



ORIGINAL ARTICLE

WILEY

Epidemiology of Allergic Disease

Tree pollen exposure is associated with reduced lung function in children

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Abstract

Background: Allergic disease is a recognized global epidemic and a significant cause of ill health and poor quality of life. The prevalence of pollen allergy is high throughout the world, and pollen exposure itself plays a role in emergency department presentations and hospitalizations for asthma. Lung function and airway inflammation are important measures of asthma activity and control.

Objective: To examine associations between exposure to multiple pollen types and lung function and markers of airway inflammation at 8 and 14 years of age, and to explore potential modification by residential greenness.

Methods: A cohort of high-risk children living in Sydney, Australia had spirometry and fractional exhaled nitric oxide (FeNO) measured at 8 and 14 years of age. Ambient pollen concentration on the day of lung function measurement and up to three days prior was used as the exposure measure. Residential greenness was derived from satellite imagery. We modelled the association between six pollen types and lung function and FeNO. We also assessed modifying effects of residential greenness.

Results: *Casuarina*, cypress and *Pinus* pollen in the air the day before measurement and 3 days prior respectively, were associated with reduced lung function in 8-year-olds. The pollen exposures were associated with decreases in FEV₁ and FVC; however, the FEV₁/FVC ratio was not affected. Effect modification by greenness was not observed due to loss of power.

Conclusions & Clinical Relevance: Airborne tree pollen of cypress, *Casuarina* and *Pinus* and not grass in some regions may be detrimental to childhood lung function.

KEYWORDS

environment, epidemiology, pediatrics

1 | INTRODUCTION

Allergic disease is a recognized global epidemic.¹ An increasing proportion of asthma can be classed as allergic asthma.² In children, asthma remains a significant cause of ill health, disability and poor quality of life.³ Lung function and exhaled markers of airway

inflammation are important measures of asthma activity and overall lung health. Identifying modifiable factors that influence these markers is important to understand asthma and for asthma control.

The role of pollen in allergic respiratory disease cannot be understated, especially when considering the severe effects of “thunderstorm asthma.” While climatic conditions were important, the high

ambient pollen concentration was a key contributor to the devastating thunderstorm asthma event that overwhelmed emergency departments in Melbourne, Australia in November 2016 and resulted in fatalities.⁴ Grass pollen is most commonly implicated in "thunderstorm asthma" events⁵ and emergency department presentations for asthma in children and adolescents.⁶ In some regions, including Sydney, Australia, weed and tree pollen have been implicated in emergency department presentations and hospitalizations.^{7,8}

The prevalence of pollen allergy worldwide is high; estimated at 18.0% in the United States,⁹ 17.6% in China,¹⁰ 19.5% in Australia¹¹ and a staggering 40% in Europe.¹² These rates are predicted to rise as the global climate changes, along with more severe symptoms as a consequence of higher pollen levels and an extended pollen season.¹³

Most allergenic pollen is produced from abundantly distributed wind-pollinating trees, grasses and weeds.¹⁴ Studies investigating the effect of these pollen on lung function in children and adolescents are comparatively rare.¹⁵⁻¹⁷

Exposure to natural vegetation (greenness) may benefit human health through the promotion of activities such as exercise and socializing, the reduction of harmful exposures such as noise, heat, pollution and stress relief.¹⁸ The Normalised Difference Vegetation Index (NDVI) provides a measure of greenness around the home that is of increasing interest to children's health.^{19,20} Our earlier work²¹ suggested residential greenness may modify the effects of early life pollen exposure on lung function in a high-risk cohort of children residing in Melbourne, Australia. Assessing the modifying effects of residential greenness may be important in better understanding the role of pollen exposure in temperate regions.

Using the Childhood Asthma Prevention Study (CAPS),²² an established birth cohort of children with a family history of asthma or allergic disease, we examined associations between exposure to multiple pollen types and lung function and markers of airway inflammation at 8 and 14 years of age, and explored potential modification by residential greenness.

2 | METHODS

2.1 | Study design and population

CAPS was a randomized, parallel-group controlled trial using a factorial design to test the combined and separate effects of HDM avoidance and omega-3 supplementation.²³ Pregnant women, whose unborn children were considered to be at risk for asthma (due to having one or more parents or siblings with asthma or wheezing), were recruited between September 1997 and November 1999 from western and south-western Sydney. Exclusion criteria included: cat ownership, strict vegetarians, non-singleton pregnancy, and infants born earlier than 36 weeks gestation. A total of 616 children were randomized to the interventions. The CAPS interventions were implemented for the first 5 years of a child's life, after which the study has been analysed as a birth cohort study.²² The study was approved by the Human Research

Ethics Committees of the University of Sydney, Children's Hospital at Westmead, and Sydney South West Area Health Services.

2.2 | Data collection

Baseline demographic details about the families were collected at the first home visit, approximately 4 weeks before the birth of the child, and subsequent birth details recorded from the hospital birth summary data. Home visits took place every 3 months for the first year of life, then biannually until age 5 years with questionnaires assessing home environment; family history, pregnancy and perinatal data; symptoms and illness; diet; clinical factors; and puberty administered at the time of visit.²² Medical assessment was performed at ages 18 months and 3, 5, 8, 11.5 and 14 years.

The 8-year follow-up was conducted from October 2005 to January 2008 close to the child's 8th birthday. The 14-year follow-up was conducted from October 2011 to January 2014 close to the child's 14th birthday. The following analysis has been restricted to children who participated in both the 8- and 14-year follow-ups.

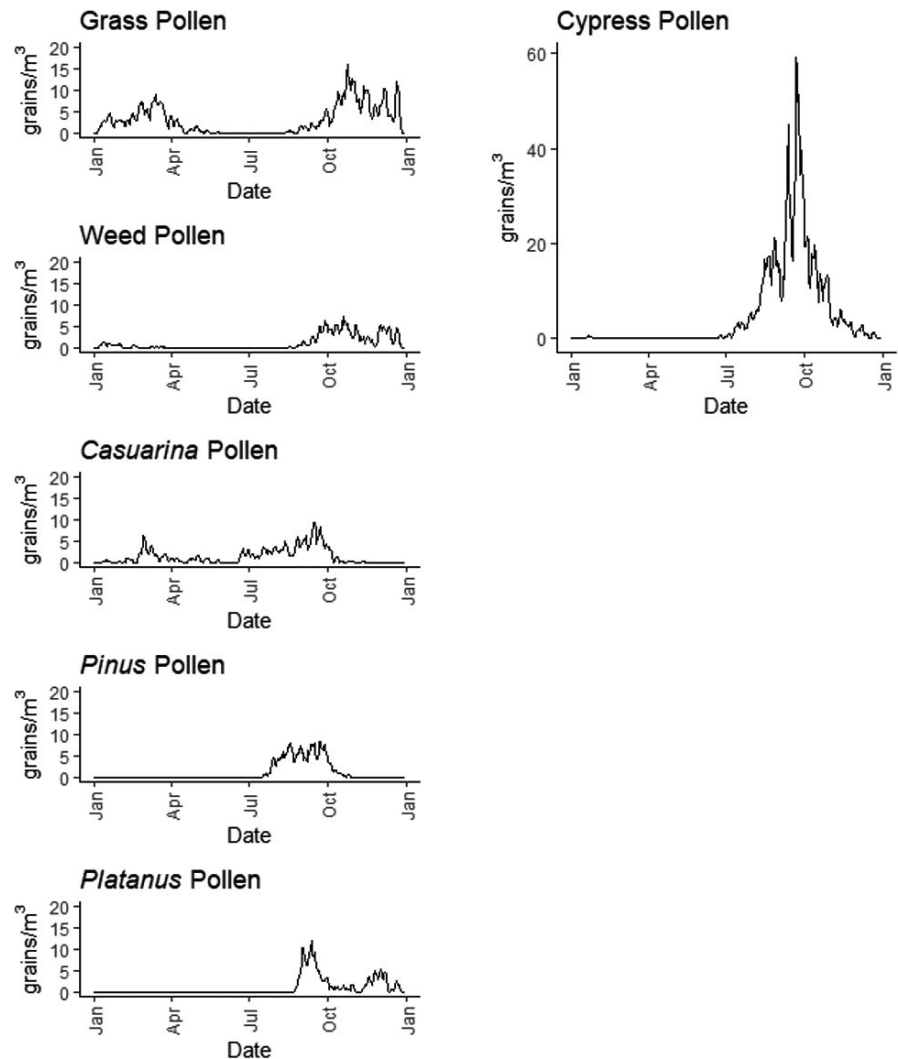
2.3 | Pollen exposure

Daily, 24-hour average pollen concentrations (grains/m³) were collected from a Burkard volumetric trap.⁸ Between 2005 and 2007, daily grass and tree pollen samples were collected from August to November each year from a trap located at Westmead hospital in Western Sydney. Grass, weed, cypress, *Casuarina* (She-oak), *Pinus* (Pine), *Platanus* (Plane) and *Liquidambar* (Liquid Amber) pollen were captured and identified. These pollen counts were assigned as the pollen exposure measure at 8 years. From the 1st of January 2008 to present, daily grass and tree pollen were collected for the whole year from a trap located at Campbelltown hospital. These pollen counts were assigned as the pollen exposure measure at 14 years. Participants living more than 150km from the pollen trap were excluded from the analysis, with the aim of increasing the validity of the pollen exposure. Three participants were excluded by this from the analysis. Ambient pollen concentration on the day of lung function measurement (lag 0), the day before measurement (lag 1), and two (lag 2) and three (lag 3) days prior were considered individually and combined (lag 0-3). The median pollen count for each day of the year during the period 2005-2013 was plotted as a three-day running mean for the seven pollen types to show the seasonal differences for each pollen and between the pollen types (Figure 1).

2.4 | Residential greenness

Local residential greenness was calculated by the Normalised Difference Vegetation Index (NDVI) derived from the satellite which provides publicly available Landsat 7 Surface Reflectance images (<https://earthexplorer.usgs.gov/>), with one image taken every 16 days at a 30 by 30-meter pixel resolution. Buffers of 100 and 500 m around

FIGURE 1 Smoothed median pollen counts for each day of the year across all years of the study



the residential home address were calculated using the NDVI in QGIS 3.0.2 (Open Source Geospatial Foundation). A 100 m buffer was chosen to represent the immediate residential environment,²⁴ and 500 m to align with previous asthma and allergy research.²⁵

Each participant was matched to a cloud-free image (<10% cloud cover) from 2008 correlating to the season (Spring, Summer, Autumn or Winter) of their lung function measurement.

2.5 | Lung function

Lung function assessed by spirometry was collected at the 8- and 14-year follow-up visits in accordance with American Thoracic Society criteria,²⁶ except that a 6-second expiratory time criterion was not applied. Forced expiratory volume in 1-second (FEV₁), forced vital capacity (FVC) and the FEV₁/FVC were recorded pre-bronchodilation. FEV₁ and FVC results were reported as % predicted values,²⁷ with the race set as Caucasian for the reference values, and the ratio expressed as a percentage. On the day prior to testing, participants were reminded to avoid using long-acting β -agonists for 12 hours and short-acting β -agonists for 6 hours before the test.

2.6 | Fractional exhaled nitric oxide (marker of airway inflammation)

Fractional exhaled nitric oxide (FeNO) was measured at the 8- and 14-year follow-up visits by using an offline technique,²⁸ as previously detailed.²⁹ The procedure was repeated until approximately 1 L of exhalation was collected in an impermeable polyethylene bag. Within 24 hours of collection (usually on the same day), the contents of the bag were aspirated into a chemiluminescent analyser (Model 42C; Thermo Environmental Instruments) to measure the nitric oxide concentration in parts per billion.

2.7 | Covariates

Atopy status was determined by skin prick tests to food allergens (salmon, peanuts, egg white, egg yolk and tuna) and aeroallergens (Dermatophagoides pteronyssinus (HDM), cockroach, cat, *Alternaria alternata*, rye grass and a grass mix (Hollister-Stier)). Positive (glycerol) and negative (histamine phosphate) controls were used and wheals greater than 3 mm in diameter and greater than those elicited

by the negative control after 10 minutes were classified as positive. Participants were considered sensitized if they had a positive reaction to any of the tested allergens, to account for likely cross-reactivity.³²

Current asthma was defined as a combination of wheeze in the last 12 months, and either ever-diagnosed asthma (reported at ages 18 months, 3, 5 or 8 years for 8-year-olds or ages 18 months, 3, 5, 8, 11.5 or 14 years for 14-year-olds) or airway hyperresponsiveness (at 8 years or 14 years). Airway hyperresponsiveness was defined as a $PD_{20}FEV_1$ (methacholine) value of less than 6.1 μmol or greater than 12% bronchodilator response in children who did not have a methacholine challenge.

$PM_{2.5}$ ($\mu\text{g}/\text{m}^3$), PM_{10} ($\mu\text{g}/\text{m}^3$), NO_2 (ppb) concentrations and Air Quality Index (AQI) levels for each day during the study period were sourced from the New South Wales Office of Environment and Heritage. The AQI is a combined pollutant measure expressed as a percentage of the level specified by the National Environment Protection Measure for Ambient Air. The highest AQI for each site was considered. Participants were assigned the pollution level of the closest monitoring station to their residential address. Meteorological data available from the Bureau of Meteorology included solar exposure, maximum and minimum temperature, and rainfall.

Smoking by anyone inside the house was assessed by questionnaire at each of the follow-ups visits. Maternal asthma, smoking during pregnancy and mother's education were assessed by questionnaire at baseline.

2.8 | Statistical methods

We used multiple linear regression to model the associations between lagged pollen exposure and lung function outcomes. FeNO values were analysed after logarithmic transformation due to the skewness of the data.

In order to reduce model complexity and avoid overfitting, a random sample of the models including all covariates were selected and run through automated model selection using the "glmulti"³⁰ package in R 3.3.3 (Open Source). Simply put, "glmulti" builds all possible unique models from a list of explanatory variables and returns the best model based on the Akaike Information Criterion (AIC). Covariates retained in these selected models were used for further analysis. Additional adjustment for seasonality was incorporated, and FeNO outcomes were also adjusted by age and sex.

For sensitivity analysis, the spirometry parameters were dichotomized into clinically meaningful value of <80% predicted and $\geq 80\%$ predicted. Multiple logistic regression was used to model the associations between lagged pollen exposure and the dichotomized outcomes.

To assess effect modification by residential greenness, we dichotomized NDVI into "High residential greenness" (defined 75th percentile or greater) and "Low residential greenness." The level of 75th percentile was selected a priori.²¹ We considered a P value $\leq .10$ as significant for the interaction terms and presented the strata specific effects for significant interactions.

Statistical analyses for the main models were performed using Stata release 14.1.

3 | RESULTS

3.1 | Ambient pollen concentrations

The highest pollen counts were of cypress, with pollen detected from July to January, peaking in October. High grass pollen counts occurred from August to April. Pollen distributions were highly skewed (Table S1), and *Liquidambar* pollen counts were detected in only 6% (162/3258 days) of the study period. As such, *Liquidambar* was excluded in subsequent analysis. Exposure to different pollen taxa was highly correlated; however, pollen levels were not correlated with NDVI (Figure S1).

3.2 | Participant characteristics

Half the children were male (54%), and the majority of mothers had a university or TAFE education (56%) (Table 1). There was a 37% increase in sensitization to at least one allergen between the two follow-ups (73 vs 100, $P = .016$), while the number of participants with current asthma was reduced by 14%. Current smoking inside the house was low in the eight-year follow-up (8%) and reduced further by the 14-year follow-up (46% decrease).

3.3 | Confounder/adjustment selection

Atopy status was retained in 71% of the best fitted models based on the AIC (Table S2). The variable with the next highest frequency, current asthma, appeared in 46% of the models. Air quality variables and maternal education status were not retained in any of the models. Variables relating to cigarette smoke exposure were retained in a small number of cases (smoking during pregnancy [25%] and smoking inside [21%]), and maternal asthma was retained in 13% of models.

Per cent predicted lung function models were therefore minimally adjusted for atopy status, current asthma, daily $PM_{2.5}$, daily NO_2 , smoking during pregnancy, maternal asthma and seasonality. Models with FeNO as the outcome were additionally adjusted for age and sex, as unlike the per cent predicted lung function, FeNO was not standardized.

3.4 | Lung function

Few associations were seen for exposure to pollens and decreased lung function, although increased exposure to cypress, *Casuarina* and *Pinus* pollen was associated with a reduced FEV_1 in 8-year-olds at lag 3 (−5.4% 95%CI: −8.1, −2.8 per IQR increase of 22 grains/ m^3), lag1 (−1.7% 95%CI: −3.0, −0.4 per 6 grains/ m^3) and lag 3 (−1.8% 95%CI: −2.9, −0.6 per 9 grains/ m^3), respectively (Figure 2). The pollen exposures were associated with a decrease in FVC comparable to the effect on FEV_1 ; however, the FEV_1/FVC ratio was not affected (Table S3).

TABLE 1 Characteristics of the 8- and 14-y follow-up visits for those with pollen and lung function/airway inflammation data

	8-y follow-up	14-y follow-up
N	160	160
	n (%)	n (% change)
Male	86 (54%)	
Ancestry		
Both parents born in Australia/NZ	93 (58%)	
One parent born in Australia/NZ	33 (21%)	
No parents born in Australia	34 (21%)	
Sensitized (any atopy)	73 (46%)	100 (+37%)
Current asthma	43 (27%)	37 (-14%)
Mother's education		
Low	35 (22%)	
Medium	35 (22%)	
High	90 (56%)	
Maternal asthma	90 (56%)	
Smoking inside the house	13 (8%)	7 (-46%)
Smoking during pregnancy	30 (19%)	
	Mean (95% CI)	Mean (95% CI)
Age (y)	8.01 (7.98, 8.05)	13.91 (13.88, 13.93)
Daily Air Quality Index	61.45 (51.15, 71.75)	64.51 (58.60, 70.41)
PM _{2.5} (µg/m ³)	7.24 (6.57, 7.91)	8.91 (8.16, 9.66)
PM ₁₀ (µg/m ³)	19.32 (18.03, 20.61)	18.78 (17.60, 19.96)
NO ₂ (ppb)	12.14 (11.38, 12.89)	17.15 (16.15, 18.15)
FEV ₁ (% predicted)	101.16 (99.11, 103.20)	91.53 (89.69, 93.37)
FVC (% predicted)	98.82 (96.72, 100.92)	91.29 (89.68, 92.90)
FEV ₁ /FVC (%)	89.86 (88.68, 91.04)	87.17 (86.00, 88.34)
FeNO (ppb)	9.03 (8.11, 9.96)	11.97 (10.60, 13.34)

Note: Mother's education at child's birth: low (Primary school/High school completed to the end of Year 10), medium (High school (completed to the end of Year 12)) and high (University/ TAFE education). Pollution metric measured at day of lung function. Air Quality Index represents the single highest pollutant measure at the site, expressed as a percentage of the level specified by the National Environment Protection Measure for Ambient Air.

No associations were found for grass or weed pollen exposure in the 8-year-olds. Pollen exposure was not related to lung function in the 14-year-olds (Table S4).

Similar results were seen when assessing the odds of having FEV₁ < 80% predicted. Lag 3 exposure to increased cypress pollen was associated with a 92% increase in the odds of having FEV₁ < 80% predicted (OR: 1.92 95%CI: 1.04, 3.55 per 22 grains/m³), while lag 1 exposure to *Casuarina* pollen was associated with a 34% increase (OR 1.34 95%CI: 1.02, 1.74 per 6 grains/m³). *Pinus* pollen was not associated with the odds of having FEV₁ < 80% predicted (Table S5). Only cypress pollen exposure was associated with increased odds of FVC < 80% predicted.

3.5 | Fractional exhaled nitric oxide

No significant associations were seen between pollen and FeNO in either age group.

3.6 | Effect modification by residential greenness

Statistically significant interactions between higher residential greenness and ambient pollen on both the FEV₁/FVC ratio and FeNO were seen in grass, cypress, *Casuarina* and *Platanus* pollen at 8 years of age (Table S5). A clinically meaningful effect modification was not observed (Figure 3).

4 | DISCUSSION

Our study suggests a negative association between airborne tree pollen concentrations (lagged) and lung function in 8-year-old children for three of the four tree pollen types measured. Cypress, *Casuarina* and *Pinus* pollen were associated with a reduced FEV₁ and FVC at lag 3, lag 1 and lag 3, respectively; however, this was not seen for other lags tested. The three other pollens investigated

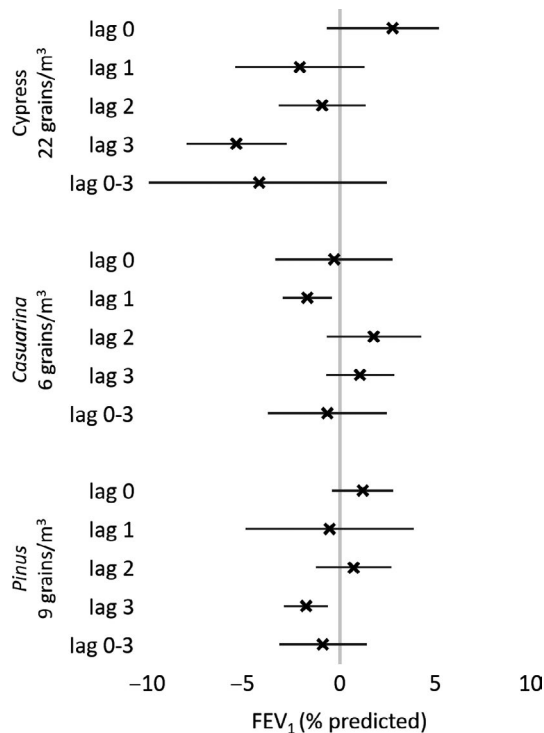


FIGURE 2 Associations between increased pollen exposures and FEV₁ in 8-y-olds

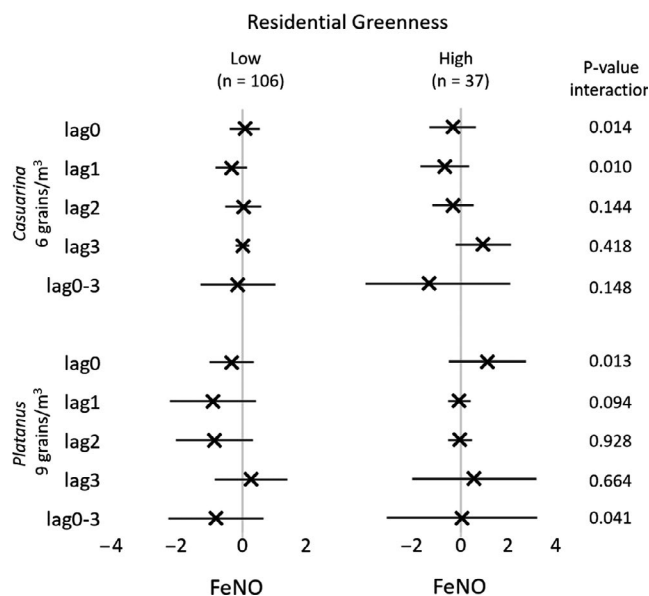


FIGURE 3 Associations between increased *Casuarina* and *Platanus* pollen exposure and FeNO in 8-y-olds, modified by residential greenness

(grass, weed and the tree *Platanus*) were not found to be associated with lung function. There were no effects found in the children at 14 years of age, suggesting a potential biological or behavioural difference between the age groups.

This difference in associations for these two age groups is consistent with the results of a Swedish cohort study.¹⁵ By 14, most of the girls had reached menarche and the boys were well on their

way through puberty—the lack of association could be explained by this physical maturation. Younger children are also likely to engage in mouth breathing,³¹ bypassing the filtering effect of the nasal passage on pollen particles. Another plausible explanation is a potential behavioural difference in the time spent outdoors and the level of physical activity engaged in between the two age groups. The Swedish study¹⁵ found associations with grass pollen (FEV₁ at 8 years: -32.4 mL; 95% CI: -50.6, -14.2 per increase of 3 grass pollen grains/m³) but not the tree pollens *Corylus*, *Alnus*, *Ulmus*, *Betula*, *Pinus*, *Salix* or *Quercus*; nor the weed *Artemisia*. A regional difference in associations between pollen and lung function is not unexpected. The grass pollen captured by Gruzdeva et al¹⁵ is likely to be Timothy grass,³² in contrast, grasses in the Sydney region of Australia are predominantly perennial rye, Bermuda and Bahia. Pollen from grasses is morphologically similar: spheroidal, psilate, with overlapping sizes from 20 to 60 µm and thus generally not speciated. Regional differences can also be seen in the tree pollen counted, with only *Pinus* pollen counted in both Sydney and Stockholm. This highlights the necessity of conducting studies in multiple geographical regions to detect associations with species prevalent to a region.

Associations between tree pollen and lung function were found at different lags for different species. *Casuarina*, an Australian native which is not generally considered to be a major contributor to pollen aeroallergens, has the smallest sized pollen grain of the three tree pollens associated with decreased lung function. This smaller size, while still too large to penetrate deeply into the lungs at 19–21 µm by 22–30 µm, could somewhat explain its association at lag 1 compared to the lag 3 associations found with cypress (25–36 µm) and *Pinus* (40–80 µm). These intact pollen grains are unlikely to penetrate deeper than the trachea and major bronchi; however, pollen grains, both grass³³ and birch,³⁴ have been shown to rupture into respirable fragments in rainfall; it is plausible that Cypress, *Casuarina* and *Pinus* pollen could do the same. This pollen fragment can also interact with other airborne particulate matter, providing a further transport mechanism to gain access into lower airways.³³ Another possible explanation is higher levels of pollen act to prime the immune system, sensitivity against pollens has been observed to increase as the pollen season progresses.³⁵

Two studies have followed small groups of seasonal allergic asthmatic children through the pollen season, taking multiple measurements of FeNO and FEV₁.^{16,17} Roberts et al¹⁷ followed n = 44 asthmatic children aged 6–16 years, sensitized to Timothy grass (*Phleum pratense*) through the grass pollen season in London, England. Unlike our findings, they showed a small positive correlation between increased FeNO and increased ambient grass pollen on the day of measurement and up to one week prior. They found no association with FEV₁. Following 11 asthmatic children aged 5–15 years, sensitized to birch pollen, through the birch pollen season in Copenhagen, Denmark; Vahlkvist et al¹⁶ reported no association between ambient pollen counts and FeNO or FEV₁ at lag 0, lag 1 or lag 2. FeNO did increase overall as the pollen season progressed. Both studies noted abnormally low pollen counts during the seasons of observation.

These studies^{16,17} have focused on a small number of asthmatic children of varying ages, taking multiple measurements whilst we have taken a snapshot of a larger number of children at two distinct ages. Further, they have looked at a single pollen type during a particular pollen season whilst we have investigated multiple pollens at the time of health outcome measurement throughout the year. Our findings cannot therefore be directly compared due to differences in study population and methodology.

Assessing the effect of pollen exposure at birth and subsequent lung function, we have previously shown effect modification by residential greenness.²¹ To our knowledge, that is the only previous study to look at the potential effect modification of pollen/lung function associations by residential greenness and is not directly comparable to this study because that study assessed pollen exposure at birth while this study assessed the acute effects of pollen exposure at time of lung function measurement. In the current analysis, there was no observable effect modification by high residential greenness, although significant interactions between residential greenness and pollen associations with FeNO were found. Replication in a larger study population may reveal further effect modification.

A major strength of this study was the access to daily counts of pollen collected through the year. We have assessed the association of a wide range of pollen species with lung function and airway inflammation, which has not been examined in an Australian context before. However, a panel study with repeated measurements of lung function and FeNO might have served as a more robust design. Several other limitations to this research exist. Daily pollen was collected from only one, centrally located, Burkard trap. While participants living more than 150 km away from the trap were excluded, the potential for exposure misclassification cannot be ignored, as it was not possible to confirm that all participants were exposed to the same levels of pollen as recorded. Pollen traps in Sydney have shown reasonable concordance over a 30 km region³⁶; however, it is not unreasonable to expect some variation at the distance required to cover the majority of the CAPS cohort. Further, while we examined concentration of the pollen grains in the atmosphere, the amount of major allergen within the pollen may be regionally and seasonal dependent.³⁷ Given the morphology similarities of grass pollen, historical records counted total grass pollen and further distinction was not available. Thus, we were unable to distinguish between perennial rye, Bermuda and Bahia grass pollens. While there was some speciation available for weeds (most being Plantain and Dock/Sorrel), the counts of each taxa were low, and results are presented as aggregated weed pollen. Local vegetation may impact both respiratory health (green space for recreational activities is associated with increased physical activities and tree canopies can reduce heat stress through cooling) and pollen (agricultural fields being a major source of grass pollen), and thus the type of vegetation is an important consideration^{38,39}. However, NDVI detects general vegetation thus providing a limitation to this research as it does not distinguish between allergenic and specific vegetation or even between trees, grass and shrubs. Further, the relatively small sample size and large number

of associations tested gives rise to the possibility of type-1 error and results should be interpreted with caution. In particular, the sub-analysis by high residential greenness is underpowered and results should be considered indicative only.

In summary, airborne tree pollen of cypress, *Casuarina* and *Pinus* were associated with a reduced FEV₁ and FVC at age 8 years but not at age 14 years. These findings contribute evidence that pollen other than grass may still be detrimental to lung function in children.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Lambert KA, Katelaris C, Burton P, et al. Tree pollen exposure is associated with reduced lung function in children. *Clin Exp Allergy*. 2020;00:1-8. <https://doi.org/10.1111/cea.13711>

Supplementary Table 1: Pollen distributions (days with non-zero pollen counts) during the period 2005-2013.

Species	Days with non-zero pollen counts							
	n (%)	Min	Max	25th %ile	Median	75 th %ile	Mean	SD
Cypress	945 (37%)	1	1266	3	8	25	31.88	81.86
Casuarina	972 (38%)	1	358	1	4	7	7.16	15.46
Pinus	599 (23%)	1	629	1	4	10	11.50	29.32
Platanus	667 (26%)	1	203	1	4	10	11.11	19.88
Liquid Amber	162 (6%)	1	29	1	3	4	3.42	3.67
Grass	1090 (43%)	1	142	3	5	10	9.24	12.82
Weed	731 (29%)	1	83	1	4	8	6.22	7.61

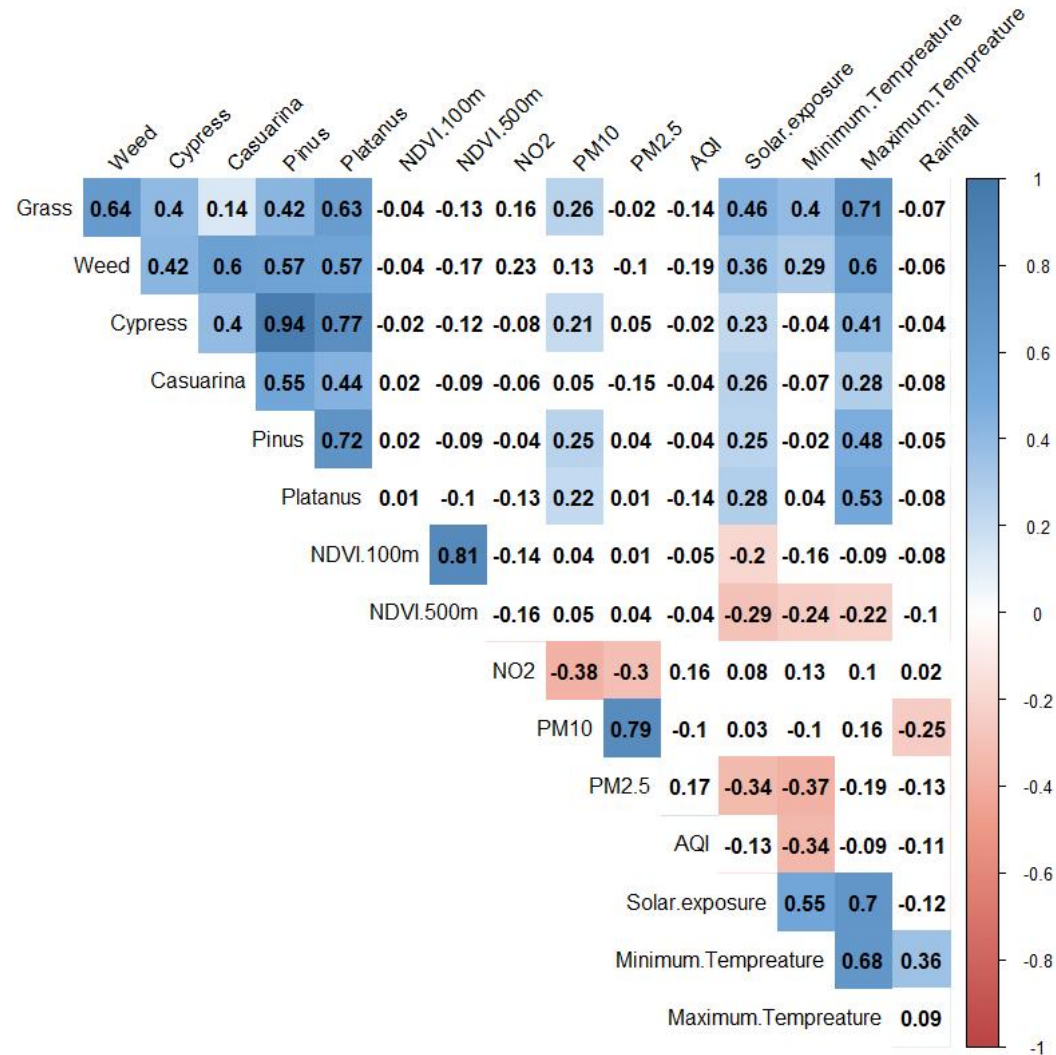


Figure S1: Correlation Matrix between pollen, residential greenness, air pollution and meteorological variables. Correlations with a p-value < 0.01 are coloured according to the strength of the correlation coefficient.

Supplementary Table 2: % retention in models.

Variable	Total Retention	% Retention in FEV₁	% Retention in FVC	% Retention in FEV₁/FVC	% Retention in FeNO
Atopy status	71%	67%	67%	50%	100%
Current asthma	46%	17%	33%	50%	83%
Smoking during pregnancy	25%	17%	33%	33%	17%
Smoking inside the house	21%	33%	17%	17%	17%
Maternal asthma	13%	17%	33%	0%	0%
Air Quality Index	0%	0%	0%	0%	0%
PM _{2.5}	0%	0%	0%	0%	0%
PM ₁₀	0%	0%	0%	0%	0%
NO ₂	0%	0%	0%	0%	0%
Maternal education	0%	0%	0%	0%	0%

Supplementary Table 3: Association between eight-year visit lung function and FeNO outcomes and pollen types by lag.

	Grass (IQR: 7gr/m ³)		Weed (IQR: 7gr/m ³)		Cypress (IQR: 22gr/m ³)		Casuarina (IQR: 6gr/m ³)		Pinus (IQR: 9gr/m ³)		Platanus (IQR: 9gr/m ³)	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
	FEV₁ (% predicted)*											
Lag 0	0.25 (-3.4, 3.8)	0.889	-1.31 (-8.1, 5.5)	0.699	2.74 (-0.7, 5.2)	0.056	-0.32 (-3.4, 2.8)	0.834	1.18 (-0.4, 2.7)	0.147	-1.35 (-3.6, 0.9)	0.240
Lag 1	-2.75 (-7.2, 1.7)	0.219	-3.21 (-9.8, 3.4)	0.337	-2.09 (-5.5, 1.3)	0.220	-1.72 (-3.0, -0.4)	0.010	-0.55 (-4.9, 3.8)	0.804	-2.29 (-4.6, 0.0)	0.051
Lag 2	-1.16 (-4.59, 2.25)	0.496	-0.77 (-3.9, 2.5)	0.636	-0.93 (-3.2, 1.4)	0.414	1.77 (-0.7, 4.3)	0.155	0.71 (-1.2, 2.6)	0.476	0.85 (-1.1, 2.7)	0.373
Lag 3	1.25 (-2.18, 4.68)	0.467	-3.32 (-13.5, 6.9)	0.515	-5.44 (-8.1, -2.8)	0.001	1.05 (-0.7, 2.8)	0.243	-1.8 (-2.9, -0.6)	0.003	1.52 (-0.4, 3.5)	0.117
Lag 0-3	-0.72 (-6.98, 5.54)	0.819	-1.50 (-6.6, 3.6)	0.553	-4.3 (-10.9, 2.5)	0.208	-0.67 (-3.7, 2.4)	0.668	-0.90 (-3.2, 1.4)	0.435	0.01 (-2.8, 2.8)	0.999
	FVC (% predicted)*											
Lag 0	0.66 (-3.4, 4.7)	0.746	3.06 (-4.5, 10.6)	0.419	2.80 (-0.2, 5.4)	0.057	-1.28 (-4.7, 2.2)	0.457	1.24 (-0.6, 3.0)	0.176	-1.03 (-3.6, 1.6)	0.426
Lag 1	-1.03 (-5.9, 3.9)	0.675	-2.67 (-9.9, 4.5)	0.460	-1.20 (-4.9, 2.5)	0.520	-1.90 (-3.3, -0.5)	0.008	-0.07 (-4.8, 4.7)	0.975	-1.50 (-4.1, 1.1)	0.247
Lag 2	-0.58 (-4.3, 3.2)	0.757	-1.28 (-4.8, 2.2)	0.467	-1.25 (-3.7, 1.2)	0.314	1.24 (-1.5, 4.0)	0.367	0.62 (-1.5, 2.8)	0.564	1.20 (-0.9, 3.3)	0.256
Lag 3	0.03 (-3.7, 3.8)	0.988	-4.1 (-15.2, 7.0)	0.460	-5.31 (-8.3, -2.4)	0.001	0.84 (-1.1, 2.8)	0.392	-1.74 (-3, -0.5)	0.009	1.27 (-0.9, 3.4)	0.237
Lag 0-3	-0.30 (-7.2, 6.6)	0.932	-2.21 (-7.8, 3.4)	0.428	-3.9 (-11.4, 3.6)	0.303	-1.66 (-5.1, 1.7)	0.331	-0.81 (-3.4, 1.7)	0.524	0.49 (-2.7, 3.7)	0.758
	FEV₁/FVC (%)*											
Lag 0	-0.3 (-2.3, 1.8)	0.794	-3.2 (-7, 0.5)	0.086	-0.2 (-1.7, 1.2)	0.739	0.7 (-1.0, 2.5)	0.395	0.0 (-0.9, 0.9)	0.975	-0.3 (-1.6, 1.0)	0.617
Lag 1	-0.5 (-2.9, 1.8)	0.658	0.0 (-3.4, 3.5)	0.984	0.0 (-1.8, 1.7)	0.968	0.2 (-0.5, 0.9)	0.555	0.0 (-2.3, 2.3)	0.994	-0.4 (-1.6, 0.8)	0.510
Lag 2	-0.2 (-2.0, 1.6)	0.823	0.6 (-1.0, 2.3)	0.452	0.3 (-0.9, 1.5)	0.633	0.5 (-0.8, 1.8)	0.427	0.1 (-1.0, 1.1)	0.920	-0.2 (-1.2, 0.8)	0.645
Lag 3	1.1 (-0.6, 2.9)	0.195	0.9 (-4.4, 6.1)	0.739	-0.3 (-1.9, 1.2)	0.664	0.2 (-0.8, 1.1)	0.715	-0.1 (-0.8, 0.5)	0.718	0.3 (-0.7, 1.3)	0.526
Lag 0-3	0.6 (-2.7, 3.9)	0.723	1.0 (-1.6, 3.7)	0.436	0.1 (-3.6, 3.7)	0.972	0.9 (-0.7, 2.5)	0.280	-0.1 (-1.3, 1.1)	0.872	-0.3 (-1.8, 1.2)	0.667
	FeNO (ppb)**											
Lag 0	0.05 (-0.1, 0.2)	0.615	-0.02 (-0.4, 0.3)	0.901	-0.01 (-0.1, 0.1)	0.862	-0.12 (-0.3, 0.0)	0.124	0.02 (-0.1, 0.1)	0.618	-0.08 (-0.2, 0.0)	0.176
Lag 1	0.06 (-0.2, 0.3)	0.610	-0.03 (-0.4, 0.3)	0.880	-0.06 (-0.2, 0.1)	0.515	-0.03 (-0.1, 0.0)	0.431	-0.08 (-0.3, 0.2)	0.501	-0.02 (-0.1, 0.1)	0.779
Lag 2	0.13 (-0.1, 0.3)	0.170	0.12 (-0.1, 0.3)	0.190	-0.03 (-0.2, 0.1)	0.603	0.08 (-0.1, 0.2)	0.235	-0.07 (-0.2, 0.0)	0.199	0.00 (-0.1, 0.1)	0.933
Lag 3	-0.10 (-0.3, 0.1)	0.255	0.53 (0.0, 1.0)	0.053	-0.03 (-0.2, 0.1)	0.727	0.01 (-0.1, 0.1)	0.854	0.00 (-0.1, 0.1)	0.958	-0.08 (-0.2, 0.0)	0.129
Lag 0-3	-0.03 (-0.4, 0.3)	0.861	-0.10 (-0.4, 0.2)	0.473	-0.18 (-0.5, 0.2)	0.315	-0.04 (-0.2, 0.1)	0.630	-0.03 (-0.1, 0.1)	0.658	-0.06 (-0.2, 0.1)	0.405

*Adjusted for atopy, current asthma, PM_{2.5}, NO₂, smoking during pregnancy, maternal asthma and seasonality **Adjusted for age, sex, atopy, current asthma, PM_{2.5}, NO₂, smoking during pregnancy, maternal asthma and seasonality. All values presented as per IQR increase in pollen grains/m³.

Supplementary Table 4: Association between 14-year visit lung function and FeNO outcomes and pollen types by lag.

	Grass (IQR: 7gr/m ³)		Weed (IQR: 7gr/m ³)		Cypress (IQR: 22gr/m ³)		Casuarina (IQR: 6gr/m ³)		Pinus (IQR: 9gr/m ³)		Platanus (IQR: 9gr/m ³)	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
	FEV₁ (% predicted)*											
Lag 0	0.42 (-0.03, 0.9)	0.067	0.27 (-0.6, 1.2)	0.563	0.01 (0.0, 0.0)	0.345	-0.10 (-0.9, 0.7)	0.818	0.07 (-0.1, 0.2)	0.324	0.59 (-0.6, 1.8)	0.337
Lag 1	-0.07 (-0.4, 0.2)	0.655	0.29 (-0.7, 1.3)	0.576	0.01 (0.0, 0.0)	0.720	-0.03 (-0.9, 0.9)	0.952	0.04 (-0.2, 0.3)	0.788	0.04 (-0.5, 0.6)	0.881
Lag 2	-0.11 (-0.8, 0.6)	0.746	0.14 (-0.8, 1.1)	0.769	-0.03 (-0.2, 0.1)	0.750	0.34 (-0.4, 1.1)	0.390	0.02 (-0.5, 0.5)	0.946	-0.09 (-0.6, 0.5)	0.756
Lag 3	0.43 (-0.3, 1.1)	0.228	0.01 (-0.7, 0.7)	0.973	-0.09 (-0.3, 0.1)	0.372	-0.19 (-0.6, 0.2)	0.347	-0.09 (-0.3, 0.1)	0.366	0.06 (-0.7, 0.8)	0.879
Lag 0-3	0.73 (-1.4, 2.9)	0.496	4.71 (-4.7, 14.1)	0.323	0.1 (-0.1, 0.3)	0.425	-1.07 (-5.5, 3.3)	0.631	0.20 (-0.9, 1.3)	0.722	0.38 (-1.9, 2.6)	0.738
	FVC (% predicted)*											
Lag 0	0.18 (-0.2, 0.6)	0.394	0.34 (-0.5, 1.2)	0.418	0.00 (-0.0, 0.0)	0.556	0.02 (-0.7, 0.8)	0.967	0.03 (-0.1, 0.2)	0.633	0.06 (-1.0, 1.1)	0.915
Lag 1	-0.03 (-0.3, 0.2)	0.837	0.37 (-0.6, 1.3)	0.434	0.01 (-0.0, 0.0)	0.504	-0.32 (-1.1, 0.5)	0.436	0.09 (-0.2, 0.3)	0.473	0.01 (-0.5, 0.5)	0.978
Lag 2	-0.04 (-0.7, 0.6)	0.892	0.10 (-0.7, 0.9)	0.805	0.00 (-0.2, 0.2)	0.977	0.33 (-0.4, 1.1)	0.357	0.02 (-0.4, 0.5)	0.925	0.15 (-0.3, 0.6)	0.553
Lag 3	0.04 (-0.6, 0.7)	0.899	-0.19 (-0.8, 0.4)	0.548	-0.07 (-0.2, 0.1)	0.441	-0.16 (-0.5, 0.2)	0.398	-0.09 (-0.3, 0.1)	0.335	-0.16 (-0.9, 0.5)	0.645
Lag 0-3	0.32 (-1.6, 2.2)	0.745	3.28 (-5.3, 11.8)	0.449	0.07 (-0.2, 0.3)	0.544	-1.14 (-5.1, 2.8)	0.573	0.07 (-0.9, 1.1)	0.892	0.41 (-1.6, 2.4)	0.693
	FEV₁/FVC (%)*											
Lag 0	0.20 (-0.0, 0.5)	0.103	0.00 (-0.6, 0.5)	0.875	0.00 (0.0, 0.0)	0.543	-0.1 (-0.6, 0.4)	0.703	0.00 (-0.1, 0.1)	0.430	0.60 (-0.1, 1.3)	0.113
Lag 1	0.00 (-0.2, 0.1)	0.664	-0.10 (-0.7, 0.5)	0.812	0.00 (0.0, 0.0)	0.774	0.2 (-0.3, 0.7)	0.503	0.00 (-0.2, 0.1)	0.630	0.00 (-0.3, 0.3)	0.978
Lag 2	-0.10 (-0.5, 0.3)	0.661	0.00 (-0.5, 0.6)	0.948	0.00 (-0.1, 0.1)	0.734	0.1 (-0.4, 0.6)	0.682	0.00 (-0.3, 0.3)	0.941	-0.20 (-0.5, 0.1)	0.223
Lag 3	0.30 (-0.1, 0.7)	0.108	0.10 (-0.3, 0.5)	0.519	0.00 (-0.1, 0.1)	0.729	0.0 (-0.3, 0.2)	0.809	0.00 (-0.1, 0.1)	0.993	0.20 (-0.2, 0.6)	0.381
Lag 0-3	0.30 (-0.9, 1.6)	0.589	0.70 (-4.8, 6.2)	0.796	0.00 (-0.1, 0.2)	0.685	0.1 (-2.4, 2.7)	0.912	0.10 (-0.5, 0.8)	0.686	0.00 (-1.3, 1.3)	0.972
	FeNO (ppb)**											
Lag 0	-0.04 (-0.3, 0.2)	0.723	-0.10 (-0.5, 0.3)	0.634	0.00 (0.0, 0.0)	0.351	0.03 (-0.4, 0.4)	0.878	-0.04 (-0.1, 0.0)	0.252	-0.18 (-0.7, 0.4)	0.530
Lag 1	-0.08 (-0.2, 0.1)	0.236	-0.40 (-0.9, 0.1)	0.088	-0.01 (0.0, 0.0)	0.229	-0.26 (-0.7, 0.2)	0.217	-0.08 (-0.2, 0.0)	0.167	0.09 (-0.2, 0.4)	0.502
Lag 2	-0.33 (-0.6, 0.0)	0.139	0.12 (-0.3, 0.6)	0.563	-0.07 (-0.2, 0.0)	0.084	-0.18 (-0.6, 0.2)	0.330	-0.18 (-0.4, 0.1)	0.127	-0.14 (-0.4, 0.1)	0.261
Lag 3	-0.13 (-0.5, 0.2)	0.436	0.00 (-0.3, 0.3)	0.976	0.03 (-0.1, 0.1)	0.561	0.05 (-0.1, 0.2)	0.630	0.01 (-0.1, 0.1)	0.866	-0.24 (-0.6, 0.1)	0.186
Lag 0-3	-0.92 (-1.9, 0.1)	0.063	-2.33 (-6.7, 2.0)	0.290	-0.07 (-0.2, 0.1)	0.248	-0.39 (-2.4, 1.7)	0.705	-0.37 (-0.9, 0.1)	0.150	-0.91 (-1.9, 0.1)	0.081

*Adjusted for atopy, current asthma, PM_{2.5}, NO₂, smoking during pregnancy, maternal asthma and seasonality **Adjusted for age, sex, atopy, current asthma, PM_{2.5}, NO₂, smoking during pregnancy, maternal asthma and seasonality. All values presented as per IQR increase in pollen grains/m³.

Supplementary Table 5: Odds ratio for association between eight-year visit lung function (<80%predicted) and pollen types by lag.

	Grass (IQR: 7gr/m ³)	Weed (IQR: 7gr/m ³)	Cypress (IQR: 22gr/m ³)	<i>Casuarina</i> (IQR:6gr/m ³)	<i>Pinus</i> (IQR: 9gr/m ³)	<i>Platanus</i> (IQR: 9gr/m ³)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	FEV₁ (<80% predicted)*					
Lag 0	1.22 (0.53, 2.79)	1.26 (0.33, 4.33)	0.58 (0.12, 2.87)	0.48 (0.09, 4.04)	1.12 (0.71, 1.77)	1.35 (0.84, 2.17)
Lag 1	0.71 (0.34, 2.47)	2.03 (0.69, 5.92)	1.21 (0.52, 2.79)	1.34 (1.02, 1.74)	1.02 (0.21, 5.00)	1.46 (0.87, 2.45)
Lag 2	0.74 (0.36, 2.42)	0.98 (0.45, 2.17)	1.12 (0.71, 1.77)	1.06 (0.51, 2.22)	1.10 (0.71, 1.71)	1.18 (0.80, 1.72)
Lag 3	0.48 (0.08, 2.81)	3.70 (0.99, 7.78)	1.92 (1.04, 3.55)	1.07 (0.63, 1.83)	1.41 (0.78, 2.57)	1.08 (0.70, 1.68)
Lag 0-3	0.68 (0.13, 3.74)	1.43 (0.71, 2.87)	2.38 (0.59, 5.56)	1.32 (0.67, 2.62)	1.41 (0.91, 2.19)	1.35 (0.75, 2.42)
	FVC (<80% predicted)*					
Lag 0	1.10 (0.56, 2.19)	0.97 (0.29, 3.19)	0.60 (0.14, 2.56)	0.17 (0.01, 2.87)	0.91 (0.42, 1.99)	1.11 (0.70, 1.78)
Lag 1	1.19 (0.46, 3.03)	1.56 (0.93, 5.06)	1.47 (0.77, 2.81)	1.21 (0.94, 1.57)	0.85 (0.19, 3.60)	1.16 (0.72, 1.87)
Lag 2	0.91 (0.42, 1.99)	1.24 (0.75, 2.04)	1.94 (0.99, 3.83)	0.75 (0.34, 1.71)	1.00 (0.66, 1.51)	1.15 (0.82, 1.61)
Lag 3	1.06 (0.53, 2.11)	3.02 (0.73, 7.24)	2.44 (1.16, 5.14)	0.85 (0.47, 1.53)	1.43 (0.87, 2.37)	0.95 (0.60, 1.51)
Lag 0-3	1.32 (0.46, 3.83)	1.79 (0.95, 3.37)	3.28 (1.10, 10.65)	0.96 (0.48, 1.92)	1.19 (0.79, 1.78)	1.12 (0.66, 1.90)

*Adjusted for atopy, current asthma, PM_{2.5}, NO₂, smoking during pregnancy and maternal asthma. All values presented as per IQR increase in pollen grains/m³.

Supplementary Table 6: p-values for the interaction term between pollen and the Normalised Difference Vegetation Index in the 8 year follow up visit.

8 years	FEV ₁	FVC	FEV ₁ /FVC	FeNO
Grass				
Lag 0	0.516	0.871	0.215	0.573
Lag 1	0.758	0.955	0.561	0.021
Lag 2	0.501	0.883	0.142	0.207
Lag 3	0.531	0.620	0.925	0.192
Lag 0-3	0.371	0.527	0.012	0.259
Weed				
Lag 0	0.717	0.916	0.478	0.106
Lag 1	0.902	0.619	0.291	0.522
Lag 2	0.758	0.946	0.682	0.510
Lag 3	0.310	0.536	0.626	0.748
Lag 0-3	0.900	0.789	0.741	0.044
Cypress				
Lag 0	0.295	0.470	0.630	0.293
Lag 1	0.998	0.737	0.402	0.756
Lag 2	0.455	0.625	0.022	0.871
Lag 3	0.318	0.347	0.664	0.765
Lag 0-3	0.614	0.388	0.704	0.886
Casuarina				
Lag 0	0.785	0.692	0.739	0.014
Lag 1	0.876	0.934	0.806	0.010
Lag 2	0.455	0.438	0.925	0.144
Lag 3	0.221	0.457	0.481	0.418
Lag 0-3	0.991	0.788	0.484	0.148
Pinus				
Lag 0	0.779	0.930	0.612	0.492
Lag 1	0.297	0.391	0.666	0.066
Lag 2	0.441	0.210	0.531	0.339
Lag 3	0.938	0.833	0.424	0.950
Lag 0-3	0.548	0.546	0.830	0.863
Platanus				
Lag 0	0.786	0.796	0.844	0.013
Lag 1	0.810	0.811	0.363	0.094
Lag 2	0.443	0.079	0.042	0.928
Lag 3	0.306	0.170	0.379	0.664
Lag 0-3	0.988	0.352	0.062	0.041