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High ambient levels of grass, weed and other pollen are associated with asthma admissions in children and adolescents: A large 5-year case-crossover study

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Summary

Background: Pollen is an important aeroallergen that triggers asthma exacerbations in children, but we know little about the impact of different pollen types in cities with varying climatic conditions and pollen seasons.

Objectives: We aimed to assess the role of ambient level of different types of pollen on a large time series of child and adolescent asthma hospitalizations in Sydney, Australia.

Methods: Childhood asthma hospitalization and the daily ambient pollen concentrations of different species were collected in South-West Sydney. With a bidirectional case-crossover design, we fitted conditional logistic regression models to measure the associations between instantaneous and up to 3 days lagged effects of pollen concentrations on asthma hospitalizations after controlling for potential confounders and testing for interactions.

Results: A total of 2098 children, more boys (59.7%) and 2-5 years old (62.6%), were hospitalized due to asthma. The geometric mean concentration of *Cupressus*, 7.88 [5.02] grains/m^3, was the highest during the study period. The increase from 75th to 90th percentile of grass (OR = 1.037, 95% CI 1.005-1.070), weed other than *Plantago* species (OR = 1.053, 95% CI 1.009-1.098) and unclassified pollen (OR = 1.034, 95% CI 1.010-1.058) were significantly associated with the odds of asthma hospitalizations. Boys were at greater risk of asthma exacerbations associated with grass (OR = 1.046, 95% CI 1.003-1.090) and unclassified pollen (OR = 1.041, 95% CI 1.010-1.073). There was evidence of effect modification by age groups for *Cupressus*, conifer, total tree and total pollen.

Conclusions: Although boys are more vulnerable to grass pollen, weed, and other pollen are also important triggers of asthma exacerbations in all children and adolescents. These findings are important for urban green space planning and the development of pollen monitoring systems for families with children at risk of asthma exacerbations during peak pollen seasons.

KEYWORDS

Asthma, case-crossover, children, hospitalization, pollen

1 | INTRODUCTION

Asthma remains a significant global chronic public health problem[1] and the burden of disease is greatest in children.[2,3] Although childhood asthma prevalence varies significantly ranging from 1% to 18% across different countries,[2] it is highest among high income countries including Australia.[4] Asthma admissions are a huge burden on children, families and the health care system with short-term triggers occurring during peak seasonal periods such as winter associated with respiratory viral infections and spring as a marker of pollen load.[5,6] Understanding the role of these environmental triggers would allow better management of those at risk enabling them to take additional precautions for limiting exposures.

Pollen is an important aeroallergen, especially grass due to its significant allergy producing capabilities.[7] High pollen grain allergen release during peak pollen seasons trigger asthma exacerbations.[8] The effects can be fatal in combination with changing extreme weather patterns as was observed in Melbourne, Australia in November 2016 during the outbreak of thunderstorm asthma where ten people died and nearly 10 000 presented to emergency department (ED).[9] Studies evaluating associations in large cities with urban demographics and different magnitude and timing of the pollen seasons are still lacking. As pollen seasons vary both spatially and temporally, the effect of pollen on respiratory health could also differ in various geographical and climatic conditions. With climate change, including changing extreme weather patterns, the allergenic effect of pollen is projected to increase,[10] especially in urban areas.[11]

Although studies including our own have strengthened our understanding of the link between ambient pollen levels and childhood asthma hospitalizations,[12-14] no study has examined different pollen types and their impacts over a long period only focusing on children and adolescents who have been admitted to hospital for asthma. Our earlier studies found significant associations between grass pollen in Melbourne and asthma admissions but over short period.[12,13] Im et al assessed effects of only weed and ragweed pollen during the fall season on asthma admissions in children 0-14 years of age. They found increases in 13 counts of weed pollen (per cubic metre) 3 days prior increased daily hospital admissions in this age group.[14] Chen et al conducted a comprehensive analysis of environmental variables including total pollen and admissions for all age groups in Adelaide, Australia. Among children, total pollen was a significant predictor of asthma admissions in multipollutant distributed lag models (IRR = 1.01 95% CI 1.010, 1.034).[15]

A better understanding of the role of different types of pollen as triggers for asthma exacerbations requiring hospitalization in cities with complex pollen seasons is critical for the management of asthma. Such knowledge may be used to better inform plant choices for greening cities. Therefore, the aim of this study was to assess the role of ambient levels of different types of pollen on asthma hospitalization over a 5 year period in children and adolescents in Sydney, Australia.

2 | METHODS

2.1 | Study design

We used a case-crossover design over a 5-year period, between May 1, 2008 and May 31, 2013. The case-crossover study is suitable for measuring transient and acute health outcomes,[16] such as asthma hospitalization and exposure to daily environmental factors such as ambient pollen concentrations. Case status was defined as the date of admission, while the control status was defined as periods on the same day of week in the same month as the case date. In this design, each case serves as his/her own control and eliminates the potential confounding effects that result from individual differences due to selection of other controls. Also, the bidirectional approach for selection of control dates from the same day of the week and month also prevents any time trend biases resulting from the time series nature of the data.[16] We excluded cases readmitted within the period of one month (1-28 days) to avoid confusion related to the definition of the case (index) and control dates.

2.2 | Study population and asthma hospitalization data

The study sample included a total of 2098 children and adolescents, aged between 2 and 18 years, admitted to hospital for asthma in three hospitals: Campbelltown, Camden and Liverpool in Sydney. Attributed to variations in coding between different hospitals, three classification systems for the diagnosis coding were included: (a) ICD10-AM[17]: Asthma (J45), Status asthmaticus (J46); (b) SNOMED CT-AU[18]: Asthma (195967001), Asthma NOS (266365004); (c) ICD-9[19]: Extrinsic asthma (493.0); Intrinsic asthma (493.1); Asthma unspecified (493.9); Chronic obstructive asthma (493.2); Other forms of asthma (493.8) and Cough variant asthma (493.82). Data on the age, gender, admission date and re-admission cases within 28 days were also available. Children below the age of 2 years were excluded because diagnosis of asthma in this group is difficult.[20]

2.3 | Pollen data

Daily ambient concentrations of pollen, expressed as total pollen grains per cubic metre (m^3) of air, were collected using a 7-day Burkard volumetric spore trap. The trap was located on the rooftop of Campbelltown hospital free from obstruction. The pollen was collected in the trap by air drawn into the chamber, at a rate of 10 L/min, through the 2 mm by 14 mm slit. The constantly moving adhesive tape/slide captured the pollen over 1-7 day period. A trained technician counted the pollen by family, since it is difficult to identify to taxa level by microscopy. The pollen was classified into eight different categories: grass (Poaceae), *Plantago* (weed), Other weeds (*Echium plantagineum* and *Parietaria pollen*) and pollen from the tree *Cupressus*, *Casuarina*, *Eucalyptus*, conifer and *Platanus*. In addition, “Total tree” and “Total pollen” categories were also created that included the sum of the tree and all pollen counts, respectively. The "unclassified" group included pollen that were not identified into any of the categories specified above. Earlier studies in Sydney have shown two distinct grass pollen peaks: the first smaller peak occurs between January and April and the second major pollen peak between July to October[21,22] but we do acknowledge that other species maybe present in the atmosphere throughout the year.

2.4 | Air quality and meteorological data

Daily air quality data were obtained from the Environment Protection Authority in NSW with fixed monitoring stations located in Liverpool and Campbelltown. Air pollutant data were available including 24-hour average daily concentrations of particulate matter (μg/m^3) $PM_{2.5}$ and PM_{10} (<2.5 and <10 μm diameter, respectively). Daily maximum one hour average of nitrogen dioxide (NO_2) in parts per billion (ppb) and daily maximum four hour average of ozone (O_3) in ppb were also available. The data from Liverpool were used in the study as they contained the most complete data for the time period. Daily maximum temperature, daily total rainfall (mm) and average daily relative humidity (%) were also available from the Bureau of Meteorology station in Liverpool.

2.5 | Statistical methods

Conditional logistic regression models were used to assess the association between different pollen taxa and the asthma hospitalizations outcome using daily pollen concentration as a continuous exposure variable. In most studies of environmental exposures and hospital related outcomes where the unit of analysis is per day, Poisson regression or General Additive Models that assume a Poisson distribution for the outcome have been commonly used. The conditional logistic model we used was based on a bidirectional approach to a case crossover design with reduced bias. Although our choice of method has potentially reduced efficiency,[23] our result may be somewhat conservative (less precise CI) but the estimates are accurate. Furthermore, the assumption of a Poisson process was not justified by our data based on a deviance goodness-of-fit and a Pearson goodness of fit test ($P < 0.001$). Therefore, our choice of the use of a conditional logistic regression is appropriate in this instance. We modelled instantaneous (L0) and up to 3 days lagged (L1, L2 and L3) effects of various pollen types. Results are presented as the odds ratio of asthma hospitalization for the 75th-90th percentile increase in pollen concentrations (grains/m^3) with 95% confidence intervals (CI). Possible confounding variables such as rainfall, relative humidity, temperature and pollutants such as O_3, NO_2, $PM_{2.5}$ were included in the models if they changed the associations between pollen and asthma hospitalization by 10% or more or were statistically significant at the 5% level of significance.

We conducted stratified analyses for gender and age group (categorised into three groups: 2-5 years, 6-12 years and 13-18 years) for assessing the effect modification by these variables on pollen and asthma association. The stratum specific odds ratio of pollen effect on asthma hospitalization and the *P*-value of the interaction terms were calculated. For the age categories, the 13-18 years age group was taken as the reference group for calculating *P*-value of interaction for other two categories. We constructed smooth time series plots of daily asthma hospitalization count smoothed using the LOWESS-locally Scatterplot Smoothing over the daily pollen counts. All analyses were conducted using statistical analysis package Stata SE 14.1 (StataCorp, College Station, TX).

2.6 | Ethics

Ethics approvals for the study were obtained from South West Sydney Local Health District Human Research Ethics Committee (HREC Number: LNR/13/LPOOL/189) and La Trobe University.

3 | RESULTS

A total of 2098 children were admitted for asthma between 25th May 2008 and 3rd May 2013. Among them, 44.3% (n = 929) children were admitted during the first pollen peak, 21.5% (n = 450) in the second peak and 34.3% (n = 719) during other months. More boys than girls were admitted during the study period, but no significant association was observed between age group and asthma hospitalization during pollen and nonpollen peaks (Table 1). Smoothed graphs of daily asthma hospitalization cases and pollen counts were plotted for grass (Figure 1), *Cupressus* (Figure 2), conifer (Figure 3) and total tree pollen (Figure 4). The plots suggest variations in asthma and distribution patterns for different pollen taxa across different time points. Table 2 shows the summary statistics of the daily pollen grain concentrations from 1st May 2008 to 31st May 2013. Most pollen counts remained relatively low for the most part of the year (50th percentile = 0), while very high pollen counts of *Cupressus* (over 500 grains/m^3) were recorded for a total of 8 days in the entire period. The high pollen counts occurred mainly during the second pollen period that peaked during September to November reaching over 1000 grains/m^3. The distribution of the grass species was distributed more consistently over the years, reaching the peak concentration (142 grains/m^3) during October to January. Conifer and total tree pollen peaked during the second peak season between July and October. *Eucalyptus* pollen reached peak concentration during the October to January, while other weeds were predominant during October-December.

Attributed to the large positive skewness of the pollen data, we present the geometric means (GM) and geometric standard deviation of daily pollen concentrations. *Cupressus*, 7.9 [5.0] grains/m^3, had the highest geometric mean, followed by grass, 4.8 [3.2] grains/m^3 (Table 2).

The adjusted odds ratios for asthma hospitalization, per unit increase in the same day and 4-day (Lag0, Lag1, Lag2 and Lag3) cumulative lagged pollen concentrations along with 95% confidence intervals are presented in Table 3. The same day grass (OR = 1.037, 95% CI: 1.005, 1.070), other weeds (OR = 1.053, 95% CI: 1.009,

TABLE 1 Descriptive statistics of asthma hospitalization segregated by pollen peaks periods in Sydney

	All	First pollen peak January-April	Second pollen peak July-October	Other months	*P*-value
N (% of All)	2098	929 (44.3)	450 (21.5)	719 (34.3)	
Gender					
Boys	1253	564 (45.0)	263 (21.0)	426 (34.0)	0.69*
Girl	845	365 (43.2)	187 (22.1)	293 (34.7)	
Age group					
2-5 years	1314	597 (45.4)	276 (21.0)	441 (33.6)	0.63†
6-12 years	644	272 (42.3)	140 (21.7)	232 (36.0)	
13-18 years	140	60 (42.9)	34 (24.3)	46 (32.9)	

*X^2 test for association between gender and pollen seasons.
†X^2 test for association between age groups and pollen seasons.

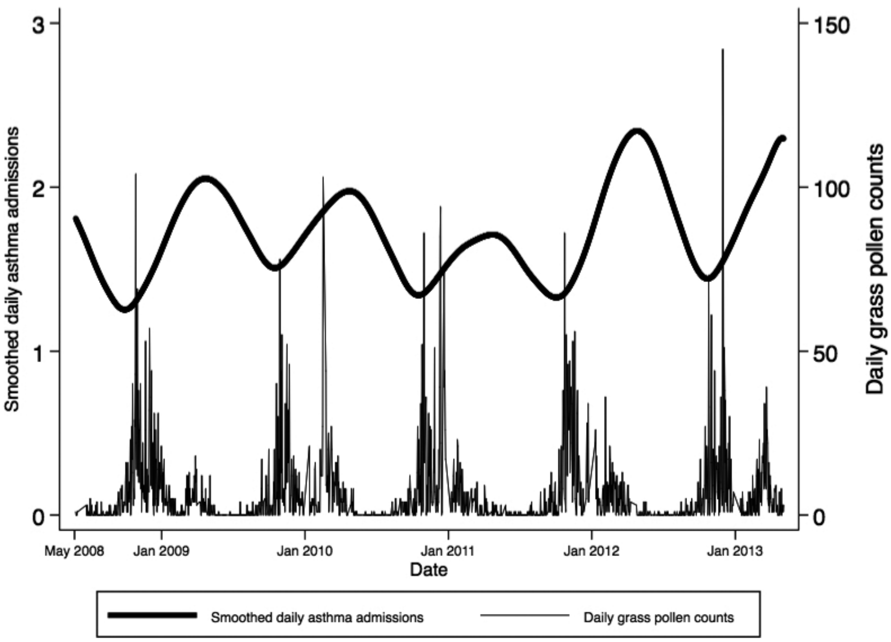

FIGURE 1 Daily smoothed asthma admissions counts and daily grass pollen count during the study period

1.098), and unclassified pollen (OR = 1.034, 95% CI: 1.010, 1.058) were significantly associated with increased likelihood of asthma hospitalization. The cumulative lagged concentrations of unclassified pollen (OR = 1.008, 95% CI: 1.001, 1.015) and *Platanus* (OR = 0.996, 95% CI: 0.991, 0.999) were also associated with asthma hospitalizations (Table 3). Few associations were observed for Lag1 and Lag3 pollen concentrations. *Plantago* (OR = 0.948, 95% CI: 0.907, 0.992) and unclassified pollen (OR = 1.016, 95% CI: 1.000, 1.032) were significant at Lag3 and *Platanus* (OR = 0.981, 95% CI: 0.965, 0.996) was significant at Lag1 (result not shown).

Gender stratified analysis was also conducted and *P*-values of the interaction terms between the gender and pollen estimated. There was a trend for grass (OR = 1.046, 95% CI: 1.003, 1.090) and other unidentified pollens (OR = 1.041, 95% CI: 1.010, 1.073) to increase odds of asthma hospitalizations in boys when stratified, but the *P*-value for the interaction term in the main effects model was not statistically significant (Table S1).

Age stratification showed that grass (OR = 1.047 95% CI: 1.005-1.091), other weeds (OR = 1.075, 95% CI: 1.024-1.129), *Platanus* (OR = 1.017, 95% CI: 1.003-1.032) and unclassified pollens (OR = 1.059, 95% CI: 1.027-1.091) were associated with asthma hospital admissions among 2-5 year old children. However, the *P*-value for the interaction term was only significant for conifer (*P* = 0.008), total tree (*P* = 0.004) and total pollen (*P* = 0.004). Conifer was significant among 6-12 year olds (OR = 1.051, 95% CI: 1.011-1.092, *P* = 0.003 for the interaction term; Table S2).

4 | DISCUSSION

Our study suggests that grass, weeds (*Echium plantaginium* & *Parietaria*) and unclassified pollen were significantly associated with childhood asthma hospitalizations in South-West Sydney, a city with two peak pollen seasons. Boys and children aged 2-5 years were

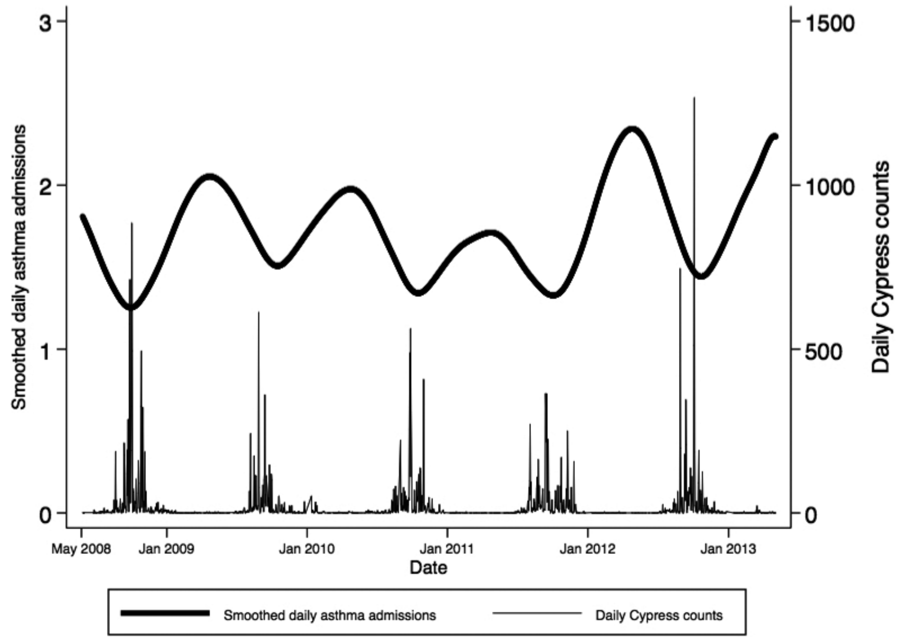

FIGURE 2 Daily smoothed asthma admissions counts and daily *Cypress* pollen count during the study period

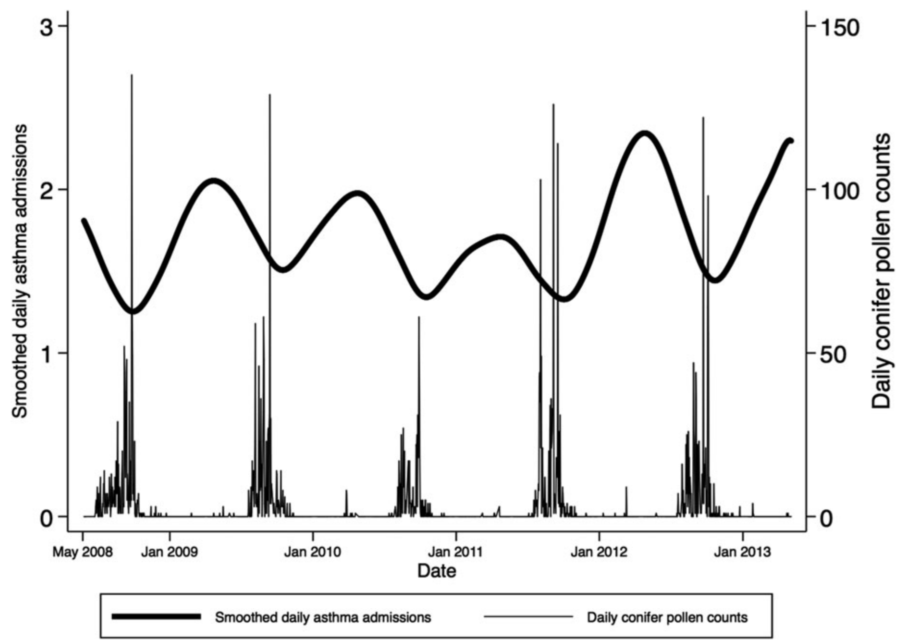

FIGURE 3 Daily smoothed asthma admissions counts and daily conifer pollen count during the study period

more vulnerable than girls or older children to grass and unclassified pollen. This is the first study to assess the role of different types of pollen concurrently on a large time series of asthma admissions in children and adolescents.

Our findings on grass pollen are consistent with others including a case-crossover study by our group that showed an increase in grass pollen concentration of 50 grains/m^3 was significantly associated with the risk of asthma hospital admissions (OR = 1.11, 95% CI 1.00-1.22) in children.[12] A large study in Adelaide reported significant associations between total pollen counts and childhood asthma hospitalizations in a multipollutant moving average model (OR = 1.013 95% CI 1.001, 1.025) but not in a multipollutant distributed lag model.[15] They also reported stronger effects in the cooler seasons. It is uncertain why the effects were observed in cooler seasons, but the effect may be modified by respiratory viral infections during winter, which were not accounted for. It was also unclear if grasses were the prominent trigger of child admissions as they only used total pollen counts as their exposure.

In addition to grass, we found other species were important too in this region including weed pollens, such as *E. plantaginium* and *Parietaria species*. This finding confirms a much earlier study by Bass et al[24] that indicated a possible association between weed species, *Parietaria Judaica* and IgE-mediated rhinitis and asthma in Sydney. Weed pollen seems to be important in the USA too especially on

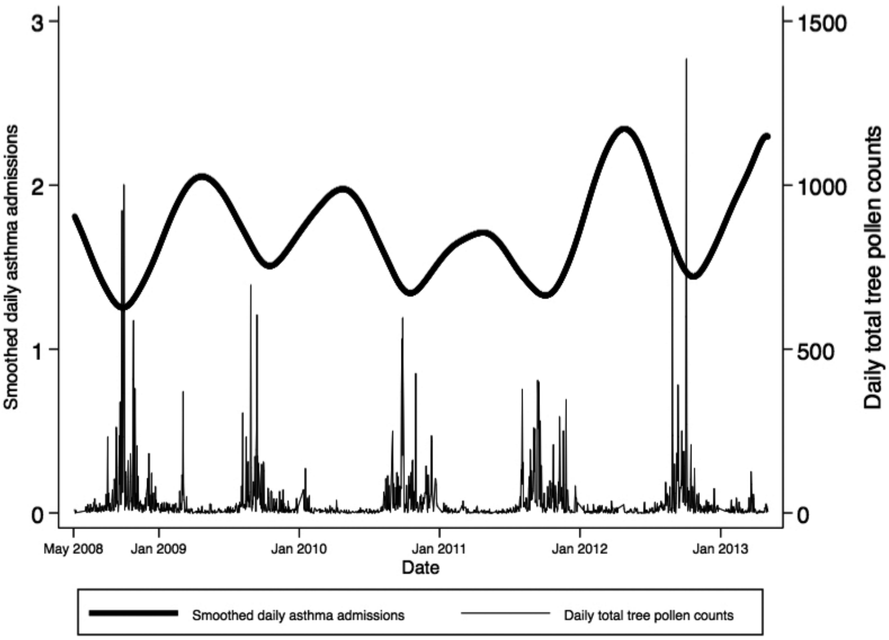

FIGURE 4 Daily smoothed asthma admissions counts and daily total tree pollen count during the study period

TABLE 2 Descriptive statistics and percentile distribution of pollens from 1st May 2008 to 31st May 2013

			Percentiles				
Pollen types	Geometric mean (SD)	Min	25th	50th	75th	90th	Max
Grass	4.8 (3.2)	0	0	1	5	14	142
Plantago	3.6 (2.9)	0	0	0	3	8	83
Other weeds[a]	2.9 (2.6)	0	0	0	1	5	51
Cupressus	7.9 (5.0)	0	0	0	5	29	1266
Casuarina	3.3 (2.9)	0	0	0	3	7	358
Eucalyptus	3.8 (2.9)	0	0	1	5	10	146
Conifer	4.7 (3.5)	0	0	0	0	7	135
Platanus	4 (3.6)	0	0	0	1	5	203
Unclassified pollen	4.4 (2.8)	0	0	3	7	12	264
Total Tree	15.1 (4.0)	0	2	11	29	75	1401
Total Pollen	20.8 (3.9)	0	4	15	42	106	1426

[a]Sporadic and lower number weeds (*Echium plantagineum* & *Parietaria* pollen).

severity of asthma symptoms in asthmatic children.[14,25] Im et al's study of asthma hospital admissions in children age 0-14 years focused only on weed including ragweed as these were the prominent pollen during the fall season. In regression models, they found 3-day lag of elevated weed pollen was significantly associated with admissions.[14] We cannot directly compare our findings with theirs as they only presented beta coefficients from a linear regression model. As overall weed taxa constitute a significant proportion of total pollen counts in Sydney,[26] urban vegetation planning needs to be carefully monitored and these factors need to be taken into consideration. In contrast to studies that have focused on tree pollen and childhood asthma exacerbation[5,8,27] we found no associations.

TABLE 3 Adjusted odds ratios and 95% confidence intervals (CI) of childhood asthma hospitalizations associated with 75th-90th percentile increase in same day (lag 0) and cumulative lagged pollen concentrations

Pollen types	Lag 0 OR (95% CI)	Cumulative Lag OR (95% CI)
Grass	**1.037 (1.005-1.070)***	1.005 (0.995-1.015)
Plantago	1.003 (0.962-1.045)	0.994 (0.983-1.005)
Other weeds[a]	**1.053 (1.009-1.098)***	1.002 (0.990-1.015)
Cupressus	1.007 (0.986-1.027)	1.001 (0.994-1.008)
Casuarina	1.004 (0.992-1.015)	1.003 (0.997-1.009)
Eucalyptus	0.991 (0.962-1.022)	0.995 (0.986-1.005)
Conifer	1.015 (0.987-1.045)	1.004 (0.995-1.012)
Platanus	1.002 (0.987-1.017)	**0.996 (0.991-0.999)***
Unclassified pollen	**1.034 (1.010-1.058)***	**1.008 (1.001-1.015)***
Total tree	1.015 (0.988-1.042)	1.002 (0.993-1.010)
Total pollen	1.026 (0.992-1.060)	1.002 (0.992-1.013)

(Adjusted for maximum temperature, mean humidity and average $PM_{2.5}$).
[a]Sporadic and lower number weeds (*Echium plantagineum* & *Parietaria* pollen).
*$P < 0.05$.

Our study suggests that pollen is a contributing trigger for asthma exacerbations mostly in young children. Grass, certain weed and other unclassified pollen were significant risk factors for asthma hospitalization in 2-5 year old children. However other studies have observed the pollen sensitisation peaks in the second decade of life.[28,29] We observed an effect modification by age group for *Cupressus*, conifer, total tree and total pollen. Similar to other studies, we also observed a trend toward a greater pollen effect in boys,[12] but it did not reach statistical significance when we included an interaction term in the main effects analysis.

This study has several strengths. It was based on a robust design extended over a period of 5 years with a large sample size. This study is unique in that it has also assessed the association of a wide range of pollen species with asthma. This has not been examined in the Australian context before and has been addressed in few studies only elsewhere. The case-crossover design increased the power of this study and controlled for confounding factors that result from individual differences.

However, this study also had some limitations. The potential for exposure misclassification cannot be excluded, since it was not possible to confirm that the population were exposed to the same levels of pollen as recorded in our study. Although pollen counts might vary across larger distances,[30] the three hospitals included in the study were located within 30 km distance of pollen trap station to minimize the exposure differences across distances. We did not have information on respiratory viruses or pollen sensitisation, which may be important on the pollen trigger pathways to asthma admissions. However, our Melbourne study showed consistent effects of grass as significant predictors of asthma exacerbation, even after adjusting for human rhinovirus and taking pollen sensitisation into account.[12] Therefore, at least for grass, we are reasonably confident that our result is close to a true estimate of asthma hospitalization risk in children. We also acknowledge the differences in coding between hospitals as a potential limitation.

In summary, grass and weed pollen were associated with asthma hospitalizations in children. Boys and 2-5 year old children were more vulnerable than girls or older children to the adverse effects of pollen. These findings further contribute to the evidence that different species of pollen are important triggers of asthma exacerbations. These factors are important for urban planning and greening cities. In countries with varying climatic conditions and different pollen species, standardized national pollen monitoring with advanced warning systems could assist patients at risk of pollen induced asthma exacerbations.

CONFLICT OF INTEREST

MJA holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. The other authors have no potential conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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