

Children With Food Allergy Are at Risk of Lower Lung Function on High-Pollen Days



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What is already known about the topic? Grass pollen exposure is a risk factor for childhood asthma hospital attendances, but its influence on lung function, especially among those with other allergic conditions, is almost nonexistent.

What does this article add to our knowledge? This is the first study to show that increasing ambient grass pollen concentration was associated with obstructive lung function deficits in children with food allergy and eczema.

How does this study impact current management guidelines? Treatment and management guidelines in relation to high-grass pollen concentrations should incorporate children with allergic disease in general rather than those with asthma or hay fever only.

BACKGROUND: Grass pollen exposure is a risk factor for childhood asthma hospital attendances. However, its short-term influence on lung function, especially among those with other allergic conditions, has been less well-studied.

OBJECTIVE: To investigate this association in a population-based sample of children.

METHODS: Within the HealthNuts cohort, 641 children performed spirometry during the grass pollen season. Grass pollen concentration was considered on the day of testing (lag 0), up to 3 days before (lag 1–lag 3), and cumulatively (lag 0–3).

We used linear regression to assess the relevant associations and examined potential interactions with current asthma, hay fever or eczema, and food allergy.

RESULTS: Associations were observed only in children with allergic disease (P value for interaction ≤ 0.1). In children with food allergy, grass pollen concentration was associated with a lower ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) and lower mid-forced expiratory flows ($FEF_{25\%–75\%}$) at all lags (eg, at lag 2, FEV_1/FVC z-score = -0.50 [95% CI -0.80 to -0.20] and $FEF_{25\%–75\%}$ z-score = -0.40).

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Conflicts of interest: In the past 5 years, J. A. Douglass has received honoraria for educational presentations from Astra-Zeneca, GlaxoSmithKline (GSK), Novartis, Shire, and CSL; has served on advisory boards at Sanofi-Aventis, Novartis, GSK, Astra-Zeneca, Shire, Immunosis, Equilium, and CSL; has undertaken contracted or investigator-initiated research on behalf of GSK, Novartis, Immunosis, Astra-Zeneca, Sanofi-Aventis, Grifols, CSL, BioCryst, and Equilium; and has a personal superannuation shareholding in CSL. J. L. Perret, A. J. Lowe, C. J. Lodge, and S. C. Dharmage received an investigator-initiated grant from GSK for unrelated work. A. J. Lowe has received in-kind contributions of study intervention (EpiCeram) from Primus Pharmaceuticals for unrelated research. M. L. K. Tang is an employee of Prota Therapeutics and has received research funding from Prota Therapeutics and NHMRC for unrelated work; has also received consultant fees from Pfizer; has royalties from Wilkinson Publishing; and is an inventor on patents owned by the Murdoch Children's Research Institute. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

BDR-Bronchodilator responsiveness

FEF_{25%–75%}-Mid-forced expiratory flow

FEV₁-Forced expiratory volume in 1 second

FVC-Forced vital capacity

OFC-Oral food challenge

SPTs-Skin prick test

[−0.60 to −0.04] per 20 grains/m³ pollen increase), and increased bronchodilator responsiveness (BDR) at lag 2 and lag 3 (eg, at lag 2, BDR = (31 [95% CI −0.005 to 62] mL). In children with current asthma, increasing grass pollen concentration was associated with lower FEF_{25%–75%} and increased BDR, whereas children with current hay fever or eczema had increased BDR only.

CONCLUSIONS: A proactive approach needs to be enforced to manage susceptible children, especially those with food allergy, before high-grass pollen days. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2144-53)

Key words: Atopy; Eczema; Food allergy; Grass pollen; Lung function; Pediatrics

INTRODUCTION

Asthma is among the top 10 causes of disability-adjusted life years in children aged 5 to 14 years.^{1,2} Ambient pollen is an important risk factor of childhood asthma hospital attendances.^{3–6} Although this association is known especially in those with diagnosed asthma, it may represent only the tip of the iceberg. The community's risk of such exacerbations has not yet been established (eg, those with no known allergic respiratory disease or those with eczema or food allergy). This is important to assess because high-ambient pollen exposure together with convergence line weather events can lead to catastrophic community-wide thunderstorm asthma events, such as the recent one in Melbourne, Australia, where people with no known overt asthma also proved susceptible.^{7–10}

Lung function can be a good marker of asthma exacerbation risk because exposure to ambient pollen may cause mild but acute measurable changes. However, the relationship between ambient pollen exposure and lung function is underinvestigated, especially within the community as evidenced by our own recent systematic review.¹¹ Lag effects of ambient pollen exposure on lung function using population-based studies and identifying those who are most susceptible to pollen exposure were highlighted as gaps that are yet to be addressed.¹¹ Understanding these lag relationships could help inform the development of a management or preventive treatment guideline for high-risk groups during likely high-pollen periods.

Findings of population-based studies investigating daily lung function are limited because most have used pollen season as a proxy marker of exposure.¹¹ Few have investigated exposure using daily average pollen concentrations but only some have assessed lag effects and potential effect modifiers to identify high-risk groups.¹¹ Previously, we found that exposure to increasing ambient grass pollen concentration 2 to 3 days prior (lag 2 and lag 3) was associated with lower lung function with an

obstructive pattern (ie, lower mid-forced expiratory flow [FEF_{25%–75%}] and lower ratio of forced expiratory volume in 1 second to forced vital capacity [FEV₁/FVC ratio]) in those 18 years or older but not in those younger.¹² This suggests that the effects of pollen may be limited to adults. However, a population-based study in 8-year-old children reported exposure to increasing tree pollen concentration up to 3 days prior was associated with reduced FEV₁.¹³ Another study showed increased ambient grass pollen concentration 1 day prior (lag 1) was associated with lower FEV₁ and FVC in 8 year olds, with stronger associations observed in pollen sensitized individuals.¹⁴ Interestingly, none of these studies examined effect modification by food allergy or eczema.

Children with food allergies or eczema typically have an increased risk of asthma and lower lung function.^{15–19} We hypothesize that, at least for some of these children, ambient pollen may especially cause airway obstruction owing to increased type 2 immune activation in the airways and/or allergen cross-reactivity.¹¹ Ambient grass pollen can increase the risk of asthma hospitalizations in food-sensitized children and asthma itself is a risk factor for fatal food anaphylaxis.^{20,21} Besides that, children with eczema experienced increased intensity of itchiness and extent of skin lesions on high-grass pollen days.²² Hence, investigation into eczema and food allergy as potential effect modifiers is warranted to tease out the synergistic effects of grass pollen on lung function.

To address these gaps, we investigated the associations between ambient grass pollen concentration and lung function in 6-year-old children within the HealthNuts cohort, a population-based study aimed to investigate the burden of food allergy in children residing in Melbourne, Australia. In this city, temperate grass pollen, specifically perennial ryegrass (*Lolium perenne*), is abundant in spring and summer,²³ which provides an ideal opportunity to investigate such associations. Owing to mounting evidence on allergic diseases and family history being modifiers of exposure-outcome associations,^{12,24,25} our secondary aims were to assess effect modification by these factors, which included eczema, food allergy, and family history of allergic disease.

METHODS

Study sample

Our study sample consisted of children who participated in the 6-year follow-up of HealthNuts. Because grass pollen data were only available during the Melbourne grass pollen season (October to December), the study sample was restricted to those who performed spirometry during this period. Nonetheless, approximately 90% of the annual pollen load occurs during this time and the levels are low or clinically irrelevant outside this period.^{26,27}

The recruitment process, study methods, and participation of the HealthNuts cohort have been described elsewhere.^{28,29} Briefly, 5,276 infants were recruited at local government-run immunization clinics across Melbourne, Australia, at 1 year of age. At the 4-year follow-up, a subsample of children underwent clinical testing, but this did not include spirometry.²⁸ At the next follow-up (2013–2016), all parents were contacted to book a clinic visit for their child once they turned 6, but the appointment date depended on the convenience of the parent and the availability of clinic appointments. Approximately 60% of children underwent clinical examination, which included spirometry, skin prick tests (SPT) to various food and pollen allergens, and eczema assessment. In order to

be eligible for the spirometry testing, participants had to (1) be well, (2) not have taken asthma medication within 24 hours of appointment, and (3) not have taken antihistamine or cough medication within 72 hours of appointment. Those who did not meet these criteria were asked to reschedule. In addition, parents also completed a questionnaire on behalf of their children, which included validated questions on asthma, hay fever, and eczema.³⁰

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). The parents provided informed consent on behalf of their children.

Lung function measurements and definitions

We measured pre- and post-bronchodilator (ie, 10 min after administering 4 puffs of 100 µg of salbutamol) spirometry based on the American Thoracic Society and European Respiratory Society guidelines³¹ using the EasyOne Spirometer (ndd Medical Technologies Inc., Andover, Mass). Participants were not asked to abstain from using short-acting bronchodilators before the spirometry, but their parents recorded recent medication use in a questionnaire.

The following pre- and post-bronchodilator spirometry measures were investigated and reported as z-scores (in SD units) using the Global Lung Function Initiative reference values³²: FEV₁; FVC; FEV₁/FVC ratio; and FEF_{25%–75%}. The z-scores represent the deviations from the height-, age-, sex- and ethnicity-adjusted population mean predicted value.

We also investigated bronchodilator responsiveness (BDR) for FEV₁ and FVC, separately, as a continuous and dichotomous variable. The definitions were

- Absolute BDR (mL): the absolute change from pre- to post-bronchodilator values.³³
- Absolute BDR (%): the percent change from pre- to post-bronchodilator values relative to the pre-bronchodilator values.³³
- Positive BDR: at least 12% and 200 mL increase from pre- to post-bronchodilator values.³⁴

Potential effect modifiers

The effect modifiers considered were current asthma, hay fever, eczema, food sensitization or allergy status, grass pollen sensitization, and family history of allergic disease. The definitions were

- Current asthma: parent-reported doctor-diagnosed asthma plus either wheeze or asthma medication use in the past 12 months.
- Current hay fever: parent-reported sneezing, runny, or blocked nose plus itchy eyes without a cold in the past 12 months.
- Current eczema: parent-reported itchy rash that had affected typical locations related to eczema (eg, knees, folds of elbows) in the past 12 months, or a non-0 SCORing Atopic Dermatitis (SCORAD)³⁵ total score (based on area affected, intensity, and subjective symptoms) on the day of testing.
- Food-sensitized tolerant: positive SPT of 3 mm or greater without meeting the criteria for definite food allergy, to either peanut, cashew, hazelnut, almond, egg, sesame, milk, wheat, or soy. The procedure involved placing a single drop of the allergen extract (ALK-Abelló, Spain, Hollister-Stier, and Stallergènes, France) on the child's back and then pricking with a lancet (Stallergènes, France).

- Food-allergic: having any of the following to either 1 of the food allergens listed previously, or pecan, walnut, pistachio, or macadamia (these were not in the predetermined food panel for SPT assessment): (1) a positive oral food challenge (OFC) (at least 3 noncontact hives lasting more than 5 minutes, angioedema, persistent vomiting, or anaphylaxis within 2 h of the last dose) plus a SPT of 3 mm or greater at age 6 years, or (2) a strong history of a reaction (consistent with OFC stopping criteria) in the past 12 months plus a SPT of 3 mm or greater at age 6 years, or (3) a positive OFC at age 4 years plus a SPT greater than 8 mm at age 6 years. The method of OFC administration is detailed in a previous paper.³⁶

We investigated effect modification by any food sensitization and allergy status, which consisted of not food-sensitized or -allergic, food-sensitized tolerant, and food-allergic. For specific foods, we only had sufficient power to investigate peanut and cashew:

- Grass pollen sensitization: positive SPT of 3 mm or greater to either rye grass or Bermuda grass.
- Family history of allergic disease: parents or siblings with a history of asthma, hay fever, eczema, or food allergy. This was investigated as a binary (yes/no) and an ordinal variable (none/only 1/2 or more allergic family members).

Environmental data collection

Daily average grass pollen concentrations (expressed in grains/m³) during the Melbourne grass pollen season (October to December in 2013–2016) were collected by the School of BioSciences at the University of Melbourne. Airborne grass pollen was collected as described³⁷ using a single Burkard volumetric spore trap located 28 m above ground. Daily maximum temperature (°C) and relative humidity (%) data were obtained from the Bureau of Meteorology.

Statistical analysis

We investigated ambient grass pollen concentration on the day of clinical testing (lag 0), lagged 1, 2, and 3 days prior and cumulatively (sum of lag 0–3 days) for each participant. The associations between ambient grass pollen concentration and lung function measures except positive BDR were assessed using linear regression models. We checked linear regression assumptions using residual plots and histograms (Figures E1–E4; available in this article's Online Repository at www.jaci-inpractice.org). For 2 of the outcomes (Figures E1 and E3), the model residuals were skewed to the left, but robust standard error and bootstrapping showed little change in standard errors (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). In addition, likelihood ratio tests comparing generalized additive nonlinear and linear models³⁸ indicated that the extra degrees of freedom for the nonlinear fits were not justified. Quantile regression models were also used to determine whether solely a mean change was an adequate summary of association. The model fits for the 10th, 50th, and 90th quantiles were largely parallel across the outcome distributions (Figure E5 as an example; available in this article's Online Repository at www.jaci-inpractice.org). Owing to these reasons, linear regression was used in the final models because it was deemed a reliable summary of the data. The associations with positive BDR were assessed using logistic regression models.

All models were adjusted for temperature and humidity as *a priori* confounders.^{39–42} Because BDR outcomes were not presented as z-scores, the models were also adjusted for age, sex, ethnicity, and height. Potential interactions were investigated using likelihood ratio

tests. The coefficients and odds ratio can be interpreted as the effect size per interquartile range^{4,13} (ie, 20 grass pollen grains/m³) increase. Trends of results were interpreted, and strata-specific associations were reported in which *P* value for interactions (*P* int) were less than 0.1. All statistical analyses were conducted using either Stata IC 16.1 (College Station, TX: StataCorp LLC) for the linear and logistic regression models, or R⁴³ for the general additive⁴⁴ and quantile regression models.⁴⁵

Sensitivity analyses

Because the study sample was restricted to only those tested during the grass pollen seasons, the sample size was relatively small (*n* = 641). The strict definition of acceptable spirometry (grades A–C) was also based on 2 or more acceptable tests with repeatability within 150 mL, or 10% of highest value, whichever is greater.⁴⁶ Thus, if participants with good technique but poor reproducibility (ie, with only 1 acceptable blow) had been excluded, we would have lost 74 individuals with good representation of lung function. Therefore, our main analysis included all lung function observations regardless of the quality grades (grades A–F⁴⁶). Nonetheless, a sensitivity analysis was conducted by restricting the analysis to lung function measures that were of conventionally acceptable qualities (*n* = 567).

Another sensitivity analysis was conducted by excluding those who still attended the clinic appointment despite using either 1 of the following: (1) inhaler, puffer, or other for-breathing medication up to 24 hours prior, or (2) antihistamines or cough medication up to 72 hours prior. This was to ensure that our results were consistent with the inclusion criteria.

Pollen season of testing as an exposure

To utilize the entire cohort who performed spirometry (*n* = 3,082), we also investigated the associations between pollen season of testing and lung function measures using the same statistical methods as the main analysis. The coefficients and odds ratios can be interpreted as the effect size inside the pollen season compared with outside the pollen season.

RESULTS

Sample and environmental characteristics

Of the 641 participants who performed spirometry during the 2013 to 2016 grass pollen seasons, 53% were males. Most participants were tested in 2014 and 2015 (Figure E6; available in this article's Online Repository at www.jaci-inpractice.org). The median (range) age was 6.3 years (5.8–8.7 years). Compared with participants tested outside of the grass pollen season, the study sample had a higher proportion of participants with current hay fever and pollen sensitization (Table 1).

Four grass pollen seasons (2013–2016) were captured (Figure E6). Of the 368 in-season days included, 69% were defined as low (<20 grains/m³), 20% as moderate (20–49 grains/m³), and 11% as high (≥50 grains/m³).⁴⁷ The summary statistics for grass pollen levels, temperature, and humidity are detailed in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

Main and effect modification analysis

Although there was no evidence of an overall association between grass pollen concentration and pre- or post-bronchodilator lung function, multiple interactions were observed with allergic diseases for pre-bronchodilator lung function. Specifically, grass

pollen concentration was associated with obstructive lung function deficits only in children with food allergy, current asthma, hay fever, or eczema. The findings are summarized visually in Figures 1 and 2. The results for absolute BDR (mL) and BDR (%) were consistent for both FEV₁ and FVC. Hence, here we only present the results for absolute BDR (mL) for FEV₁.

Any food sensitization and allergy status. There was evidence of an interaction for FEV₁/FVC ratio (.002 < *P* int < .04), FEF_{25%–75%} (.003 < *P* int < .07) and absolute BDR (.02 < *P* int < .1) but not for FEV₁ or FVC alone. Increasing ambient grass pollen concentration was associated with a lower FEV₁/FVC ratio and FEF_{25%–75%} at every lag and increased BDR at lag 2 and lag 3 in food-allergic participants but not in those who were food-sensitized tolerant, or not food-sensitized or -allergic (Figure 3 and Table E3; available in this article's Online Repository at www.jaci-inpractice.org). The results for FEV₁ and FVC alone are presented in the Online Repository (Table E3). Similar findings were observed for peanut and cashew (Table E4; available in this article's Online Repository at www.jaci-inpractice.org).

Current asthma. There was evidence of an interaction for absolute BDR (*P* int = .04) and FEF_{25%–75%} (*P* int = .08). Increasing ambient grass pollen concentration was modestly associated with reduced FEF_{25%–75%} (Coefficient [95% CI] –0.2 [–0.4 to 0.05]) at lag 1 and increased BDR (Coefficient [95% CI] 26 [–2.0 to 54] mL) at lag 2 in participants with current asthma but not in those without.

Current hay fever or eczema. Similarly, there was evidence of an interaction for absolute BDR (*P* int = .09). Increasing ambient grass pollen concentration at lag 2 was modestly associated with increased BDR in participants with current hay fever (Coefficient [95% CI] 24 [–0.4 to 50] mL) or eczema (Coefficient [95% CI] 18 [–8.0 to 44] mL) but not in those without.

Grass pollen sensitization or family history of allergic disease. No evidence of an interaction was found.

Sensitivity analysis

We did not find any substantive differences when restricting observations to acceptable spirometry (*n* = 567) or when excluding those who had used recently used antihistamines or asthma or cough medications (*n* = 36) prior to spirometry (Tables E5 and E6; available in this article's Online Repository at www.jaci-inpractice.org).

Pollen season of testing as an exposure

There was no evidence for an association between pollen season of testing *per se* and lung function, either overall or in stratified groups (data not shown).

DISCUSSION

To the best of our knowledge, this is the first study to investigate effect modification by eczema, food sensitization, and food allergy for the association between short-term grass pollen exposure and lung function abnormalities in children. We observed the greatest and most consistent increase in risk of obstructive lung function deficits in children with food allergy. In children with this condition, increasing ambient grass pollen

TABLE I. Characteristics of the HealthNuts participants at the 6-y follow-up

Variables	Entire HealthNuts cohort who performed spirometry	HealthNuts participants who performed spirometry outside the grass pollen season (January–September)	Present study sample	χ^2 test
			HealthNuts participants who performed spirometry in the grass pollen season (October–December)	Those who performed spirometry in vs out of grass pollen season (<i>P</i> value)
n (total)	3,082	2,441	641	-
Median age, y (range)	6.4 (5.0–9.6)	6.4 (5.0–9.6)	6.3 (5.8–8.7)	-
Mean height $\pm$ SD (cm)	119 $\pm$ 5.6	119 $\pm$ 5.6	119 $\pm$ 5.6	-
Male sex, n (%)	1,597 (51.8)	1,256 (51.5)	341 (53.2)	.43
Current eczema, n (%) [*]	665 (21.6)	520 (21.3)	145 (22.6)	.63
Current hay fever, n (%) [†]	442 (14.3)	332 (13.6)	110 (17.2)	.02
Family history of allergic disease, n (%)	2,216 (71.9)	1,749 (71.7)	467 (72.9)	.60
Grass pollen sensitization (SPT $\geq$ 3 mm), n (%) [‡]	323 (10.5)	221 (9.05)	102 (15.9)	<.001
Current asthma, n (%) [§]				
Total	414 (13.4)	320 (13.1)	94 (14.7)	.36
Used inhaled corticosteroids	70 of 414 (16.9)	51 of 320 (15.9)	19 of 94 (20.2)	.33
Any food sensitization and allergy status, n (%)				
Food-sensitized tolerant	125 (4.06)	96 (3.9)	29 (4.5)	.13
Food-allergic [¶]	217 (7.0)	160 (6.6)	57 (8.9)	
SEIFA quintiles, n (%)				
Least disadvantaged	579 (18.8)	476 (19.5)	103 (16.1)	.20
2	609 (19.8)	485 (19.9)	124 (19.3)	
3	673 (21.8)	516 (21.1)	157 (24.5)	
4	603 (19.6)	477 (19.5)	126 (19.7)	
Most disadvantaged	599 (19.4)	472 (19.3)	127 (19.8)	

SCORAD, SCORing Atopic Dermatitis; SEIFA, Socioeconomic Indexes for Areas measure.

^{*}Current eczema = parent-reported itchy rash that had affected typical locations related to eczema such as the knees and folds of elbows in the past 12 mo or a non-0 SCORAD score.[†]Current hay fever = sneezing/runny/blocked nose plus itchy eyes without cold/flu in the past 12 mo.[‡]Sensitization to either rye grass or Bermuda grass.[§]Current asthma = parent-reported doctor-diagnosed asthma plus either wheeze/asthma medication use in the past 12 mo.^{||}Food-sensitized tolerant = food-sensitized without meeting the criteria for definite food allergy.[¶]Food allergic = any of the following: (1) a positive OFC plus a SPT $\geq$ 3 mm at age 6 y, or (2) history of a reaction in the past 12 mo plus a SPT $\geq$ 3 mm at age 6 y, or (3) a positive OFC at age 4 y plus a SPT $>$ 8 mm at age 6 y.

Food-allergic • *FEV₁/FVC ratio = −0.5 (−0.8 to −0.2) at every lag • *FEF_{25–75%} = −0.4 (−0.6 to −0.04) at every lag • BDR = 31 (−0.005 to 62) mL at lag 2; 36 (2.2 to 72) mL at lag 3
Current asthma • FEF_{25–75%} = −0.2 (−0.4 to 0.05) at lag 1 • BDR = 26 (−2.0 to 54) mL at lag 2
Current hay fever • BDR = 24 (−0.4 to 50) mL at lag 2
Current eczema • BDR = 18 (−8.0 to 44) mL at lag 2

FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity; FEF_{25–75%} = mid-forced expiratory flow, BDR = bronchodilator responsiveness

Results were interpreted as the effect size per increase in IQR (20 grains/m³) in grass pollen. All lung function measures except BDR were reported as z-scores.

FIGURE 1. Changes in lung function measures as ambient grass pollen concentration increased in stratified groups (where there was evidence of interaction). Results were interpreted as the effect size per increase in interquartile range (20 grains/m³) in grass pollen. All lung function measures except BDR were reported as z-scores. *Effect size was shown for lag 1 but the effect sizes at other lags were similar (see Table E3).

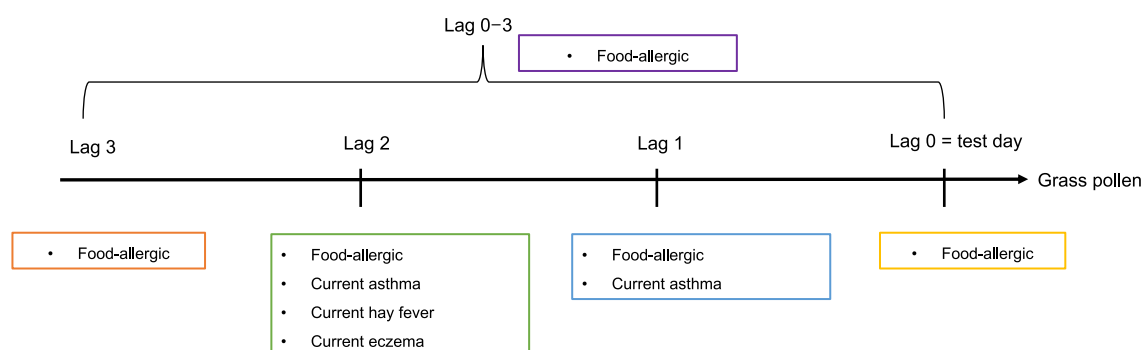


FIGURE 2. The timeline for the associations between grass pollen at different lags and lung function measures in stratified groups (where there was evidence of interaction).

concentration was associated with increased BDR and airway obstruction, including large and medium-small airways, as reflected by the FEV₁/FVC ratio and FEF_{25%–75%} respectively.

Sherenian et al¹⁷ found 10-year-old children with asthma and 2 or more food allergies had lower FEF_{25%–75%} but normal FEV₁, FVC, and FEV₁/FVC ratio, implying that they were at risk of medium-small airway obstruction only. Our findings indicate that high-grass pollen exposure may worsen global airway disease in children with food allergy because there was evidence of both large and medium-small airway involvement. This could be from a priming effect of grass pollen, a hypothesis that has been underlined in previous studies.^{9,11,13,48} We found no evidence of an association between grass pollen concentration and lung function in food-sensitized tolerant children (n = 27). This could be due to limited power, but some studies have reported that, while food allergy was associated with asthma, food sensitization only was not.^{15,49,50}

We also found the association between grass pollen concentration and lung function to be modified by current asthma. Children with current asthma had modestly lower FEF_{25%–75%} and higher absolute BDR with increased ambient grass pollen concentration, but not in those without. Our findings support previous studies that reported children with active asthma experienced elevated respiratory symptoms even when pollen levels were as low as 2 grains/m³,⁵¹ and that allergen inhalation can trigger increased airway responsiveness in children with a preexisting airway inflammatory condition.⁵² These findings were also in line with our previous investigation that showed people with current asthma had increased absolute BDR with increased ambient grass pollen concentrations.¹² Comparably, children with current eczema or hay fever exhibited more modest increases in absolute BDR with increased ambient grass pollen concentration. Given that eczema is a risk factor for aeroallergen sensitization⁵³ and asthma,¹⁹ our findings were not unexpected.

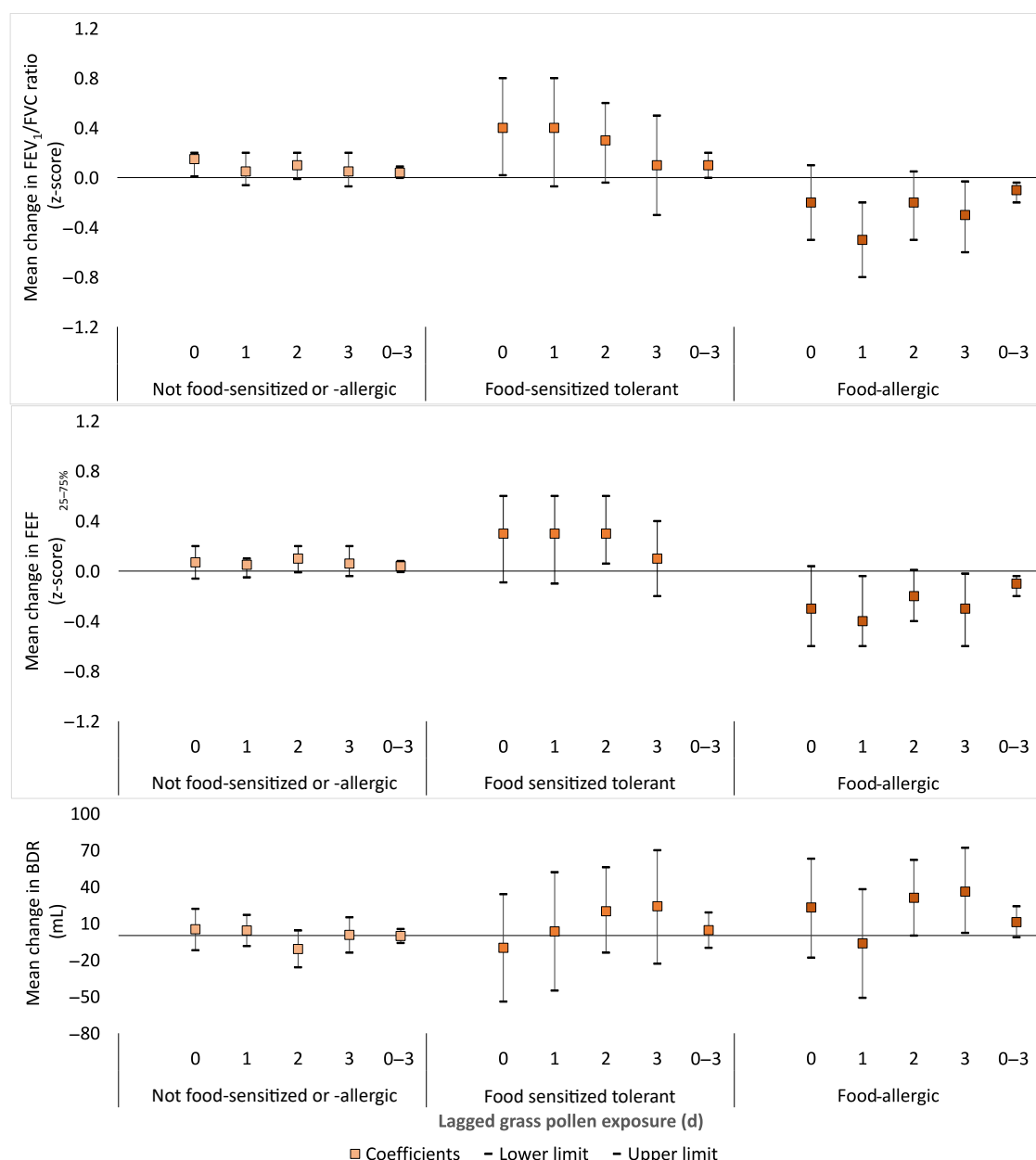


FIGURE 3. Coefficients for the change in means, at different lags, owing to the associations between ambient grass pollen concentration and some pre-bronchodilator lung function measures, stratified by any food sensitization and food allergy status (not food-sensitized or -allergic = 526, food-sensitized tolerant = 29, food-allergic = 57).

Moreover, we observed most associations at lag day 2, indicating the ambient grass pollen may only affect the lungs approximately 48 hours after exposure. This is consistent with our earlier findings and known pathophysiology of induced allergic airway inflammation, in which peak immune response to pollen, such as eosinophils recruitment, has shown to occur within 3 days of exposure.^{12,54} Better understanding of this relationship can inform the timing and targeting of preventive therapy during the pollen season.

Surprisingly, there was no evidence of interaction between grass pollen concentrations and grass pollen sensitization on lung function. Only 16% of participants were grass pollen-sensitized

so this finding could be explained by insufficient power. Furthermore, we did not collect data on serum pollen specific immunoglobulin E levels so we were unable to investigate the variation that could have been provided by this measure. Moreover, although there was evidence of interaction for current asthma, hay fever, and eczema, the differences in the associations across strata were modest. Children with these conditions may have poorer lung function at baseline so the changes may not be as significant and/or they may have their conditions deliberately well controlled (eg, using by asthma-preventive medications and/or by limiting time outdoors) during the grass pollen season. We had information on asthma-preventive medication use but it was

for the last 12 months, so we were unable to restrict to the grass pollen season only, and information on time spent outdoors was not collected.

In addition, no evidence of an association was found when investigating grass pollen season of testing as an exposure. Because pollen concentrations vary each year owing to different climatic conditions, daily average pollen concentration is a better marker of exposure and is not directly comparable with pollen season of testing.¹¹ In contrast, pollen season could be a proxy marker for ultraviolet exposure, which has been associated with increased vitamin D levels.⁵⁵ Vitamin D is protective of food allergy,⁵⁶ and so the effects of pollen season may be negated by this. Unfortunately, we did not have vitamin D measurements to test this hypothesis.

In terms of the clinical importance of our findings, 0.5 SD has been suggested to be physiologically relevant,⁵⁷ and our point estimates were approaching this threshold, especially for children with food allergy. Furthermore, small changes in lung function at an individual level do not necessarily mean that it is not clinically important at a population level. For example, a 0.5 SD shift to the population mean would result in approximately 1.6% being below the lower limit of normal. In other words, the percentage of children below the critical lung function levels will increase by 1.6% at a population level. In addition, although we did not find any evidence of an association with positive BDR, it has been reported that there is poor sensitivity associated with the 12% cutoff in children.⁵⁸

Strengths and limitations

The HealthNuts study used a population-based sampling frame. Although we had to restrict the study sample to those tested during the grass pollen season, most of the sociodemographic characteristics were similar to those tested outside the grass pollen season, and therefore, selection bias was likely to be minimal. In addition, we essentially used gold standard measures to determine the outcomes and potential modifiers, which minimized measurement bias.

Although grass pollen allergen content varies between different grass species,^{59,60} grass pollen has been used as a single-exposure variable because it cannot be identified below the family level. A main limitation of the study is that grass pollen concentration may not be representative of individual-level exposure because data were collected from a single trap. Nevertheless, this trap is arguably an acceptable proxy of exposure for most, if not all, participants because pollen concentrations from this trap are associated with allergic rhinitis symptoms for residents living within 50 km from it⁶¹ and a 50-km radius encompasses nearly all of the Melbourne population.⁶² In addition, most participants were tested at a hospital located within a short distance of the trap. Moreover, we had insufficient power to investigate specific food allergies other than peanut and cashew, and multiple interactions among allergic diseases that usually coexist within an individual.⁶³ In addition, 95.6% of participants underwent spirometry when grass pollen concentration was low-moderate, so this could have reduced the power to observe associations. Compared with participants tested outside of the grass pollen season, those tested during the pollen season were more likely to have current hay fever symptoms and pollen sensitization. This is not surprising because symptoms are likely to manifest more recently during the pollen season and this could have affected recall. The priming effect also suggests that there could be

increased sensitivity to allergens upon repeated exposure,⁶⁴ which would explain why participants tend to demonstrate grass pollen sensitization more during the pollen season. Because participants were contacted to attend the follow-up close to their sixth birthday, another explanation could be that those tested in the pollen season were more likely to also be born during the pollen season and had a higher risk of developing allergic disease in childhood.⁶⁵⁻⁶⁷ Given the study design, we cannot exclude the possibility of selection bias. Lastly, there is the possibility of type 1 error given the number of hypotheses tested, but unlikely as our findings were biologically plausible, and the associations were quite consistent across groups. We have not just focused on *P* values when interpreting our findings. The trends of effect sizes and confidence intervals have all been important when assessing the associations.⁶⁸ In addition, investigating lagged effects of environmental risk factors such as pollen, fungi, and air pollutants is biologically plausible and common in studies with *a priori* defined hypotheses.^{6,69,70}

In conclusion, we provided evidence that increasing short-term ambient grass pollen exposure was associated with reversible obstructive lung function deficits in children with allergic disease, with the greatest risk of symptomatic exacerbation in food allergic children. If these findings are confirmed in further research, we need to incorporate this knowledge into clinical guidelines so that children with food allergy or eczema are also proactively managed for asthma activity during, and preferably before, high-grass pollen periods. In the interim, pollen communication outreach, which is often a cost-effective tool, could include all families with children with any allergic disease, rather than only those with asthma or hay fever. Future investigations should also consider the impact of other pollen types on lung health in children with any allergic disease.

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ONLINE REPOSITORY

EM by food sensitisation and allergy

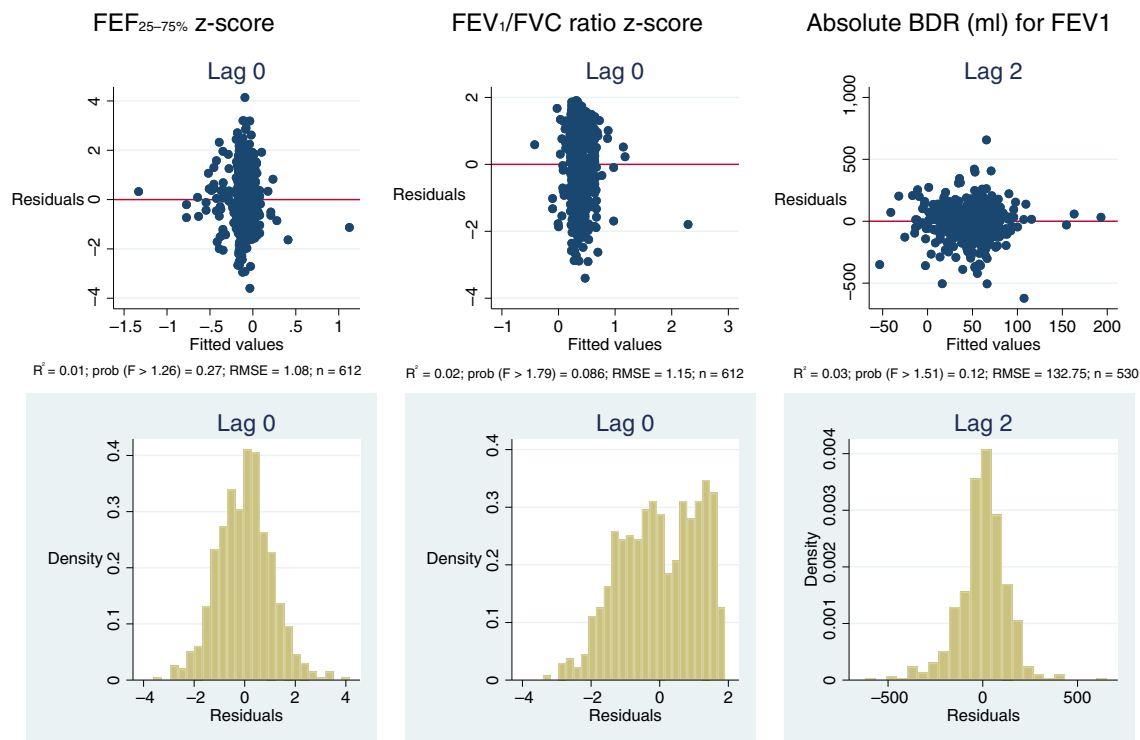


FIGURE E1. Residual plots and histograms for the linear regression model assessing effect modification by food sensitization and allergy for the associations between grass pollen and FEF_{25%–75%} (lag 0), FEV₁/FVC ratio (lag 0), and absolute BDR (lag 2).

EM by current asthma

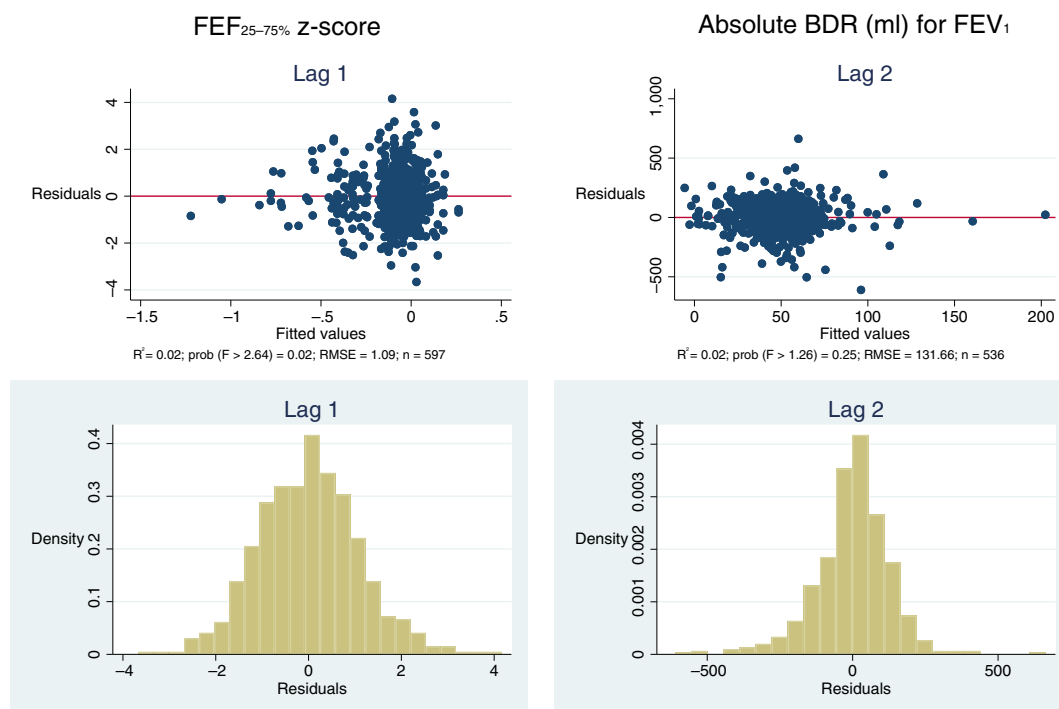


FIGURE E2. Residual plots and histograms for the linear regression model assessing effect modification by current asthma for the associations between grass pollen and FEF_{25%–75%} (lag 1) and absolute BDR (lag 2).

EM by current hayfever

Absolute BDR (mL) for FEV₁

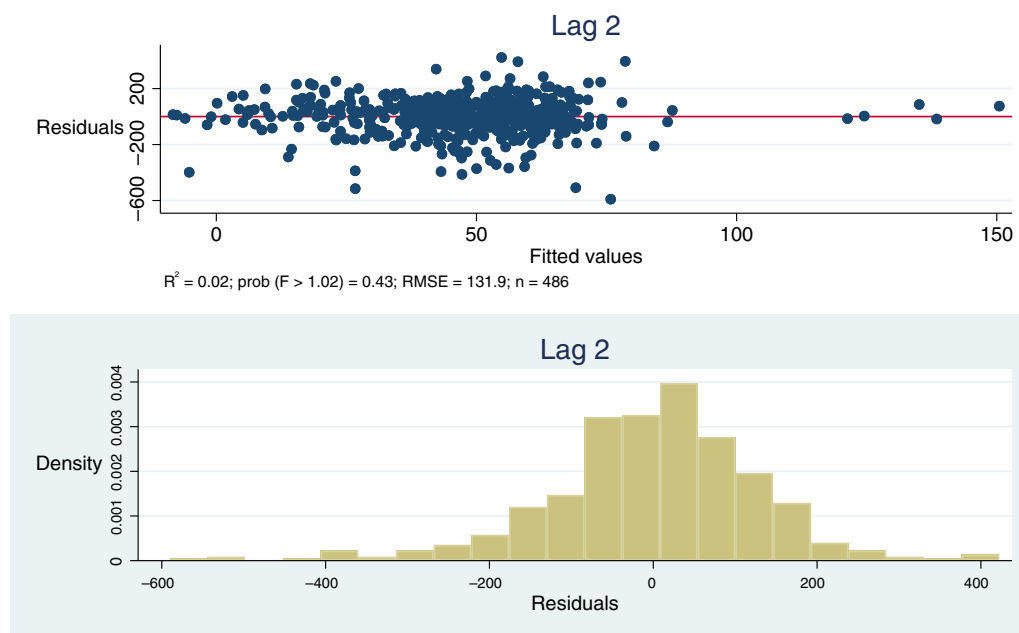


FIGURE E3. Residual plots and histograms for the linear regression model assessing effect modification by current hay fever for the associations between grass pollen and absolute BDR (lag 2).

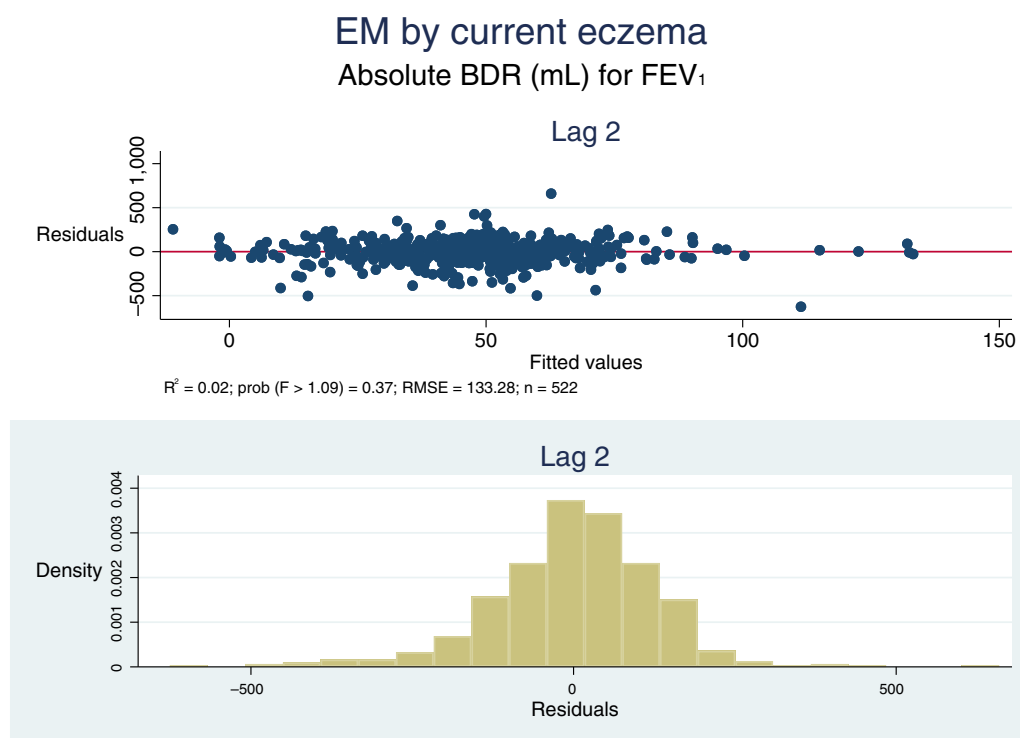


FIGURE E4. Residual plots and histograms for the linear regression model assessing effect modification by current eczema for the associations between grass pollen and absolute BDR (lag 2).

TABLE E1. The estimates, *P* values, and SEs for the interaction term comparing ordinary linear regression model, linear regression model with robust SE, and linear regression model with bootstrapped SE

Models	Ordinary linear regression				Linear regression with robust SE				Linear regression with bootstrapped SE			
	Coefficient	95% CI	<i>P</i>	SE	Coefficient	95% CI	<i>P</i>	SE	Coefficient	95% CI	<i>P</i>	SE
Interaction with food sensitization and allergy for the association between grass pollen at lag 0 and FEV ₁ /FVC ratio	−0.017	−0.03 to 0.00004	.05	0.009	−0.017	−0.03 to −0.002	.03	0.008	−0.017	−0.04 to 0.0006	.058	0.009
Interaction with current hay fever for the association between grass pollen at lag 2 and absolute BDR (mL) for FEV ₁	1.27	−0.19 to 2.7	.087	0.74	1.27	0.06 to 2.5	.04	0.62	1.27	−0.04 to 2.6	.06	0.67

SE, Standard error.

TABLE E2. Summary statistics of grass pollen and other environmental variables during the study period (grass pollen season, 2013–2016)

Variables	n (d)	Mean (SD)	Minimum	25th percentile	50th percentile	75th percentile	90th percentile	Maximum
Grass pollen (grains/m ³)								
Study period (2013–2016)	368	18.6 (24.5)	0	3	9	23	51	154
2013	92	21.2 (26.6)	0	3	10	25.5	65	104
2014	92	13.0 (13.4)	0	2.5	9	20	36	54
2015	92	11.1 (13.7)	0	2	5	14.5	29	58
2016	92	28.9 (33.8)	0	3	17	45	73	154
Weather variables in 2013–2016								
Maximum temperature (°C)	368	23.2 (5.8)	13.2	18.5	21.8	26.6	31.8	41.2
Relative humidity (%)	368	51.2 (18.3)	12	40.5	51.5	59	66	100

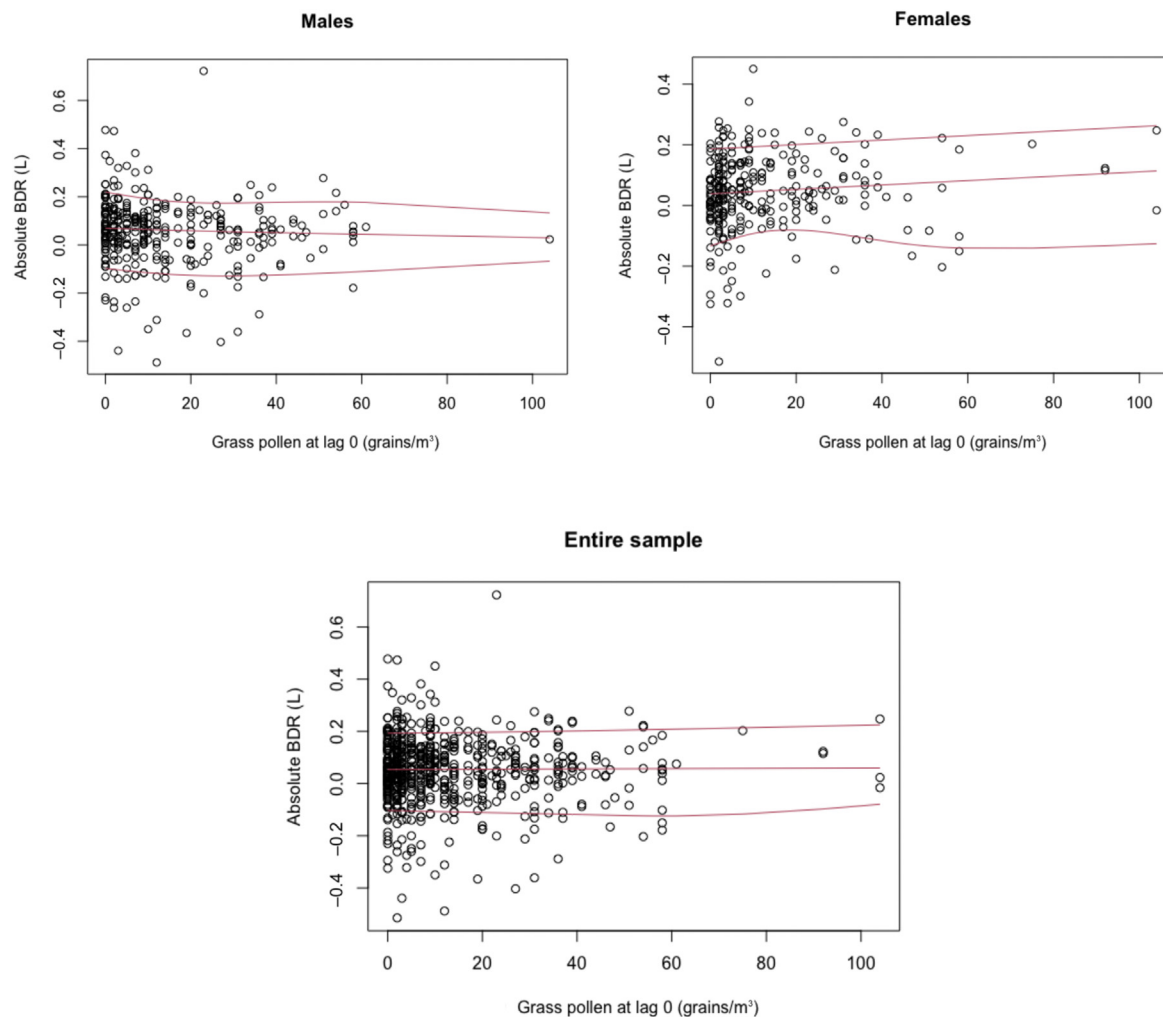


FIGURE E5. The quantile regression model fits for the 10th, 50th, and 90th quantiles (shown by 3 lines) assessing the association between grass pollen at lag 0 and absolute BDR.

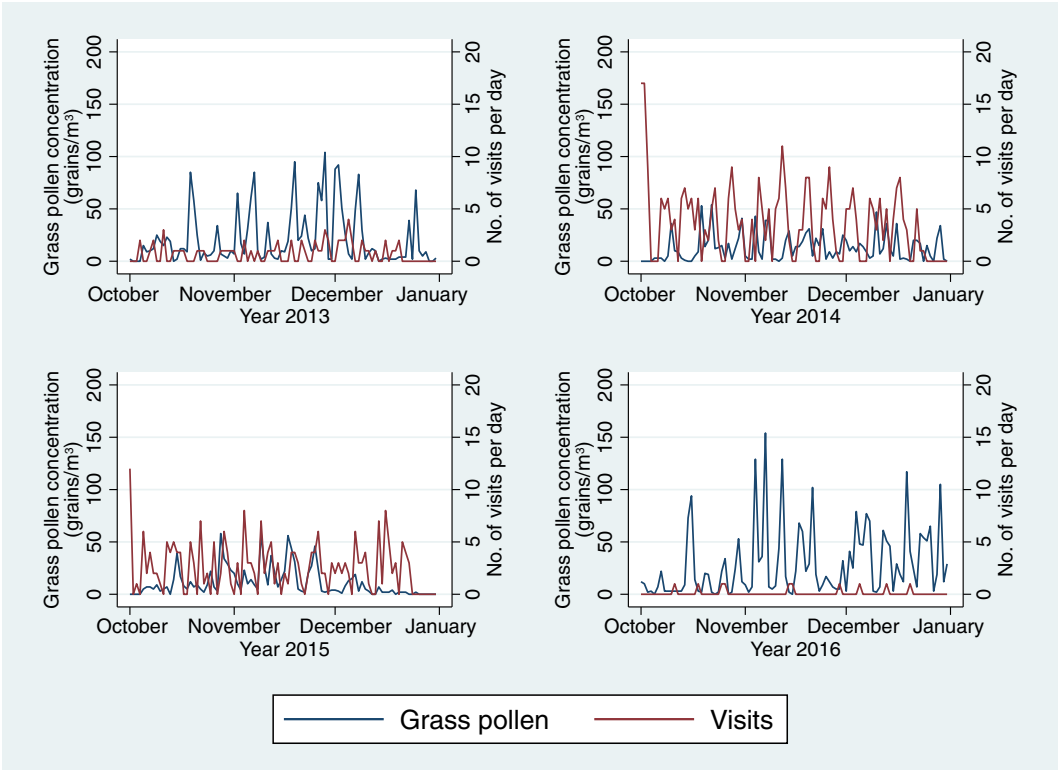


FIGURE E6. Daily grass pollen concentration and number of clinic visits per day for each year during the study period.

TABLE E3. Associations between grass pollen levels at different lags and some pre-bronchodilator lung function measures, stratified by any food sensitization and allergy status*

Grass pollen	FEV ₁ (z-score)				FVC (z-score)			
	Not food-sensitized or -allergic n = 526	Food-sensitized tolerant n = 29	Food-allergic n = 57	P int	Not food-sensitized or -allergic n = 526	Food-sensitized tolerant n = 29	Food-allergic n = 57	P int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	−0.004 (−0.1 to 0.10)	0.06 (−0.3 to 0.4)	−0.08 (−0.4 to 0.2)	.81	−0.07 (−0.2 to 0.06)	−0.2 (−0.5 to 0.2)	0.07 (−0.2 to 0.4)	.61
Lag 1	−0.07 (−0.2 to 0.03)	−0.09 (−0.4 to 0.3)	−0.2 (−0.5 to 0.1)	.78	−0.1 (−0.2 to 0.002)	−0.1 (−0.6 to 0.3)	0.08 (−0.3 to 0.4)	.58
Lag 2	0.01 (−0.1 to 0.1)	0.1 (−0.1 to 0.4)	−0.2 (−0.5 to 0.03)	.14	−0.05 (−0.2 to 0.07)	−0.03 (−0.3 to 0.3)	−0.1 (−0.3 to 0.1)	.92
Lag 3	0.03 (−0.09 to 0.1)	0.02 (−0.4 to 0.4)	−0.2 (−0.5 to 0.06)	.26	0.006 (−0.1 to 0.1)	−0.02 (−0.4 to 0.4)	−0.08 (−0.4 to 0.2)	.85
Lags 0–3	−0.008 (−0.05 to 0.04)	0.02 (−0.09 to 0.1)	−0.1 (−0.2 to 0.004)	.21	−0.03 (−0.08 to 0.02)	−0.04 (−0.2 to 0.08)	−0.02 (−0.1 to 0.08)	.98

	FEV ₁ /FVC (z-score)				FEF _{25%–75%} (z-score)			
	Not food-sensitized or -allergic n = 526	Food-sensitized tolerant n = 29	Food-allergic n = 57	P int	Not food-sensitized or -allergic n = 526	Food-sensitized tolerant n = 29	Food-allergic n = 57	P int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	0.15 (0.01 to 0.2)	0.4 (0.02 to 0.8)	−0.2 (−0.5 to 0.1)	.046†	0.07 (−0.06 to 0.2)	0.3 (−0.09 to 0.6)	−0.3 (−0.6 to 0.04)‡	.065†
Lag 1	0.05 (−0.06 to 0.2)	0.4 (−0.07 to 0.8)	−0.5 (−0.8 to −0.2)†	.003†	0.05 (−0.05 to 0.1)	0.3 (−0.1 to 0.6)	−0.4 (−0.6 to −0.04)†	.03†
Lag 2	0.1 (−0.01 to 0.2)	0.3 (−0.04 to 0.6)	−0.2 (−0.5 to 0.05)‡	.04†	0.1 (−0.01 to 0.2)	0.3 (0.06 to 0.6)	−0.2 (−0.4 to 0.01)‡	.01†
Lag 3	0.05 (−0.07 to 0.2)	0.1 (−0.3 to 0.5)	−0.3 (−0.6 to −0.03)†	.088†	0.06 (−0.04 to 0.2)	0.1 (−0.2 to 0.4)	−0.3 (−0.6 to −0.02)†	.07†
Lags 0–3	0.04 (−0.002 to 0.09)	0.1 (−0.001 to 0.2)	−0.1 (−0.2 to −0.04)†	.002†	0.04 (−0.008 to 0.08)	0.1 (−0.002 to 0.2)	−0.1 (−0.2 to −0.04)†	.003†

Absolute BDR for FEV ₁ (mL)				
Not food-sensitized or -allergic n = 526		Food-sensitized tolerant n = 29		Food-allergic n = 57
Coefficient (95% CI)		Coefficient (95% CI)		Coefficient (95% CI)
Lag 0		Lag 0		Lag 0
5.2 (−12 to 22)		−10 (−54 to 34)		23 (−18 to 63)
Lag 1		Lag 1		Lag 1
4.2 (−8.6 to 17)		3.4 (−45 to 52)		−6.4 (−51 to 38)
Lag 2		Lag 2		Lag 2
−11 (−26 to 4.2)		20 (−14 to 56)		31 (−0.005 to 62)†
Lag 3		Lag 3		Lag 3
0.6 (−14 to 15)		24 (−23 to 70)		36 (2.2 to 72)†
Lags 0–3		Lags 0–3		Lags 0–3
−0.3 (−6.0 to 5.4)		4.4 (−10 to 19)		11 (−1.3 to 24)‡

*Results are interpreted as the effect size per increase in 20 grains/m³. All models were adjusted for temperature and humidity. Models involving BDR outcomes were adjusted for age, sex, ethnicity, and height in addition to temperature and humidity. The results for absolute BDR (mL & %) for FEV₁ and FVC were consistent, so we only present the results for absolute BDR (mL) for FEV₁. Absolute BDR (mL) was defined as the absolute change from pre- to post-BD values.

†Significant interactions ($P_{\text{int}} \leq .1$) or stratified associations ($P \leq .05$). P_{int} is the p-value for the interaction term while P is the p-value for the association.

‡Stratified associations ($P \leq .1$).

TABLE E4. Associations between grass pollen levels at different lags and some pre-bronchodilator lung function measures, stratified by sensitization and allergy status to peanut or cashew*

Grass pollen	FEV ₁ (z-score)				FVC (z-score)			
	Not peanut-sensitized or -allergic n = 565	Peanut-sensitized tolerant n = 21	Peanut-allergic n = 30	P int	Not peanut-sensitized or -allergic n = 565	Peanut-sensitized tolerant n = 21	Peanut allergic n = 30	P int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	−0.02 (−0.2 to 0.1)	0.1 (−0.3 to 0.5)	−0.2 (−0.5 to 0.2)	.62	−0.08 (0.2 to 0.06)	−0.02 (−0.4 to 0.4)	−0.2 (−0.6 to 0.2)	.89
Lag 1	−0.09 (−0.2 to 0.006)	0.2 (−0.4 to 0.8)	−0.2 (−0.6 to 0.2)	.49	−0.1 (−0.2 to −0.01)	0.2 (−0.4 to 0.8)	−0.08 (−0.4 to 0.4)	.58
Lag 2	−0.01 (−0.1 to 0.1)	0.05 (−0.2 to 0.4)	−0.2 (−0.6 to 0.06)	.30	−0.06 (−0.2 to 0.05)	−0.06 (−0.4 to 0.2)	−0.1 (−0.4 to 0.2)	.90
Lag 3	0.01 (−0.09 to 0.1)	−0.2 (−0.6 to 0.3)	−0.4 (−0.8 to 0.06)	.20	0.008 (−0.1 to 0.1)	−0.2 (−0.6 to 0.2)	−0.2 (−0.6 to 0.2)	.47
Lags 0–3	−0.02 (−0.06 to 0.02)	0.02 (−0.1 to 0.2)	−0.1 (−0.2 to 0.004)	.25	−0.03 (−0.08 to 0.01)	−0.02 (−0.2 to 0.1)	−0.08 (−0.2 to 0.06)	.81

Grass pollen	FEV ₁ /FVC (z-score)				FEF _{25%–75%} (z-score)			
	Not peanut-sensitized or -allergic n = 565	Peanut-sensitized tolerant n = 21	Peanut-allergic n = 30	P int	Not peanut-sensitized or -allergic n = 565	Peanut-sensitized tolerant n = 21	Peanut-allergic n = 30	P int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	0.1 (0.01 to 0.3)	0.2 (−0.2 to 0.6)	−0.06 (−0.4 to 0.4)	.59	0.06 (−0.07 to 0.2)	0.2 (−0.2 to 0.6)	−0.2 (−0.6 to 0.1)	.22
Lag 1	0.04 (−0.06 to 0.1)	0.05 (−0.6 to 0.6)	−0.3 (−0.8 to 0.1)‡	.27	0.02 (−0.07 to 0.1)	0.6 (−0.005 to 1.1)	−0.4 (−0.8 to 0.02)‡	.03‡
Lag 2	0.1 (−0.01 to 0.2)	0.2 (−0.1 to 0.6)	−0.2 (−0.6 to 0.04)‡	.047‡	0.1 (−0.02 to 0.2)	0.3 (−0.06 to 0.6)	−0.4 (−0.6 to −0.02)‡	.02‡
Lag 3	0.02 (−0.1 to 0.1)	0.1 (−0.3 to 0.5)	−0.4 (−0.8 to 0.08)‡	.22	0.05 (−0.06 to 0.2)	−0.06 (−0.4 to 0.4)	−0.4 (−0.8 to 0.01)‡	.10‡
Lags 0–3	0.04 (−0.01 to 0.08)	0.08 (−0.08 to 0.2)	−0.1 (−0.2 to 0.02)‡	.07‡	0.03 (−0.01 to 0.06)	0.1 (−0.05 to 0.3)	−0.2 (−0.2 to −0.04)‡	.01‡

Grass pollen	Absolute BDR for FEV ₁ (mL)			P int
	Not peanut-sensitized or -allergic n = 565	Peanut-sensitized tolerant n = 21	Peanut-allergic n = 30	
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	2.4 (−14 to 19)	−2.0 (−54 to 50)	41 (−7.4 to 89)	.31
Lag 1	2.4 (−10 to 14)	29 (−45 to 103)	0.6 (−54 to 56)	.78
Lag 2	−7.0 (−21 to 7.0)	26 (−16 to 68)	34 (−4.2 to 72)‡	.06‡
Lag 3	4.2 (−9.6 to 18)	10 (−41 to 61)	40 (−10 to 90)‡	.39
Lags 0–3	0.18 (−5.0 to 5.4)	7.0 (−12 to 26)	14 (−2.2 to 30)‡	.24

Grass pollen	FEV ₁ (z-score)				FVC (z-score)			
	Not cashew-sensitized or -allergic n = 573	Cashew-sensitized tolerant n = 24	Cashew-allergic n = 17	P int	Not cashew-sensitized or -allergic n = 573	Cashew-sensitized tolerant n = 24	Cashew-allergic n = 17	P int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	−0.01 (−0.1 to 0.1)	−0.09 (−0.5 to 0.3)	−0.3 (−0.9 to 0.3)	.60	−0.06 (−0.2 to 0.06)	−0.2 (−0.6 to 0.2)	−0.03 (−0.6 to 0.6)	.85
Lag 1	−0.07 (−0.2 to 0.02)	−0.4 (−0.9 to 0.03)	−0.9 (−2.0 to 0.3)	.15	−0.09 (−0.2 to 0.004)	−0.2 (−0.6 to 0.3)	−0.2 (−1.4 to 1.0)	.88
Lag 2	−0.01 (−0.1 to 0.1)	−0.2 (−0.6 to 0.2)	−0.008 (−0.5 to 0.4)	.65	−0.06 (−0.2 to 0.04)	0.004 (−0.4 to 0.4)	−0.2 (−0.6 to 0.4)	.88
Lag 3	0.005 (−0.1 to 0.1)	−0.2 (−0.6 to 0.2)	−0.2 (−0.7 to 0.3)	.46	−0.02 (−0.1 to 0.09)	0.05 (−0.4 to 0.4)	−0.05 (−0.6 to 0.4)	.95
Lags 0–3	−0.01 (−0.05 to 0.03)	−0.09 (−0.2 to 0.04)	−0.1 (−0.3 to 0.1)	.39	−0.04 (−0.08 to 0.008)	−0.04 (−0.2 to 0.1)	−0.05 (−0.2 to 0.2)	.99

	FEV ₁ /FVC (z-score)				FEF _{25%-75%} (z-score)			
	Not cashew-sensitized or -allergic n = 573	Cashew-sensitized tolerant n = 24	Cashew-allergic n = 17	<i>P</i> int	Not cashew-sensitized or -allergic n = 573	Cashew-sensitized tolerant n = 24	Cashew-allergic n = 17	<i>P</i> int
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	
Lag 0	0.1 (0.01 to 0.3)	0.2 (−0.2 to 0.6)	−0.5 (−1.2 to 0.1)	.13	0.06 (−0.06 to 0.2)	0.002 (−0.4 to 0.4)	−0.5 (−1.1 to 0.06)	.15
Lag 1	0.06 (−0.05 to 0.2)	−0.4 (−0.8 to 0.1)	−1.3 (−2.6 to −0.04) [†]	.02 [†]	0.05 (−0.04 to 0.1)	−0.4 (−0.8 to 0.02)	−1.4 (−2.6 to −0.2) [†]	.007 [†]
Lag 2	0.1 (−0.01 to 0.2)	−0.3 (−0.7 to 0.1)	0.2 (−0.3 to 0.6)	.16	0.1 (0.0002 to 0.2)	−0.3 (−0.6 to 0.07)	−0.09 (−0.6 to 0.4)	.09 [†]
Lag 3	0.04 (−0.06 to 0.2)	−0.4 (−0.8 to 0.09)	−0.4 (−0.9 to 0.1)	.075 [†]	0.06 (−0.04 to 0.2)	−0.3 (−0.8 to 0.08)	−0.4 (−0. to 0.1) [‡]	.05 [†]
Lags 0–3	0.04 (−0.001 to 0.08)	−0.09 (−0.2 to 0.06)	−0.1 (−0.4 to 0.08)	.08 [†]	0.04 (−0.005 to 0.08)	−0.1 (−0.3 to 0.02)	−0.2 (−0.4 to 0.02) [‡]	.02 [†]

Absolute BDR for FEV ₁ (mL)				
Not cashew-sensitized or -allergic n = 573	Cashew-sensitized tolerant n = 24	Cashew-allergic n = 17	<i>P</i> int	
Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)		
Lag 0	2.4 (13 to 18)	20 (−29 to 69)	29 (−50 to 108)	.64
Lag 1	2.4 (−10 to 15)	4.8 (−53 to 63)	38 (−120 to 16)	.90
Lag 2	−5.0 (−18 to 8.4)	26 (−23 to 74)	49 (−12 to 109) [‡]	.12
Lag 3	1.4 (−12 to 14)	41 (−13 to 95)	77 (13 to 140) [†]	.03 [†]
Lags 0–3	−0.05 (−5.2 to 5.0)	10 (−6.0 to 27)	26 (0.02 to 52) [†]	.08 [†]

*Results are interpreted as the effect size per increase in 20 grains/m³. All models were adjusted for temperature and humidity. Models involving BDR outcomes were adjusted for age, sex, ethnicity, and height in addition to temperature and humidity. The results for absolute BDR (mL & %) for FEV₁ and FVC were consistent so we only present the results for absolute BDR (mL) for FEV₁. Absolute BDR (mL) was defined as the absolute change from pre- to post-bronchodilator values.

[†]Significant interactions (*P* int ≤ 0.1) or stratified associations (*P* ≤ 0.05). *P* int is the p-value for the interaction term while *P* is the p-value for the association.

[‡]Stratified associations (*P* ≤ 0.1).

TABLE E5. Associations between grass pollen concentrations and pre-bronchodilator lung function measures (all qualities and acceptable qualities only)*

All qualities, A–F										
Outcomes	Grass pollen									
	Lag 0		Lag 1		Lag 2		Lag 3		Lags 0–3	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
FEV ₁ z-score	−0.01 (−0.1 to 0.1)	.85	−0.08 (−0.2 to 0.01)	.09	−0.03 (−0.1 to 0.1)	.55	−0.01 (−0.1 to 0.1)	.83	−0.02 (−0.06 to 0.02)	.27
FVC z-score	−0.04 (−0.2 to 0.08)	.43	−0.09 (−0.2 to 0.01)	.09	−0.08 (−0.2 to 0.04)	.19	−0.009 (−0.1 to 0.1)	.88	−0.03 (−0.07 to 0.01)	.15
FEV ₁ /FVC ratio z-score	0.10 (−0.02 to 0.2)	.10	0.01 (−0.1 to 0.1)	.87	0.08 (−0.03 to 0.18)	.16	0.004 (−0.1 to 0.1)	.94	0.02 (−0.02 to 0.06)	.32
FEF _{25%–75%} z-score	0.01 (−0.1 to 0.1)	.81	0.008 (−0.1 to 0.1)	.86	0.06 (−0.04 to 0.16)	.24	0.02 (−0.09 to 0.1)	.77	0.01 (−0.03 to 0.05)	.64
Absolute BDR for FEV ₁ (mL)	4.6 (−10 to 19)	.55	2.5 (−9.0 to 14)	.66	−1.2 (−14 to 11)	.84	6.2 (−6.2 to 19)	.32	1.4 (−4.0 to 6.0)	.57
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Positive BDR for FEV ₁	1.2 (0.9 to 1.8)	.11	1.0 (0.8 to 1.5)	.91	1.2 (0.8 to 1.5)	.30	1.2 (0.96 to 1.8)	.09	1.0 (0.98 to 1.2)	.12
Qualities A–C only										
Outcomes	Grass pollen									
	Lag 0		Lag 1		Lag 2		Lag 3		Lags 0–3	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
FEV ₁ z-score	−0.04 (−0.2 to 0.08)	.52	−0.06 (−0.20 to 0.03)	.17	−0.02 (−0.14 to 0.08)	.57	−0.03 (−0.13 to 0.08)	.57	−0.02 (−0.06 to 0.01)	.22
FVC z-score	−0.08 (−0.2 to 0.04)	.2	−0.06 (−0.16 to 0.04)	.20	−0.06 (−0.16 to 0.04)	.25	−0.01 (−0.12 to 0.09)	.81	−0.03 (−0.06 to 0.01)	.14
FEV ₁ /FVC ratio z-score	0.10 (−0.02 to 0.24)	.10	0.01 (−0.10 to 0.10)	.88	0.06 (−0.04 to 0.17)	.26	−0.02 (−0.12 to 0.08)	.71	0.02 (−0.02 to 0.06)	.41
FEF _{25%–75%} z-score	0.03 (−0.10 to 0.14)	.66	0.03 (−0.06 to 0.12)	.52	0.06 (−0.04 to 0.16)	.21	−0.01 (−0.1 to 0.08)	.79	0.01 (−0.02 to 0.06)	.57
Absolute BDR for FEV ₁ (mL)	10 (−4.0 to 24)	.16	4.4 (−6.0 to 15.0)	.42	−4.8 (−16 to 6.6)	.42	6.2 (−5.6 to 18)	.31	1.3 (−3.2 to 5.8)	.56
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Positive BDR for FEV ₁	1.5 (1.0 to 2.2)	.05	1.2 (0.8 to 1.5)	.54	1.0 (0.8 to 1.5)	.62	1.2 (0.96 to 1.8)	.09	1.2 (0.98 to 1.2)	.11

OR, Odds ratio.

*Results are interpreted as the effect size per increase in 20 grains/m³. All models were adjusted for temperature and humidity. Models involving BDR outcomes were adjusted for age, sex, ethnicity, and height in addition to temperature and humidity. The results for absolute BDR (mL & %) for FEV₁ and FVC were consistent so we only present the results for absolute BDR (mL) for FEV₁. Absolute BDR (mL) was defined as the absolute change from pre- to post-bronchodilator values.

TABLE E6. Associations between grass pollen concentrations and pre-bronchodilator lung function measures (excluded participants who recently used either any medication or breathing medication only prior to spirometry)*

Excluded participants who recently used any medication prior to spirometry										
Outcomes	Grass pollen									
	Lag 0		Lag 1		Lag 2		Lag 3		Lags 0–3	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
FEV ₁ z-score	−0.01 (−0.1 to 0.1)	.93	−0.08 (−0.2 to 0.02)	.14	−0.04 (−0.2 to 0.06)	.39	−0.01 (−0.1 to 0.1)	.85	−0.02 (−0.06 to 0.02)	.26
FVC z-score	−0.04 (−0.2 to 0.09)	.53	−0.06 (−0.2 to 0.03)	.18	−0.08 (−0.2 to 0.04)	.18	−0.008 (−0.1 to 0.1)	.88	−0.03 (−0.06 to 0.01)	.19
FEV ₁ /FVC ratio z-score	0.09 (−0.03 to 0.2)	.15	−0.006 (−0.1 to 0.09)	.90	0.05 (−0.06 to 0.2)	.37	0.006 (−0.1 to 0.1)	.92	0.01 (−0.03 to 0.05)	.53
FEF _{25%–75%} z-score	−0.004 (−0.1 to 0.1)	.94	−0.01 (−0.1 to 0.08)	.87	0.02 (−0.08 to 0.1)	.66	0.02 (−0.08 to 0.1)	.76	−0.001 (−0.04 to 0.04)	.96
Absolute BDR for FEV ₁ (mL)	6.4 (−8.6 to 21)	.40	1.2 (−11 to 13)	.84	−1.6 (−14 to 11)	.81	6.0 (−6.6 to 18)	.35	1.2 (−3.4 to 6.0)	.59
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Positive BDR for FEV ₁	1.2 (0.9 to 1.8)	.12	0.9 (0.7 to 1.2)	.77	1.2 (0.9 to 1.5)	.20	1.2 (1.0 to 1.8)	.05	1.0 (1.0 to 1.2)	.10
Excluded participants who recently used breathing medication only prior to spirometry										
Outcomes	Grass pollen									
	Lag 0		Lag 1		Lag 2		Lag 3		Lag 0–3	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
FEV ₁ z-score	−0.01 (−0.1 to 0.1)	.82	−0.08 (−0.2 to 0.01)	.1	−0.03 (−0.1 to 0.08)	.64	−0.004 (−0.1 to 0.1)	.95	−0.02 (−0.06 to 0.02)	.3
FVC z-score	−0.04 (−0.2 to 0.08)	.50	−0.08 (−0.2 to 0.02)	.12	−0.06 (−0.2 to 0.04)	.28	0.001 (−0.1 to 0.1)	.99	−0.03 (−0.06 to 0.02)	.22
FEV ₁ /FVC ratio z-score	0.08 (−0.04 to 0.2)	.17	−0.004 (−0.1 to 0.1)	.93	0.06 (−0.04 to 0.2)	.24	0.0004 (−0.1 to 0.1)	.995	0.01 (−0.03 to 0.06)	.50
FEF _{25%–75%} z-score	0.06 (−0.1 to 0.1)	>0.99	−0.004 (−0.1 to 0.09)	.95	0.06 (−0.04 to 0.2)	.26	0.02 (−0.08 to 0.1)	.67	0.006 (−0.04 to 0.04)	.77
Absolute BDR for FEV ₁ (mL)	6.6 (−8.4 to 22)	.39	2.6 (−9.2 to 14)	.67	−2.6 (−15 to 10)	.69	4.2 (−8.4 to 17)	.51	1.2 (−3.6 to 6.0)	.62
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Positive BDR for FEV ₁	1.5 (1.0 to 2.2)	.085	1.0 (0.8 to 1.5)	.86	1.0 (0.8 to 1.5)	.64	1.2 (0.9 to 1.8)	.015	1.0 (0.96 to 1.2)	.18

OR, Odds ratio.

*Results are interpreted as the effect size per increase in 20 grains/m³. All models were adjusted for temperature and humidity. Models involving BDR outcomes were adjusted for age, sex, ethnicity, and height in addition to temperature and humidity. The results for absolute BDR (mL & %) for FEV₁ and FVC were consistent so we only present the results for absolute BDR (mL) for FEV₁. Absolute BDR (mL) was defined as the absolute change from pre- to post-bronchodilator values.