Importance of allergen–environment interactions in epidemic thunderstorm asthma

Kira Morgan Hughes, Dwan Price and Cenk Suphioglu

Abstract: Australia is home to one of the highest rates of allergic rhinitis worldwide. Commonly known as ‘hay fever’, this chronic condition affects up to 30% of the population and is characterised by sensitisation to pollen and fungal spores. Exposure to these allergens has been strongly associated with causing allergic reactions and worsening asthma symptoms. Over the last few decades, incidences of respiratory admissions have risen due to the increased atmospheric concentration of airborne allergens. The fragmentation and dispersion of these allergens is aided by environmental factors like rainfall, temperature and interactions with atmospheric aerosols. Extreme weather parameters, which continue to become more frequent due to the impacts of climate change, have greatly fluctuated allergen concentrations and led to epidemic thunderstorm asthma (ETSA) events that have left hundreds, if not thousands, struggling to breathe. While a link exists between airborne allergens and led to epidemic thunderstorm asthma (ETSA) events that have impacted hospital admission rates need to be determined. After the epidemic thunderstorm asthma (ETSA) event that impacted Melbourne in 2016, it is clear that more research needs to be undertaken to prevent future cases of severe and fatal asthma from occurring. This review will investigate the underlying causes of allergic rhinitis, determine how exposure can be altered by meteorological factors and improve our understanding of how allergen–environment interactions affect respiratory health.

Keywords: asthma, climate, fungal spore, pollen, pollen allergy

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Introduction

The relationship between airborne allergens and respiratory health has not yet been fully understood. Along with the continued increase in asthma prevalence across Australia, and the world, the factors that have influenced the unprecedented rise in atmospheric allergenicity and impacted hospital admission rates need to be determined. After the epidemic thunderstorm asthma (ETSA) event that impacted Melbourne in 2016, it is clear that more research needs to be undertaken to prevent future cases of severe and fatal asthma from occurring. This review will investigate the underlying causes of allergic rhinitis, determine how exposure can be altered by meteorological factors and improve our understanding of how allergen–environment interactions affect respiratory health.

Allergic rhinitis and asthma

Characteristics of allergic rhinitis

Seasonal allergic rhinitis, commonly referred to as ‘hay fever’, affects approximately 20% of people in developed countries. This condition is characterised by an allergic response to airborne allergens, resulting in inflammation and discharge from the mucous membranes. In a majority of the cases, individuals afflicted with allergic rhinitis experience mild symptoms that are considered self-treatable and manageable. In addition, it is estimated up to 40% of individuals with allergic rhinitis also suffer from chronic respiratory diseases such as asthma, and if exposed to allergens this could lead to acute respiratory presentations that may prove fatal. Aside from physical symptoms, allergic rhinitis negatively affects physical health and quality of life. Over the last few decades, incidences of respiratory admissions have risen due to the increased atmospheric concentration of airborne allergens. The fragmentation and dispersion of these allergens is aided by environmental factors like rainfall, temperature and interactions with atmospheric aerosols. Extreme weather parameters, which continue to become more frequent due to the impacts of climate change, have greatly fluctuated allergen concentrations and led to epidemic thunderstorm asthma (ETSA) events that have impacted Melbourne in 2016. It is clear that more research needs to be undertaken to prevent future cases of severe and fatal asthma from occurring. This review will investigate the underlying causes of allergic rhinitis, determine how exposure can be altered by meteorological factors and improve our understanding of how allergen–environment interactions affect respiratory health.

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Conclusion

Understand the potential threat these events pose on our susceptible populations and ensure our health infrastructure is prepared for the next epidemic.
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impacts an individual’s quality of life, affecting their sleep quality, economic well-being and mental health.4 Australia’s prevalence of allergic sensitisation and asthma is one of the highest, despite the country having a smaller population compared with the rest of the developed world. Up to 30% of Australians are estimated to suffer from allergic rhinitis and at least 20% are reported to have experienced some degree of asthmatic symptoms.9 Allergic rhinitis is estimated to cost the Australian economy approximately $9 billion annually, with a majority of the financial burden attributed to lost productivity and expenditure of the health system.6

Characteristics of allergic asthma

Allergic asthma is the most common phenotype of asthma, contributing to 80% of chronic asthma cases, and typically manifests in early childhood.7,8 It is defined by exposure to airborne allergens triggering an asthmatic response through airway inflammation and bronchoconstriction.8 Allergic asthma shares similar physiology with allergic rhinitis as both are IgE-mediated and exhibit hypersensitiveness to bioaerosols in the respiratory tract.9 This can result in patients with one of these chronic diseases being diagnosed with the other later in life, making allergic rhinitis a risk factor for developing asthma and vice versa.9 Family history of asthma also increases the risk of developing allergic asthma.10,11 Compared with the economic burden of all diseases, 2% of the world’s economy is spent covering asthma-related costs.12

IgE-mediated response to aeroallergens

Allergic rhinitis and allergic asthma manifest in genetically predisposed individuals following a two-step process: the primary and secondary. During the primary response, individuals are first exposed to airborne allergens via inhalation or contact with the skin. Antigen-presenting cells, located within the mucous membranes of the eyes, nasal cavity, and oral cavity, complex with these allergens and process them to be presented to allergen-specific T cells.13 The presence of foreign antigens activates T cells and induces the production of immunoglobulin E (IgE) via B plasma cells14 specific to the antigens of these airborne allergens. IgE released into circulation bind to high-affinity receptors on mast cells, effectively ‘arming’ them against the allergen.15 Coinciding with this response, B memory cells are also produced to ensure the immune system promptly recognises and responds to the foreign antigen if future exposure was to occur. At this point, the individual is now sensitised to the allergen. When these airborne allergens make contact with the mucous membranes again, the secondary response occurs. Subsequent exposure leads to antibody–antigen binding with the allergen and the allergen-specific IgE attached to mast cells. This signals mast cells to activate and commence the allergenic immune response by releasing inflammatory mediators.16 For those who are sensitised but remain asymptomatic, they will possess allergen-specific IgE but it may never progress to atopic diseases and they could lose their sensitisation over time.17,18 In sensitised symptomatic individuals, inflammatory mediators, like histamine, are released from mast cells, which triggers inflammation and irritation in response to the presence of the allergen.19 However, if the immune response occurs in the lower airways of sensitised symptomatic individuals, it can trigger breathing issues ranging from mild to severe. Pharmacological solutions are widely available to help alleviate symptoms in these situations, but hospitalisation may be required in more serious circumstances.

Pollen

Pollen allergy

Over the last few decades, incidence of respiratory diseases has been increasing drastically due to the higher prevalence of airborne pollutants, including airborne allergens, across Australia.20 Pollen grains are one of the most common aeroallergens in the country. Grass pollen (Poaceae), for instance, has been recognised as a major cause of allergic rhinitis across a wide range of age groups.21 Exposure to grass pollen has also been linked to a rise in asthma-related hospital admissions in rural New South Wales22 and associated with increased antihistamine sales in Darwin, Northern Territory.23 IgE-mediated allergic reactions can occur quickly in sensitised hosts, usually 15–30 min following contact from inhalation.24

History of pollen allergy

Originally, pollen grains were not considered as a significant cause of asthma. While skin prick tests performed on young children proved that exposure caused a positive allergic response, pollen had not yet been linked to contributing to acute
respiratory issues. It was assumed that due the size of intact pollen grains averaging 20–60 μm in diameter\(^2\) (see Figure 1), it would be difficult for pollen to reach the lower airways, where inflammation commonly occurs in asthma. However, it was discovered that they can naturally fragment into microscopic respirable particles due to high levels of moisture in the atmosphere.\(^3\) Pollen grains were found to rupture from osmotic shock, causing them to release extremely fine particles that are able to penetrate further into the lower airways compared with intact pollen\(^4\) (see Figure 2) and provoke asthmatic symptoms within susceptible populations.\(^5\) Group 1 and 5 allergens were found to expel from ruptured grass pollens at respirable sizes when hydrated excessively.\(^6\) Intact grass pollen contains approximately 700 starch granules loaded with these allergenic particles that, when released, trigger IgE-mediated responses in sensitised individuals.\(^7\)

**Severity of pollen allergy**

The severity of allergic rhinitis symptoms has been shown to lessen over the duration of the pollen season. Sensitised individuals from the Netherlands reported symptoms more frequently at the start of the season compared with the end, despite pollen counts staying relatively consistent.\(^8\) This may be due to tolerance gradually building up over a long period of constant exposure to these airborne allergens. Constant high exposure to pollen allergens may reduce the severity of symptoms over time, but has still been linked to high rates of sensitisation in Northern Europe.\(^9\) Currently, a majority of studies on the influence of seasonal pollen have taken place in the United States and Europe. However, there is little to no available data available regarding the impact of seasonal pollen on sensitised populations in Australia.

**Figure 1.** Aeroallergen scale bar.

**Figure 2.** Visualisation of aeroallergens traversing the upper and lower airways. Intact pollens, due to their size, get stuck along the mucosal membrane of the upper airways, which induces allergies. Ruptured pollen particles are caught up in the airflow and able to travel deep into the lower airways, which triggers asthmatic symptoms.
Fungi

**Fungal spore allergy**
Fungal spores make up a large proportion of aeroallergen concentrations in the atmosphere. At least 80 fungi taxa have been identified as the cause of respiratory symptoms and in a majority of cases, fungal allergy presents as rhinitis. Most spores do not exceed 10 µm in size, which enables them to penetrate deeper into the lower airways and cause asthmatic symptoms. Most airborne fungal spores are hydrophobic, which enables them to reach greater distances when dispersed and leads to increased cases of exposure.

**Fungal sensitisation**
Fungal sensitisation has been greatly associated with causing allergic reactions and worsening asthma symptoms. Decreased lung function and increased inflammation have also been linked to fungal spore exposure in sensitised individuals. *Alternaria sp.* for example, has been observed to significantly worsen asthma symptoms in sensitised children and adults susceptible to respiratory infections. Sensitisation to *Alternaria sp.* spores has also been linked to an increased risk of experiencing severe asthma episodes that result in acute respiratory admission. While fungal spores exist in large quantities in the external environment, they have also been discovered to be common indoors due to mould growth and dispersal via ventilation systems. This suggests that spores could contribute equally, if not more, given their wider dispersal, to allergy-related hospital admissions compared with pollen grains.

**Prevalence of fungi sensitisation**
Currently, the prevalence of fungal allergy is estimated to be up to 10% globally. However, among individuals regularly exposed to fungi and moulds, the rate of sensitisation is much higher. Occupational allergic asthma induced by fungal sensitisation has been primarily reported across eastern Asia and parts of Europe. Approximately 32% of farmers and 16% of bakers who were suffering from asthmatic symptoms were also found to be sensitised to at least one fungal spore taxa, with *Aspergillus sp.* being the most common allergen.

**Differences between pollen and fungal spore allergy**
Fungal spores are prevalent within the air for a much longer period of time, in contrast to pollen where the season only spans a few months. For example, in Canada, ragweed starts production of pollen between August and September. In contrast, most *basidiomycetes* have been shown to release noticeable levels of spores between April and October, resulting in an extremely long period of exposure for sensitised individuals. Despite a substantial number of fungi taxa contributing to the presence of allergens in the atmosphere, only a small number of species like *Alternaria spp.* are recognised by allergy specialists and associated with respiratory symptoms. This may be in part due to the highly specific nature of fungi allergy where different spore taxa results in distinctly different respiratory presentations. The increased exposure time, inconsistencies in allergic presentation, and lack of fungal diversity during allergic testing calls for increased research into further identifying the allergenic fungi present in the air and understanding the contribution of fungal sensitisation to respiratory hospital admissions.

**Climate**

**Weather and allergic rhinitis**
In order to understand the prevalence of different airborne allergens, we should first acknowledge how environmental factors have contributed to these fluctuating levels. Climate, for instance, has a major influence on the production of and our exposure to airborne allergens. While their prevalence is seasonal, the impact of climate change and meteorological factors on the number and distribution of these aeroallergens has increased allergy-induced hospitalisations across urban areas, despite improvements in pharmacological treatment. Originally, daily changes to weather parameters were not believed to have a significant impact on asthma or allergic rhinitis, despite asthma sufferers frequently reporting that the extent of their symptoms was dependent on the climate. Studies in Europe have now found correlations between the weather and respiratory health, with a 7% increase in respiratory-related deaths at higher temperatures, and at colder temperatures a 4% increase in hospital admissions.
Impact of weather on aeroallergen prevalence

Weather conditions have been shown to greatly impact atmospheric concentrations of pollen and fungal spores (see Figure 3). Birch pollen allergens form a respirable aerosol when ruptured, with the allergen concentration further increasing following rainfall. Low humidity levels have been observed to compliment the release and distribution of airborne allergens into the atmosphere. Temperature may also influence interactions between pollen grains and other airborne allergens or pollutants, causing them to adhere to the pollens’ surfaces and express higher allergenicity, which will increase the risk of exposure for sensitised individuals. Dry ascomycete spores rely on conditions with warm temperatures, low humidity and wind to enhance dispersion. This was observed in Southern India, where monsoons significantly increased Aspergillus sp. and Cladosporium sp.

Climate change and allergic rhinitis

Studies have begun to find that the warming of the Earth’s climate has had a detrimental effect on human health, which has been associated with a rising prevalence of allergic respiratory diseases since the 1990s. Climate change has led to longer pollen seasons, increasing the duration and severity of respiratory symptoms among allergy sufferers. The average pollen season of ragweed, a primary allergenic pollen in the United States, has lasted for at least 2–4 weeks longer since 1995. This may be due to changes in the growth and reproduction of the allergenic plant’s life, resulting in temporal variation of allergen distribution. Findings have shown across multiple continents that higher temperatures have caused allergenic pollen loads to significantly increase, which will continue to rise as global temperatures become more extreme.

Impact of atmospheric aerosols on aeroallergens

Plants can also be significantly influenced by changes in atmospheric concentrations. Increased levels of atmospheric carbon dioxide have been linked to adjustments in the flowering periods of allergenic plants. The pollen seasons are consequently extended, which increases the risk of sensitised individuals being exposed to a greater airborne allergen count. Alternaria sp., when exposed to high carbon dioxide levels, altered the spore loads so they produced three times greater counts when compared with fungi cultivated in lower carbon dioxide concentrations. High carbon dioxide levels were also linked to increased allergenicity within these fungal spores, with twice as many allergenic proteins found when grown under these elevated conditions. If atmospheric conditions continue to worsen, we can expect the duration of pollen seasons to keep increasing and allergenic symptoms to become more frequent and severe among sensitised individuals.

The future of allergic rhinitis

Pollen allergy is a common health issue in many parts of Europe, with ragweed being the most common cause of symptoms, making up 50% of total atmospheric pollen concentration. Research into the future impacts of climate change suggests that allergic rhinitis will affect a greater proportion of the general population over the next few decades. Allergic rhinitis prevalence had previously almost doubled, as well as asthma prevalence increasing by approximately 50%, over a ten year period in Sweden. Studies predict that the population susceptible to ragweed

Figure 3. Hypothesised representation of airborne allergen levels during various climates and its impact on susceptible individuals. From left to right: dry and cold conditions lead to moderate pollen levels and mild allergy (a), dry and hot conditions lead to high pollen levels and acute allergy (b), thunderstorms lead to high pollen & fungal spore levels and acute allergy & asthma (c), wet and warm conditions lead to high fungal spore levels and acute allergy (d), wet and cold conditions lead to moderate fungal spore levels and mild allergy (e).
sensitisation will double as early as 2041, even in countries with a lower prevalence of pollen allergy and will experience a higher frequency of severe symptoms. Climate change could result in more frequent extreme weather events that increase the production and distribution of airborne allergens. The risk of a large proportion of the world population developing allergic rhinitis will result in higher cases of allergy-related hospital admissions. The different aeroallergen biology in the southern hemisphere, compared with the northern hemisphere, suggests that unique strategies will need to be developed to cope with the consequences of climate change. As Australia is already experiencing one of the highest rates of asthma worldwide, the heavy burden this could possibly place on unprepared public health systems in the coming years may be devastating.

Thunderstorm asthma

The Melbourne epidemic thunderstorm asthma event

On 21 November 2016, Melbourne experienced the world’s most severe case of thunderstorm asthma. This catastrophic event caused thousands to be hospitalised due to respiratory issues and has been associated with at least 10 deaths. Approximately 87% of admitted patients suffered from allergic rhinitis and 28% had been diagnosed with asthma.

Characteristics of thunderstorm asthma

Thunderstorm asthma is categorised as an epidemic of acute asthma attacks triggered by environmental conditions. The outflow of cold air collects and concentrates a large proportion of airborne allergens near ground level, increasing the risk of sensitised individuals inhaling allergenic particulates and experiencing asthmatic symptoms. Electric fields generated by thunderstorms increase the rate of pollen fragmentation and aid the dispersion of allergenic particles. Lightning can also cause airborne allergens to ionise, which results in longer adherence to the mucous membranes of lower airways and an increased risk of asthmatic symptoms. While rain usually washes pollen out of the air, under certain conditions it can generate a high concentration of ruptured fragments that will remain for several hours after a storm has passed.

History of thunderstorm asthma in Australia

ETSA events have been reported in Australia since 1984, but the impact of thunderstorms on respiratory health in Australia has been well known since two consecutive events unfolded in Melbourne in 1987 and 1989. Both epidemics resulted in a significant increase in hospital admissions for asthma exacerbations, with rye grass allergy a common factor among patients. While the impact of these events could not be solely attributed to pollution levels or the storm itself, the trend of allergic rhinitis among patients suggested airborne allergens contributed significantly to these asthma epidemics. This association between pollen and respiratory health was further explored following the Wagga Wagga epidemic in 1997. On the 30th of October, the airborne concentration of grass pollen over the town increased exponentially over a short period of time. Over 200 people were reported to have visited the emergency department that night, all suffering from symptoms related to their pollen allergies; 41 of these patients needed to be hospitalised to treat severe exacerbations. Some sensitised individuals who reported asthmatic symptoms during the thunderstorm event had never been diagnosed with asthma.

Thunderstorm asthma in Australia

Epidemic thunderstorm asthma is a rare event that will not occur unless factors such as specific weather parameters, high airborne allergen concentrations and a susceptible population are present. Twenty-six events have been reported worldwide since 1983. Despite the low probability, Australia has recorded 11 separate events of thunderstorm asthma, 7 of which occurred in Melbourne (see Figure 4(a)). The pollen season varies across Australia due to the country’s diverse climate and its impact on the distribution and production of airborne allergens (see Figure 4(b)). Urban areas are especially vulnerable as slight changes in climate can influence duration, start date and end date of the pollen season. Peaks in concentrations can occur at almost any point during the season depending on when certain species are flowering more prominently. Melbourne is reported to have the largest concentration of individuals suffering from allergic rhinitis. The high frequency of events implies that Australia, specifically Melbourne, is at a greater risk of thunderstorm asthma occurring regularly,
with the probability estimated to be two events for every 3 years.\(^7\)

**Limitations of current thunderstorm asthma models**
Researchers have found, from studying asthma epidemics, that a strong correlation exists between severe weather parameters, such as elevated temperature and rainfall, pollen concentrations and increased asthma presentations.\(^7\) However, the number of papers published previously on the subject of thunderstorm asthma was extremely low, with publications only starting to rapidly rise following the 2016 Melbourne epidemic event.\(^6\) Existing studies primarily quantify grass pollen loads while ignoring the wider range of prevalent aeroallergens.\(^\text{77} \) When used to predict epidemic asthma events, the practical application of this data becomes limited. The lack of prior investigations into these impacts on respiratory health left the country unprepared for the extent and severity of the Melbourne asthma epidemic of 2016.\(^6\)

**Predicting airborne allergen prevalence**
Most health specialists in Australia rely on static seasonal pollen calendars to advise their patients suffering from allergic rhinitis and asthma. They aid in visualising the distribution trends of different pollen during the year so they can administer tests and treatments accordingly. In Melbourne, some tree taxa like *Ulmus* and *Cupressaceae* produce higher pollen concentrations between late winter and early spring while *Poaceae* pollen is more abundant in late spring and early summer.\(^7\) However, the rate and severity of pollen allergy is primarily determined by environmental factors that influence allergen concentrations such as flora, climate, and air pollution.\(^7\) Due to the temporal and local variability, and the increasing impact of climate change, these calendars can be highly inaccurate when used across different suburbs and should not be solely relied upon.

**Conclusion**
When visualising aeroallergen trends, it is important to consider the potential interactions with weather and how that will impact rates of asthma presentations. Health officials need more accurate data in order to prepare for or prevent the surge in respiratory admissions during future asthma epidemics. Thus, we need to identify the missing links between weather parameters, respiratory health and airborne allergens. By analysing pollen and spore counts during and outside of the standard pollen season, and correlating these data with daily weather events, pollution and asthma presentations, we can fill in these gaps of knowledge and improve our ability to make accurate predictions about the seasonal impact of airborne allergens in the environment.

**Author contribution(s)**
Kira Morgan Hughes: Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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**Figure 4.** Visualisation of epidemic thunderstorm asthma prevalence (a) and ryegrass distribution (b) in Australia. Epidemic thunderstorm asthma events are characterised by an influx of asthmatic symptoms brought about by severe weather changes and high atmospheric pollen loads. Ryegrass is a key allergenic grass species responsible for triggering asthmatic symptoms during epidemic thunderstorm asthma (ETSA). Numbers signify total ETSA events per state (a). Blue represents ryegrass density; pink represents reported locations of known ETSA events (b).
Dwan Price: Supervision; Validation; Writing – review & editing.

Cenk Suphioglu: Conceptualization; Formal analysis; Funding acquisition; Project administration; Supervision; Validation; Writing – review & editing.

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