

Phl p 5 levels more strongly associated than grass pollen counts with allergic respiratory health



Elaine Fuertes, PhD,^{a,b} Debbie Jarvis, MBBS, MD,^{a,b} Holly Lam, PhD,^{a,b} Bethan Davies, PhD,^{b,c} Daniela Fecht, PhD,^{b,c,d} Joana Candeias, PhD,^e Carsten B. Schmidt-Weber, PhD,^e Abdel Douiri, PhD,^f Anna Slovic, MBBS, BSc, PhD, DOHNS, FRCS (ORL-HNS),^g Enrico Scala, MD,^h Thomas E. L. Smith, PhD,ⁱ Mohamed Shamji, PhD, FAAAAI,^{a,j} Jeroen T. M. Buters, PhD,^{e,*} Lorenzo Cecchi, MD,^{k,l,*} and Stephen J. Till, PhD, FRCP^{g,m,*}

London, United Kingdom; Munich, Germany; and Rome, Florence, and Prato, Italy

Background: Studies have linked daily pollen counts to respiratory allergic health outcomes, but few have considered allergen levels.

Objective: We sought to assess associations of grass pollen counts and grass allergen levels (Phl p 5) with respiratory allergic health symptoms in a panel of 93 adults with moderate-severe allergic rhinitis and daily asthma hospital admissions in London, United Kingdom.

Methods: Daily symptom and medication scores were collected from adult participants in an allergy clinical trial. Daily counts of asthma hospital admissions in the London general population were obtained from Hospital Episode Statistics data. Daily grass pollen counts were measured using a volumetric air sampler, and novel Phl p 5 levels were measured using a ChemVol High Volume Cascade Impactor and ELISA analyses (May through August). Associations between the 2 pollen variables and daily health scores (dichotomized based on within-person 75th percentiles) were assessed using generalized estimating equation

logistic models and with asthma hospital admissions using Poisson regression models.

Results: Daily pollen counts and Phl p 5 levels were each positively associated with reporting a high combined symptom and medication health score in separate models. However, in mutually adjusted models including terms for both pollen counts and Phl p 5 levels, associations remained for Phl p 5 levels (odds ratio [95% CI]: 1.18 [1.12, 1.24]), but were heavily attenuated for pollen counts (odds ratio [95% CI]: 1.00 [0.93, 1.07]). Similar trends were not observed for asthma hospital admissions in London.

Conclusions: Grass allergen (Phl p 5) levels are more consistently associated with allergic respiratory symptoms than grass pollen counts. (*J Allergy Clin Immunol* 2024;153:844-51.)

Key words: Air pollution, allergens, allergies, asthma, pollen

Allergic airways disease due to grass pollen is a major problem in many countries. Studies have demonstrated associations between increases in daily grass pollen counts and worsening of health outcomes, including more frequent allergic and asthmatic respiratory symptoms¹ and increases in daily hospital admissions for asthma.^{2,3}

Nearly all existing studies assessing the short-term health impacts of pollen have used the number of airborne grass pollen grains (ie, pollen count) as a proxy for the concentration of airborne grass allergen. This exposure assessment approach may be inadequate to capture the true potential of airborne allergens to exacerbate allergic respiratory symptoms, as subpollen particles may be small enough to reach the lower airways, whereas intact pollen grains are larger and cannot enter the lower respiratory tract. Further, it is recognized that the relationship between airborne grass pollen count and grass pollen allergen levels is nonlinear and that the amount of allergen released from pollen grains varies significantly (>10-fold) per location and time.⁴ Similar observations have been made for molds.⁵ These observations may explain why allergy symptoms are experienced even on days with low pollen counts^{6,7} and suggest that epidemiologic studies based only on grass pollen counts are limited in their ability to estimate the true health burden of grass pollen exposure.

The current novel analysis fills this gap by examining associations between daily grass pollen counts and Phl p 5 allergen levels, both measured simultaneously during a grass

From ^athe National Heart and Lung Institute, Imperial College London, London; ^bthe MRC Centre for Environment and Health, Imperial College London, London; ^cthe Small Area Health Statistics Unit, School of Public Health, Imperial College London, London; ^dthe NIHR Health Protection Research Unit in Chemical Radiation Threats and Hazards, School of Public Health, Imperial College London, London; ^eCenter of Allergy and Environment, Technische Universität München and Helmholtz Center Munich, Member of the German Center for Lung Research (DZL), Munich; ^fthe School of Life Course and Population Sciences, King's College London, London; ^gKing's Centre for Lung Health, School of Immunology and Microbial Sciences, King's College London, London; ^hthe Clinical and Laboratory Molecular Allergy Unit, IDI IRCCS, Rome; ⁱthe Department of Geography and Environment, London School of Economics and Political Science, London; ^jthe NIHR Imperial Biomedical Research Centre, London; ^kCentre of Bioclimatology, University of Florence, Florence; ^lSOS Allergy and Clinical Immunology, USL Toscana Centro, Prato; and ^mthe Department of Allergy, Guy's and St Thomas' NHS Foundation Trust, London.

*These authors are joint senior authors.

Received for publication December 7, 2022; revised November 1, 2023; accepted for publication November 9, 2023.

Available online November 22, 2023.

Corresponding author: Elaine Fuertes, PhD, Emmanuel Kaye Building, 1B Manresa Road, London, SW3 6LR UK. E-mail: e.fuertes@imperial.ac.uk.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

© 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaci.2023.11.011>

Abbreviations used

IQR: Interquartile range
LSOA: Lower layer Super Output Area
NO₂: Nitrogen dioxide
O₃: Ozone
OR: Odds ratio
PM: Particulate matter
PM₁₀: PM with diameter smaller than 10 μm
PM_{2.5}: PM with diameter smaller than 2.5 μm

pollen season in central London, United Kingdom, and daily symptom and medication scores from a panel of 93 adults with moderate-severe allergic rhinitis and daily hospital admissions for asthma in London. Although different groups of allergens related to grass pollen are known to induce IgE responses,⁸ we studied Phl p 5, as this is a major timothy grass allergen recognized by almost all individuals with grass pollen allergy, which induces strong IgE antibody responses and clinical allergic outcomes.⁹ Further, Phl p 5 levels are known to have a nonlinear relationship with grass pollen counts, which is influenced by environmental and meteorological factors.^{6,10,11}

METHODS

Symptom and medication scores from randomized controlled trial panel study

In 2013, 93 adult participants with moderate-severe grass pollen-induced allergic rhinitis (mean age = 33.5 years, 66% male, 80% White) were recruited for the PollenLITE (Pollen Low dose Intradermal Therapy Evaluation) study, a single-center, randomized controlled double-blind phase 2 trial, at Guy's Hospital in London. Participants completed diary cards recording daily symptoms and medication use. Grass pollen group 5-specific IgE levels were measured in blood. Written informed consent was obtained. These data were previously used to determine that intradermal allergen immunotherapy was not clinically effective.¹²

The primary outcome of interest was a combined symptom and medication score, hereafter referred to as the total score, as used previously.¹² Predefined secondary outcomes were the overall medication score and overall symptom score analyzed separately. Details of the study design, ethical approval, and symptom and medication scoring in the PollenLITE population have been published previously¹² and are included in this article's Online Repository (at www.jacionline.org). The previous study found that intradermal allergen immunotherapy (the treatment group) was not clinically effective.

Hospital admissions for asthma

Daily counts of hospital admissions and emergency department visits for asthma were obtained from Hospital Episode Statistics data held by the Small Area Health Statistics Unit at Imperial College London and provided by NHS England for the period covering the pollen exposure measurements (May to August 2013). Counts were obtained for all ages and by age groups (<15 years, 15-44 years, and >44 years). Hospital admissions for asthma were identified using the *International Classification of Disease, Tenth Revision* codes J45 and J46 recorded in the first

diagnosis field only. As an alternative outcome, we used emergency department visits for asthma coded in the first 2 diagnosis fields using the diagnostic code 251 (respiratory conditions—bronchial asthma). We included individuals located within 100 km of the pollen measurement site, defined as individuals with a home address in a Lower layer Super Output Area (LSOA) with a population-weighted centroid within 100 km of the site (11,963 LSOAs).¹³ This included Greater London and most of the East of England and South East regions. We selected a 100-km buffer to obtain enough hospital admissions for asthma per day to sufficiently power the statistical analysis.

Daily grass pollen count and allergen (Phl p 5) levels

Daily airborne pollen counts (grains/m³) were obtained using a standardized Hirst-type volumetric air sampler (Burkard Manufacturing, Rickmansworth, Hertfordshire, United Kingdom) deployed on the southwest corner on the roof of the Strand Building, King's College London, from May 17, 2013, to August 31, 2013.¹⁴ To determine Phl p 5 allergen levels (pg/m³), air was sampled using a ChemVol High Volume Cascade Impactor (800 L/minutes; Butracco Inc, Son, The Netherlands) located within 5 m of the pollen trap during the same time frame, and the filters collected on the particulate matter (PM) > 10 μm and 10 μm > PM > 2.5 μm stages of the impactor were analyzed by ELISA according to HIALINE (Health Impacts of Airborne Allergen Information Network) study protocols.¹⁵ Full details are provided in the Online Repository (at www.jacionline.org).

Meteorological and air pollution data

Daily mean temperature, mean precipitation, and mean relative humidity data were obtained from all monitors within 100 km of the pollen measurement site from the Medical and Environmental Data Mash-up Infrastructure project.¹⁶ A daily average across all sites was calculated per variable. The daily mean concentrations of PM with diameter smaller than 10 μm (PM₁₀) and 2.5 μm (PM_{2.5}) and nitrogen dioxide (NO₂) and mean daily maximum 8-hour concentration for ozone (O₃) were calculated using data from the Automatic Urban and Rural Network¹⁷ and following imputation for missing values (details are in Table E1 in the Online Repository at www.jacionline.org).

Statistical analysis

All analyses were conducted in R v4.3.1.¹⁸ A data access statement and the statistical code used for statistical modeling are provided at the end of the Online Repository at www.jacionline.org.

The range of daily health scores reported by each participant in the panel study varied substantially and were non-normally distributed (Fig E1 in the Online Repository at www.jacionline.org). As such, they were dichotomized per day as being below/equal to versus above the 75th percentile for that participant. Associations between this binary outcome (≤ vs > within-person 75th percentile) and the 2 pollen variables were assessed using generalized estimating equations logistic regression models (geepack R package).¹⁹⁻²¹ All generalized estimating equations models included adjustments for sex; age; trial arm (treatment vs control)¹²; month; and daily mean temperature, relative humidity, precipitation, and NO₂. An autoregressive lag 1 correlation structure was specified to account for the clustering of the daily

measurements taken within participants. Effect estimates represent the increase in odds ratio (with 95% CI) of reporting a health score above a given participant's 75th percentile per interquartile range (IQR) increase of each pollen variable.

Associations between the 2 pollen variables and daily hospital admissions for asthma were assessed using quasi-Poisson generalized linear regression models accounting for overdispersion. Models were adjusted for a binary variable specified as weekday versus weekends/holidays; month; and daily mean temperature, precipitation, relative humidity, and NO₂. Effect estimates represent the percentage change in hospital admissions for asthma per IQR increase of each pollen variable.

Mutually adjusted models containing pollen counts and Phl p 5 were tested. In these mutually adjusted models, the effect estimate for pollen counts represents the increase in odds of reporting a health score > within-person 75th percentile (or percent change in hospital admissions for asthma) associated with an IQR increase in pollen counts, after accounting for the effect of airborne Phl p 5 levels and that of the other covariates. Similarly, the effect estimate for Phl p 5 levels represents the increase in odds of reporting a health score > within-person 75th percentile (or percent change in hospital admissions for asthma) associated with an IQR increase in Phl p 5 levels, after accounting for the effect of pollen counts and that of the other covariates. Variance inflation factors were examined as a measure of the increase in the variance of the regression coefficients due to collinearity. Values less than 4 are typically accepted to indicate that multicollinearity is not a concern.

Sensitivity analyses

Sensitivity analyses included adjusting for other air pollutants (daily mean PM_{2.5}, PM₁₀, and O₃) to test for residual confounding, restricting the dataset to the peak grass pollen season, defined as starting after the first consecutive 3 days with pollen counts > 30 (grains/m³) and ending after the first 3 days when pollen counts < 30 (grains/m³) (June 12, 2013, to July 25, 2013), to see if associations are stronger and adjusting for pollen counts and Phl p 5 levels the day before to assess the impact of considering 1-day lag effects on the results. Effect modification by air pollution was assessed by including an interaction term between each pollutant and pollen variable and stratifying the models into tertiles of air pollution. Additional analyses for the panel study health score data included adjusting for blood IgE levels specific to Phl p 5 and analyzing the symptom scores separately (nose, eyes, mouth/throat, chest). The models on hospital admissions for asthma were restricted to LSOAs with a population-weighted center within 50 km (7702 LSOAs) and 20 km (4400 LSOAs) of the pollen measurement site to see whether associations may be stronger in smaller buffers that presumably have lower exposure misclassification. Finally, emergency department visits for asthma was considered as an alternative outcome to hospital admissions for asthma.

RESULTS

Descriptive statistics

Descriptive statistics of the health outcomes and environmental variables included in the models are presented in **Tables I and II**. Spearman correlation coefficients between all environmental factors are presented in **Table E2** (in the Online Repository at www.jacionline.org).

Daily Phl p 5 levels were highly correlated with grass pollen counts ($\rho = 0.769$) (scatterplot in **Fig E2** in the Online Repository at www.jacionline.org).

Associations between grass pollen exposures and daily health scores in the panel study

Daily pollen counts were positively associated with reporting a score in the top quarter of each individual's health score range (ie, > within-person 75th percentile) for all 3 outcomes (total score: odds ratio [95% CI]: 1.11 [1.05, 1.17]; symptom score: OR [95% CI]: 1.10 [1.05, 1.16]; medication score: OR [95% CI]: 1.09 [1.02, 1.15]). Elevated associations were also observed with Phl p 5 levels (total score: OR [95% CI]: 1.18 [1.14, 1.22]; symptom score: OR [95% CI]: 1.17 [1.13, 1.22]; medication score: OR [95% CI]: 1.16 [1.11, 1.21]). In mutually adjusted models including terms for both pollen count and Phl p 5 levels, effect estimates for pollen counts were attenuated to the null, whereas those for Phl p 5 levels remained stable (**Fig 1**; **Table E3** in the Online Repository at www.jacionline.org). Variance inflation factors were < 3.5, suggesting that regression coefficients are not artificially inflated due to collinearity.

Results remained consistent after adjusting for participant blood IgE levels specific to Phl p 5 and daily mean PM_{2.5}, PM₁₀, and O₃ and restricting the analysis to the height of the grass pollen season (**Table E4** in the Online Repository at www.jacionline.org). Adjusting the models for pollen counts and Phl p 5 levels the day before (ie, including 1-day lag terms) reduced the differences in the size of the effect estimates between pollen counts and Phl p 5 levels, although this should be interpreted with caution given the high number of correlated exposure variables in this model (**Table E5** in the Online Repository at www.jacionline.org).

Although some interaction terms between the pollen variables and daily mean PM_{2.5} and PM₁₀ concentrations were statistically significant ($P < .05$), stratifying the models into tertiles of pollution yielded no consistent patterns. When considering the symptom scores individually, the effect estimates for pollen counts were again null in mutually adjusted models, whereas those for Phl p 5 were elevated for eye, nose, and mouth/throat symptoms (**Table III**).

Associations between grass pollen exposures and daily counts of hospital admissions for asthma

Daily pollen counts were positively associated with percentage change in asthma admissions in the overall population (percent change [95% CI]: 6.7 [3.4, 10.2]) and individuals < 15 years old (percent change [95% CI]: 13.2 [7.6, 19.2]) and 15 to 44 years old (percent change [95% CI]: 7.5 [3.0, 12.3]). Associations in individuals > 44 years old were null (percent change [95% CI]: -1.7 [-6.1, 2.9]). Similar results were observed for daily Phl p 5 levels (percent change [95% CI] for the overall, < 15 years, 15-44 years, and > 44 years populations: 4.5 [1.5, 7.5], 9.9 [4.8, 15.2], 4.0 [0.0, 8.1], and -0.8 [-4.5, 3.1], respectively). In mutually adjusted models, only the effect estimates for pollen counts remained elevated; however, CIs overlapped with the effect estimates for Phl p 5 levels (**Fig 2**; **Table E6** in the Online Repository at www.jacionline.org). Variance inflation factors were < 3.6.

Associations with Phl p 5 levels remained null throughout all sensitivity analyses. For pollen counts, adjusting the models for PM_{2.5}, PM₁₀, and O₃ did not change the findings, but restricting

TABLE I. Frequency of participants reporting high health scores in the panel study*

Health scores	Total observations	No. of participants	Score > within-participant 75th percentile, n (%)
Total	9715	93	2291 (23.6)
Overall symptoms	9715	93	2105 (21.7)
Overall medication	9016	86	1439 (16.0)
Eye symptoms	9608	92	1665 (17.3)
Nose symptoms	9715	93	1720 (17.7)
Chest symptoms	7362	71	859 (11.7)
Mouth/throat symptoms	8859	85	1041 (11.8)

*Total potential is 9951 observations (93 participants × 107 observation days); however, some values are lower due to missing data and the removal of individuals who always reported scores of 0 for specific outcomes throughout the study period.

TABLE II. Descriptive daily data on the modeled variables*

	Daily variable	Mean	SD	Median	P25	P75
Hospital admissions for asthma	All ages	49.5	16.9	48.0	36.0	62.5
	< 15 years	14.0	10.8	15.0	9.0	22.0
	15-44 years	15.5	7.8	16.0	13.0	20.5
	> 44 years	16.5	7.4	16.0	12.0	22.0
Environmental exposures	Grass pollen count (grains/m ³)	43.5	68.5	17.0	3.0	55.5
	Phl p 5 level (pg/m ³)	169.0	303.0	17.9	1.3	198.3
	Mean PM _{2.5} (μg/m ³)	13.0	5.8	10.9	9.0	14.9
	Mean PM ₁₀ (μg/m ³)	17.7	6.2	15.8	13.5	19.8
	Mean NO ₂ (μg/m ³)	18.3	6.3	17.4	14.1	23.0
	Mean O ₃ (μg/m ³)	70.5	17.3	67.4	60.7	78.8
	Mean temperature (°C)	15.9	3.4	16.3	13.5	18.1
	Precipitation (mL)	0.0	0.1	0.0	0.0	0.0
	Mean relative humidity (%)	74.9	7.9	74.1	69.7	79.1

*Observation days from May 17, 2013, to August 31, 2013 (n = 107 days). Percentiles presented for the 25th (P25) and 75th (P75) intervals.

the analyses to daily hospital admissions within 50 km and 20 km of the pollen measurement site and using hospital emergency department visits for asthma as an alternative outcome slightly attenuated the associations for the overall population and individuals 15 to 44 years old (Table E7 in the Online Repository at www.jacionline.org). Limiting to the height of the grass pollen season attenuated the associations for all ages (Table E7). Including 1-day lag terms for pollen counts and Phl p 5 levels did not change the main findings (Table E8 in the Online Repository at www.jacionline.org). A few interaction terms between the pollutants and the pollen variables were statistically significant ($P < .05$), but again no consistent pattern was apparent in models stratified by tertiles of pollutant concentrations.

DISCUSSION

This study is the first to demonstrate that levels of airborne Phl p 5, an important grass pollen allergen, are more consistently associated with the occurrence of allergic and respiratory symptoms than pollen counts, after accounting for meteorological and environmental factors. In mutually adjusted models that allowed us to compare the relative importance of each pollen variable, only associations with daily Phl p 5 levels and the occurrence of high health scores in a panel study of 93 adults with moderate-severe allergic rhinitis remained consistent throughout various analyses. Associations with daily pollen counts were heavily attenuated when Phl p 5 levels were accounted for. These trends were observed not only for the total score, but also for the symptom and medication scores independently, suggesting that airborne allergen levels impact how a patient experiences symptoms and their attempts to control them through medication use.

These trends were not replicated for hospital admissions for asthma, for which associations with pollen counts appeared more robust than those with Phl p 5 levels among individuals ≤ 44 years of age. However, these results should be interpreted with caution, as CIs overlapped between the estimates for pollen counts and Phl p 5 levels. The lack of any associations in individuals > 44 years of age may reflect that asthma in older age has a more complex phenotype (allergic or secondary nonallergic, linked to other risk factors such as smoking and comorbidities, and overlaps with chronic obstructive pulmonary disease²²).

Implications

It may be intuitive that Phl p 5 levels should strongly predict health outcomes, as it is the allergen that elicits the IgE-mediated immunologic response and not the pollen grain, as supported by experimental studies (eg, see Buters et al¹⁵). However, routine monitoring of allergen levels does not occur in the United Kingdom or elsewhere. Rather, risk assessments, pollen forecasts, and public health tools are based on pollen counts, which, although informative, may not be the best measure to allow allergic and asthmatic patients to self-manage their symptoms.

The mismatch between airborne pollen counts and allergen levels is influenced by year, location, plant growth, and various meteorological and environmental factors, such as temperature, precipitation, relative humidity, and air pollutants, which are affected by ongoing climate change.^{11,23,24} How individuals experience exacerbations of allergic diseases is also influenced by their external exposome.²⁵ We tested for interactions between the pollen variables and several air pollutants, but no clear trends were identified, which is consistent with a recent systematic

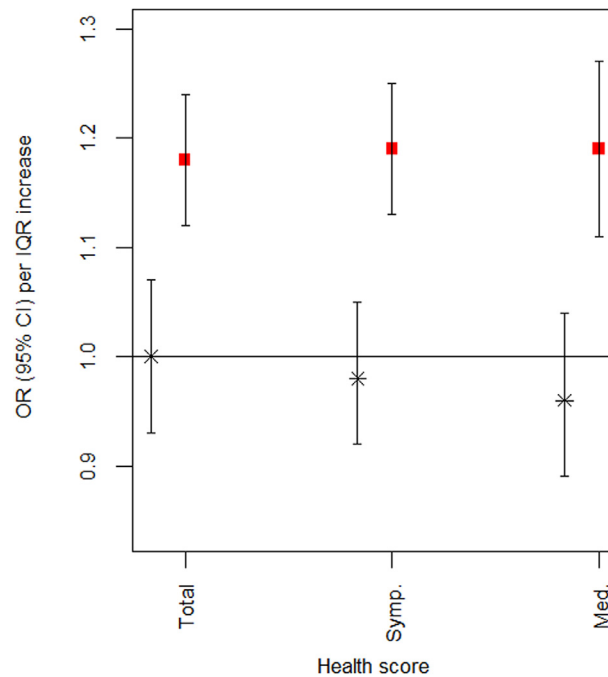


FIG 1. ORs and 95% CIs for reporting total, symptom, and medication scores > within-person 75th percentile associated with an IQR increase in pollen counts (*black stars*) and Phl p 5 levels (*red squares*), from mutually adjusted models. The effect estimate for pollen counts (*black stars*) can be interpreted as the increase in odds of having a score > within-person 75th percentile associated with an IQR increase in pollen counts, after accounting for the effects of airborne Phl p 5 levels and other covariates. The effect estimate for Phl p 5 levels (*red squares*) can be interpreted as the increase in odds of having a score > within-person 75th percentile associated with an IQR increase in Phl p 5 levels, after accounting for the effects of pollen counts and other covariates.

TABLE III. OR [95% CI] for having a symptom score > within-person 75th percentile associated with an IQR increase in grass pollen counts and Phl p 5 levels*

Health scores	Grass pollen counts	Phl p 5 levels
Eye symptoms	1.00 [0.93, 1.08]	1.13 [1.06, 1.21]
Nose symptoms	0.97 [0.91, 1.03]	1.22 [1.15, 1.30]
Chest symptoms	1.01 [0.92, 1.11]	1.02 [0.93, 1.11]
Mouth/throat symptoms	1.03 [0.95, 1.11]	1.09 [1.00, 1.19]

*Generalized estimating equations logistic models contain terms for grass pollen counts, Phl p 5 levels, sex, age, trial arm, month, daily mean temperature, daily mean relative humidity, daily precipitation, and daily mean NO₂.

review.²⁶ However, our study had a limited number of days with exposure information, which reduced statistical power and the precision of the effect estimates in the interaction and stratified analyses. Further, the ChemVol High Volume Cascade Impactor used to measure Phl p 5 levels did not capture very small particles (cutoff was 2.5 μ m), so very small allergen released via direct cell damage of the pollen grain wall by pollutants may have been missed. However, long-term measurements to detect pollen allergen in this size fraction suggest that there are very few days with significant allergen in the PM_{2.5} fraction.¹¹ Despite the lack of interactions with air pollutants in this work, we encourage future studies to continue examining interactions between pollen grains, their allergens, meteorological factors, and air pollutants, as it is increasingly clear that these all have independent and joint effects on allergic and respiratory health, which are influenced by urbanization and climate change.^{23,27}

Strengths and limitations

To the best of our knowledge, this study is the first to compare the strength of associations of grass pollen counts and Phl p 5 levels with respiratory health outcomes in models adjusted for both meteorological factors and air pollutants. One previous study reported similar effect estimates for associations between birch and grass pollen counts and allergen levels with nasal and ocular allergic symptoms but in only 15 adults with pollen allergy.²⁸ A second study reported that allergic symptoms in Austria, Germany, France, and Finland in an online data tool had higher Spearman correlations with allergen levels (Bet v 1 and Phl p5) than pollen counts (birch and grass) for certain study years.²⁹ However, in both previous studies, as allergen levels and pollen counts were considered in separate analyses and their effects were not mutually adjusted for, it is difficult to determine which may be most relevant for health. Further, neither considered the confounding effects of meteorological factors.²⁹ Further strengths of this work include the use of the PollenLITE trial study population, a highly characterized group of adults with grass allergen allergy, and an attempt at replication using daily hospital admissions for asthma as a second independent set of health data. However, we acknowledge that symptom reporting is subjective and that asthma admissions are influenced by many factors that are unrelated to asthma severity (eg, social factors, comorbidities). It is possible that the results for hospital admissions for asthma might have been more consistent had serologic data been available to restrict the analysis to individuals sensitized to grass pollen.

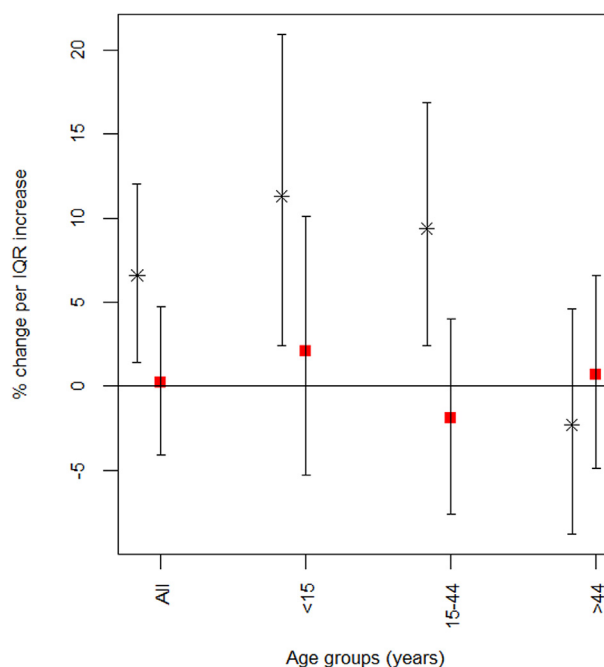


FIG 2. Percent change in daily hospital admissions for asthma, for the whole population, and among individuals < 15, 15 to 44, and > 44 years of age, associated with an IQR increase in pollen counts (*black stars*) and Phl p 5 levels (*red squares*), from mutually adjusted models. The effect estimate for pollen counts (*black stars*) can be interpreted as the percent change in daily hospital admissions for asthma associated with an IQR increase in pollen counts, after accounting for the effects of airborne Phl p 5 levels and other covariates. The effect estimate for Phl p 5 levels (*red squares*) can be interpreted as the percent change in daily hospital admissions for asthma associated with an IQR increase in Phl p 5 levels, after accounting for the effects of pollen counts and other covariates.

The daily pollen measurements made at one site in central London were explicitly assumed to represent exposure equally to all participants in the PollenLITE trial for the health scores and all residents living within broadly 100 km for the hospital admissions for asthma. There is published evidence that daily pollen count measurements up to 41 km are in near-perfect agreement for 2 English cities,³⁰ and others show supporting results for up to 30 km.³¹ However, as no studies exist to support this assumption for Phl p 5 levels, it is possible that the spatial variation in Phl p 5 levels is higher than pollen counts. This may be one reason why associations were not observed between Phl p 5 levels and hospital admissions for asthma in mutually adjusted models. Sensitivity analyses in which we restricted to hospital admissions for asthma within 50 km and 20 km of the pollen measurement site to reduce potential exposure misclassification did not elicit a clear trend, although effect estimates were greatest for Phl p 5 levels for the smallest (20 km) buffer.

The short available time frame of the pollen measurement data is a notable limitation of this work. Seasonality in pollen counts and Phl p 5 levels exist, and it is likely that their association with respiratory health is also seasonal. Although we included calendar month in all models and examined smoothing splines (ultimately deemed unnecessary), we had data only on Phl p 5 levels for one season, which limited our ability to account for long-term time trends and seasonality. Further, despite adjusting for calendar month and specifying an autoregressive lag 1 correlation structure in the models, diagnostic plots revealed some remaining autocorrelation in the model residuals for the health scores (Fig E3 in the Online Repository at www.jacionline.org). We hypothesize that this could be improved by analyzing data from multiple years, in which seasonality and time trends could be better accounted

for. Multiyear data would also substantially increase the statistical power of the analyses, possibly allowing the identification of interactive effects with other environmental factors. The health score results were nonetheless robust to many sensitivity analyses in which we tested our model parameters.

A final limitation is that we examined only grass pollen. Further work should consider other allergen components of grass pollen, such as the group 1 allergens (eg, Phl p 1), and birch, ragweed, olive pollen, and molds, for which a mismatch between pollen grains or fungal spore counts and airborne allergen levels has been documented.^{5,15,32,33}

In conclusion, grass allergen (Phl p 5) levels were more consistently associated with the occurrence of allergic respiratory symptoms in a panel study of adults with grass pollen allergy than were pollen counts. Results for daily hospital admissions were less consistent than those from the panel study. As allergens are the biologically active component of pollen, and their release is affected by factors influenced by climate change and urbanization, there is a need to assess, using multiyear data, whether increased efforts should be invested in modeling airborne allergen content and whether allergen levels should become the standard for measuring the allergic potential of the air.

DISCLOSURE STATEMENT

The PollenLITE trial was awarded by the Efficacy and Mechanism Evaluation Programme, is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership, and is jointly sponsored by King's College London and Guy's and St Thomas' NHS Foundation Trust. Additional funding

was provided by the King's Health Partners Research and Development Challenge Fund. This work was also supported by the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The work of the UK Small Area Health Statistics Unit is overseen by the UK Health Security Agency and partly funded by the MRC Centre for Environment and Health (grant no. MR/L01341X/1), the NIHR through its Health Protection Units at Imperial College London in Environmental Exposures and Health and in Chemical and Radiation Threats and Hazards, Health Data Research UK, and infrastructure support to the Department of Epidemiology and Biostatistics provided by the NIHR Imperial Biomedical Research Centre. This paper does not necessarily reflect the views of the UK Health Security Agency, the NIHR, or the Department of Health and Social Care. E.F. is supported by the Imperial College Research Fellowship. J.T.M.B. was supported by a Higher Education Funding Council for England Clinical Senior Lectureship Award during the period the PollenLITE study was conducted. The funding sources had no role in the study design, collection, analysis and interpretation of data, writing of the report, and decision to submit the paper for publication.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

We gratefully acknowledge the following individuals who contributed to the design and conduct of the PollenLITE clinical trial: Stephen Durham, Andrea Guerra, Rachel Muir, Konstantinos Tsioulos, Joanna Kelly, Caroline Murphy, Tao Chen, and Paul Tunstell. We are indebted to the participants in the PollenLITE trial and members of the public who provided input to the project; to James Dobbyn, John Brooks, Sharon Jones, and Gerry Trillana of the NIHR Clinical Research Facility at Guy's Hospital; the UK Meteorological Office for managing the UK pollen network and Bhopal Pandey, Kris Chan, Natalia Acero Martinez, Dr Trevor Blackall, and Dr Robert Francis for collection and provision of pollen count data. We acknowledge the Small Area Health Statistics Unit database team for support with the NHS England data, Hima Daby and Gajanan Natu. The Small Area Health Statistics Unit holds approvals both from the London-South East Research Ethics Committee, reference 22/LO/0256, and from the Health Research Authority Confidentiality Advisory Group, reference 20/CAG/0028. Hospital Episode Statistics data are copyright © 2022, reused with the permission of NHS England. All rights reserved.

Key messages

- A mismatch between daily pollen counts and allergen levels is affected by environmental factors and climate change, but routine monitoring of allergen levels does not occur in the United Kingdom or elsewhere.
- Grass allergen (Phl p 5) levels were shown to be more consistently associated with allergic respiratory symptoms in a panel study than grass pollen counts.
- These results suggest that measuring airborne allergen levels (instead or in addition to grass pollen counts) may improve risk prediction and help patients better control their allergic and respiratory symptoms.

REFERENCES

1. Kitinoja MA, Hugg TT, Siddika N, Yanez DR, Jaakkola MS, Jaakkola JJK. Short-term exposure to pollen and the risk of allergic and asthmatic manifestations: a systematic review and meta-analysis. *BMJ Open* 2020;10:e029069.

2. Erbas B, Jazayeri M, Lambert KA, Katelaris CH, Prendergast LA, Tham R, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: a systematic review and meta-analysis. *Allergy* 2018;73:1632-41.
3. Osborne NJ, Alcock I, Wheeler BW, Hajat S, Saran C, Clewlow Y, et al. Pollen exposure and hospitalization due to asthma exacerbations: daily time series in a European city. *Int J Biometeorol* 2017;61:1837-48.
4. Tegart LJ, Johnston FH, Borchers Arriagada N, Workman A, Dickinson JL, Green BJ, et al. 'Pollen potency': the relationship between atmospheric pollen counts and allergen exposure. *Aerobiologia* 2021;37:825-41.
5. Grewling L, Nowak M, Szymańska A, Kostecki L, Bogawski P. Temporal variability in the allergenicity of airborne *Alternaria* spores. *Med Mycol* 2019;57:403-11.
6. Buters J, Prank M, Sofiev M, Pusch G, Albertini R, Annesi-Maesano I, et al. Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season. *J Allergy Clin Immunol* 2015;136:87-95.e6.
7. D'Amato G, Chong-Neto HJ, Monge Ortega OP, Vitale C, Ansotegui I, Rosario N, et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy* 2020;75:2219-28.
8. Andersson K, Lidholm J. Characteristics and immunobiology of grass pollen allergens. *Int Arch Allergy Immunol* 2003;130:87-107.
9. Hrabina M, Peltre G, Van Ree R, Moingeon P. Grass pollen allergens. *Clin Ex Allergy Rev* 2008;8:7-11.
10. Ščevková J, Vašková Z, Sepšiová R, Dušička J, Kováč J. Relationship between Poaceae pollen and Phl p 5 allergen concentrations and the impact of weather variables and air pollutants on their levels in the atmosphere. *Heliyon* 2020;6:e04421.
11. Maya-Manzano JM, Oteros J, Rojo J, Traidl-Hoffmann C, Schmidt-Weber C, Buters J. Drivers of the release of the allergens Bet v 1 and Phl p 5 from birch and grass pollen. *Environ Res* 2022;214:113987.
12. Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Hay E, et al. Intradermal grass pollen immunotherapy increases TH2 and IgE responses and worsens respiratory allergic symptoms. *J Allergy Clin Immunol* 2017;139:1830-9.e13.
13. Output areas (December 2011) population weighted centroids - data.gov.uk. Office for National Statistics. 2020. Available at: <https://www.ons.gov.uk/peopolepopulationandcommunity/populationandmigration/populationestimates/datasets/10wersuperoutputareamidyearpopulationestimates>. Accessed February 5, 2020.
14. Rojo J, Oteros J, Pérez-Badía R, Cervigón P, Ferencova Z, Gutiérrez-Bustillo AM, et al. Near-ground effect of height on pollen exposure. *Environ Res* 2019;174:160-9.
15. Buters JTM, Thibaudon M, Smith M, Kennedy R, Rantio-Lehtimäki A, Albertini R, et al. Release of Bet v 1 from birch pollen from 5 European countries. Results from the HIALINE study. *Atmos Environ* 2012;55:496-505.
16. Medical & Environmental Data Mash-up Infrastructure (MEDMI). European Center for Environment and Human Health; 2022. Available at: <https://www.data-mashup.org.uk/>. Accessed February 12, 2020.
17. UK Air: Air Information Resource: Data Archive. Department for Environment Food and Rural Affairs. Available at: <https://uk-air.defra.gov.uk/data/>. Accessed December 11, 2019.
18. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021 Available at: <https://www.R-project.org/>. Accessed July 15, 2023.
19. Højsgaard S, Halekon U, Yan J. The R package geepack for generalized estimating equations. *J Stat Softw* 2006;15:1-11.
20. geepack Yan J. yet another package for generalized estimating equations. *R News* 2002;2/3:12-4.
21. Yan J, Fine J. Estimating equations for association structures. *Stat Med* 2004;23:849-80.
22. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med* 2015;373:1241-9.
23. Pacheco SE, Guidos-Fogelbach G, Annesi-Maesano I, Pawankar R, D'Amato G, Latour-Staffeld P, et al. Climate change and global issues in allergy and immunology. *J Allergy Clin Immunol* 2021;148:1366-77.
24. Cecchi L. From pollen count to pollen potency: the molecular era of aerobiology. *Eur Respir J* 2013;42:898-900.
25. Cecchi L, D'Amato G, Annesi-Maesano I. External exposures and allergic respiratory and skin diseases. *J Allergy Clin Immunol* 2018;141:846-57.
26. Lam HCY, Jarvis D, Fuertes E. Interactive effects of allergens and air pollution on respiratory health: a systematic review. *Sci Total Environ* 2021;757:143924.
27. Eguiluz-Gracia I, Mathioudakis AG, Bartel S, Vijverberg SJH, Fuertes E, Comber-iat P, et al. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. *Allergy* 2020;75:2170-84.
28. Riediker M, Monn C, Koller T, Stahel WA, Wüthrich B. Air pollutants enhance rhinoconjunctivitis symptoms in pollen-allergic individuals. *Ann Allergy Asthma Immunol* 2001;87:311-8.
29. Bastl K, Kmenta M, Pessi AM, Prank M, Saarto A, Sofiev M, et al. First comparison of symptom data with allergen content (Bet v 1 and Phl p 5 measurements) and pollen data from four European regions during 2009–2011. *Sci Total Environ* 2016;548-549:229-35.

30. Pashley CH, Fairs A, Edwards RE, Bailey JP, Corden JM, Wardlaw AJ. Reproducibility between counts of airborne allergenic pollen from two cities in the East Midlands, UK. *Aerobiologia* 2009;25:249-63.
31. Oteros J, Valencia RM, del Río S, Vega AM, García-Mozo H, Galán C, et al. Concentric ring method for generating pollen maps. *Quercus* as case study. *Sci Total Environ* 2017;576:637-45.
32. Galán C, Antunes C, Brandao R, Torres C, Garcia-Mozo H, Caeiro E, et al. Airborne olive pollen counts are not representative of exposure to the major olive allergen Ole e 1. *Allergy* 2013;68:809-12.
33. Wang W, Wang Q, Lu S, Lin Y, Suzuki M, Saito Y. Behavior of autumn airborne ragweed pollen and its size-segregated allergens (Amb a 1): a study in urban Saitama, Japan. *Atmosphere* 2023;14:247.