Ambient pollen concentrations and emergency department visits for asthma and wheeze

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Background: Previous studies report associations between aeroallergen exposure and asthma exacerbations. Aeroallergen burdens and asthma prevalence are increasing worldwide and are projected to increase further with climate change, highlighting the importance of understanding population-level relationships between ambient pollen concentrations and asthma.

Objective: We sought to examine short-term associations between ambient concentrations of various pollen taxa and emergency department (ED) visits for asthma and wheeze in the Atlanta metropolitan area between 1993 and 2004.

Methods: We assessed associations between the 3-day moving average (lag 0-1-2) of Betulaceae (except *Alnus* species), Cupressaceae, *Quercus* species, Pinaceae (except *Tsuga* species), Poaceae, and *Ambrosia* species pollen concentrations and daily asthma and wheeze ED visit counts, controlling for covarying pollen taxa and ambient pollutant concentrations.

Results: We observed a 2% to 3% increase in asthma- and wheeze-related ED visits per SD increase in *Quercus* species and Poaceae pollen and a 10% to 15% increased risk on days with the highest concentrations (comparing the top 5% of days with the lowest 50% of days). An SD increase in Cupressaceae concentrations was associated with a 1% decrease in ED visits. The association for *Quercus* species pollen was strongest for children aged 5 to 17 years. Effects of *Ambrosia* species pollen on asthma exacerbations were difficult to assess in this large-scale temporal analysis because of possible confounding by the steep increase in circulating rhinoviruses every September.

Conclusion: Poaceae and *Quercus* species pollen contribute to asthma morbidity in Atlanta. Altered *Quercus* species and Poaceae pollen production caused by climate change could affect allergen-induced asthma morbidity in the southeastern United States. (J Allergy Clin Immunol 2012;130:630-8.)

Key words: *Pollen, asthma exacerbation, wheeze, pollinosis, aeroallergens, bioaerosols, ozone, climate change, epidemiology*

Previous epidemiologic studies have reported associations between ambient pollen levels and various measures of asthma morbidity.[1-6] However, the specific pollen taxa implicated have not been consistent across studies, which might be partially attributable to geographic differences in the prevalence of plant species and their related allergens, pollen concentrations, and allergic sensitization profiles of the populations under study. In addition, determining the shape of the exposure-response curve for highly skewed pollen distributions and controlling adequately for time and meteorology in time-series studies present methodological challenges and might explain differences in results among studies.[7]

The incidence of asthma and other allergic respiratory diseases has increased dramatically worldwide in the last 3 decades.[8] Projected changes in pollen production caused by climate change magnify the importance of understanding relationships between asthma exacerbations and pollen concentrations.[9] Improved understanding of specific exposure-outcome relationships can facilitate a wide range of adaptation activities that might reduce the associated health impacts.[10]

We investigated short-term associations between pollen levels and asthma exacerbations in the metropolitan Atlanta area using a large time series of more than 400,000 emergency department (ED) visits for asthma and wheeze between 1993 and 2004. We assessed associations for 4 tree taxa (Betulaceae, Cupressaceae, *Quercus* species, and Pinaceae), Poaceae (grasses), and *Ambrosia* species (ragweeds). The large sample size allowed for tight control of time trends and temperature, as well as secondary analyses in which we explored the shape of the dose response, confounding among the pollen taxa, age-specific effects, and confounding and effect modification by ambient pollutant concentrations.

METHODS

Pollen data

Airborne pollen concentrations were measured by the Atlanta Allergy and Asthma Clinic, a member of the National Allergy Bureau, between January 1, 1993, and December 31, 2004 (Fig 1). The monitoring site was moved once on January 1, 2000; pollen was sampled from the same rooftop height at both locations and away from vegetation, air conditioners, and building vents.

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Supported by the Centers for Disease Control and Prevention (TKC Global Solutions, LLC: JR5000139), the US Environmental Protection Agency (USEPA; RD834799), and the National Institute of Environmental Health Sciences (NIEHS; R03ES018963). Creation of the emergency department database was supported by the USEPA (RD833626), the NIEHS (R01ES11294), and the Electric Power Research Institute (EP-P277231/C13172). The content of this publication is solely the responsibility of the grantee and does not necessarily represent the official views of the USEPA. Furthermore, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication.

Disclosure of potential conflict of interest: L. A. Darrow and M. Klein have received research support from the National Institute of Environmental Health Sciences, the US Environmental Protection Agency (EPA), the Electric Power Research Institute, and the Centers for Disease Control and Prevention (CDC). J. Hess has received research support from the CDC. P. E. Tolbert has received research support from the EPA, the Electric Power Research Institute, the National Institutes of Health, and the CDC. S. E. Sarnat has received research support from the EPA and the Electric Power Research Institute. C. A. Rogers declares that she has no relevant conflicts of interest.

Received for publication November 21, 2011; revised May 14, 2012; accepted for publication June 18, 2012.

Available online July 26, 2012.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.06.020

Abbreviations used
CO: Carbon monoxide
ED: Emergency department
ICD-9: International Classification of Diseases, Ninth Revision
NO_2: Nitrogen dioxide
$PM_{2.5}$: Twenty-four-hour average particulate matter of less than 2.5 μm in diameter
PM_{10}: Twenty-four-hour average particulate matter of less than 10 μm in diameter
SO_2: Sulfur dioxide
URI: Upper respiratory tract infection

National Allergy Bureau–certified Atlanta Allergy and Asthma Clinic staff analyzed air samples 5 days per week (Sunday-Thursday) using a Rotorod sampler (Model 40; SDI Company, Plymouth Meeting, Pa). The Rotorod was set to spin for 30 seconds every 10 minutes, and pollen was collected on a plastic I rod (dimensions, 23 mm × 1.59 mm) coated with silicone grease. After each 24-hour sampling period, the I rod was placed in a stage adapter and stained with Calberla solution. As per Rotorod manufacturer's instructions, the entire surface (using 3 and 1/3 longitudinal sweeps) was examined microscopically at ×400 magnification, and counts of individual pollen taxa were converted to concentrations (pollen grains per cubic meter of air). Because pollen grains deposit on the rods in a random manner along the collector surface,[11] during peak pollen seasons, counts were obtained from one longitudinal sweep over the rod, with concentration conversion calculations adjusted accordingly.

We selected several pollen taxa *a priori* for evaluation in epidemiologic analyses based on allergenic potential and prevalence in Atlanta, including Betulaceae (birches, hornbeam, hophornbeam, and hazelnut but excluding alder), Cupressaceae (junipers, cedars, and bald cypress), *Quercus* species (oaks), and Pinaceae (pines, spruces, and fir, except hemlock). Pinaceae were selected as a "control" pollen taxon because they are thought to only infrequently cause serious allergic responses.[12,13] We also included Poaceae (grasses) and *Ambrosia* species (ragweeds). For our main epidemiologic analyses, the 2 days (Friday-Saturday) of missing pollen data each week were estimated by using linear interpolation. In a model validation exercise, imputations for Tuesdays and Wednesdays were reasonably correlated with corresponding measured pollen levels, with Spearman correlation coefficients ranging from 0.65 (Cupressaceae) to 0.84 (*Quercus* species). In sensitivity analyses we excluded the Friday-Saturday imputed data from the epidemiologic models.

Ambient air pollution data

Monitoring data from available monitoring networks in the study area were used to create daily, population-weighted, spatial average pollutant concentrations for 8-hour maximum ozone; 1-hour maximum carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2); and 24-hour average particulate matter of less than 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$) in diameter, as described in detail elsewhere.[14] We have examined associations between ED visits and these air quality metrics in previous analyses.[15]

ED visit data

We obtained individual-level data on ED visits for the 20-county (7964 m^2) Atlanta population through computerized billing records collected from 41 acute-care hospitals for the 1993-2004 time period (Fig 1).[16] For each patient visit, hospitals provided the date of admission; International Classification of Diseases, Ninth Revision (ICD-9), diagnostic codes; and patient's date of birth and residential ZIP code.

We defined ED visits for asthma and wheeze as all visits with a primary or secondary ICD-9 code indicating asthma (493.0-493.9) or wheeze (786.09 before October 1, 1998; 786.07 beginning October 1, 1998) that did not also have a code for an external injury or poisoning (E800-E999).[15] Asthma-related ED visits were grouped into 3 age categories: 0 to 4 years, 5 to 17 years, and 18 years or older. We identified ED visits for acute upper respiratory tract infections (URIs; 460.0-466.0) without a concurrent ICD-9 code for asthma or wheeze. We also created a control outcome group for finger wounds (883) because these visits were unlikely to be causally related to pollen levels. The study protocol was approved by the Emory University Institutional Review Board.

Analysis

We examined associations between pollen concentrations and asthma ED visits using a case-crossover design matched on same-day temperature, a strong confounder.[15] Because the exposure (ie, ambient pollen) was shared among all patients, we implemented the analysis in Poisson regression using indicator variables for month, year, and maximum temperature (lag 0), as well as their interactions.[17] Conceptually, this is analogous to creating strata in which case days (day of the ED visit) are matched to control days in the same calendar month with the same temperature (exact degree Celsius). Models included indicator variables for hospital, day of week and holidays, cubic polynomial terms for lag 1-2 minimum temperature, and lag 0-1-2 average dew point. Potential confounding by URIs was controlled by including a term for the logarithm of the age-specific daily count of URI-related ED visits. Primary analyses assessed associations between continuous 3-day moving average pollen levels (average of today [lag 0], yesterday [lag 1], and 2 days ago [lag 2]) and asthma-related ED visits. Analyses were limited to the relevant pollen season for each taxon: Betulaceae (February-May), Cupressaceae (January-April), *Quercus* species (February-May), Pinaceae (February-June), Poaceae (March-June), and *Ambrosia* species (August-November). Months outside of these seasons were excluded because of minimal variation in concentrations.

We conducted several secondary analyses, including examination of the shape of the dose-response relationship, using distributional categories, single-day lag models (lag 0 through lag 7), age-specific effects, confounding by ambient air pollutants, and effect modification by ozone, a known pulmonary irritant. We also created a multi-taxa model to assess whether individual tree pollen results were confounded by each other; although the tree pollen taxa did not peak at exactly the same time each year, airborne levels were correlated between taxa within a calendar month, creating the potential for confounding. The multi–tree pollen model time period (January-June of every year) captured the peak concentration periods for all 4 tree taxa.

Although the case-crossover approach inherently controls for all time-invariant risk factors (eg, socioeconomic status and race), it is vulnerable to confounding by factors that vary within the time windows selected, in this case months.[18] An example of within-month trends in asthma exacerbations is the steep increase that occurs at the beginning of the school year every September because of circulating rhinoviruses.[19] In sensitivity analyses we added controls for within-month trends by including a cubic polynomial on day of season (with "season" defined for each pollen taxa as described above). We also conducted analyses excluding days with imputed pollen values and stratified analyses by study year to assess whether associations were driven by a small number of influential years. All analyses were carried out with SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Descriptive statistics

Over the 1993-2004 time period, there were 400,819 ED visits for asthma and wheeze (0-4 years = 108,147 visits; 5-17 years = 91,386 visits, and ≥18 years = 201,286 visits). ED visits are further described in Table E1 in this article's Online Repository at www.jacionline.org. Raw data plots shown in Fig E1 in this article's Online Repository at www.jacionline.org demonstrate recurrent seasonal patterns of ED visits. Ambient pollen concentrations were highly skewed, with concentrations that

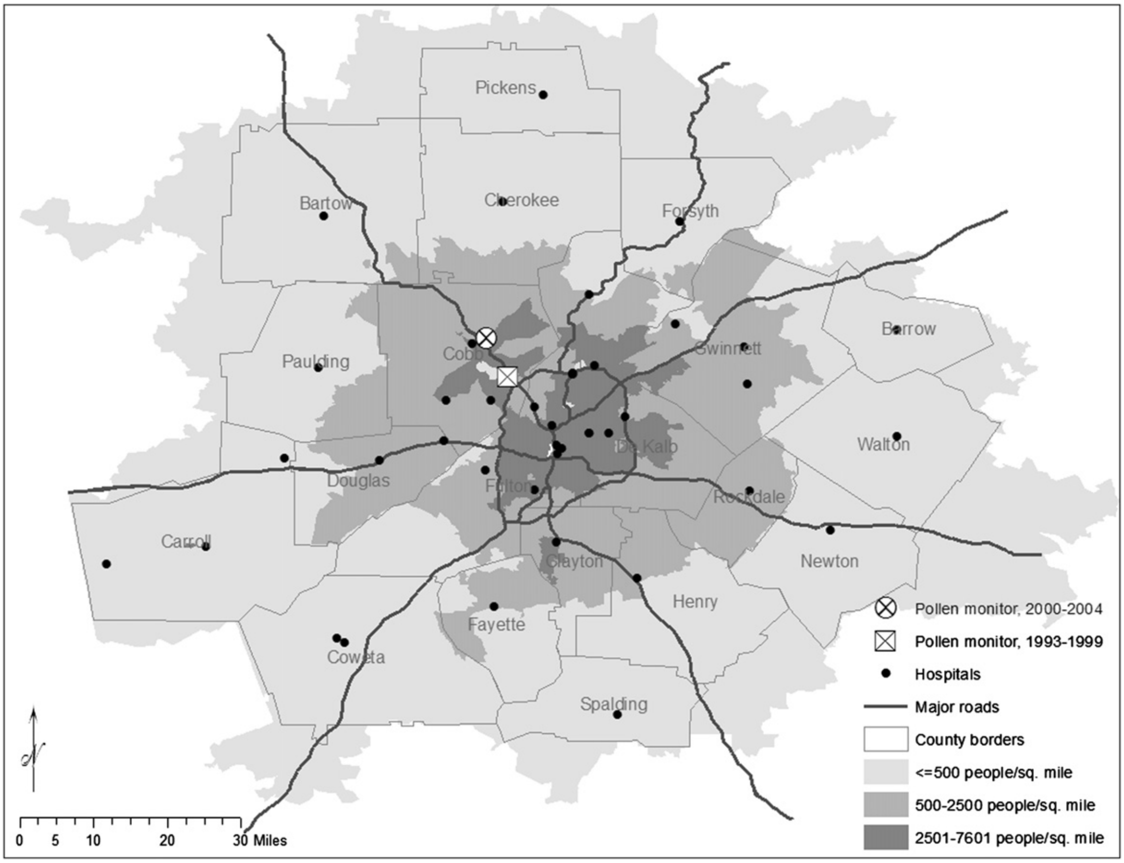

FIG 1. Twenty-county Atlanta study area.

were low or zero for large parts of the year (eg, Fig 2 presents daily pollen time series for 2004). Descriptive statistics (Table I) for each pollen taxon for the months included in epidemiologic analyses show that concentrations differed among taxa by orders of magnitude. Table II displays overall Spearman correlation coefficients among the 3-day average pollen and pollutant concentrations; 3-day average concentrations of *Quercus* species, Pinaceae, and Betulaceae pollen were strongly correlated ($r = 0.68\text{-}0.77$).

Single-taxon models

Risk ratios and 95% CIs for associations between continuous (ie, linear) 3-day moving average pollen levels for the 6 pollen taxa and asthma-related ED visits for all ages combined are presented in Table III. Relative risks were scaled to approximate SD increases in the season-specific pollen data (Table III). We observed positive associations for Betulaceae, *Quercus* species, Pinaceae, and Poaceae pollen; a negative association for Cupressaceae pollen; and no association for *Ambrosia* species.

Multitaxa models

Because tree pollen levels were correlated between taxa (Table II and Fig 2), we examined whether results from the single-taxon models were confounded by covarying pollen types. Among the tree taxa, the *Quercus* species–asthma relationship was strongest; the effects of Betulaceae and Pinaceae were consistent with the null when controlling for *Quercus* species pollen (Table III). These results suggest that the positive associations observed in the single-taxon models for Betulaceae and Pinaceae were likely due to covarying *Quercus* species pollen concentrations. On the basis of observed positive associations, we also modeled *Quercus* species and Poaceae together in the same model. Results shown in Table III demonstrate independent associations for these 2 taxa.

Categorical exposure

We investigated the potential for a nonlinear dose response with a focus on the top end of the pollen distributions. We examined effects of the 50th to 75th, 75th to 90th, 90th to 95th, and 95th to 100th percentiles relative to the 0 to 50th percentile of pollen concentrations within the predefined pollen season for each taxon. Concentration percentiles are shown in Table I, and median concentrations for each category are shown on the x-axis in Fig 3. Because of the apparent confounding of the effects of Pinaceae and Betulaceae by *Quercus* species, as described above, results for Betulaceae and Pinaceae are adjusted for *Quercus* species pollen concentrations.

We observed positive associations for *Quercus* species and Poaceae, with a pattern of progressively stronger risk ratios for higher concentrations relative to the lowest concentrations (Fig 3). For Poaceae, statistically significant increased risks were observed for all concentration categories of greater than the 50th

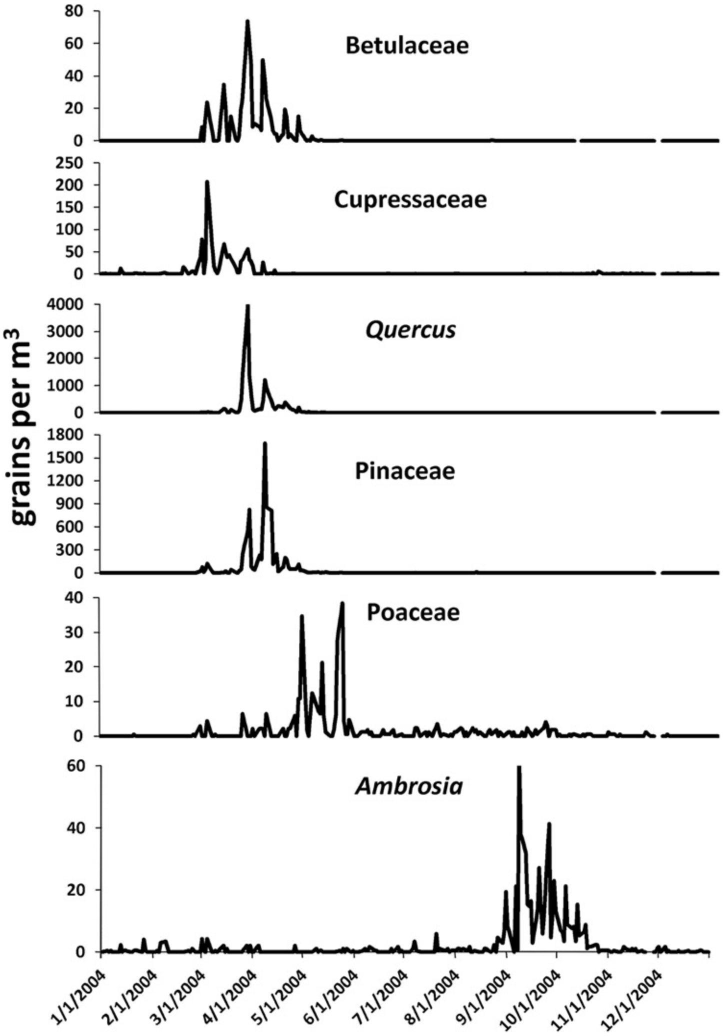

FIG 2. Daily time series of pollen concentrations (in grains per cubic meter) for 2004.

TABLE I. Descriptive statistics of 3-day moving average pollen concentrations (in grains per cubic meter) from the Atlanta Allergy and Asthma Clinic, 1993-2004

				Percentiles				
Pollen	**Months**	**No.***	**Mean ± SD**	**50th**	**75th**	**90th**	**95th**	**Maximum**
Betulaceae	February-May	1423	8.1 ± 17.6	1.2	7.2	26.3	38.6	177.5
Cupressaceae	January-April	1408	10.0 ± 21.2	2.4	9.9	27.4	46.0	183.2
Quercus species	February-May	1423	123.0 ± 333.8	5.1	71.6	390.9	692.0	3793.2
Pinaceae	February-June	1782	74.1 ± 219.9	4.9	33.3	193.1	412.1	2753.4
Poaceae	March-June	1443	6.1 ± 9.1	2.9	7.9	15.9	21.8	73.8
Ambrosia species	August-November	1426	8.9 ± 13.8	2.4	11.6	27.5	39.4	128.4

*Number of days included in analysis.

percentile, whereas for *Quercus* species, associations were only observed for concentrations of greater than the 90th percentile (relative to the bottom 50%). There was little evidence of association with other pollen taxa. Risk ratios for the highest category of Betulaceae and *Ambrosia* species (95th-100th percentile) were increased but were not significant. Because only *Quercus* species and Poaceae were associated with ED visits in the primary analyses, secondary analyses focused exclusively on *Quercus* species and Poaceae.

Assessment of lag structure

We assessed the lag structure of the pollen-asthma associations using single-day lag models of lags 0 through 7. Fig 4 presents the results of these analyses for *Quercus* species and Poaceae pollen. For *Quercus* species, the strongest associations were observed for lags 2 through 4, whereas for Poaceae, the strongest association was for lag 0. The 3-day moving average (of lags 0, 1, and 2) exposure window yielded stronger associations than any single-day lag.

TABLE II. Spearman correlation coefficients among 3-day moving average pollen and pollutant concentrations

	Betulaceae	Cupressaceae	*Quercus*	Pinaceae	Poaceae	*Ambrosia*	Ozone	CO	NO_2	SO_2	PM_{10}	$PM_{2.5}$
Betulaceae	1	0.47	0.77	0.68	0.33	−0.30	0.15	0.01	0.18	−0.04	−0.02	−0.10
Cupressaceae		1	0.44	0.34	−0.19	−0.22	−0.26	0.05	0.15	0.08	−0.26	−0.25
Quercus species			1	0.74	0.43	−0.32	0.16	−0.02	0.15	−0.06	−0.03	−0.09
Pinaceae				1	0.48	−0.33	0.26	−0.06	0.10	−0.10	0.03	−0.03
Poaceae					1	0.02	0.58	−0.10	0.04	−0.19	0.34	0.26
Ambrosia species						1	0.01	−0.03	0.00	−0.13	0.11	0.12
Ozone							1	0.14	0.26	0.04	0.67	0.58
CO								1	0.58	0.32	0.45	0.42
NO_2									1	0.43	0.43	0.39
SO_2										1	0.14	0.12
PM_{10}											1	0.89
$PM_{2.5}$												1

Correlation coefficients are for all days between January 1, 1993, and December 31, 2004, except PM_{10} (began January 1, 1996) and $PM_{2.5}$ (began August 1, 1998).

TABLE III. Associations between 3-day moving average pollen levels and asthma- and wheeze-related ED visits

		Single-taxon models		Multi–tree pollen model*		*Quercus*–Poaceae model†	
Pollen taxa	**Per unit (grains/m^3)**	**Risk ratio (95% CI)**	***P* value**	**Risk ratio (95% CI)**	***P* value**	**Risk ratio (95% CI)**	***P* value**
Betulaceae	20	1.022 (1.013-1.032)	<.001	1.004 (0.993-1.016)	.439	NA	
Cupressaceae	25	0.986 (0.975-0.996)	.007	0.988 (0.978-0.998)	.024	NA	
Quercus species	300	1.028 (1.021-1.035)	<.001	1.028 (1.020-1.037)	<.001	1.026 (1.019-1.033)	<.001
Pinaceae	200	1.007 (1.001-1.013)	.015	0.995 (0.988-1.001)	.123	NA	
Poaceae	10	1.022 (1.012-1.033)	<.001	NA		1.019 (1.008-1.029)	<.001
Ambrosia species	15	1.001 (0.990-1.013)	.849	NA		NA	

NA, Not applicable.
*Multipollen results are from the model including all 4 tree pollen taxa together for the season January through June of every year.
†*Quercus*–Poaceae results are from the model including both *Quercus* species and Poaceae for the for the season March through May of every year.

Age-specific effects

We examined age-stratified associations using the continuous 3-day moving average pollen levels for *Quercus* species and Poaceae pollen (Fig 5). The magnitude of associations differed by age group, with the strongest associations for *Quercus* species occurring in school-aged children 5 to 17 years (risk ratio, 1.046; 95% CI, 1.033-1.059 per SD increase) and the strongest associations for Poaceae occurring in adults 18 years or older (risk ratio, 1.030; 95% CI, 1.017-1.043). Further stratification of the adult age group into 18- to 39-year (n = 96,622), 40- to 59-year (n = 67,227), and 60-year or older (n = 37,437) age groups showed similar results as the overall adult age group (results not shown).

Assessment of confounding and effect modification by air pollution

We examined whether ozone, CO, NO_2, SO_2, PM_{10}, or $PM_{2.5}$ concentrations confounded the observed pollen-asthma associations by controlling for the 3-day moving average of these pollutants. The observed pollen-asthma associations were nearly identical to those without controlling for these pollutants, indicating that these air pollutants are not confounders of the observed associations with pollen. Likewise, pollen did not affect the estimated associations between these pollutants and asthma- and wheeze-related ED visits, as previously reported.[15]

We also assessed effect modification of the *Quercus* species and Poaceae pollen associations by ozone by including interaction terms between ozone and pollen (3-day moving average concentrations of both). Interaction terms for *Quercus* species and Poaceae were not significant. However, there was limited variation in ozone concentrations over the narrow windows when pollen concentrations peaked.

Sensitivity analyses

Risk ratios for Cupressaceae and *Ambrosia* species but not the other taxa were sensitive to inclusion of a cubic polynomial to smoothly control for within-month trends. In this analysis the negative association between Cupressaceae and asthma- and wheeze-related ED visits shown in Table III was no longer evident. Conversely, inclusion of the cubic polynomial in the *Ambrosia* species model induced a negative association between *Ambrosia* species and asthma-related ED visits. Similarly, omission of a control for URI visits led to a slight downward bias in the effect estimate for *Ambrosia* species but not the other pollen taxa.

Sensitivity analyses excluding days with imputed pollen concentrations led to similar results as seen with the primary analyses. Results excluding imputed pollen values and results from spatial subanalyses restricted to hospitals within 10 miles (16 km) or 6 miles (10 km) of the pollen-monitoring station showed similar patterns to those seen with the primary analyses (see Table E2 and Fig E2 in this article's Online Repository at www.jacionline.org). Year-stratified analyses showed similar associations across years, suggesting that results were not attributable to a small number of influential years. For both *Quercus*

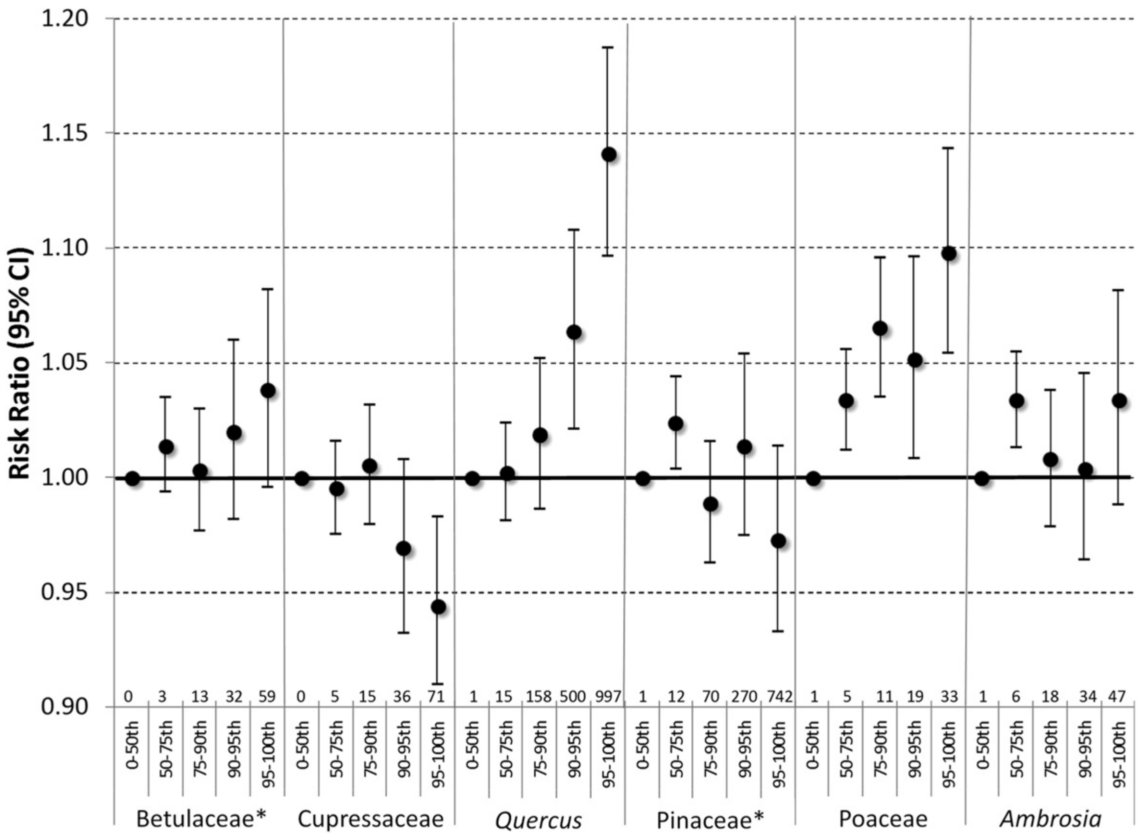

FIG 3. Risk ratios and 95% CIs for categories of 3-day moving average pollen levels. Numbers above the *x-axis* indicate median pollen concentrations for each category. *Risk ratios for Betulaceae and Pinaceae are controlled for *Quercus* species concentrations.

species and Poaceae, risk ratios were increased (ie, >1.00) for 9 of the 12 study years. Finally, models assessing relationships between pollen levels and ED visits for finger wounds, a control outcome group, did not suggest any systematic bias in the modeling approach; the risk ratio for *Quercus* species was 0.997 (95% CI, 0.987-1.007), and that for Poaceae was 1.003 (95% CI, 0.989-1.018).

DISCUSSION

Overall, these results suggest that ambient pollen, in particular *Quercus* species and Poaceae pollen, independently contribute to asthma morbidity in Atlanta. We observed a 2% to 3% increased risk of asthma-related ED visits per SD increase in pollen levels and a corresponding 10% to 15% increase in risk on days with the highest concentrations (comparing the top 5% of days with the lowest 50% of days) for *Quercus* species and Poaceae pollen. The magnitudes of association observed are similar to those reported in studies of air pollution's health effects and other population-level studies of ambient pollen levels and asthma morbidity.[2,15,20] We also observed a negative association between Cupressaceae pollen concentrations and asthma- and wheeze-related ED visits. However, when smooth control for within-month trends was added to the model, the association was consistent with the null.

In this analysis we observed consistent independent associations for *Quercus* species and Poaceae pollen, whereas the associations for Betulaceae and Pinaceae were not evident when *Quercus* species levels were controlled. *Quercus* species pollen concentrations were the highest of all pollen taxa examined, reaching a 3-day average maximum concentration of 3793 grains/m^3. Pinaceae concentrations were also high, but Pinaceae pollen is thought to be less frequently allergenic.[13] Although Betulaceae pollen is considered highly allergenic,[21] it is possible that the aggregate population response to Betulaceae pollen was dwarfed by the population response to *Quercus* species pollen because *Quercus* species concentrations were orders of magnitude higher than Betulaceae concentrations, even when Betulaceae concentrations were peaking. Furthermore, pollen measurements were available from only 1 monitor, and differing degrees of measurement error among the pollen taxa caused by local vegetation effects, for example, could have distorted our results. Of the lag periods examined, our *a priori* 3-day moving average yielded the strongest risk ratios. It is possible that asthma exacerbations are greatest when pollen concentrations remain increased for several consecutive days, leading to the development of a full allergic response in susceptible subjects.

The null association observed between ambient *Ambrosia* species pollen levels and ED visit counts for asthma and wheeze was unexpected given that *Ambrosia* species pollen is known to be highly allergenic and is a major cause of hay fever.[13,21] However, there is evidence to suggest that our results for *Ambrosia* species were confounded. *Ambrosia* species pollen levels increased steeply every September around the same time or just after steep increases in daily asthma-related ED visits (see Fig E1). Previous studies have also noted September increases in asthma

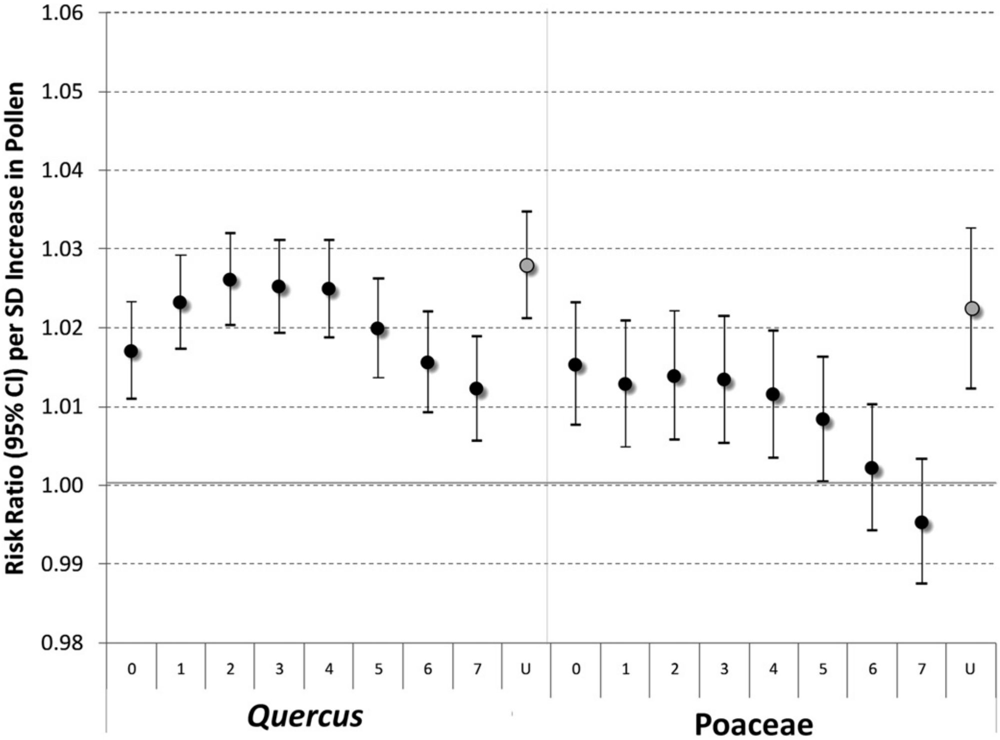

FIG 4. Risk ratios and 95% CIs of models assessing lag 0 through lag 7 and 3-day moving average pollen levels. Risk ratios from the *a priori* model assessing 3-day moving average pollen levels are shown in *gray* and denoted by a *U* on the *x-axis*.

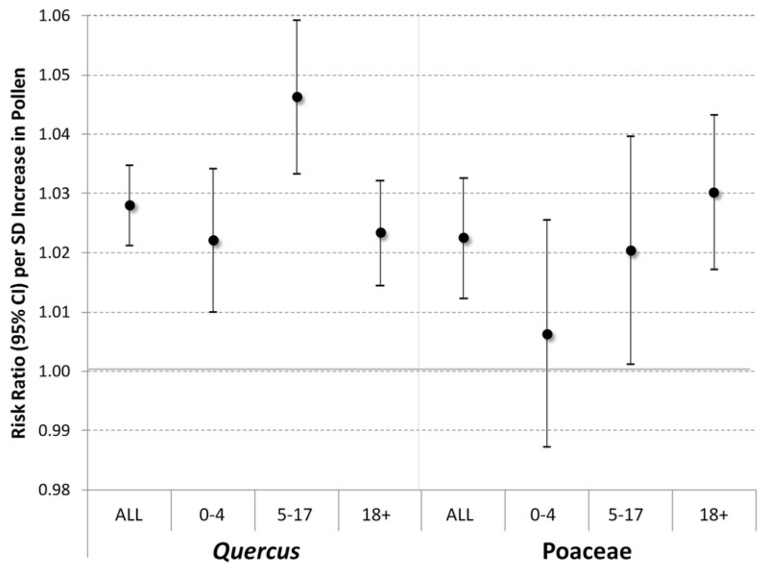

FIG 5. Age-specific risk ratios and 95% CIs for 3-day moving average pollen levels.

exacerbations, attributing the pattern to circulating rhinoviruses.[19] Unfortunately, we did not have an accurate population-level measure of circulating rhinoviruses to include as a covariate in our models; few ED visits indicated rhinovirus (ICD-9 code 079.3), and URI-related visits are likely a poor surrogate. Nonetheless, controlling for URI-related visits slightly increased the effect estimate for *Ambrosia* species, suggesting that a better surrogate might allow positive associations to be observed between *Ambrosia* species and asthma-related ED visits. The strong increasing trend in asthma-related visits every September might also explain the sensitivity of the *Ambrosia* species results to control for within-month time trends. For these reasons, our *Ambrosia* species results should be interpreted cautiously. Results from previous time-series and case-crossover studies of *Ambrosia* species might also be confounded by this back-to-school effect.[20] Although there is a corresponding spring and summer decrease in the number of asthma-related ED visits, the trend is not as strong as the September increase and does not coincide with dramatic increases or decreases in other pollen taxa. Effect estimates for the spring and summer pollen taxa (ie, trees and grasses) were not sensitive to within-month time trend control, suggesting that the results for these taxa were not confounded.

Positive associations for Poaceae and *Quercus* species were observed for all age groups, with the exception of Poaceae pollen in the 0- to 4-year year group. Asthma is difficult to diagnose in children younger than 5 years,[22] and weaker associations in the youngest age group might reflect a less specific outcome group. Respiratory symptoms in early life also tend to be unrelated to allergy[23]; thus the respiratory response to an inhalant allergen might be expected to be weaker. Different sensitivities to pollen concentrations and behavioral management of those sensitivities in adults versus children could also explain differences in effects observed between the 5- to 17-year age group and adults (≥18 years of age). Unfortunately, there were no data available on the allergy status of the ED patients. Finer stratification of the adult age group suggested similar patterns between older and younger adults. Some true asthma-related visits were likely coded as chronic obstructive pulmonary disease, particularly in the oldest age group (≥60 years); chronic obstructive pulmonary disease–related visits were not included in our outcome group unless accompanied by an ICD-9 code for asthma or wheeze. Although disease misclassification resulting from the use of ICD-9 codes might have biased true associations toward the null, it would be unlikely to induce spurious associations because coding preferences are likely independent of day-to-day changes in pollen concentrations.

A limitation of our study was the use of 1 monitoring site to represent citywide population exposures. Exposure measurement error because of spatial heterogeneity in ambient pollen levels, as well as differences between ambient and personal exposures, could have biased risk ratios toward the null but would be unlikely to induce a spurious association in this context. Spatial subanalyses of ED visits from hospitals within 10 or 6 miles around the pollen-monitoring stations showed similar patterns of association across pollen taxa despite the loss of precision. Previous studies have indicated that single monitoring sites can be suitable for representing study areas up to 30 to 40 km wide, especially for geographies like Atlanta, for which air flow is not restricted by mountains or bodies of water.[24,25]

Ambient pollutant concentrations are also associated with asthma- and wheeze-related ED visits in this population[15] but were not confounders of the associations with pollen. Effect estimates for pollen were virtually identical between the models including and excluding control for ozone, NO_2, CO, SO_2, PM_{10}, and $PM_{2.5}$. Clinical and epidemiologic reports have suggested that exposure to ozone might enhance the respiratory response to airborne allergens.[2,26,27] We found no evidence of effect modification for *Quercus* species or Poaceae pollen; however, it is important to note the difficulty of assessing this interaction in the current study. Pollen concentrations exhibit sharp peaks at specific times of year; hence there was little variation in ozone concentration during the time periods when concentrations of these taxa were high. For example, ozone concentrations were rarely high in February and March, when tree pollen concentrations were peaking, thus limiting our ability to compare days with high tree pollen and high ozone levels with days with high tree pollen and low ozone levels.

As our climate changes, the temporal distribution and concentration of ambient pollen will likely be altered. Increased carbon dioxide levels have been shown to increase *Ambrosia* species pollen production.[28-30] Trends of longer pollen seasons and increased concentrations in response to increasing temperatures have already been observed for specific taxa, including *Quercus* species.[31] Our results and those of previous investigators suggest that these changes can have implications for asthma morbidity. The most important taxa can differ by region, but in Atlanta, of the taxa we considered, Poaceae and *Quercus* species pollen appear to be of particular concern for asthmatic patients. Additional research is needed to determine whether these relationships hold in other locations.

A 10% to 15% increase in asthma-related ED visits for the highest pollen concentration days has large public health implications; for a common health outcome and ubiquitous exposure, even modest increases in risk affect large numbers of persons. To put these increased risks in context, a 10% increase in ED visits in the later years of our study would represent approximately 16 additional visits per day on the highest-concentration days (approximately 6 days per year fell into the top 5% of days for each pollen taxon). However, the affected number of persons is likely much greater because we did not capture every ED visit in the study area and the effects of pollen on asthma exacerbation are presumably not limited to those that result in an ED visit. In addition, ED visits for asthma represent a heterogeneous mix of subjects with severe or uncontrolled asthma, those without health insurance, or those who use the ED as a source of primary health care; for some of these subgroups, associations with pollen might be stronger or weaker.

As others have noted, additional research on exposure-outcome associations can facilitate a wide range of public health measures to improve primary, secondary, and tertiary prevention of aeroallergen-related disease.[10] Primary prevention includes management of allergenic plants, pollen surveillance and warning systems, and building and ventilation strategies. Secondary prevention includes patient education and medical management to reduce the development of allergic disease. Tertiary prevention includes enhanced access to medical care to palliate the symptoms of allergic respiratory disease and reduce the severity of exacerbations when they occur.

We thank the Atlanta Allergy and Asthma Clinic and Marie McFalls for providing the pollen data and participating hospitals for providing the ED data.

Clinical implications: Pollen levels contribute to asthma-related ED visit risk. Increased patient education and access to treatment, aeroallergen surveillance, and early warning systems might be relevant adaptation measures under a changing climate.

REFERENCES

1. Dales RE, Cakmak S, Judek S, Coates F. Tree pollen and hospitalization for asthma in urban Canada. Int Arch Allergy Immunol 2008;146:241-7.
2. Dales RE, Cakmak S, Judek S, Dann T, Coates F, Brook JR, et al. Influence of outdoor aeroallergens on hospitalization for asthma in Canada. J Allergy Clin Immunol 2004;113:303-6.

3. Galan I, Prieto A, Rubio M, Herrero T, Cervigon P, Cantero JL, et al. Association between airborne pollen and epidemic asthma in Madrid, Spain: a case-control study. Thorax 2010;65:398-402.
4. Jariwala SP, Kurada S, Moday H, Thanjan A, Bastone L, Khananashvili M, et al. Association between tree pollen counts and asthma ED visits in a high-density urban center. J Asthma 2011;48:442-8.
5. Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. Ann Allergy Asthma Immunol 2003;90:28-33.
6. Tobias A, Galan I, Banegas JR, Aranguez E. Short term effects of airborne pollen concentrations on asthma epidemic. Thorax 2003;58:708-10.
7. Atkinson RW, Strachan DP. Role of outdoor aeroallergens in asthma exacerbations: epidemiological evidence. Thorax 2004;59:277-8.
8. D'Amato G, Cecchi L, D'Amato M, Liccardi G. Urban air pollution and climate change as environmental risk factors of respiratory allergy: an update. J Investig Allergol Clin Immunol 2010;20:95-102.
9. Shea KM, Truckner RT, Weber RW, Peden DB. Climate change and allergic disease. J Allergy Clin Immunol 2008;122:443-53.
10. Beggs PJ. Adaptation to impacts of climate change on aeroallergens and allergic respiratory diseases. Int J Environ Res Public Health 2010;7:3006-21.
11. Frenz DA, Scamehorn RT, Hokanson JM, Murray LW. A brief method for analyzing Rotorod samples for pollen content. Aerobiologia 1996;12:51-4.
12. Behrendt H, Becker WM. Localization, release and bioavailability of pollen allergens: the influence of environmental factors. Curr Opin Immunol 2001;13:709-15.
13. Frenz DA. Interpreting atmospheric pollen counts for use in clinical allergy: allergic symptomology. Ann Allergy Asthma Immunol 2001;86:150-8.
14. Ivy D, Mulholland JA, Russell AG. Development of ambient air quality population-weighted metrics for use in time-series health studies. J Air Waste Manag Assoc 2008;58:711-20.
15. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med 2010;182:307-16.
16. Sarnat SE, Klein M, Sarnat JA, Flanders WD, Waller LA, Mulholland JA, et al. An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J Expo Sci Environ Epidemiol 2010;20:135-46.
17. Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. Biostatistics 2007;8:337-44.
18. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. Epidemiology 2005;16:717-26.
19. Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. J Allergy Clin Immunol 2006;117:557-62.
20. Heguy L, Garneau M, Goldberg MS, Raphoz M, Guay F, Valois MF. Associations between grass and weed pollen and emergency department visits for asthma among children in Montreal. Environ Res 2008;106:203-11.
21. Lewis WH, Vinay P, Zenger VE, editors. Airborne and allergenic pollen of North America. Baltimore: Johns Hopkins University Press; 1983.
22. National Heart Lung and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health; 2007. NIH publication no. 07-4051.
23. Wright AL. Epidemiology of asthma and recurrent wheeze in childhood. Clin Rev Allergy Immunol 2002;22:33-44.
24. Katelaris CH, Burke TV, Byth K. Spatial variability in the pollen count in Sydney, Australia: can one sampling site accurately reflect the pollen count for a region? Ann Allergy Asthma Immunol 2004;93:131-6.
25. 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.
26. Peden DB, Setzer RW Jr, Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. Am J Respir Crit Care Med 1995;151:1336-45.
27. Vagaggini B, Taccola M, Cianchetti S, Carnevali S, Bartoli ML, Bacci E, et al. Ozone exposure increases eosinophilic airway response induced by previous allergen challenge. Am J Respir Crit Care Med 2002;166:1073-7.
28. Rogers CA, Wayne PM, Macklin EA, Muilenberg ML, Wagner CJ, Epstein PR, et al. Interaction of the onset of spring and elevated atmospheric CO2 on ragweed (*Ambrosia artemisiifolia* L.) pollen production. Environ Health Perspect 2006;114:865-9.
29. Ziska LH, Caulfield F. The potential influence of rising atmospheric carbon dioxide (CO2) on public health: pollen production of common ragweed as a test case. World Resource Review 2000;12:449-57.
30. Wayne P, Foster S, Connolly J, Bazzaz F, Epstein P. Production of allergenic pollen by ragweed (*Ambrosia artemisiifolia* L.) is increased in CO(2)-enriched atmospheres. Ann Allergy Asthma Immunol 2002;88:279-82.
31. Garcia-Mozo H, Galan C, Jato V, Belmonte J, de la Guardia CD, Fernandez D, et al. *Quercus* pollen season dynamics in the Iberian Peninsula: response to meteorological parameters and possible consequences of climate change. Ann Agric Environ Med 2006;13:209-24.

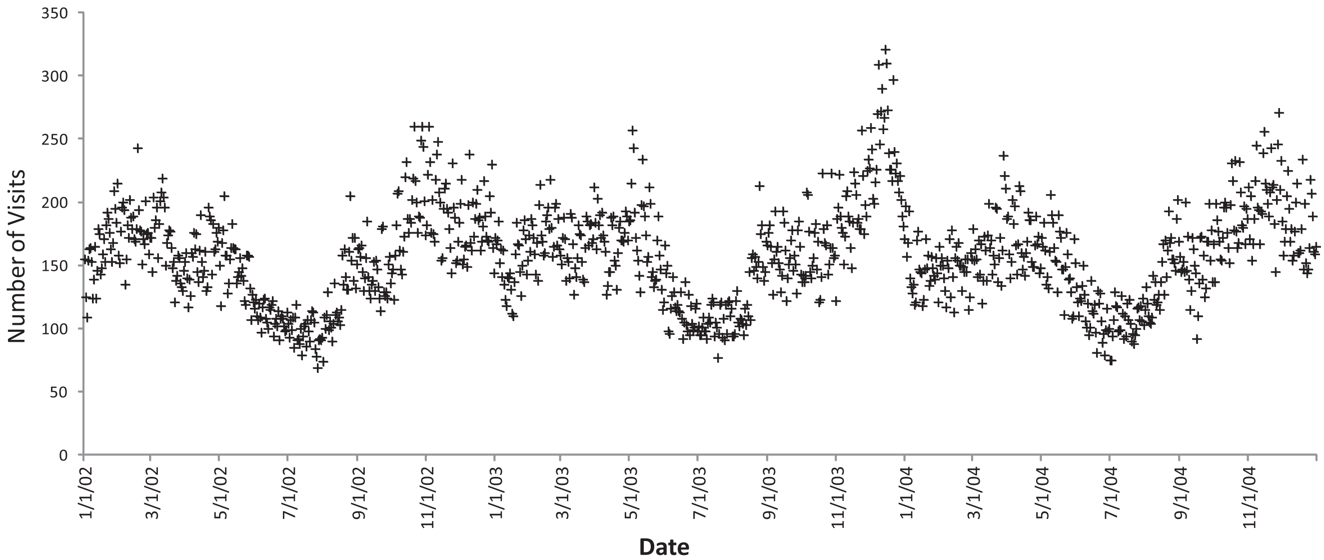

FIG E1. Daily counts of ED visits for asthma and wheeze, 2002-2004.

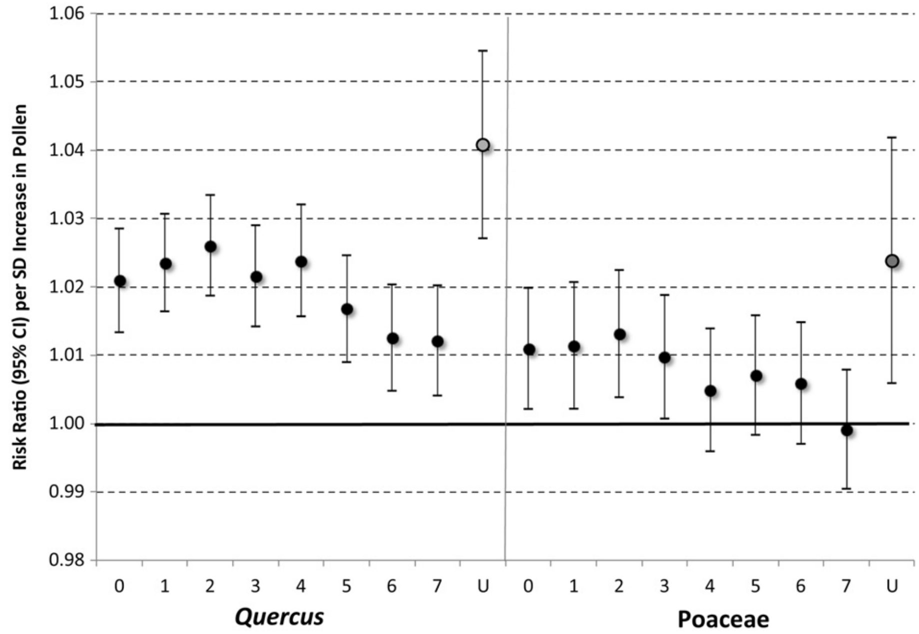

FIG E2. Risk ratios and 95% CIs of models assessing lag 0 through lag 7 and 3-day moving average pollen levels excluding imputed pollen measurements. Risk ratios from the *a priori* model assessing 3-day moving average pollen levels are shown in *gray* and denoted by a *U* on the *x-axis*.

TABLE E1. Characteristics of ED visits for asthma and wheeze

	No.	Percent
Age (y)		
0-4	108,147	27
5-11	62,654	16
12-17	28,732	7
18-39	96,622	24
40-59	67,227	17
≥60	37,437	9
Sex		
Female	213,208	54
Male	181,676	46
Missing	5,935	<1
ICD-9 code		
Asthma (493)	318,628	79
Wheeze (786.09,* 786.07†)	66,273	17
Asthma and wheeze	15,918	4

*Before October 1, 1998.
†On or after October 1, 1998.

TABLE E2. Associations among 3-day moving average pollen levels restricted to hospitals within a specified distance of the pollen-monitoring site

		ED within 10 miles of pollen monitoring*		ED within 6 miles of pollen monitoring*	
Pollen taxa	**Per unit (grains/m^3)**	**Risk ratio (95% CI)**	***P* value**	**Risk ratio (95% CI)**	***P* value**
Betulaceae	20	1.014 (0.998-1.031)	.095	0.997 (0.968-1.027)	.852
Cupressaceae	25	0.986 (0.965-1.008)	.200	0.965 (0.929-1.003)	.074
Quercus species	300	1.030 (1.017-1.043)	<.001	1.020 (0.997-1.043)	.090
Pinaceae	200	1.009 (0.996-1.023)	.164	1.004 (0.982-1.026)	.721
Poaceae	10	1.026 (1.005-1.047)	.013	1.031 (1.000-1.064)	.053
Ambrosia species	15	0.999 (0.975-1.025)	.961	1.011 (0.970-1.053)	.609

*There were 8 hospitals within 10 miles (16 km) and 3 hospitals within 6 miles (10 km) of the pollen monitors. Associations are from single-taxon models.