acting through different biological pathways. Murray et al[4] previously reported an increased risk for admission following a combination of allergen exposure and rhinovirus infection,[4] although they did not separately report results for grass pollen exposure and rhinovirus. The combination of these 2 triggers particularly in boys needs further exploration. The "two-hit hypothesis"[9] is one such possible mechanism where viral infections combined with atopy in early life may increase asthma exacerbations in children.

Our findings further indicate that food sensitization presents an increased risk of admission related to pollen exposure in girls, and highlights the value of identifying concomitant food sensitization/allergy in children with asthma. Significant effects of grass pollen exposure in girls sensitized to food could suggest a more severe atopic phenotype, rather than cross-reactivity to allergens as was previously thought.[10,11] Additional studies are required to confirm our findings and investigate mechanisms.

A major strength of our study is the case-crossover design, which was chosen to address the hypothesis of pollen exposure, cosensitization, and the presence of respiratory viral infection. One potential limitation should be considered when interpreting the results: pollen measurements were performed at only 1 outdoor site, and it is possible that the counts did not reflect airborne pollen levels across the city. However, in previous studies, the exposures to grass pollen were similar for residents across Melbourne.[2]

In summary, boys with HRV infection at admission on days with high concentrations of outdoor grass pollen are at risk of asthma exacerbations requiring hospitalization. In contrast, girls sensitized to food were at an increased risk of admission on high pollen days. With climatic conditions continuing to have an impact on the duration and intensity of the pollen season coupled with likely increases in allergen exposures,[12] it is imperative to

better understand the relationship between pollen exposure and risk for adverse respiratory health outcomes. Interventions to reduce pollen exposure to better manage asthma and allergies may reduce the potential for these factors to interact, and can help to prevent serious asthma exacerbations in children and adolescents.

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Alternate methods of nasal epithelial cell sampling for airway genomic studies

To the Editor:

Recent translational studies of airway inflammation have shown that nasal epithelial cells are a good surrogate for bronchial epithelial cells[1,2] in asthmatic patients.[3,4] However, the standard method of nasal sampling requires use of a nasal speculum and specialized training. In pediatric studies requiring longitudinal specimen collection, sampling by this method can be limited by subject refusal and technical challenges.

Alternate methods of nasal sampling have been proposed. Different instruments for collection have been used, ranging from polyester-tipped swabs to plastic curettes to cytology brushes. Different sampling locations have been proposed, such as beneath the inferior turbinate or the anterior nares, where respiratory epithelial cells are also located.[5] Obtaining nasal epithelial cells beneath the inferior turbinate with a cytology brush has been the most commonly used method. These cells have been validated as a surrogate for bronchial epithelial cells[2] and have been shown to be clinically important in translational asthma studies.[4] This method has also been shown in preliminary studies to be more difficult to tolerate.[6] Whether a more comfortable method of sampling exists and whether this method can provide equivalent cytologic, gene expression, and epigenetic results is undetermined.

Here we compared nasal epithelial cells sampled from the anterior nares with either a polyester swab or a cytology brush with the standard collection method of cytology brush sampling from beneath the inferior turbinate. The benefit of the former method is that it does not require the use of a speculum to visualize nasal anatomy, is technically easy to perform, and, with

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TABLE E1. Selected characteristics of Melbourne Air Pollen Children and Adolescent Health study participants

Variable	N = 644 (%)	Boys, n (%)	Girls, n (%)	*P* value
Sex		407 (63)	237 (37)	<.00005
Age (y), mean ± SD	5.2 ± 3.3	5.0 ± 3.2	5.5 ± 3.5	.11
Age (y), categories				
2-5	416 (65)	273 (66)	143 (34)	<.00005
6-12	201 (31)	119 (59)	82 (41)	.01
13+	27 (4)	15 (56)	12 (44)	.56
Presence of respiratory virus at admission	N = 642			
HRV	447 (70)	292 (72)	155 (66)	.12
Other viruses	16 (2)	10 (2)	6 (3)	.94
Allergen sensitization (wheal size ≥3 mm)	N = 643	N = 406		
Grass pollen	269 (42)	181 (45)	88 (37)	.07
Any pollen	311 (48)	206 (51)	105 (44)	.12
	N = 640	N = 405		
Food	145 (23)	87 (21)	58 (25)	.35
	N = 642	N = 406		
Cat	179 (28)	118 (29)	57 (24)	.18