Allergies in the workplace

AIR POLLUTION, POLLENS AND CHILDHOOD ASTHMA – IS THERE A LINK?

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ABSTRACT

While the interplay between ambient air pollutants and their role in the development of asthma continues to remain a subject of detailed study, a link appears to be postulated between ambient air pollutants and airborne pollens in the increasing prevalence of allergic airway disease. With an increasing focus on climate change and the effects of global warming, pollen allergy has become the focus of recent studies looking at the interrelationship between ambient air pollutants and pollen exposures in individuals with allergic respiratory disease. At the population level, little is known about the potential synergistic effects between pollen allergens and air pollutants since this type of association poses challenges in uncontrolled real-life settings. The current knowledge of the pathogenesis of allergies and asthma due to the combined exposure to biological agents such as pollens and air pollutants has been based primarily on animal or *in vitro* studies. This article highlights possible mechanisms involved in the interrelationship between air pollutants and pollen allergens with asthma, and summarises the evidence on the independent and/or co-effect of multiple environmental exposures (ambient air pollutants and pollens) on childhood asthma.

INTRODUCTION

Childhood asthma is the most common chronic disease in children globally and ranks among the top 20 contributors to global disability-adjusted life years (DALY) in all children; it also ranks among the top ten causes of DALY in 5–14-year-olds.[1] The growing increase in the prevalence of childhood asthma symptoms has been correlated with the global increase in outdoor air pollution.[2] Ambient air pollution is a major environmental health concern globally that affects populations in highly industrialised and developing countries. As recently documented by the World Health Organisation (WHO), 98% of cities in low- and middle-income (LMI) countries with more than 100 000 inhabitants do not meet WHO air-quality guidelines, whereas in high-income countries the percentage decreases to 56%.[3] According to recent global burden of disease indicators, the estimated ambient air pollution (especially particulate matter) was responsible for 5.5 million deaths per year in 2013 and 141.5 million DALY (14% of global total DALY); in terms of DALY, it is the fifth leading global risk factor.[4] The WHO has reported 3.7 million premature deaths in both urban and rural areas caused by air pollution, which is due mainly to small particulate matter of 10 microns or less in diameter (PM_{10}). LMI countries, in which air-pollution emissions from power plants, traffic, open waste burning and other combustion sources are very common, account for approximately 88% of these deaths.[5]

While the relationship between ambient air pollutants and their role in the development of asthma continues to remain an area of detailed study, with our increasing understanding of the implications of climate change and global warming, a link has been postulated between ambient air pollutants and airborne pollens in the increasing prevalence of allergic airway diseases, including the exacerbation of asthma and the role of air pollutants in modifying the effect of pollen exposures. Pollen allergy has been used more recently to study the interrelationship between ambient air pollutants and respiratory allergy, including asthma in sensitised individuals.[6]

The aim of this article is to identify the mechanisms involved in the interrelationship between air pollutants

Figure 1: Power plants' pollution and pollen

Figure 2: Traffic-related pollution and pollen

and pollen allergens with asthma and to summarise the evidence for the independent and/or co-effect of environmental exposures (ambient air pollutants and pollens) on childhood asthma.

AMBIENT AIR POLLUTANTS

Ambient air pollutants commonly arise from primary and secondary sources. The primary pollutants are emitted directly from sources that include gaseous pollutants – for example, suphur dioxide (SO_2) and mono-nitrogen oxides (NO_x) as well as particulate matter (PM) (e.g. soot). The secondary pollutants arise from primary pollutants in the atmosphere that combine with UV-rays from sunlight and/or moisture (e.g. ozone (O_3), secondary particles such as sulphates). The air pollutants referred to in this article are the four key primary sources – PM, SO_2, nitrogen dioxide (NO_2) and O_3 – identified by the WHO 2005 Air Quality Guidelines (AQG), reviewed previously.[1]

ALLERGENIC POLLEN AND POLLEN ALLERGY

Although airborne pollens comprise a small proportion of the atmosphere, they are important causative agents of allergic respiratory disease in sensitised individuals. Allergic respiratory disease has become a public health problem due to the increased prevalence of airborne allergenic pollen causing clinical disease and resulting in escalating costs to patients and society at large.[7] Globally, the common non-animal-related allergens that are common sensitisers are pollens from trees, weeds, grass and fungal spores. Important grass-pollen allergens are Cynodon dactylon (Bermuda grass) and Lolium perenne (Rye grass). These tropical grasses are commonly found along latitudes between 30°N and 31.4° + 7.5°S and have their optimal growth at temperatures between 24°C and 37°C. Bermuda grass has been linked to allergic conjunctivitis, asthma, seasonal allergic rhinitis exacerbation and asthma.[8] Grass-pollen allergy is also a common respiratory allergy (median prevalence of 16.9%) in most European countries and also in South Africa.[9] Approximately 80% of South Africans react to Eragrostis (lovegrass) and Buffalo grass pollens.[10] Besides grass, birch (mostly in east-central Europe) and ragweed (predominantly in northern countries) are among the major pollens responsible for causing rhinitis and asthma. Cypress and Parietaria (wall pellitory) also play a major role in southern countries.

INTERACTION BETWEEN AIR POLLUTANTS AND POLLEN IN ASTHMA AETIOLOGY

Exposure to single pollutants has been the focus of many studies on respiratory and allergic risk factors. However, multiple exposures to several pollutants occur in 'real life'. There are always complex mixtures of pollutants from various sources in the environment, which often contribute jointly to synergistic or additive toxic effects.[11,12] Owing to the intrinsic electrostatic properties and porous surfaces of ambient respirable PM, they readily adhere to airborne allergens released from pollens. PM interacts with aero-allergens via modulation of the allergenicity of airborne allergens, in this way promoting airway sensitisation.[13,14] Phleum pratense pollen releases more allergen-containing granules when treated with various concentrations of O_3 and NO_2 under experimental conditions compared to exposure to air only (see Figure 3).[15] The bio-availability of airborne pollen allergens has also been identified to increase owing to the effect of traffic-related pollutants.[15] Air pollutants may increase acute responses to allergens in various ways:

- increasing epithelial permeability;
- 'priming' allergen-induced responses caused by airway inflammation, in this way enhancing the recruitment and activation of inflammatory cells;
- increasing airway oxidative stress, and
- increasing the release of neuropeptide.[7]

The access of inhaled allergens to the immune system may be facilitated by impaired mucociliary clearance and airway mucosal damage, which enhances atopic sensitisation risk and symptoms exacerbation in sensitised individuals.[16,17]

MECHANISMS BY WHICH AIR POLLUTANTS CAUSE ASTHMA

The development of asthma has been better understood owing to the availability of techniques for investigating gene polymorphisms and variants associated with the increased risk of asthma. There are four groups of genes attributed to conferring susceptibility to the development of

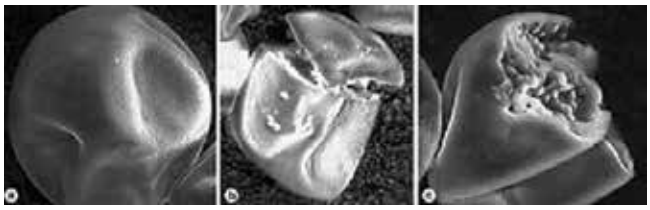

Figure 3: (a) Intact pollen; (b) damaged pollen following the treatment of 50 ppm of NO2; (c) damaged pollen following treatment with 0.7 ppm of O_3, showing visible pollen cytoplasmic granules from the broken grain (Reproduced with permission)[15]

asthma. They are those controlling:

- airway repair and remodelling, including airway development;
- immune system responses;
- bronchial hyperresponsiveness, and
- the endogenous production of anti-oxidants in the airways (see Figure 4).

Various mechanisms enable either different gene types on their own or those interacting with environmental exposures (pollutants and allergens) through gene-environment interactions to cause asthma. These mechanisms include oxidative stress and damage, airway wall remodelling, immunological effects and inflammatory pathways, and the enhancement of respiratory sensitisation to allergens.[18] It is postulated that air pollution increases the likelihood of sensitisation to allergens by:

- acting as a carrier for allergens to the lower respiratory tract and parts of the lungs that would otherwise be difficult for allergens to reach;
- increasing the permeability of the epithelium and thereby increasing the surface area of immunological cells responding to allergens;
- interacting with antigenic protein and in this way increasing its potency, and
- air pollutants (especially PM), acting as adjuvants, serving as a depot and in this way preventing antigens from dispersing.

During this process, PM stimulates the division of Type-2-helper T cells or activates antigen-presenting cells.[19]

EXPOSURE-RESPONSE STUDIES BETWEEN AMBIENT AIR POLLUTANTS AND EXACERBATION, PREVALENCE AND INCIDENCE OF CHILDHOOD ASTHMA

In the literature, the evidence for the association between ambient air pollution exposure and asthma prevalence or asthma induction in children is inconclusive.[20,21] A systematic review by Anderson et al[22] of 21 studies on the prevalence of wheeze symptoms or asthma diagnosis and levels of air pollution in five or more communities demonstrated that only 11% of studies showed a positive, statistically significant association between the pollution-outcome estimates. Epidemiological evidence from a pooled analysis of five European birth-cohort studies – GINI and LISA (both Germany, divided into north and south areas), MAAS (England, United Kingdom), PIAMA (the Netherlands), and BAMSE (Sweden)[20] – showed no association with an increased prevalence of childhood asthma, while some suggested effects on only a sub-population of age-groups[23] and girls.[24] The results of a systematic review and a meta-analysis by Bowatte et al[21] of pooled five birth-cohort studies (PIAMA, Oslo, BAMSE, Vancouver and BCO[25–29]) showed a modest association between the incidence of asthma and longitudinal childhood exposure to NO_2: OR 1.09; 95% CI 0.96 to 1.23 per 10 µg/m^3 increase in pollutant. However, the association was highly variable between all the studies pooled together, with a heterogeneity of 75.5%. A recent study evaluating the association with traffic-related pollution found no association between incidence of asthma with the measured pollutants at baseline and follow-up.[30] However, there is evidence from epidemiological studies that exposure to ambient air pollutants in early childhood plays an important role in the exacerbation of asthma and other respiratory symptoms, with a greater effect being observed in asthmatic children.[31–36]

EXPOSURE-RESPONSE STUDIES BETWEEN AIR POLLUTANTS AND AIRWAY INFLAMMATION AND LUNG FUNCTION DEFICITS IN CHILDHOOD ASTHMA

AIRWAY INFLAMMATION

There is growing evidence of an association between ambient air pollution and increased exhaled nitric-oxide (FeNO) levels, a subclinical marker of airway inflammation in children. In the Southern California Children's Health Study (SCCHS), higher FeNO levels were associated with both background and traffic-related pollutants. Among children aged seven to 11 years, cumulative lagged averages of daily O_3 (over 1–23 days), PM_{10} (over 1–7 days), and $PM_{2.5}$ (over 1–8 days) were associated with 14.3% ($p<0.01$), 9.3% ($p<0.05$), and 17.4% ($p<0.001$) higher FeNO levels across an IQR of 15.42 ppb of O_3, 12.97 µg/m^3 of PM_{10}, and 7.5 µg/m^3 of $PM_{2.5}$.[37] Similarly, longitudinal analysis of chronic exposures to $PM_{2.5}$ and NO_2 (scaled to the IQR of 2.4 µg/m^3 and 1.8 ppb, respectively) showed that $PM_{2.5}$ and NO_2 exposures were associated with 4.94 ppb ($p = 0.005$) and 2.29 ppb ($p = 0.02$) increase in FeNO, respectively.[37]

LUNG FUNCTION DEFICITS

There is more consistent evidence for the role of ambient air pollution exposure, particularly traffic-related pollutants, in reducing lung function, especially in young children. A large proportion of epidemiological studies[38–43] found a consistent association between ambient air pollution exposure and reduced lung function in children, with three studies showing mixed results[23,44,45] Some studies demonstrated significant associations with only traffic-related pollutants such as NO_2, $PM_{2.5}$ and PM_{10}[39,42,44,45] in younger children[23,42] non-asthmatics[38] and boys.[39] Findings from the SCCHS were consistent in demonstrating a significant positive association with lung-function deficits.[46]

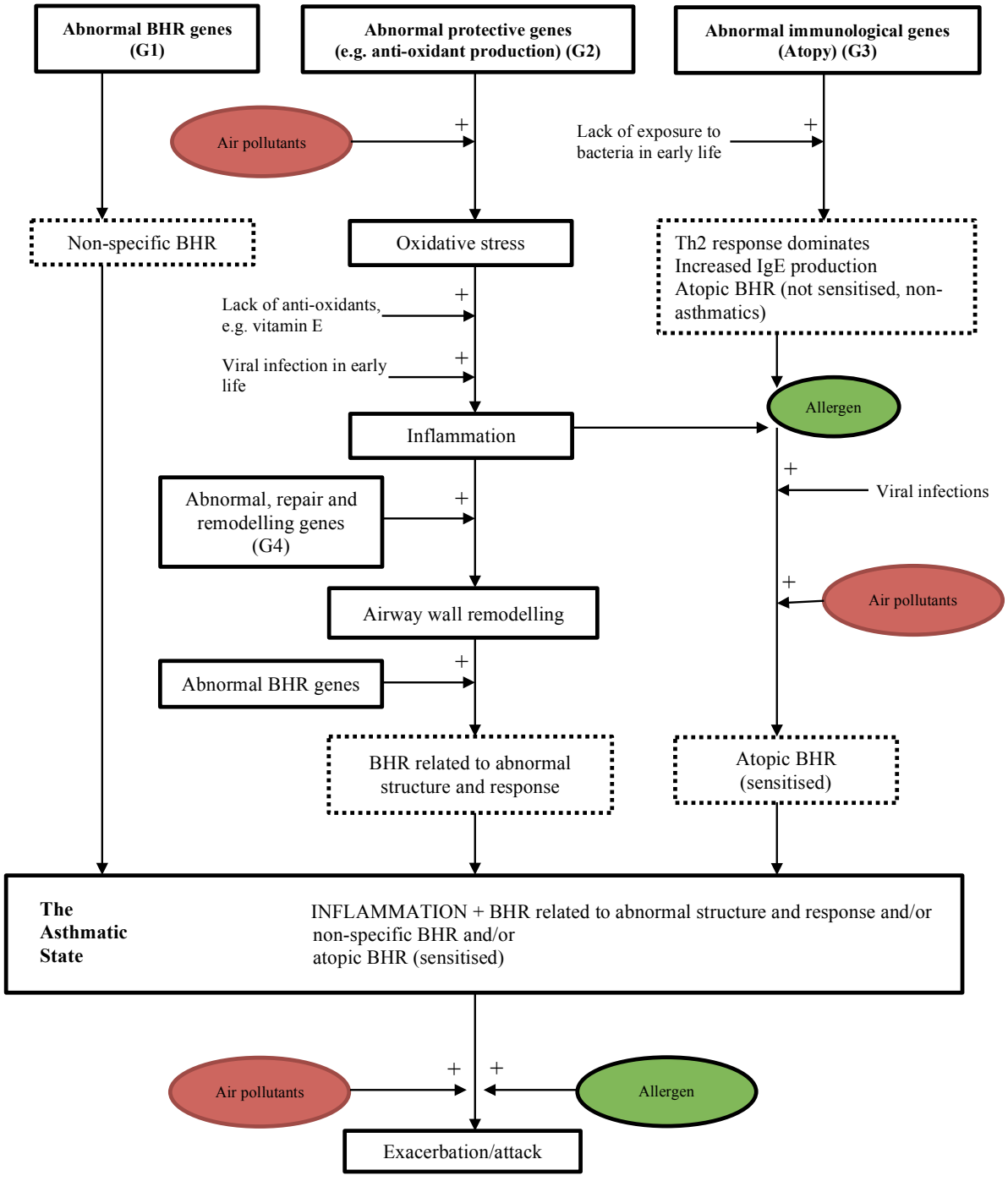

Figure 4: Hypothetical network of causation of asthma in relation to ambient air pollution exposure. BHR, bronchial hyperresponsiveness; IgE, immunoglobulin E; Th2, Type 2 helper cells (adapted and reproduced with permission)18

For example, exposures to NO_2, $PM_{2.5}$, elemental carbon (EC), and acid vapour were significantly associated with reduced FEV_1 in children followed from age ten to 18 years. Similarly, the proportion of low FEV_1 (defined as the per cent FEV_1 below 80%) was four times greater in children from communities with the highest level of $PM_{2.5}$ compared to those with the lowest level (7.9% vs 1.6%, p = 0.002).[46]

EXPOSURE-RESPONSE STUDIES BETWEEN POLLEN EXPOSURE AND THE EXACERBATION, PREVALENCE AND INCIDENCE OF CHILDHOOD ASTHMA

The association between pollens and the onset of allergic disease and exacerbations has also been reported in various studies (Table I);[47,48] however, inconsistencies

were evident in the reported associations in these studies. Positive correlations between cedar-pollen counts and asthma in six- to seven-year-old children have been reported in the Japanese ISAAC study.[47] In contrast, no association between increased prevalence of asthma and airborne pollen was found in a Hungarian study.[49] In a large international epidemiological study,[50] grass-pollen allergy was associated with seasonal asthma exacerbations, with elevated risks for sensitised participants in early summer in southern Europe (OR March/April = 2.60, 95% CI: 1.70–3.97; OR May/June = 4.43, 95% CI: 2.34–8.39). In northern Europe, a similar association was observed for birch-sensitised individuals (OR May/June = 2.94, 95% CI: 1.92–4.50; OR July/August = 2.01, 95% CI: 1.38–2.94). A significant association was also observed between grass pollens and hospital visits for asthma attacks in a French study,[51] with an interquartile range increase of 17.6 grains/m^3 of the Poaceae grass family for a 54% increased risk of asthma attacks. However, three of the reviewed studies showed no association between pollen exposure and asthma exacerbation in children (see Table I).[52–54] With regard to asthma incidence, a nine-year German longitudinal study[48] found a significant association between new onset of asthma with previous sensitisation to grass pollen (RR 1.79, 95% CI: 1.01–3.19). In an Australian birth cohort study,[55] cumulative exposure to pollen between four and six months was associated with asthma among 620 children aged six to seven years (OR 1.4 95% CI: 1.1–1.7). Similarly, in a birth-cohort study of 514 children followed from birth to 24 months of age, children exposed to pollen and spores in the first three months of life were reported to be at increased risk of early wheezing, independent of other seasonal factors, lower respiratory infections and ambient air pollutants.[56]

EXPOSURE-RESPONSE STUDIES BETWEEN CO-EXPOSURE TO AIR POLLUTANTS AND POLLEN AND ASTHMA

At the population level, little is known about the possible synergistic effect between allergens and air pollutants since this association is difficult to analyse in uncontrolled settings. The current knowledge of the pathogenesis of allergies and asthma due to combined exposure to biological agents (e.g. pollen, mites) and air pollutants has been based primarily on animal or in vitro laboratory studies.[2] Several clinical laboratory studies have demonstrated that, following prior exposure to ambient air pollutants, there was a greater effect of allergen challenge on asthma.[57,58] In 2015, Brandt et al demonstrated a significantly higher house-dust mite (HDM)-specific memory T cells in the lungs of mice exposed to both HDM and diesel exhaust particles (DEPs) compared to mice exposed to only saline, DEPs or HDM alone.[57] The authors' hypothesised that early-life exposures to DEP may increase the risk of allergic asthma development in children, should exposure to DEPs potentiate recall responses to allergen. The same authors further tested the hypothesis by assessing the effect of early-life exposure to DEP in children sensitised and non-sensitised to HDM. Their result showed a two-fold higher prevalence of asthma at seven years in sensitised children exposed to DEP at birth, compared to non-sensitised children.[57] However, the clinical relevance of such modification in the wider population is unclear, because inconsistent results were found in other epidemiological studies.

A number of the reviewed articles demonstrated a positive association between increased pollen exposures and asthma exacerbation (see Table I).[33,59,56,60–62] However, the effects persisted after controlling for several air pollutants and meteorological factors, indicative of non-modifiable effects of air pollution and seasonality. Similarly, in a Spanish study of 3 939 participants, an increase of 10 µg/m^3 in SO_2 and NO_2 was associated with a higher risk of asthma emergency room visits (RR 5.2 95% CI: 0.5–10.1 for SO2 and RR 2.6 95% CI: 0.3–5.0 for NO2), while the risk level remained the same with the combined effect of plant species such as Urticaceae and Poaceae (RR 5.7 95% CI: 0.9–10.6 for SO_2 and RR 2.7 95% CI: 0.4–5.1 for NO_2).[63]

In conclusion, although the synergistic effect of the combined exposure to air pollutants and allergens has been demonstrated in experimental studies, studies of this association at the population level remain inconclusive, indicating the need for more research to explore this further.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

REFERENCES

1. Olaniyan TA, Dalvie MA, Jeebhay MF. Ambient air pollution and childhood asthma: A review of South African epidemiological studies. Curr Allergy Clin Immunol 2015;28:122–127.
2. World Health Organization. Review of evidence on health aspects of air pollution – REVIHAAP Project 2013.
3. Prüss-Ustün A, Wolf J, Corvalán C, Bos R, et al for WHO. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. (2016).
4. Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386: 2287.
5. World Health Organization. Burden of disease from household and ambient air pollution for 2012 summary of results. 2014:35.
6. D'Amato G, Liccardi G, D'Amato M, Holgate S. Environmental risk factors and allergic bronchial asthma. Clin. Exp. Allergy 2005;35:1113–1124.
7. D'Amato G, Liccardi G, D'Amato M, Cazzola M. Outdoor air pollution, climatic changes and allergic bronchial asthma. Eur Respir J 2002;20:763–776.
8. D'Amato G, Holgate ST, Pawankar R, Ledford DK, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. World Allergy Organ J 2015;8:25.

TABLE I: STUDIES OF THE ASSOCIATION BETWEEN AMBIENT POLLEN AND/OR AIR POLLUTANTS AND CHILDHOOD ASTHMA

AUTHOR(S)	AIM	STUDY DESIGN	STUDY POPULATION	EXPOSURE MEASUREMENTS	OUTCOME MEASUREMENTS	RESULTS	CONCLUSION
Gleason et al, 2014[33]	Studied transient impact of ozone, $PM_{2.5}$ and pollen on emergency department visit for childhood asthma	Time-stratified case-crossover design	Children aged 3–17 years residing in New Jersey, United States between 2004 and 2007	Daily concentrations of pollen. Daily averages of $PM_{2.5}$ and daily eight-hour average of O_3 from fixed-monitoring station, and meteorological data from New Jersey State Climatologist	Daily number of emergency visits for childhood asthma	Multipollutant model showed positive associations between daily emergency department visits and same-day O_3 (RR_{IQR} = 1.08, 95% CI 1.06–1.10), three-day tree pollen average (RR_{IQR} = 1.19, 95% CI 1.17–1.20), three-day grass pollen average (RR_{IQR} = 1.08, 95% CI 1.09–1.11) respectively	Ozone, grass and weed pollen are independent risk factors for asthma exacerbation
Tosca et al, 2014[64]	Investigated relationship between asthma exacerbation, pollen, air pollution and meteorological factors	Time-series ecological study design	Children residing in Genoa, Italy between 2002 and 2011	Daily concentrations of pollen (*Betulaceae, Utricaceae, Gramineae, Oleaceae*), outdoor air pollutants, and meteorological variables	Number of emergency calls for asthma exacerbation	Number of emergency calls associated with pollens in spring (r = 0.498), SO_2 (r = 0.622), NO_2 = 0.58, NO (r = 0.699), rainfall (r = 0.0.818), and wind speed (r = 0.727)	Environmental factors may induce exacerbation of asthma
Yoshida et al, 2013[47]	Evaluated association between pollen exposure and prevalence of allergic diseases	Ecological analysis	Children aged between six and seven years and those aged between 13 and 14 years residing in Japan	Daily pollen data on Japanese cedar and Japanese cypress	Allergic diseases assessed using International Study of Asthma and Allergy in childhood (ISAAC) questionnaire	Cedar but not cypress pollen counts positively associated with prevalence of asthma in six- to seven-year-old children (r = 0.49, p = 0.003) but not in other age group.	Evidence of ecological associations between pollen counts and prevalence of asthma
DellaValle et al, 2012[59] night symptoms, shortness of breath, chest tightness, persistent cough, and rescue medication use were recorded in a cohort of 430 children with asthma (age 4-12 years)	Investigated relationship between ambient pollen concentration and severity of asthma symptoms among asthmatic children	Cross-sectional study	430 asthmatic children aged 4–12 years in Connecticut, MA and New York	Mixed-effect models used to estimate daily exposures to tree, grass, weed, and total pollen	Daily symptoms of rescue medication use, night symptoms, wheeze, persistent cough, chest tightness, shortness of breath, and night symptoms	23% increased likelihood of any respiratory symptoms (95% CI; 1.01–1.50) and 11% increased likelihood in rescue medication use (95% CI; 1.02–1.21), comparing the highest quintile of weed pollen to the lowest, while adjusting-for O_3, $PM_{2.5}$, maximum temperature, antibiotic use, and season	Daily asthmatic symptoms are associated with pollen exposure
Harley et al, 2009[56]	Assessed risk of early childhood wheezing following fungal and pollen exposure in first months of life	Birth-cohort study	514 children enrolled before birth and followed for 24 months	Ambient aeroallergens measured throughout study period	Early wheezing obtained from medical records	Positive association between seasonal patterns (spore season) and odds of early wheezing (adjusted OR = 3.1, 95% CI; 1.3–7.4) controlling for $PM_{2.5}$ and lower respiratory infections	Early wheezing in children exposed to pollen and spores in first three months of life is independent of air pollutant exposure and lower respiratory infections

AUTHOR(S)	AIM	STUDY DESIGN	STUDY POPULATION	EXPOSURE MEASUREMENTS	OUTCOME MEASUREMENTS	RESULTS	CONCLUSION
Heguy et al, 2008[60]	Explored short-term effects of grass and weed pollen exposure on childhood asthma (re) admission to emergency department	Time-series analysis	Children aged 0–9 years living in Montreal, Canada between 1994 and 2004	Daily concentrations of pollen. Bi-hourly measurements of CO, SO_2, NO_2, and O_3 from fixed-monitoring stations, and meteorological data from Meteorological Service of Canada	Daily number of emergency visits for childhood asthma	Positive association between emergency department visit and grass pollen concentration three days following exposure (mean per cent change = 1.73%; 95% CI: 0.24–3.25%) after adjusting for air pollutants and meteorological variables	Increasing risk of emergency department visit with increasing grass pollen concentrations
Endre et al, 2007[49]	Measured prevalence of childhood asthma in relation to air pollution and total pollen count	Time-series ecological study design	Children under care of paediatricians between 1995 and 2003 in Budapest, Hungary	Online measurements of CO, NO_2, and SO_2 at eight points in Budapest, O_3 measurements at two stations, while pollen and fungal counts were calculated in Budapest	Doctors reported childhood asthma from response to survey questionnaire	Significant increase in prevalence of reported asthma from 1.88% in 1995 to 2.68% in 2003 ($p < 0.0001$). No increase in levels of air pollutants and pollens across studied years	Increase of 50% in prevalence of asthma in study period, independent of air pollution and pollen exposures
Atkinson et al, 2006[61]	Investigated short-term effects of daily counts of fungal spores on asthma exacerbation	Time-series ecological study design	Children aged 0–14 years residing in London between 1992 and 1993	Daily concentrations of fungal spores, pollen, outdoor air pollutants, and meteorological variables	Daily counts of visit for childhood asthma to family doctors, emergency department, and hospital admissions	Changes in fungal spore concentrations from lower to upper quartiles showed increase risk of emergency department visit (RR 1.06 95% CI: 0.94–1.18) and hospital admissions (RR 1.07 95% CI: 0.97–1.19). Observed effect was independent of air pollutants	Exacerbation of asthma may be induced by increased fungal spore concentrations independent of other environmental factors such as air pollution
Dales et al, 2000[52]	Explored association between emergency department visit for asthma and daily concentrations of both pollen and fungal spores	Time-series ecological study design	Children reporting to children's hospital between 1993 and 1997	Daily concentrations of fungal spores, pollen, outdoor air pollutants (SO_2, NO_2, O_3), and meteorological variables (barometric pressure, relative humidity, temperature)	Emergency department visit for asthma reporting at the children's hospital	Fungal spores, but not pollen, associated with percentage increase in number of asthma visits to emergency department (8.8%, $p < 0.05$)	Fungal spores implicated in exacerbation of asthma in children
Newson et al, 2000[53]	Explored association between fungal spore counts and asthma admission	Time-series ecological study design	Children and adults residing in Trent, England between 1987 and 1994	Daily counts of 25 spore taxa measured in Derby	Hospital admission for asthma including spore counts on six days of asthma epidemics	No association found between total spore count and hospital admission, except for total spore count above the 90th percentile showing associations with four of the six epidemic days (OR = 9.92, 95% CI: 1.41–109.84)	Although no specific taxon was implicated, there is some evidence that high rates of asthma admissions tend to occur on days with high total mould spore counts

AUTHOR(S)	AIM	STUDY DESIGN	STUDY POPULATION	EXPOSURE MEASUREMENTS	OUTCOME MEASUREMENTS	RESULTS	CONCLUSION
Garty et al, 1998[54]	Examined association between emergency department asthma visit and air pollution, weather, and airborne allergens	Prospective cohort study	Asthmatic children aged 1–18 years reporting at Children's ER between January and December, 1993	Daily concentrations of airborne allergens, air pollutants, and meteorological variables	Number of emergency room visits for asthma	Positive correlation between number of emergency room visits and SO_2 and NO_x, high barometric pressure and negative associations with O_3 and temperature, but no association with airborne pollens and spores	High levels of NO_x and SO_2 associated with emergency room visits for asthma but not airborne pollen
Rosas et al, 1998[62]	Assessed the relationship between environmental factors such as aeroallergens, air pollution and weather and emergency department admissions for asthma	Time-series ecological study design	Children under 15 years of age residing in Mexico City, Mexico	Daily concentrations of airborne allergens, air pollutants, and meteorological variables	Number of emergency room admissions for asthma	Both grass and fungal spores associated with asthma admissions in both wet and dry seasons, adjusting for air pollution	Positive association between pollen and asthma exacerbation in children

9. D'Amato G, Cecchi L, Bonini S, Nunes C, et al. Allergenic pollen and pollen allergy in Europe. Allergy 2007;62:976–990.
10. Potter PC. Common indoor and outdoor aero-allergens in South Africa. Contin Med Educ 2010;28:426–432.
11. Billionnet C, Sherrill D, Annesi-Maesano I. Estimating the health effects of exposure to multi-pollutant mixture. Ann Epidemiol 2012;22:126–141.
12. Eggleston PA. Complex interactions of pollutant and allergen exposures and their impact on people with asthma. Pediatrics 2009;123 Suppl:S160–S167.
13. García-Gallardo MV, Algorta J, Longo N, Espinel S, et al. Evaluation of the effect of pollution and fungal disease on Pinus radiata pollen allergenicity. Int Arch Allergy Immunol 2013;160:241–250.
14. D'Amato G. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. Multidiscip Respir Med 2011;6:28–37.
15. Motta AC, Marliere M, Peltre G, Sterenberg PA, et al. Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. Int Arch Allergy Immunol 2006;139:294–298.
16. D'Amato G. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. Multidiscip Respir Med 2011;6:28–37.
17. D'Amato G. Environmental urban factors (air pollution and allergens) and the rising trends in allergic respiratory diseases. Allergy 2002;57 Suppl:30–33.
18. Gowers AM, Cullinan P, Ayres JG, Anderson HR, et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. Respirology 2012;17:887–898.
19. Peltre G. Inter-relationship between allergenic pollens and air pollution. Allerg Immunol (Paris) 1998;30:324–326.
20. Mölter A, Simpson A, Berdel D, Brunekreef B, et al. A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. Eur Respir J 2015;45:610–624.
21. Bowatte G, Lodge C, Lowe AJ, Erbas B, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. Allergy 2015;70:245–256.
22. Anderson HR, Favarato G, Atkinson RW. Long-term exposure to outdoor air pollution and the prevalence of asthma: meta-analysis of multi-community prevalence studies. Air Qual Atmos Heal 2011;6:57–68.
23. Mölter A, Agius RM, De Vocht F, Lindley S, et al. Long-term exposure to PM10 and NO2 in association with lung volume and airway resistance in the MAAS birth cohort. Environ Health Perspect 2013;121:1232–1238.
24. Sahsuvaroglu T, Jerret M, Sears MR, McConnell R, et al. Spatial analysis of air pollution and childhood asthma in Hamilton, Canada: comparing exposure methods in sensitive subgroups. Environ Health 2009;8:14.
25. Oftedal B, Nystad W, Brunekreef B, Nafstad P. Long-term traffic-related exposures and asthma onset in schoolchildren in oslo, norway. Environ Health Perspect 2009;117:839–844.
26. Clark NA, Demers PA, Karr CJ, Koehoorn M, et al. Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect 2010;118: 284–290.
27. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, et al, Traffic-related air pollution and incident asthma in a high-risk birth cohort. Occup Environ Med 2011;68:291–295.
28. Gehring U, Wijga AH, Brauer M, Fischer P, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 2010;181:596–603.
29. Gruzieva O, Bergström A, Hulchiy O, Kull I, et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. Epidemiology 2013;24:54–61.
30. Hasunuma H, Sato T, Iwata T, Kohno Y, et al. Association between traffic-related air pollution and asthma in preschool children in a national Japanese nested case-control study. BMJ Open 2016;6: e010410.
31. Evans K, Halterman J, Hopke P, Fagnano M, et al. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbationa among urban children. Environ Res 2014;129:11–19.
32. Alangari AA, Riaz M, Mahjoub MO, Malhis N, et al. The effect of sand storms on acute asthma in Riyadh, Saudi Arabia. Ann Thorac Med 2015;10:29–33.
33. Gleason JA, Bielory L, Fagliano JA. Associations between ozone, PM2.5, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: a case-crossover study. Environ Res 2014;132:421–429.
34. Strickland MJ, Klein M, Flanders WD, Chang HH, et al. Modification of the effect of ambient air pollution on pediatric asthma emergency visits: susceptible subpopulations. Epidemiology 2014;5:843–850.
35. Ho WC, Hartley WR, Myers L, Lin MH, et al. Air pollution, weather, and associated risk factors related to asthma prevalence and attack rate. Environ Res 2007;104:402–409.
36. Loyo-Berríos NI, Irizarry R, Hennessey JG, Tao XG, et al. Air pollution sources and childhood asthma attacks in Catano, Puerto Rico. Am J Epidemiol 2007;165:927–935.
37. Berhane K, Zhang Y, Linn WS, Rappaport EB, et al. The effect of ambient air pollution on exhaled nitric oxide in the Children's Health Study. Eur Respir J 2011;37:1029–1036.
38. Jacobson Lda S1, Hacon Sde S, Castro HA, Ignotti E, et al. Association between fine particulate matter and the peak expiratory flow of schoolchildren in the Brazilian subequatorial Amazon: a panel study. Environ Res 2012;17:27–35.
39. Lee YL, Wang WH, Lu CW, Lin YH, et al. Effects of ambient air pollution on pulmonary function among schoolchildren. Int J Hyg

Environ Health 2011;214:369–375.
40. Neophytou AM, White MJ, Oh SS, Thakur N, et al. Air Pollution and Lung Function in Minority Youth with Asthma in the GALA II (Genes-Environments and Admixture in Latino Americans) and SAGE II (Study of African Americans, Asthma, Genes, and Environments) Studies. Am J Respir Crit Care Med 2016;193(11):1271–1280
41. He QQ, Wong TW, Du L, Jiang ZQ, et al. Effects of ambient air pollution on lung function growth in Chinese schoolchildren. Respir Med 2010;104:1512–1520.
42. Chen CH, Chan CC, Chen BY, Cheng TJ, et al. Effects of particulate air pollution and ozone on lung function in non-asthmatic children. Environ Res 2015;137:40–48.
43. Ierodiakonou D1, Zanobetti A, Coull BA, Melly S, et al. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol 2016;137:390–399.
44. Castro HA, Cunha MF, Mendonça GA, Junger WL, et al. Effect of air pollution on lung function in schoolchildren in Rio de Janeiro, Brazil. Rev Saude Publica 2009;43(1):26–34.
45. Barone-Adesi F, Dent JE, Dajnak D, Beevers S, et al. Long-term exposure to primary traffic pollutants and lung function in children: cross-sectional study and meta-analysis. PLoS One 2015;10(11):e0142565.
46. Chen Z, Salam MT, Eckel SP, Breton CV, et al. Chronic effects of air pollution on respiratory health in Southern California children: findings from the Southern California Children's Health Study. J Thorac Dis 2015;7:46–58.
47. Yoshida K, Adachi Y, Akashi M, Itazawa T, et al. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. Allergy 2013;6:757–763.
48. Schäfer T, Wölke G, Ring J, Wichmann HE, et al. Allergic sensitization to cat in childhood as major predictor of incident respiratory allergy in young adults. Allergy 2007;62:1282–1287.
49. Endre L, Láng S, Vámos A, Bobvos J, et al. Increase in prevalence of childhood asthma in Budapest between 1995 and 2003: correlation with air pollution data and total pollen count. Orv Hetil 2007;148:211–216.
50. Canova C, Heinrich J, Anto JM, Leynaert B, et al. The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks. Eur Respir J 2013;42:935–945.
51. Huynh BT, Tual S, Turbelin C, Pelat C, et al. Short-term effects of airborne pollens on asthma attacks as seen by general practitioners in the Greater Paris area, 2003-2007. Prim Care Respir J 2010;19:254–259.
52. Dales RE, Cakmak S, Burnett RT, Judek S, et al. Influence of ambient fungal spores on emergency visits for asthma to a regional children's hospital. Am J Respir Crit Care Med 200;162:2087–2090.
53. Newson R, Strachan D, Corden J, Millington W. Fungal and other spore counts as predictors of admissions for asthma in the Trent region. Occup Environ Med 2000;57:786–792.
54. Garty BZ, Kosman E, Ganor E, Berger V et al. Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. Ann Allergy Asthma Immunol 1998;81:563–570.
55. Erbas B, Lowe AJ, Lodge CJ, Matheson MC, et al. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clin Exp Allergy 2013;43:337–343.
56. Harley KG, Macher JM, Lipsett M, Duramad P, et al. Fungi and pollen exposure in the first months of life and risk of early childhood wheezing. Thorax 2009;64:353–358.
57. Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, et al. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. J Allergy Clin Immunol 2015;136:295–303.
58. Cakmak S, Dales RE, Coates F. Does air pollution increase the effect of aeroallergens on hospitalization for asthma? J Allergy Clin Immunol 2012;129:228–231.
59. DellaValle CT, Triche EW, Leaderer BP, Bell ML. Effects of ambient pollen concentrations on frequency and severity of asthma symptoms among asthmatic children. Epidemiology 2012;23:55–63.
60. Héguy L, Garneau M, Goldberg MS, Raphoz M, et al. Associations between grass and weed pollen and emergency department visits for asthma among children in Montreal. Environ Res 2008;106:203–211.
61. Atkinson RW, Strachan DP, Anderson HR, Hajat S, et al. Temporal associations between daily counts of fungal spores and asthma exacerbations. Occup Environ Med 2006;63:580–590.
62. Rosas I, McCartney HA, Payne RW, Calderón C, et al. Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy 1998;53:394–401.
63. Baldacci S, Maio S, Cerrai S, Sarno G, et al. Allergy and asthma: Effects of the exposure to particulate matter and biological allergens. Respir Med 2015;109:1089–1104.
64. Tosca MA, Ruffoni S, Canonica GW, Ciprandi G. Asthma exacerbation in children: relationship among pollens, weather, and air pollution. Allergol Immunopathol (Madr) 2014;42(4):362–368.