

ENVIRONMENTAL DETERMINANTS

Associations between Pollen Counts, Pollutants, and Asthma-Related Hospital Admissions in a High-Density Indian Metropolis

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Background. The seasonal pattern of asthma-related hospitalization has often been correlated with ambient allergen/pollutant levels. **Objective.** To examine the relationship between asthma-related hospital admissions (ARHA) and outdoor pollen, spore, and pollutant levels for adult patients in a densely populated Indian megacity Kolkata. **Methods.** ARHA data were obtained from two major teaching hospitals of the city. Pollen and spores causing allergic sensitization were identified by skin prick tests (SPTs) among respiratory allergic subjects ($N = 1353$). Outdoor concentrations of aeroallergens were determined using a Burkard sampler for five consecutive years (2004–2009). Levels of NO_2 , SO_2 , suspended particulate matters (SPMs), and respirable particulate matters (RPMs) were made available by West Bengal Pollution Control Board (WBPCB, Government of West Bengal). Poisson multivariate Poisson regression (with adjustments for overdispersion) was used to model the data. **Results.** We found that ARHA in Kolkata increased with predictable regularity in March and September, while remaining low in January and July. SPT showed highly positive skin reactions with grass/weed and palm pollens in respiratory allergic patients, while *Aspergilli* spores also evoked good sensitivity. In our regression model, the airborne pollen types, Cheno-Amaranthaceae and Cyperaceae, and the inorganic pollutant, SO_2 and RPM, were significantly associated with ARHA ($p < .05$).

Conclusion. ARHA in the megacity of Kolkata shows two seasonal peaks that can be correlated with outdoor grass/weed pollen and RPM concentrations. In contrast, the city's ambient fungal spore counts were not found to be significantly associated.

Keywords asthma, hospital admissions, molds, pollen, pollutants

INTRODUCTION

Environmental pollution has become a major concern in rapidly growing economies like China and India (1). It is known that the urban population of India is exposed to some of the world's highest pollution levels (2). In fact, 3 of 26 megacities of the world are located in India, contributing significantly to the region's atmospheric pollution. India also has a large population of asthmatics—around 15–20 million (3)—and the number is on the rise, especially in the megacities such as Kolkata and Mumbai. This has put an enormous burden on the existing health care services. Therefore, identifying environmental factors behind asthma exacerbation could be helpful in determining the region's public health policy.

Ambient aeroallergens and organic or inorganic air pollutants are known to cause asthma exacerbation

and subsequent asthma-related hospital admissions (ARHAs) (4, 5). This study was done in Kolkata (Figure 1), an Indian megacity with an estimated 16.6 million inhabitants. Rich tropical vegetation surrounding the city is the major source of Kolkata's atmospheric pollen and spores (6), while the sources of air pollutants are gaseous exhausts from vehicular traffic and industries located in and around the city (7). Previous studies have emphasized the role of indoor pollutants and house dust mite sensitization on the asthmatics of Mumbai (8). However, due to recent urbanization, outdoor pollutants have become much more significant. However, to date, no detailed study has been done relating ambient aeroallergens or pollutants to ARHA in the region.

The objective of this study was to examine the role of aeroallergens and other gaseous or particulate air pollutants in influencing ARHA in Kolkata. It is known that asthmatics suffer from periodic exacerbations of the disease, which, in addition to causing morbidity and mortality, frequently lead to hospital admissions and a significant economic burden (9). Sensitization to aeroallergens (e.g., allergenic pollen and spore) is a risk factor for asthma (10). We therefore examined the pattern of aeroallergen sensitization among patients suffering from respiratory allergies and determined the concentrations of both

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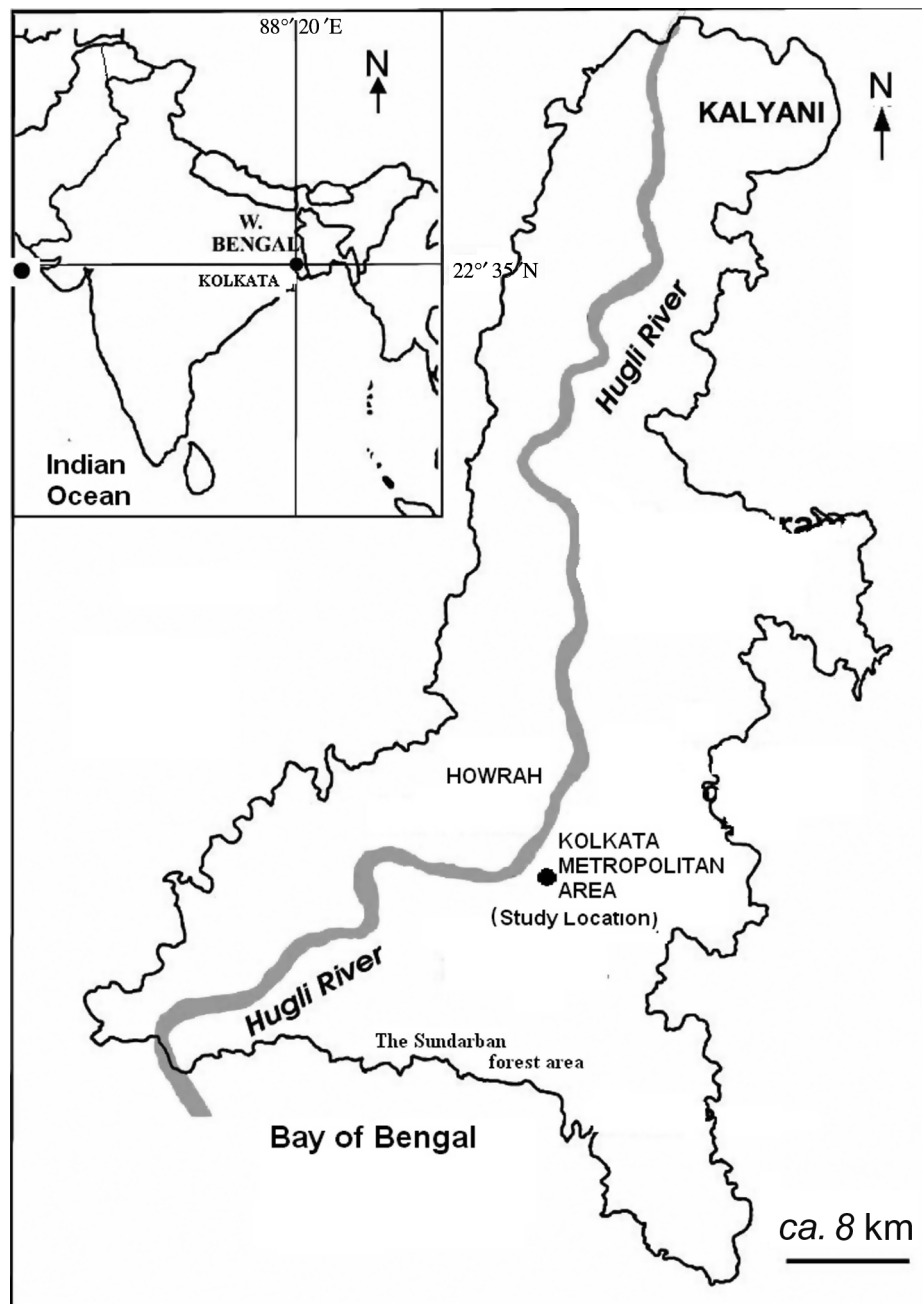


FIGURE 1.—Map showing the location of Kolkata metropolitan area.

aeroallergens and gaseous or particulate air pollutants to study their association with the city's ARHAs. Our report will serve as a useful groundwork for more detailed studies and better asthma management in one of the most densely populated megacities of the world.

MATERIALS AND METHODS

Subjects for Sensitization Studies

Data pertaining to allergen sensitization among the population were obtained by studying patients with respiratory allergies visiting the outpatients' department of the Institute of Child Health (ICH, Park Circus,

Kolkata, India). A detailed questionnaire was used to obtain demographic and medical history data from the patients. The project proposal was approved by the Institutional Ethics Committee, and prior informed consents were obtained from all subjects. Subjects, who had no personal and family history of allergic diseases were randomly recruited from the same locality to serve as non-allergic adult healthy controls. Pulmonary function tests (PFTs) were performed to determine the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and other parameters, using a standard spirometer and following American Thoracic Society guidelines. Each measurement comprised of at least two consistent maneuvers with variation of less than

5% in FEV1. The highest FEV1 and FVC were used in the analyses. Allergic asthmatics with controlled symptoms were included in the study. All subjects stopped taking anti-histamines for 2 weeks prior to skin tests to avoid drug-mediated suppression of results.

Asthma-Related Hospitalization Cases

The number of daily ARHA was collected from two major state-funded teaching hospitals located in the city. These two hospitals, located at strategic points inside the city, represent a significant portion of the total ARHA in Kolkata.

Skin Prick Test to Study the Sensitization Pattern

The allergic subjects as well as 15 healthy volunteers underwent skin prick test (SPT) to common aeroallergens. Briefly, antigenic extracts were prepared from a panel of 16 common pollen types and 8 common spore types for skin testing. Extracts were extensively dialyzed, micro-filtered, and checked for their protein contents as already described (6, 11–13). Tests were performed by placing a drop of glycerinated (50% v/v) allergen extracts on the volar side of the forearm and gently pricking the skin underneath with a sterile lancet (Prick Lancetter, Bayer, USA). Phosphate-buffered saline (PBS, 0.1 M Sodium phosphate, 150 mM NaCl, pH 7.2) and histamine di-phosphate (10 mg/ml) were included as negative and positive controls, respectively. A conventional 0–4 grading system was used to evaluate the skin test results following McCann and Ownby (14), where 0 indicated no reaction/reactions no different than the negative control, +1 indicated erythema less than 21 mm, +2 indicated wheal less than 3 mm and erythema larger than 21 mm, +3 indicated wheal greater than 3 mm with surrounding erythema, and +4 indicated wheal with pseudopods and surrounding erythema (14). Skin test data were collected for five consecutive years (2003–2008).

Pollen and Spore Load of the Ambient Air

Airborne pollen grains and spores were monitored in the city using a Burkard volumetric sampler (Burkard Inc., UK) and a pollen–spore calendar was prepared as previously described (6, 15). The aeroallergen monitoring station was situated between 16–20 miles from the two hospitals included in the study. After microscopic analyses, a list of pollen grains and fungal spores present in the ambient atmosphere of the city was prepared and circulated to the allergy clinic, ICH.

Inorganic Pollutants of the Ambient Air

Atmospheric pollutant levels were monitored and kindly made available by the West Bengal Pollution Control Board (WBPCB). An automatic ambient air quality monitoring station was used throughout the study (http://www.wbpcb.gov.in/html/environmental_publication.shtml. Accessed December 10, 2011). The WBPCB sampling station was equipped to monitor the oxides of nitrogen (by

gas phase chemiluminescence), SO₂ (by ultraviolet (UV) emission at 214 nm after irradiated with light of 300–400 nm wavelength), ozone (absorption of UV radiation 253.7 nm), and particulate matter (by Beta Ray C14 deflection method using Geiger–Muller tube detector).

Data Presentation and Statistical Analyses

Pollen and spore concentrations were expressed as average numbers per hour per cubic meter of ambient air per day. Concentrations of inorganic gaseous pollutants (NO₂ and SO₂), suspended particulate matter (SPM), and respirable particulate matter (RPM) were expressed in micrograms per cubic meter, as per conventions. The number of ARHA was recorded over a 5-year period in 10-day time-slots. Three consecutive 10-day slots in each month gave rise to 36 consecutive slots in each year, with a total of 180 slots for 5 years. The concentration of pollens (*Areca*, *Carica*, *Cheno-Amntheaceae*, *Cocos*, *Phoenix*, *Cyperaceae*, and *Poaceae*), spores (*Alternaria*, *Aspergilli*, *Basidiospores*, *Cladosporium*, and total spores) and atmospheric pollutants (NO₂, SO₂, SPM, and RPM) were also recorded in a similar manner for the same 5-year period.

In the Poisson generalized linear model (GLM), ARHA was treated as the outcome variable, while individual concentrations of airborne pollen, fungal spores, and pollutants were treated as predictor variables. While fitting the model with only airborne pollen grains and fungal spores, it was found that several pollens were significantly associated with ARHA. However, the value/(degrees of freedom) for both deviance and Pearson Chi-square statistic were much greater than 1 (data not shown). This suggested that the Poisson model fitted the observed data poorly with data points more dispersed than was expected, and the count data for hospitalization had higher variability than could be accounted for by Poisson distribution. Therefore, in order to correct for this overdispersion in the model, a dispersion parameter, based on the quasi-likelihood approach, was estimated (16). The Pearson scale was used to adjust the overdispersion. The standard errors of the regression coefficients were adjusted on the basis of this dispersion parameter. Pollutants were then added to the model and the same procedure followed. All *p*-values below .05 were considered significant. All statistical analyses were carried out using the SAS statistical package (SAS Version 9.1, SAS Inc., NC, USA).

RESULTS

Subjects for SPTs

Among patients who visited the outpatient allergy or asthma clinics of the ICH during the study period, we found that 44.39% were suffering from atopic asthma, 50.78% from allergic rhinitis, 18.98% from rhinoconjunctivitis, 6.52% from contact allergy, and 12.41% from different food allergies. For this study, only patients who were suffering from diagnosed respiratory

allergic problems (with controlled atopic asthma/allergic rhinitis) and willing to participate in the study were considered ($n = 1353$). The mean age of the study population was 34 ± 1.28 years (mean $\pm$ SD), with a male:female ratio of 100:83 and the mean FEV1/FVC ratio of $84 \pm 2\%$ (mean $\pm$ SD).

Patterns of Aeroallergen Sensitization

Figure 2 shows the results of allergy testing. *Saccharum officinarum* or common sugarcane plant (68%) and *Imperata cylindrica* or cogon grass (59.26%), both of Poaceae family, were found to elicit high sensitization responses. They were followed by *Cyperus rotundus* (43.8%) of Cyperaceae family. These were naturally occurring grass species native to the region. *Carica papaya* (papaya tree, 30.96%) also elicited high response, whereas *Trema* (Indian charcoal tree) pollen, although very abundant, showed very low response (9.5%). Among the palms, *Cocos nucifera* (coconut palm, 44.5%), *Phoenix sylvestris* (wild date palm, 35.58%), *Areca catechu* (betel nut palm, 35.26%), and *Borassus flabellifer* (Fan palm, 29.36%) were found to be relevant. Among environmental mold spores, the maximum sensitization was recorded for *Fusarium roseum* (53.92%), followed by *Aspergillus japonicus* (50.92%), *Nigrospora oryzae* (47.82%), *Aspergillus niger* (44.44%), *A. fumigatus* (43%), *Periconia digitata* (40.70%), *Cladosporium cladosporioides* (40.20%), *Penicillium citrinum* (37.12%), *Trichoderma harzianum* (27.92%), and *Alternaria alternata* (25%). The healthy volunteers, who had also been tested with the same panel of aeroallergens, were mostly found to be non-atopic (data not shown).

Pollen, Spore, and Pollutant Concentrations of Ambient Air

Detailed aerobiology of Kolkata region has been described elsewhere (15); this study was focused on the pollen grains that were found to cause higher sensitization as evident by

SPT results. Figure 3A displays the pollen calendar of the most abundant airborne allergenic pollen grains of Kolkata region. We found that the concentration of *Areca* pollen peaked twice in a year; once during mid-April (12.8 pollen/ m^3 /day) and once during September–October (4.98 pollen/ m^3 /day). *Phoenix*, another palm pollen, tended to have high values (11.21 pollen/ m^3 /day) during late January–early March. In late March, Chenopodaceae pollen was found to attain the highest concentration (15.01 pollen/ m^3 /day).

Among grasses, Poaceae pollen reached peak concentrations in March (629.3 pollen/ m^3 /day) and September (411.8 pollen/ m^3 /day), whereas the concentration of Cyperaceae peaked only once during the September to mid-October period (103 pollen/ m^3 /day). We found the highest concentration (5.91 pollen/ m^3 /day) of *Cocos* pollen between late April and June with an additional elevation (1.7 pollen/ m^3 /day) during December. Finally, *Carica* pollen concentration attained peak values (3–4.5 pollen/ m^3 /day) during the period between mid-October and early November. Total fungal spore load of the atmosphere attained peak values ($3.3\text{--}5.8 \times 10^3$ spores/ m^3 /day) in October, when the spore types of *Aspergilli*, *Cladosporium*, *Alternaria*, and Basidiomycetes were found to be present in abundance. The concentration of *Alternaria* spores was found to be higher thrice in a year: February (140.56 spores/ m^3 /day), May (84–106 spores/ m^3 /day), and the late October–early November period ($157\text{--}10^3$ spores/ m^3 /day) (Figure 3B). All of the pollutants SPM, RPM, SO_2 , and NO_2 tended to have the highest values between November and March. (Figure 3C). The daily average values of RPM and SPM went up to 256.6 ± 46 and $293.8 \pm 23 \mu g/m^3$, respectively, which are much above the (Environmental Protection Agency (EPA), USA) permissible standards ($140 \mu g/m^3$ and $60 \mu g/m^3$, respectively).

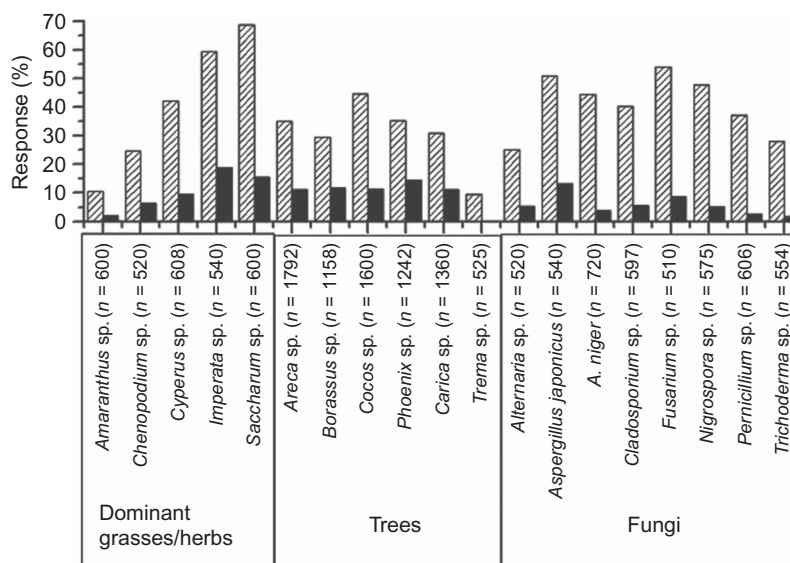


FIGURE 2.—Profile of sensitization (%) to dominant airborne pollen grains and fungal spores: Light and dark bars indicate the percentage of individuals displaying positive and highly positive (+2/higher) reactions in skin prick tests, respectively. Number of subjects tested has been indicated within brackets.

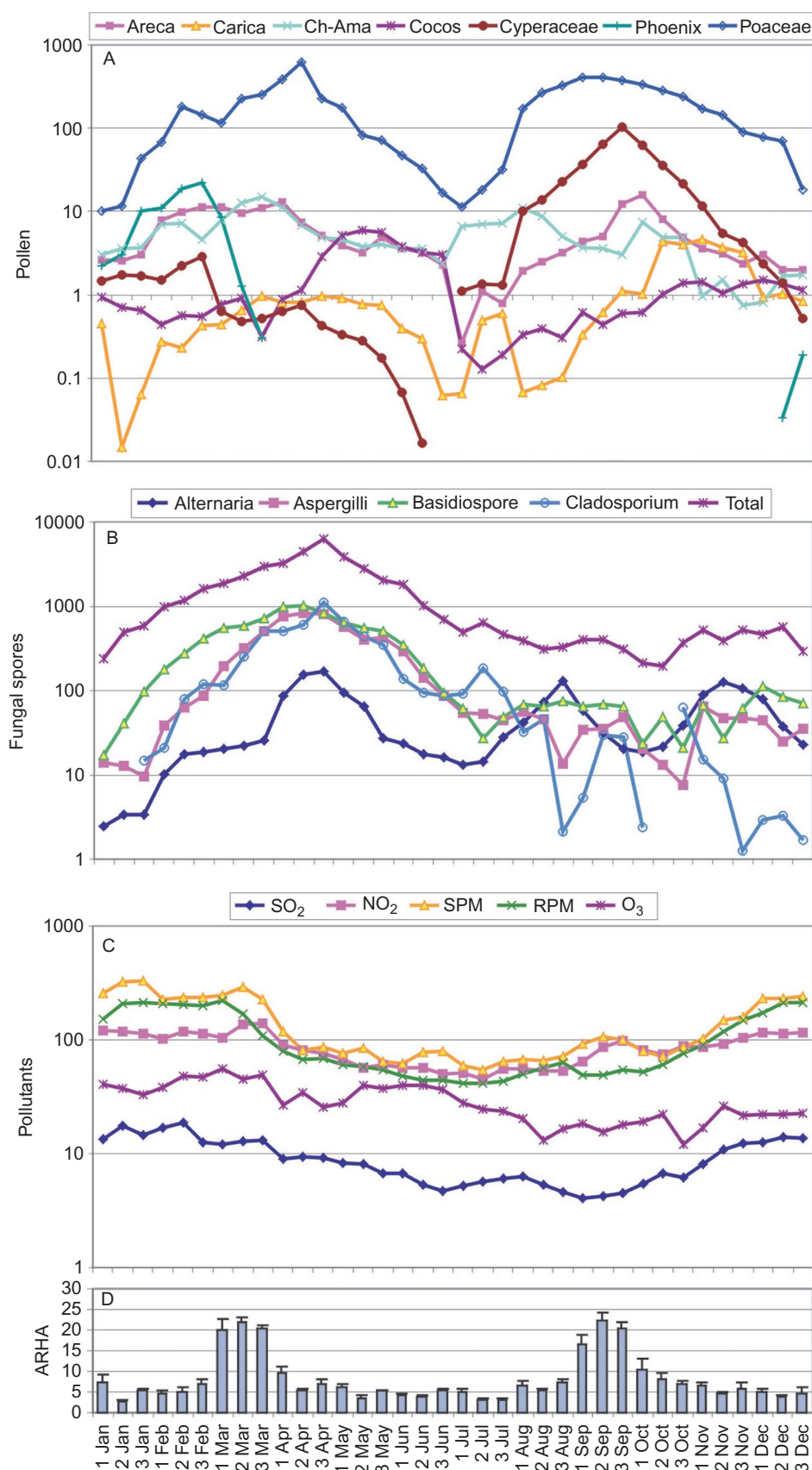


FIGURE 3.—The seasonal patterns of ambient pollen (A), spores (B), pollutants (C), and asthma-related hospital admissions (ARHAs, D) in Kolkata. Pollen and spores are expressed in numbers/m³/day, while pollutants are in µg/m³/day.

Asthma-Related Hospitalization in the City

Figure 3D shows the frequency of daily hospital admissions (mean values $\pm$ SEM), presented in 10-day average over 7 years. We noticed that in spite of the rise in allergy or asthma cases, the numbers of yearly hospitalizations did not increase significantly over the study period, possibly due to improved medication and care available at home (data not shown). The distribution of ARHA was bimodal, with maximum hospitalization cases occurring during the middle of the months March (21.83 ± 1.3) and September (22.29 ± 2.01). The numbers decreased during the middle of January (2.8 ± 0.43) and middle of July (2.9 ± 0.40).

Association between ARHA and Ambient Pollen, Spores, and Pollutants

When only pollen and spores were used as predictor variables in the regression model, the pollens *Areca*, Cheno-Amaranthaceae and Cyperaceae, but none of the spores, were significantly associated with the number of ARHA after correcting for overdispersion. When atmospheric pollutants were included in the model and corrected for overdispersion, only Cheno-Amaranthaceae, Cyperaceae, SO₂ ($p = .048$), and RPM remained significantly associated with ARHA (Table 1).

DISCUSSION

Air-borne pollen types were identified at the family, genus, or species level as previously described (6, 15). Pollen grains of grasses (Poaceae and Cyperaceae), *Trema orientalis* (Urticaceae), Cheno-Amaranthaceae, coconut (*Cocos nucifera*; Arecaceae), and betel nut (*Areca catechu*; Arecaceae) were found to be present throughout the year, although a seasonal bias existed. Some pollen taxa such as

Azadirachta indica (neem tree), *Phoenix sylvestris* (date palm), and *Brassica sp.* (mustard plant) were purely seasonal, showing a bimodal pattern. Finally, there were pollen grains like *Carica papaya* (papaya plant) that occurred sporadically. Although known to be amphiphilus or entomophilus, it can contribute significantly to local pollen load.

A sharp rise in ARHA during September has been reported from countries like Australia and Canada, which is known as the “September epidemic” (17). In contrast, our study confirms that ARHA in Kolkata increases, with predictable regularity, in March and September, with more than 40% of the annual ARHA occurring during these two months alone (18). Since the “September epidemic” primarily affects school children and correlates with their return to school after vacation; it has been suggested that they may carry the source (namely rhinoviral inoculum) for asthma exacerbation (17, 19).

The key factors for ARHA, however, vary from place to place. Several studies from around the world suggest links between either aeroallergens (20) or gaseous/particulate air pollutants (21) and asthma exacerbation. Keeping in mind the roles of both aeroallergens and pollutants, Kolkata was chosen for this study because it represents a densely populated environment with a high concentration of air pollutants as well as a rich tropical or sub-tropical vegetation. Both of these factors are known to play significant roles in influencing ARHA.

In a European community respiratory health survey, sensitization to *Cladosporium* was found to be significantly associated with increased asthma severity (22). A recent multicenter study among the asthmatic population of China reported a high prevalence of mite sensitization, followed by sensitizations to *Artemisia* pollen, cat, and cockroach allergens (23). Our skin test results, conducted with dominant pollen and spore antigens on more than 1300 respiratory allergy patients, showed that pollens of several grass species (including sugarcane) were the major sensitizing agents. Among the fungal species, *Fusarium* and *Aspergillus* spore antigens showed higher percentages of positive skin reactions, whereas sensitivity to *Alternaria* has been reported to be predominant in some other countries (24). We performed skin tests on outpatients who visited the clinic for rhinitis and asthma, since it was not possible to directly include the hospitalized asthma patients for skin testing.

Previous aerobiological studies in the region have been done either for a considerably short period of time or in specific environments such as agricultural farms (6, 15, 25). Our pollen calendar shows that the plant *Trema orientalis* (Urticaceae) is the biggest contributor of early pollen load of the city, although it shows little response to skin tests indicating little or low potential for allergenicity. On the other hand, there are pollen types like *Catharanthus roseus* and *Moringa oleifera*, which, despite showing considerably high skin test reactivity, contribute a relatively small portion of the total pollen load. However, they are of sporadic occurrence and do not change the rate of ARHA as a whole. Most importantly, there are pollen types that

TABLE 1.—Result of regression analysis using Poisson GLM showing the relationship between ARHA (data collected from two different hospitals) and ambient pollen, spore, and pollutants.

Parameter	Estimate	χ^2	Pr > χ^2
Pollens			
ARECA	1.013	0.72	0.398
CARICA	1.017	0.07	0.797
CHENO_AM	1.052	9.08	0.003
COCOS	0.977	0.18	0.667
CYPERACE	1.011	15.87	<0.0001
PHOENIX	0.978	2.09	0.149
POACEAE	1.001	3.25	0.072
Spores			
ALTERN	1.001	0.28	0.595
ASPER	0.999	0.34	0.562
BASID	1.000	0.02	0.888
CLADOS	0.999	1.33	0.249
TOTALSP	1.000	0.23	0.635
Pollutants			
SO₂	0.982	3.93	0.048
NO ₂	1.000	0.09	0.758
RPM	1.003	15.57	<0.0001
SPM	1.000	0.11	0.744

Note: Parameters showing significant associations with ARHA are in bold letters.

are abundant and also cause high rates of sensitization in the community. This third group is represented by Palms (*Areca*, *Cocos*, *Phoenix*), *Carica*, Cheno-Amaranthaceae, and grasses (Cyperaceae and Poaceae). They are the most potent pollen factors for asthma exacerbation. Similarly, the most relevant fungal species are *Alternaria* sp., *Apergilli*, Basidiospores, and Cladospores, which are allergenic and present in abundance.

Pollen grains with allergenic capacity have been found to be positively associated with ARHA or emergency room visits, with grass/weed/tree pollen often showing the strongest association (21, 26, 27). Ryegrass pollen ruptures upon contact with water, releasing granules containing the major allergen Lol p 5 and triggering IgE-mediated responses (28). A similar phenomenon has been found to occur in papaya pollen (13). In addition to carrying allergen molecules, inhaled pollens are known to cause oxidative injury resulting in airway inflammation (29). Our study suggests positive associations between ARHA and concentrations of palm, Cheno-Amaranthaceae and Cyperaceae pollens, with the last two types showing the strongest associations. Allergenicity of *Areca* pollen and its cross-reactivity with other Indian palms is well documented (12, 30). Moreover, a recent report on *Areca* pollen allergen has described it as a risk factor for higher hospitalization rate in the locality (11). Several members of the cyperaceae family are common grasses and sedges of the region (e.g., Bermuda grass *Cynodon dactylon*) producing airborne allergenic pollen. Allergy to Chenopodiaceae and Amaranthaceae pollen has also been reported from several countries and the relevant proteins have been described (31, 32). Apart from pollen, fungal spores are also known to cause asthma exacerbation and ARHA (33). However, we found no marked association of outdoor spore concentration and ARHA in our study.

Associations between the levels of inorganic air pollutants (NO₂, SO₂, particulate matter, and O₃) and asthma exacerbation (34, 35) have been described by several groups and from different regions. We studied ambient O₃ concentration (data were available for 2 years only), but found no significant association between O₃ concentration and ARHA (data not shown). On the other hand, our study demonstrated a positive association between SO₂ concentration and ARHA ($p = .048$). SO₂ can exacerbate asthma by directly causing bronchoconstriction and reduction in lung function in asthmatics (36).

Synergistic associations of pollen, spore, inorganic pollutants, and/or climatic factors have been suggested to affect ARHA by some authors (37). But the significance of this association varies. We have also explored the effects of possible aeroallergen – inorganic pollutant interactions. However, in our model, the interaction terms were not found to appreciably influence the ARHA rate indicating that individual roles of the pollen and pollutants were more important in the megacity (data not shown). This is similar to the findings of Lewis and colleagues from United Kingdom (4).

Our study revealed a strong association between RPM (Respirable Particulate Matter) and ARHA ($p < .0001$).

RPM can drive allergic inflammation through the generation of oxidative stress depending on the individual's genetic susceptibility (38). The fraction of SPM that has an aerodynamic diameter of $\leq 10 \mu\text{m}$ is usually designated as RPM, since it can penetrate deep into the pulmonary alveoli. Other sub-fractions such as PM_{2.5} and PM_{0.1} (aerodynamic diameter $\leq 2.5 \mu\text{m}$ and $\leq 0.1 \mu\text{m}$, respectively) can even penetrate into human blood vascular system and are more likely to cause cardiovascular disease (39). This study focused on total SPM and RPM only, as we did not have data regarding further sub-fractions for the entire study period. Another potential limitation was regarding the statistical model, because this type of model sometimes assigns excessive weight to parameters that sharply overlapped the peaks of hospitalization, putting less weight on others. Pollens, such as Poaceae, that are allergenic and present in the air for longer period of time, appear to be less relevant (not significant in our analysis after including all the pollen, spore, and pollutants and correcting for over-dispersion) because hospitalizations start dropping even though these pollens remain at high levels in the air. This overlooks the fact that the initial exposure to high levels of pollen is more likely to cause asthma hospitalizations than exposures later in the season. This is in part due to the development of tolerance to the allergens in question, as well as to the fact that once hospitalized, patients are much more likely to receive good preventive treatment and are much less likely to be re-hospitalized even though the pollen counts remain high. However, in spite of these limitations, our study produced useful results correlating ambient allergenic pollen, pollutants, and ARHA.

CONCLUSION

This study demonstrated that ARHA in the megacity of Kolkata exhibited a very regular seasonal pattern that was governed by the allergenic content of the atmosphere, specifically the allergenic grass or weed pollen of Cheno-Amaranthaceae and Cyperaceae family as well as by respirable particulate matter. This study is the first of its kind to describe the seasonal pattern of ARHA and its association with the outdoor pollen, spore, and pollutants in a megacity of the Indian subcontinent.

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DECLARATION OF INTEREST

The authors have no conflicts of interest to report. The authors alone are responsible for the content and writing of this paper. PC was supported by CSIR, Government of India.

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