ORIGINAL ARTICLE

The role of short-term grass pollen exposure in food skin-prick test reactivity, food allergy, and eczema flares in children

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Abstract

Background: While the relationship between pollen and respiratory allergies is well-documented, the role of short-term pollen exposure in food allergy and eczema flares has not previously been explored. We aimed to investigate these associations in a population-based sample of children.

Methods: We investigated 1- ($n = 1108$) and 6-year-old ($n = 675$) children in the grass pollen season from the HealthNuts cohort. Grass pollen concentrations were considered on the day of testing (lag 0), up to three days before (lag 1-lag 3) and cumulatively (lag 0–3). Associations between grass pollen and food skin-prick test reactivity (SPT ≥ 2 mm at age 1 year and ≥ 3 mm at age 6 years), eczema flares, challenge-confirmed food allergy, reaction threshold to oral food challenges (OFC), and serum food-specific IgE levels were analyzed using either logistic or quantile regression models. Atopy and family history of allergic disease were considered as potent effect modifiers.

Results: Grass pollen at lag 0–3 (every 20 grains/m^3 increase) was associated with an up to 1.2-fold increased odds of food SPT reactivity and eczema flares in 6-year-olds. In 1-year-olds, the associations were only observed for peanut in those with a family history of food allergy. Increasing grass pollen concentrations were associated with a lower reaction threshold to OFC and higher serum IgE levels in peanut-allergic 1-year-olds only.

Conclusion: Increasing grass pollen concentration was associated with increased risk of food SPT reactivity and eczema flares in children. The associations in peanut-allergic infants may be related to immune activation and/or peanut and grass pollen cross-reactivity leading to a lower reaction threshold.

KEYWORDS

eczema, food allergy, food sensitization, grass, pediatrics, pollen

1 | INTRODUCTION

Globally, childhood food allergy and eczema continue to be growing public health problems. Australia is particularly affected, with approximately 10% and 25% of children under five showing food allergy and eczema, respectively.[1,2] Little is known about the impacts of outdoor pollen on these conditions. Our systematic review showed that short-term outdoor pollen exposure can enhance type-2 immune responses such as immunoglobulin E (IgE), mast cell, and eosinophil production in the airways, especially among those with asthma and/or seasonal allergic rhinitis.[3] Although this is the current evidence, investigating further the adverse effects of outdoor pollen within the community is warranted because thunderstorm asthma events showed that people with no known asthma were also susceptible.[4,5] The priming hypothesis indicates that increased sensitivity towards pollen is possible with persistent exposure.[6] Therefore, we hypothesized that high pollen exposure may result in an inflammatory response that may lower the threshold for manifestation of other allergic diseases such as food allergy and eczema, and this may include those without pre-existing respiratory conditions or known grass pollen sensitization.

There is mounting evidence that pollen exposure may be associated with eczema and food allergy. Direct application of grass pollen onto the skin has been shown to induce eczematous lesions.[7,8] Krämer et al.[9] also demonstrated that children with eczema experienced more symptoms on days with high grass pollen counts. Previously, studies including our own have found that exposure to grass pollen in utero and the first few months of life was associated with food sensitization and allergy.[10–12] We have also recently demonstrated that increased residential greenness exposure was associated with an increased risk of challenge-confirmed peanut and egg allergy in infants, and this could be related to the higher pollen concentrations.[13] Antibody cross-reactivity between a specific pollen (e.g. grass) and plant-based foods that contain similar proteins (e.g. Ara h 9 of peanut) can also occur resulting in the pollen-food allergy syndrome.[14–16] Hence, outdoor pollen exposure may be linked to broad priming across all food allergens or limited to known cross-reactive food allergens only.

> **Key Message**
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> This population-based study is the first to investigate the relationship between short-term grass pollen exposure, food skin-prick test (SPT) reactivity, food allergy outcomes, and eczema flares. We found that persistent grass pollen exposure may trigger a general state of heightened immune responsiveness leading to increased odds of food SPT reactivity and eczema flares in children, but the impact may be greater if peanut allergy is already present. Research into SPTs and oral food challenges should consider pollen concentrations to limit residual confounding and/or effect modification, and additional caution for peanut avoidance may need to be taken for peanut-allergic children during the grass pollen season.

Here, we aimed to determine whether outdoor grass pollen concentration was associated with food skin-prick test (SPT) reactivity, food allergy, and eczema flares in children aged 1 and 6 years, and their potential modifiers. Additionally, we also investigated whether grass pollen concentration was associated with oral food challenge (OFC) outcomes and/or serum food-specific IgE levels in food allergic children. We have focused on grass pollen a priori because our study population consisted of children who were based in Melbourne, Australia, and grass pollen was the most abundant aeroallergen in the city.[17]

2 | METHODS

2.1 | Study sample

The study sample consisted of participants from the HealthNuts cohort.[18] The study methodology is detailed elsewhere,[19] but briefly, a total of 5276 1-year-old infants were recruited at local council-run

immunization clinics across Melbourne, Australia, from 2007 to 2011, and underwent skin-prick testing (SPT) to food allergens. A follow-up was conducted at age 6 years (2013–2016) where 3233 children underwent clinical examinations. This clinic visit included SPT to food and pollen extracts, as well as eczema assessment. At both follow-ups, participants with a food SPT ≥ 1 mm or recent history of food allergy were offered OFC. Those with food allergy were also offered blood draw for serum food-specific IgE.

The present work was restricted to participants who underwent testing during the Melbourne grass pollen season (October to January). To investigate any potential selection/participation bias, we have compared the characteristics of participants tested during the grass pollen season vs. out of the grass pollen season (Table 1). By excluding participants outside of the pollen season, we reduced possible bias of the estimates toward the null as the time of observation and of potential grass pollen exposure would not have coincided.[20] Nonetheless, a separate analysis was conducted involving all participants, where grass pollen season of testing was investigated as an exposure.

2.2 | Ethics

Ethics approval was obtained from the Victorian Department of Human Services (reference no. 10/07), the Office for Children (reference no. CDF/07/492), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047 & no. 32294). The parents provided written informed consent on behalf of their children.

2.3 | Outcome collection and definitions

The study samples varied depending on the outcome and are defined in Table S1.

2.3.1 | Food SPT reactivity

SPTs were conducted by placing a single drop of the allergen extract (ALK-Abelló, Spain at age 1 year; ALK-Abelló, Spain, Hollister-Stier, USA, and Stallergènes, France, at age 6 years) on the infant's or child's back and then pricked with a lancet (Stallergènes, France). Positive and negative controls were histamine (10 mg/ml) and saline, respectively.

Age 1 – SPT reactivity was defined as wheal ≥ 2 mm, which is the common cut-off used in young infants.[21,22] A sensitivity analysis was conducted using the 3 mm cut-off, and no significant differences were found (data not shown). The food allergens considered were peanut, egg, sesame, and cow's milk.

Age 6 – SPT reactivity was defined as wheal ≥ 3 mm. Food allergens considered were peanut, egg, sesame, cashew, hazelnut, and almond.

2.3.2 | Serum food-specific IgE

Only those with food allergy were offered blood draw for serum food-specific IgE. We collected blood samples and separated the child's plasma for serum IgE assays on the same day. The serum food-specific IgE antibodies were then analyzed using ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).[23] We only had sufficient sample size to assess this outcome in 1-year-old peanut or egg allergic infants. An infant was considered allergic if he or she had (i) a positive OFC (at least three non-contact urticaria lasting >5 min, angioedema, vomiting, or anaphylaxis within two hours of last dose[2]), or a history of a reaction (consistent with OFC stopping criteria) in the past month for egg and 2 months for peanut plus; (ii) a positive SPT (≥ 2 mm) and/or a positive in vitro test defined as ≥ 0.35kU$_A$/L.[24,25]

2.3.3 | Food allergy outcomes

The method of OFC administration was described elsewhere.[18,19] We investigated (i) the presence of challenge-confirmed food allergy, defined by a positive OFC, and (ii) the reaction threshold to OFC, defined as the cumulative total dose (ml) given to a child before a reaction occurred.

Age 1 – The food allergens considered were peanut and egg.

Age 6 – We only had sufficient power to investigate the presence of challenge-confirmed allergy to peanut.

2.3.4 | Eczema flares on the day of assessment

Age 1 – This was determined by nurses who have undergone online SCORing Atopic Dermatitis (SCORAD) training photo tutorials on different appearances of eczema and skin pigmentation. During a participant's assessment, the nurses were asked to identify cardinal signs of eczema, such as excoriation, erythema, edema/papulation, vesiculation, and lichenification and used clinical judgment (e.g. erythema on the cheeks from crying).[26]

Age 6 –This was defined as having a non-zero SCORAD[27] total score (based on area affected, intensity, and subjective symptoms[28]).

2.4 | Grass pollen data collection

A Burkard volumetric trap was used to collect daily grass pollen. This single trap is a good proxy for exposure for those living up to 50 km from the site.[29] All participants lived within this radius, and the clinical testing site was within a short distance of the trap. The methods of data collection were described elsewhere.[10,30] This present work examined grass pollen concentrations on the day of health

TABLE 1 Characteristics of the HealthNuts participants

Variables	1-year cohort			6-year cohort		
		Present study sample			Present study sample	
	Tested outside of grass pollen season[a]	Tested during the grass pollen season (Oct-Jan)[a]	p-value	Tested outside of grass pollen season	Tested during the grass pollen season (Oct-Dec)[a]	p-value
N (Total)	2013	1108	–	2551	675	–
Male sex	990 (49.2%)	573 (51.7%)	.22	1325 (51.9%)	356 (52.7%)	.69
Recent history of eczema[b]	762 (37.9%)	411 (37.1%)	.67	554 (21.7%)	160 (23.7%)	.38
Eczema in the past 12 months[c]	602 (29.9%)	326 (29.4%)	.82	400 (15.7%)	121 (17.9%)	.21
Ever wheeze	315 (15.6%)	179 (16.2%)	.57	–	–	–
Current asthma[d]	–	–	–	333 (13.1%)	97 (14.4%)	.43
Current hay fever[e]	–	–	–	348 (13.6%)	116 (17.2%)	.02
Family history of food allergy	204 (10.1%)	137 (12.4%)	.05	173 (6.8%)	55 (8.1%)	.12
Family history of eczema	600 (29.8%)	348 (31.4%)	.35	493 (19.3%)	145 (21.5%)	.09
Grass pollen sensitized[g]	–	–	–	235 (9.2%)	104 (15.4%)	<.001
SEIFA quintiles[f] Least disadvantaged	419 (20.8%)	211 (19.0%)	.62	499 (19.6%)	107 (15.9%)	.25
2	383 (19.0%)	211 (19.0%)		505 (19.8%)	139 (20.6%)	
3	426 (21.2%)	258 (23.3%)		546 (21.4%)	159 (23.6%)	
4	408 (20.3%)	220 (19.9%)		498 (19.5%)	137 (20.3%)	
Most disadvantaged	371 (18.4%)	204 (18.4%)		501 (19.6%)	131 (19.4%)	
SPT reactivity[g] Peanut	146 (7.3%)	83 (7.5%)	.81	152 (6.0%)	52 (7.7%)	.12
Cashew	–	–	–	106 (4.2%)	40 (5.9%)	.06
Hazelnut	–	–	–	68 (2.7%)	24 (3.6%)	.24
Almond	–	–	–	57 (2.2%)	17 (2.5%)	.70
Sesame	31 (1.5%)	25 (2.3%)	.15	17 (0.7%)	17 (2.5%)	<.001
Egg	260 (12.9%)	149 (13.4%)	.67	58 (2.3%)	17 (2.5%)	.76
Milk	34 (1.7%)	23 (2.1%)	.21	15 (0.6%)	2 (0.3%)	.34

Note: The 1-year cohort in and outside of grass pollen season do not add up to n = 5,276 (at recruitment) because some participants were recruited before pollen data were available (i.e. prior to the MAPCAH study which commenced in September 2009). The 6-year cohort in and outside of grass pollen season do not add up to n = 3,233 because some children did not have their date of assessment recorded. Participants tested in and out of grass pollen season were compared using chi-squared tests. – = Information not collected.

[a]Sample with pollen data available.

[b]Recent history of eczema= Nurse-observed eczema or history of parent-reported doctor-diagnosed eczema/itchy rash that had been treated with topical steroids (age 1 year); Non-zero SCORAD score or parent-reported itchy rash that had affected typical locati.

[c]Eczema in the past 12 months= History of parent-reported doctor-diagnosed eczema/itchy rash that had been treated with topical steroids (age 1 year); Parent-reported itchy rash that had affected typical locations related to eczema such as knees and folds of elbows in the past 12 months (age 6 years).

[d]Current asthma= Parent-reported doctor-diagnosed asthma plus either wheeze/asthma medication use in the past 12 months (age 6 years).

[e]Current hay fever= Sneezing/runny/blocked nose plus itchy eyes without cold/flu in the past 12 months (age 6 years).

[f]SEIFA= Socioeconomic status was defined using the Socio-Economic Indexes for Areas (SEIFA) measures, which was based on the participants' home postcodes.

[g]SPT reactivity/sensitised = SPT ≥ 2 mm (age 1 year); SPT ≥ 3mm (age 6 years).

TABLE 2 Associations between grass pollen concentrations at all lags and food SPT reactivity and eczema flares on the day of assessment in 6-year-old children

Outcomes	Lag 0 OR (95% CI)	p-value	Lag 1 OR (95% CI)	p-value	Lag 2 OR (95% CI)	p-value	Lag 3 OR (95% CI)	p-value	Lag 0–3 OR (95% CI)	p-value
SPT reactivity										
Peanut	1.0 (0.8, 1.5)	.64	0.9 (0.7, 1.2)	.65	1.0 (0.8, 1.8)	.63	0.9 (0.7, 1.2)	.66	1.17 (1.0, 1.3)	.002
Cashew	1.0 (0.7, 1.5)	.76	0.9 (0.7, 1.5)	.76	0.9 (0.5, 1.5)	.80	1.0 (0.7, 1.5)	.86	1.13 (1.0, 1.24)	.036
Hazelnut	0.9 (0.5, 1.5)	.81	1.2 (0.7, 1.8)	.55	1.2 (0.7, 2.2)	.65	0.8 (0.5, 1.5)	.50	1.15 (1.0, 1.35)	.048
Almond	0.9 (0.5, 1.5)	.80	0.8 (0.4, 1.5)	.66	1.5 (0.7, 2.7)	.33	0.96 (0.5, 1.5)	.87	1.17 (1.0, 1.37)	.047
Egg	1.0 (0.7, 1.8)	.77	0.98 (0.5, 1.8)	.94	1.2 (0.7, 2.2)	.52	0.8 (0.4, 1.5)	.48	1.22 (1.0, 1.43)	.01
Sesame	1.2 (0.7, 1.8)	.67	1.0 (0.5, 2.2)	.77	1.2 (0.5, 2.2)	.74	0.8 (0.4, 1.5)	.36	1.17 (1.0, 1.4)	.048
Eczema flares	1.2 (0.8, 1.8)	.22	0.7 (0.5, 1.0)	.10	0.7 (0.4, 1.2)	.14	1.2 (0.96, 1.8)	.08	1.13 (1.0, 1.22)	.02

Note: No confounders were adjusted for in the food SPT reactivity models. Temperature and humidity were adjusted for in the eczema models. Results were interpreted as the effect size per IQR (20 grains/m³) increase in grass pollen.

examination (lag 0) and up to three days before (lag 1, lag 2, lag 3) for each participant. This was because of previous evidence of a lagged association (up to 3 days) between pollen and asthma.[30,31] We also considered each participant's cumulative grass pollen exposure over the 4 days (lag 0–3).

Age 1 – Grass pollen data were obtained from the Melbourne Air Pollen Children and Adolescent Health (MAPCAH) study.[32] Only data collected during the grass pollen season (October to January) were utilized in this present study.

Age 6 – Grass pollen data were obtained directly from the School of Biosciences. However, data were only available in October to December.

2.5 | Potential confounders: weather

Daily temperature and humidity data were obtained from the Bureau of Meteorology. We considered temperature and humidity as potential confounders because they could influence the concentrations of allergenic pollens, the timing of pollen seasons, and other allergic diseases such as asthma and eczema exacerbations.[33–36]

2.6 | Potential modifiers: allergic disease and genetic susceptibility

Given allergic disease[37–39] and genetic susceptibility[40,41] could modify the relationships between risk factors and food SPT reactivity and/or eczema, we investigated potential interactions between grass pollen at all lags and recent history of eczema, wheeze, food sensitization, asthma, hay fever, grass pollen sensitization, and family history of either food allergy or eczema, depending on the outcome. These potential modifiers are defined in Table S2.

2.7 | Statistical analysis

The associations between daily grass pollen concentrations (continuous), food SPT reactivity, challenge-confirmed food allergy, and eczema flares were assessed using logistic regression models. Likelihood ratio tests (LRTs) comparing general additive[42] linear models to non-linear models indicated that the linear models were appropriate to assess the above associations. Pooled analyses of data from both follow-ups were not conducted, because there was evidence that the associations differed across the two follow-ups (p-value for interaction <.1). Interactions were explored separately using LRTs.

Meanwhile, the associations between grass pollen concentrations, the reaction threshold to OFC, and serum food-specific IgE levels were assessed using quantile regression models for the median. We chose to model median rather than mean outcome due to the highly skewed distributions of these outcomes and the model residuals not meeting ordinary linear regression assumptions. LRTs indicated that the

associations with reaction threshold to OFC and serum food-specific IgE levels were best fit with non-linear and linear, respectively.

Where the associations were linear, we interpreted the results as the estimated effect size per IQR (i.e. 29 grains/m^3 at the 1-year follow-up; 20 grains/m^3 at the 6-year follow-up) increase in grass pollen. This interpretation using the IQR is commonly used in studies investigating continuous environmental variables and adverse outcomes.[43,44] Food SPT reactivity and allergy models were not adjusted for temperature and humidity because there was limited understanding of the relationship and sensitivity analyses indicated little to no change in the effect size or statistical significance between the univariate (Table 2) and multivariate models (Table S3). For the eczema model, temperature and humidity were adjusted for as a priori confounders.[36]

A separate second set of analyses was performed involving the whole cohort, where the associations between grass pollen season of testing (categorical) and the outcomes were investigated at age 1 year (n = 5276) and age 6 years (n = 3226), separately. Here, the results were interpreted as the estimated effect size in those tested in the grass pollen season compared to those tested outside of the grass pollen season.

All statistical analyses were carried out in Stata IC 16.1 (College Station, TX: StataCorp LLC) for the logistic regressions and R for the general additive[42] and quantile regressions.[45]

3 | RESULTS

3.1 | Sample and environmental characteristics

In total, 1108 1-year-old infants and 675 6-year-old children participated during the grass pollen seasons and were included in the primary analyses. Most socio-demographic characteristics were similar to participants outside of the grass pollen seasons (Table 1). The summary statistics for grass pollen, temperature, and humidity are presented in Table S4. At each follow-up, there were 40 high pollen days (≥ 50 grains/m^3).[46]

Summary of the findings can be found in Table S1.

3.2 | Food SPT reactivity

Age 1 – There was no evidence of an overall association, but interactions were observed with family history of food allergy for peanut (p-int = 0.03). In infants with a family history of food allergy, grass pollen concentrations were associated with a 1.3-fold increased odds of peanut SPT reactivity at lag 0 (95% CI = 1.0, 2.4) (Table S5).

Age 6 – Grass pollen at lag 0–3 was associated with an up to 1.2-fold increased odds of SPT reactivity to peanut (p = .002), cashew (p = .036), hazelnut (p = .048), almond (p = .047), egg (p = .01), and sesame (p = .048) (Table 2). There was no consistent evidence of interactions with any of the potential effect modifiers. Stratified analyses showed that the associations were not restricted to or

amplified in grass pollen-sensitized children, but slightly higher risks were observed for non-grass pollen-sensitized children (Table S6).

3.3 | Serum food-specific IgE

Age 1 – Grass pollen concentrations were associated with a higher median serum food-specific IgE levels in peanut-allergic infants at lag 1 (Coef = 5.8 [95% CI = 0.3, 12] kU$_A$/L; p = .04) and lag 0–3 (Coef = 1.2 [95% CI = 0.6, 2.0] kU$_A$/L; p = .001) (Table S7), but no evidence was found in egg-allergic infants (data not shown).

3.4 | Food allergy outcomes

Age 1 – There was no evidence of an association between grass pollen concentrations and challenge-confirmed peanut or egg allergy (data not shown).

In peanut-allergic infants (n = 27), grass pollen concentrations at lag 0 (p < 0.001) were non-linearly associated with a lower median reaction threshold to OFC (Figure 1). There was some evidence at lag 3, but the direction of association was inconsistent. No evidence of an association was found in egg-allergic infants.

Age 6 – There was no evidence of an association between grass pollen concentrations and challenge-confirmed peanut allergy (data not shown).

3.5 | Eczema on the day of assessment

Age 1 – There was no evidence of an association between grass pollen concentrations and eczema flares nor was there consistent evidence of interactions with any of the potential effect modifiers. Stratified analyses indicated that the association was not restricted to or amplified in children with reported eczema in the past 12 months (Table S8).

Age 6 – Grass pollen at lag 0–3 was associated with a 1.13-fold increased odds of eczema flares (p = .02) (Table 2). There was no consistent evidence of interactions with any of the potential effect modifiers, and stratified analyses indicated that the association was not restricted to or amplified in children with reported eczema in the past 12 months or grass pollen sensitization (Table S9).

3.6 | Pollen season of testing as an exposure for all outcomes

The results are presented in Tables S10–S12.

Age 1 – There was no evidence of an association between pollen season of testing and all outcomes.

Age 6 – Participants in the grass pollen season had a relatively higher odds of food SPT reactivity compared to participants outside of grass pollen season. However, the association was only significant
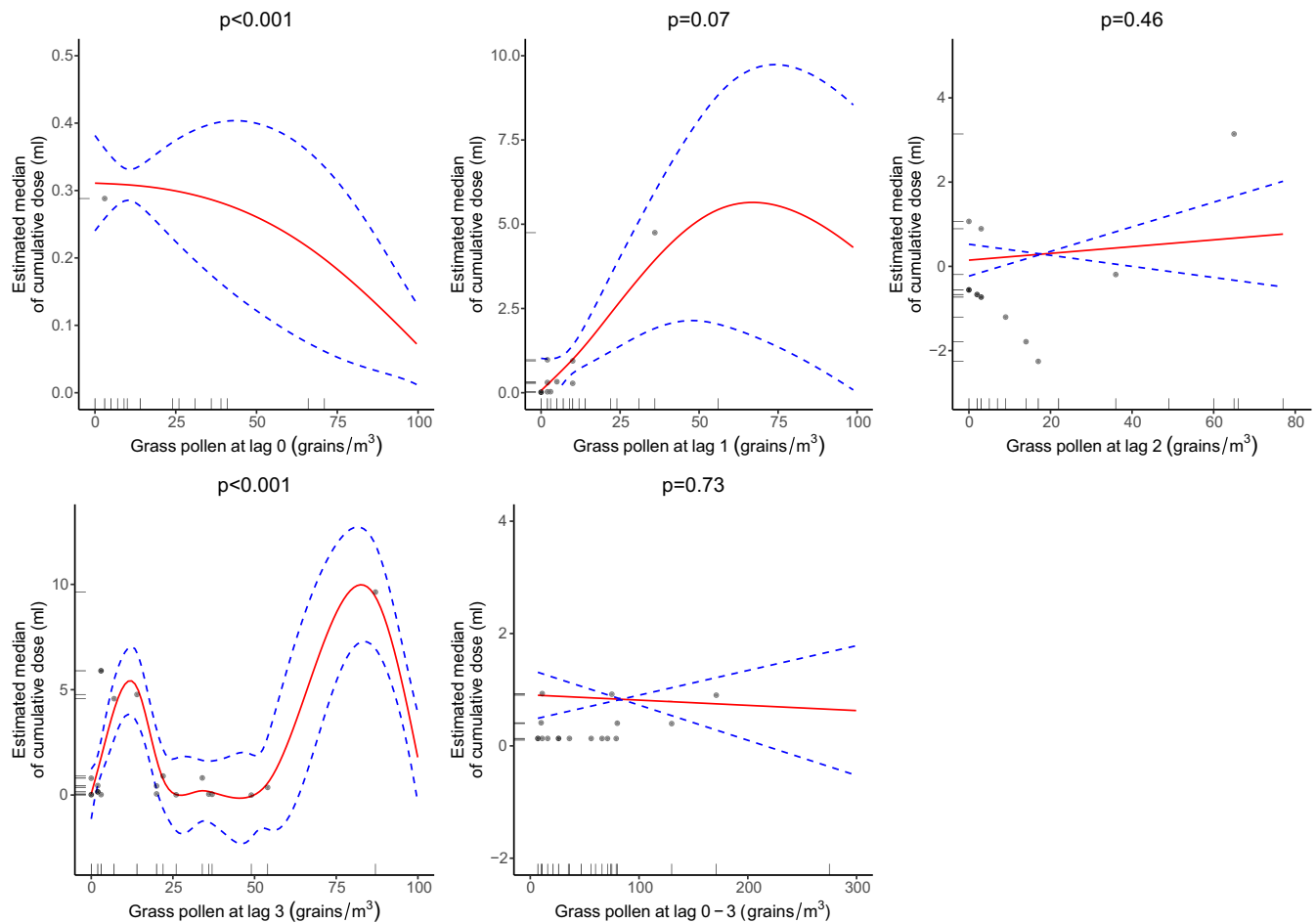
FIGURE 1 The associations between grass pollen concentrations at all lags and the estimated median of cumulative dose (ml) ingested by 1-year-old infants before they had a reaction to OFC with peanut (n = 27). The dotted blue lines represent the 95% confidence intervals, while the black dots represent the observations

for sesame ($p < .001$). No evidence of an association was found with the other outcomes.

4 | DISCUSSION

Overall, we found cumulative exposure to grass pollen over 4 days to be associated with an up to 1.2-fold increased odds of SPT reactivity to all food allergens and eczema flares in 6-year-olds. In 1-year-old infants, an association was only observed with peanut in those with a family history of food allergy. We also found grass pollen concentrations to be associated with a higher serum food-specific IgE levels and lower reaction threshold to OFC in peanut-allergic 1-year-olds. For clinical relevance, we have used the common cut-offs of SPT ≥ 2 mm at age 1 year and SPT ≥ 3 mm at age 6 years to define food SPT reactivity, but this does not imply that short-term grass pollen exposure could lead to the development of new food sensitization in children.

It is well-known that exposure to high ambient grass pollen enhances mast cell activity,[47] so we speculate that this could explain why we observed increased odds of food SPT reactivity or eczema

flares in 6-year-old children. Conversely, the associations between grass pollen concentration and food SPT reactivity were not restricted to or amplified in children with grass pollen sensitization. Similarly, the associations with eczema flares were not limited to children with reported eczema in the past 12 months or grass pollen sensitization. There could be several reasons for these unexpected findings. Firstly, there may have been small sample bias or residual confounding for which we were unable to control for. Plausibly, increased awareness in parents of children with allergic disease may have led to adoption of preventive measures during the pollen season, such as limiting time spent outdoors, utilizing asthma, hay fever, or eczema medications (which may not have been entirely captured at testing), using HEPA filters and/or closing windows to reduce the burden of exposure. Our recently published study of the same cohort also showed no evidence of an association between daily grass pollen concentrations and lung function changes in children sensitized to ryegrass and/or Bermuda grass.[48] Limited data on other grass pollen sensitization may have led to misclassification and subsequently influenced the associations observed in this cohort. Also, lack of data on serum allergen-specific IgE for grass pollen did not allow investigation

into the nuances that may be provided by the quantitative nature of this measure.

Furthermore, we observed the risk of food SPT reactivity at cumulative lag 0 to 3 to be higher in non-grass pollen-sensitized children at age 6 years. Evidence shows that people are more likely to become sensitized to inhalant allergens over time,[49,50] so we may have studied children who were in the process of becoming pollen sensitized. In terms of the potential mechanisms that could trigger pollen-induced immune responses in non-sensitized participants, we hypothesize that persistent grass pollen exposure may lead to a general state of heightened immune responsiveness. Experimental studies have shown that pollen can trigger both the innate and adaptive immune responses in allergic and non-allergic people.[51] For example, pollen grains have non-allergenic properties; they can release pro-inflammatory eicosanoid-like substances such as bioactive lipid mediators, upon contact with respiratory or mucous membranes.[51] These lipid mediators can activate polymorphonuclear leukocytes independent of sensitization status.[52] Studies involving other allergens such as house dust mite, cat and dog, have reported that exposure to high levels of these domestic allergens can significantly increase non-specific airway reactivity and trigger production of antibody responses in people who were not sensitized to them.[53–55] We believe that the impact of pollen on health is broader than just the induction of allergy. To support this, pollen has also been shown to be associated with non-allergic diseases, such as chronic obstructive pulmonary disease, cardiovascular disease, and pneumonia.[56] This is akin to air pollution effects, suggesting that particles of biological origin can have similar health impacts. Nevertheless, more studies are required to replicate our findings.

It is not clear why we found fewer associations in 1-year-olds. We postulate that young infants have lower SPT reactivity, spend less time outdoors with less opportunity for grass pollen exposure, and/or had their eczema well-controlled at the time of observation. Nonetheless, we did observe the main findings on eczema flares and food SPT reactivity to be in line at both follow-ups. Furthermore, we found grass pollen concentrations to be associated with an increased odds of peanut SPT reactivity in infants with a family history of food allergy. This indicates that genetic susceptibility and/or shared household/lifestyle factors may accentuate the effects of grass pollen on the immune system in infants. However, it is important to note that these results were based on a small subgroup, and without pollen sensitization data available in this age group, it was difficult to untangle the relationship.

Moreover, grass pollen concentration was not associated with the presence of challenge-confirmed food allergy, indicating that while persistent grass pollen exposure may trigger an immune response leading to increased odds of food SPT reactivity, it may not necessarily lead to increased odds of food allergy. Alternatively, there could be lack of power to detect associations as some participants with probable food allergy chose not to undergo OFCs. Nonetheless, infants with definite peanut allergy had a lower reaction threshold to OFC and higher serum food-specific IgE levels with increased grass pollen concentrations. This suggests that grass pollen exposure may trigger type-2 immune responses through immune activation and/or peanut and grass pollen cross-reactivity, but only if peanut allergy was already present. However, more research is needed because the associations with the reaction threshold to OFC outcome were inconsistent, and the confidence intervals were wide. This could be due to the small number of observations and/or that the outcome only had a few distinct values, which would negatively affect any model fit. In addition, we only had data for IgE and not T cell subsets or cytokines. No evidence of an association was found between grass pollen concentrations and OFC outcomes in egg-allergic infants, indicating that the reaction to non-cross-reactive allergens or non-plant-derived foods may be milder, but more research is warranted to support this hypothesis.

4.1 | Strengths and limitations

This population-based study is the first to investigate the relationship between short-term grass pollen exposure, food SPT reactivity, food allergy outcomes, and eczema flares. Validated questionnaires and gold standard measurements were utilized, limiting measurement bias. Furthermore, investigation into clinically relevant outcomes and potential effect modifiers was possible due to the range of data collected in this study.

However, some study limitations need to be acknowledged. Our cross-sectional study design does not allow us to infer causal relationships. Although repeated measures before and after high pollen exposure could strengthen the conclusions, it would not completely address the causal question because there are likely to be other environmental differences. Nonetheless, our findings generated novel hypotheses that could be tested in future studies. Additionally, grass pollen was only measured at a single site, and this may not reflect individual-level exposure. Furthermore, data on T-cell subsets, cytokines, and sensitization to peanut allergen components were also not collected, and this limited outcome assessment. We also could not comprehensively investigate the role of grass pollen sensitization or allergy in the observed associations because SPTs to grass pollen were not performed at age 1 year and data on serum allergen-specific IgE levels for grass pollen were not collected at ages 1 and 6 years. Furthermore, SPTs were only performed for ryegrass and Bermuda grass, not other grass pollen species. Moreover, we had limited power to assess important outcomes such as the severity of OFC reactions (e.g. anaphylaxis), reaction thresholds to OFC and food-specific IgE levels in 6-year-olds, severity of SCORAD-based eczema, and mutually exclusive food sensitization groups, for example SPT reactivity to egg but not peanut. Lastly, there were some inconsistencies in the results between pollen season of testing and daily grass pollen concentrations as the exposures, but daily grass pollen concentrations correspond to a more accurate representation of exposure as the magnitude of pollen exposures may vary between the years and therefore, may not be directly comparable to pollen season of testing.[3]

In conclusion, persistent grass pollen exposure may trigger dysregulation of immune responses leading to increased odds of food SPT reactivity and eczema flares in children, but the impact on food may be greater if peanut allergy is already present. These findings suggest the need for future research to better understand the physiological mechanisms that take place in the days following high grass pollen exposure. If these findings are confirmed in other studies, additional caution for peanut avoidance may be necessary for peanut-allergic children during the grass pollen season to reduce the burden of this exposure. Investigations involving SPT, OFC, food-specific IgE levels, and eczema flares in children may also need to consider pollen concentrations to minimize residual confounding and/or effect modification on observed associations.

AUTHOR CONTRIBUTIONS

Nur Sabrina Idrose: Formal analysis (lead); investigation (lead); writing – original draft (lead); writing – review and editing (lead). **Caroline J Lodge:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Rachel Louise Peters:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Jo Douglass:** Supervision (equal); writing – review and editing (equal). **Jennifer Julia Koplin:** Data curation (equal); funding acquisition (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Adrian J Lowe:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Kirsten Perrett:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Mimi Tang:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Ed Newbigin:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Michael Abramson:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Bircan Erbas:** Data curation (equal); funding acquisition (equal); resources (equal); writing – review and editing (equal). **Don Vicendese:** Conceptualization (equal); formal analysis (equal); investigation (equal); supervision (equal); writing – review and editing (equal). **Shyamali C Dharmage:** Conceptualization (lead); data curation (equal); funding acquisition (equal); resources (equal); supervision (lead); writing – review and editing (equal).

CONFLICTS OF INTEREST

MLKT has received speaker fees from Nestle Health Science, is a consultant to Bayer Pharmaceuticals, and has received research funding from NHMRC, Bayer Pharmaceuticals, Abbot Nutrition, and Prota Therapeutics. JAD has received honoraria for educational presentations from Astra-Zeneca, GSK, Novartis, Alphapharm, Shire, and CSL. She has served on advisory boards: Sanofi-Aventis, Novartis, GSK, Astra-Zeneca, Shire, Immunosis, and CSL. She has also undertaken contracted or investigator-initiated research on behalf of GSK, Novartis, Immunosis, Astra-Zeneca, Sanofi-Aventis, Grifols, CSL, BioCryst & Equilium. She has a personal superannuation shareholding in CSL. MJA holds investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. SCD, AJL & CJL have received an investigator-initiated grant from GSK for unrelated work. Other authors have no conflicts to disclose.

PEER REVIEW

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SUPPORTING INFORMATION

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