Pollen and Asthma Hospitalisations in Children and Adolescents: High Admission Days, Peak Periods, and Readmissions

Submitted by

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Abstract

Childhood asthma continues to pose a significant global public health challenge. Despite extensive progress in understanding the aetiology for childhood asthma, much still remains unclear. Childhood asthma exacerbations resulting in admissions and readmissions present a significant burden on the individual, family, carers, and hospitals. Environment risk factors, particularly pollen in the Southern Hemisphere, are important triggers of asthma admissions in children and adolescents. Little is known regarding the role of pollen on readmissions and other factors on the pathway from pollen and repeat admissions in children/adolescents. Overall, my aim was to understand the role of pollen in childhood asthma hospital admissions and readmissions in Melbourne, Australia. My objectives were:

1. To assess the association of pollen and fungal spores with high asthma admission periods.
2. To identify High asthma admission days (HAADs) and high asthma readmission days (HARDs) using the Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) method.
3. To assess the association between pollen and readmissions within 28 days.
4. To assess the association between pollen and readmissions with indoor risk factors as effect modifiers.

High asthma admission days (HAADs) are the days that report unusually high admissions; they provide important clues regarding environmental risk factors. In Melbourne, Australia, two HAADs, 25 November 2010 and 30 October 2011, were identified. Autocorrelations, two days prior and after the event, were used to define high asthma admission periods, since the impact of the environment is not always immediate. Pollen and fungal spore count two days prior admission and admission day fungal spores were associated with peak periods.

Existing methods used to identify high days in admission and readmission time series have typically used ad hoc approaches that lack statistical evidence and formal evaluation as to their accuracy. I demonstrated how the Seasonal Hybrid Extreme Studentised Deviate (S-H-ESD), which has been evaluated to have high accuracy, supply appropriate statistical evidence in identifying unusually high occurrences in time series and identify HAADs and HARDs with greater accuracy than previous ad hoc methods. It has the capacity to systematise the study of HAADs and HARDs and, with its greater accuracy, the potential to understand associated risk

factors more clearly. Using this novel method, I identified 17 days as HAADs and 25 days as HARDs

I found that daily pollen levels and pollen season were significantly associated with childhood asthma readmissions within 28 days. Also important are indoor risk factors. Therefore, it was important to assess the impact of pollen on readmissions in the presence of poor indoor environment. Exposure to smoking by parents at home was found to increase readmissions regardless of the presence of outdoor pollen.

Identification of environmental risk factors may help in devising approaches to reduce the likelihood of child asthma hospital admissions and readmissions as these are considered prominent triggers of exacerbations. My results showed an important effect of airborne allergen levels up to two days prior to hospitalisation, indicating that tracking not only ambient pollen but also spore counts can be beneficial during the pollen season for the management of children with asthma. I found that the outdoor risk factor, namely pollen, increased child asthma hospital readmissions. Readmissions can possibly be reduced by modifying these exposures.

Statement of Authorship

"This thesis includes work by the author that has been published or accepted for publication as described in the text. Except where reference is made in the text of the thesis, this thesis contains no other material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgment in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution. All research procedures reported in the thesis were approved by the relevant Ethics Committee".

Mehak Batra

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Author Contribution to Publications

Primary Publications

All publications included in this thesis have been primarily authored by me. However, the inclusion of co-authors in these papers indicates that they were produced through collaborative efforts. In my role as primary author, I took responsibility for the majority of the Research Question design, data analysis and interpretation, manuscript drafting and editing. I received guidance and support from my supervisors: Professor Bircan Erbas, and Dr Don Vicendese.

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Mehak Batra was responsible for various aspects of the research paper, including leading its development, devising the analysis plan, conducting data analysis, taking charge of the manuscript writing process, responsible for all edits and revisions, and submitting the manuscript for publication in a journal.

Edward Newbigin, Katrina A Lambert, Mimi Tang, Michael J Abramson, and Shyamali C Dharmage contributed to the study design, reviewed, and edited the manuscript, and contributed to finalising it.

Bircan Erbas and Don Vicendese contributed to the development of the Research Question and analysis plan, supervised the data analysis, initial manuscript drafting, and contributed to finalising it.

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List of Abbreviations

HAADs	High Asthma Admission Days	**SD**	Standard Deviation
HARDs	High Asthma Readmission Days	**O_3**	Ozone
S-H-ESD	Seasonal Hybrid Extreme Studentised Deviate	**AR**	Allergic Rhinitis
COVID-19	Coronavirus disease	**IRR**	Incident Rate Ratio
US	United States	**CI**	Confidence Interval
PM	Particulate Matter	**TRAP**	Traffic-Related Air Pollution
NO_2	Nitrogen dioxide	**TA**	Thunderstorm Asthma
SO_2	Sulphur dioxide	**IL**	Interleukins
MAPCAH	Melbourne Air Pollen Children and Adolescent Health	**HDM**	House Dust Mites
VAED	Victorian Admitted Episodes Dataset	**OR**	Odds Ratio
MCRI	Murdoch Children Research Institute	**RCT**	Randomised Controlled Trial
CO_2	Carbon dioxide	**IgE**	Immunoglobulin E
LMIC	Low- and Middle-Income Countries	**PEF**	Peak Expiratory Flow
NCD	Non-communicable Diseases	**FEV1**	Forced Expiratory Flow in 1 second
UK	United Kingdom	**MV**	Minute Ventilation
QoL	Quality of Life	**BR**	Bedroom
HRV	Human Rhinovirus	**BG**	Beddings
ED	Emergency Department	**LR**	Living Room
DALYs	Disability-adjusted life years	**NS**	Not significant

YLDs	Years Lived with Disability	**RR**	Relative Risk
WHO	World Health Organization	**N**	Sample size
LOWESS	Locally Weighted Scatterplot Smoothing	**PPV**	Positive Predictive Value
ICD	International Statistical Classification of Diseases and Related Health Problems	**MAD**	Median Absolute Deviation
ESD	Rosner Extreme Studentized Test	**GAM**	General Additive Model
TMQQ	Trimmed Mean Quantile Quantile plot	**qq**	quantile quantile
M.4SD	Model 4 Standard Deviation	**STL**	Seasonal and Trend decomposition
PPV	Positive Predictive Value	**GSK**	GlaxoSmithKline
EPA	Environment Protection Authority Victoria	**AIC**	Akaike Information Criterion
VEMD	Victorian Emergency Minimum Dataset	**CVDL**	Centre for Victorian Data Linkage
ICU	Intensive Care Unit	**aOR**	Adjusted Odds Ratio
CALD	Culturally and Linguistically Diverse	**GP**	General Practitioner

1 Introduction

1.1 Respiratory diseases

Asthma is the most common chronic respiratory disease. Many cells and cellular components contribute to asthma, which is– a chronic inflammatory condition of the airways. Asthma is a diverse medical condition characterised by a pattern of respiratory symptoms, such as wheezing, breathlessness, chest tightness, and coughing, which fluctuate in occurrence and intensity, accompanied by variable restrictions in expiratory airflow (1). There are now over 300 million individuals with asthma around the globe, and it is estimated that another 100 million may be impacted by the disease by 2025 (2). The incidence, severity, and death rate of asthma vary greatly among regions. Asthma affects over 30 million Europeans less than the age of 45 years (3, 4). It causes the premature deaths of almost 250,000 every year in the United States. In 2012, the top five countries with the highest prevalence of clinical asthma are Australia at 21.5%, Sweden at 20.2%, the United Kingdom at 18.2%, the Netherlands at 15.3%, and Brazil at 13.0% (5). In low- and middle-income countries, the asthma burden is increasing (6). While more people in high-income nations have asthma, most of those who die from the disease are in low- and middle-income countries, which include countries in sub-Saharan Africa, South Asia, Middle East, North Africa, East Asia and Pacific, Latin America, Caribbean, Europe, and Central Asia regions (7-9). Thus, asthma can be considered a global public health concern.

The onset of asthma often occurs at an early age (10). There are notable distinctions between the prevalence and incidence of asthma in children and adults. More than 6 million children worldwide are affected by this disease, making it one of the most widespread chronic non-communicable childhood illnesses. It is one of the top 20 causes of disability-adjusted life years worldwide among children (11). It causes many missed school days, which can have negative effects on a child's ability to learn and socialise (12). In addition, it is a major reason why children are admitted to hospital, with about 20% of these children being readmitted within a year (13, 14). A child's and their family's emotional and financial wellbeing are negatively impacted by hospital stays. Between 0 to 0.7 per 100,000 (15) children worldwide die every year from asthma complications. Childhood asthma continues over the life course. By the time a child reaches school age, lung function is reduced (16) which persists into adulthood (17, 18). The purpose of my research is to gain a deeper understanding of the impact of modifiable risk factors on childhood asthma outcomes, specifically by investigating

the relationship between pollen exposure and asthma admissions and readmissions among children and adolescents.

1.2 Childhood asthma aetiology

Childhood asthma appears to have a multifactorial aetiology, and the exact cause or causes remain unclear. Multiple genetic and environmental variables are implicated to alter the clinical manifestation and related phenotypes of asthma (19). It is commonly accepted that asthma is caused by interactions between genes and the environment. Several risk factors for the development of asthma are discussed below. Their role in childhood asthma outcomes such as admissions and readmissions are further explored in my research.

1.2.1 Environmental risk factors

Several studies (20, 21) have shown that environmental factors play an important role in the development of childhood asthma. Indoor and outdoor environmental exposures associated with childhood allergies are especially critical during the early years (22). Both outdoor environmental risk factors such as pollen and fungal spores, and indoor environmental factors such as secondhand smoke exposure, mold and other sources of unusual smells such as carpets are important and are briefly discussed below.

1.2.1.1 Outdoor environmental risk factors

1.2.1.1.1 Pollen

Pollen is a prominent aeroallergen worldwide (23), particularly grass pollen, known for its strong allergenic effects (24). Approximately 30% of Australian children suffer from clinical respiratory disease caused by pollen-related asthma and hay fever every season (23).There are three primary pollen kinds associated with asthma: grass, tree, and weed. Multiple studies have demonstrated that weed pollen affects the severity of asthma symptoms in children with asthma (25, 26). Tree pollen and asthma exacerbation were also found to be associated in multiple studies that focussed on children (27-29). This is discussed further in my literature review in section 2.12.3.

Australia has the highest prevalence of allergic sensitisation to grass pollen (29.2%; 95% CI: 25.3, 33.2)(30). When extreme weather patterns such as heavy rain, high winds, and lightning, are combined with high pollen levels, it can cause a thunderstorm asthma event resulting in death. This was observed in 2016 in Melbourne, Australia, when the occurrence of

a thunderstorm asthma event resulted in 10 fatalities and almost 10,000 emergency department presentations (31). As pollen seasons vary geographically and temporally, their effects on respiratory health may differ as well (32). Change in weather patterns, due to climate change, is projected to further increase the allergenic effects of pollen(33). Despite the extensive evidence associating pollen with emergency presentations (34) and exacerbations resulting in hospitalisations (35) in children and adolescents, no study has yet been undertaken to explore the possible role of ambient grass pollen on readmissions in Australia.

Although pollen is primarily considered an outdoor allergen, it can enter indoor spaces through open windows and doors, ventilation systems, clothing and pets. Consequently, pollen also can trigger allergies for some people even when they are indoors.

1.2.1.1.2 Outdoor fungal

The fungus kingdom is ecologically varied and successful. There are an estimated 1.5 million fungal species in existence, as of now, only 10% of these have been described (36). The method of spore production is the primary method of identifying fungi (37). There are several factors that are associated with allergic sensitisation and fungus being one possible factor triggering sensitisation through exposure to the fungal proteins (38, 39). Due to their microscopic size and ability to enter and lodge in the airways and lungs, fungal spores in the air can also trigger asthma, since many of their proteins are allergenic (40, 41). The link between outdoor fungal spores and asthma hospitalisations among children has already been well-documented. Findings from these studies suggest that certain types of outdoor fungal spores, Coprinus, Periconia, and Chaetomium may trigger asthma exacerbations in children and adolescents requiring hospitalisation (42). However, on high pollen days, when the concentration of pollen in the air exceeds 20 grains/m^3 (43), there is a potential for increased asthma exacerbations and subsequent hospital admissions, as a high correlation between aeroallergens and fungal spore exposure has been documented in some parts of the world (44). In some instances, fungi alone can trigger a response (44). Not much has been done to assess the respective impact of both these aeroallergens among children and adolescents during high asthma admission periods, which occur during pollen seasons. In this context, when examining the occurrence HAADs during the October-December period in Australia, it was observed that concentrations of grass pollen exceeding 50 grains/m^3 were more frequent in three timeframes: on a daily basis, over the past three days, and over the past seven days (45).

Fungi and pollen often coexist in outdoor environments, and their synergistic effects coupled with changing weather patterns can have implications for individuals with allergies. For example, specific weather conditions, such as rainfall, humidity, and wind, can affect both pollen and fungal spore levels. Rainfall may wash pollen from the air but can also release allergenic components from pollen, particularly during thunderstorms, potentially contributing to asthma outbreaks. Local weather conditions also influence the types and levels of airborne fungal spores. For instance, rainfall and increased humidity can trigger the release of large amounts of ascospores and basidiospores, both linked to asthma and allergic rhinitis severity, as well as asthma exacerbations (46).

1.2.1.1.3 Outdoor air pollutants

Most studies investigating the impact of air pollution have predominantly centred on Traffic-Related Air Pollution (TRAP), which encompasses pollutants stemming from traffic emissions, such as particulate matter (PM), nitrogen dioxide (NO2), carbon monoxide (CO), and others (47). This specific focus on TRAP has been driven by its significant association with adverse health outcomes in children, including heightened asthma symptoms, increased use of rescue medications, more frequent visits to emergency departments (ED), and hospitalisations (48), resulting in a large social and economic burden. Exposure to pollutants is related to daily hospital admissions for childhood asthma (49) and is a potential confounder in analyses of pollen and asthma admissions (24). However, the impact of pollen on childhood asthma readmissions while controlling for important air pollutants is unknown.

1.2.1.2 Indoor environmental risk factors

In recent years, there have been an increase in concerns about the health effects of indoor environments(50), including indoor allergens such as dust mites, mold, and environmental tobacco smoke. The allergen produced by dust mites is a significant indoor allergen source; it is estimated that 84% of houses in HICs (high income countries) such as the US contain dust mites at measurable levels (51). Evidence indicates that allergens from house dust mites play a major role as a contributor on the causal pathway to exacerbations in children (52).

Exposure to mold and indoor humidity is linked to an increased risk of developing asthma and related morbidity. It is uncertain how much or how long exposure to fungi needs to be to initiate asthma or exacerbate an existing asthma condition (53). A review indicated that *Cladosporium*, *Aspergillus*, *Penicillium*, and *Alternaria* can worsen current asthma symptoms,

and *Aspergillus*, *Penicillium*, and *Cladosporium* may increase the chance of acquiring asthma symptoms (54). It is likely that carpets release volatile organic compounds (VOCs) into the air that irritate mucous membrane. Children are particularly vulnerable to these pollutants due to their increased exposure and heightened susceptibility to the harmful effects of VOCs (55). A comprehensive review of the literature revealed consistent evidence of a relationship between ante or post-natal exposure to ambient cigarette smoke and an elevated risk of asthma development in children (56). Environmental tobacco smoke (ETS) may be the most important known environmental modulator of child asthma induction and development, notably in early life but less significantly in later life, according to a review of long-term cohort studies (57).

All the above-mentioned indoor risk factors have been investigated in relation to asthma readmissions among children and adolescents (58-68) . However, the extent to which pollen and these indoor risk factors interact and impact asthma readmissions is yet to be determined.

1.2.2 Genetics

Family and twin studies have shown that genetic factors have a significant influence on the development of asthma and allergy (69), most likely via many genes of moderate impact (70, 71). The development of asthma may result from a combination of both genetic and environmental variables. It is estimated that 40-60% of the probability of developing asthma can be attributed to genetics. Asthma's genetic and environmental variations are most prominent in children, suggesting that these variations are the result of interactive processes (72). A few studies (73-79) have explored the possible interactions between early environmental exposures and parental history of asthma. No significant association was observed between wheeze and house dust mite following stratification by maternal (73, 74) and paternal history of asthma (73). However, a significant association was observed in two studies between cat allergen and wheezing among children with a history of maternal asthma (74, 75). Also, increased risk of asthma and allergy is reported among children who were breastfed and had maternal history of asthma (76, 77). These studies suggest that asthma is a polygenic, multifactorial disorder, with many factors contributing to its development.

1.3 Rationale

Based on the above-mentioned research gaps I now give this project's rationale:

1.3.1 High asthma admission periods

High asthma admission periods with HAADs (days with a significantly high number of asthma admissions which does depend on the location, regular hospital admission rates and other factors) may give crucial information about the cause of asthma admissions. In the literature, multiple environmental variables, including pollen (80), fungal spores (81), viral infections (82) and seasons have been associated with high admission days (83-87). In addition, changes in flora, higher pollen/mold spore concentrations and extended pollen seasons are correlated with climate change (33). Consequently, it is essential to identify the significant risk factors connected with high asthma admission periods during pollen seasons that might create enough problems to warrant an early warning system (88).

Few studies (89) (90) have focused on identifying HAADs among children. Currently, the methods used to identify high admission days are ad hoc (90) (91) and lack statistical evidence and proper evaluation of their accuracy. There is a requirement for a method that is highly accurate that provides sufficient statistical evidence to systematically study high admission days and a clearer understanding of the related risk factors.

1.3.2 Readmissions

A sizeable proportion of asthma admissions in children are readmissions(92). To measure the disease burden, readmission rates are considered. These rates are defined as the number of index admissions for asthma, each of which is followed by at least one subsequent admission, divided by the total number of index admissions for asthma (93). Readmission rates are often masked or underreported in studies of asthma hospitalisations (94, 95). Furthermore, nearly a third of the total national paediatric asthma costs are attributable to hospitalisations (96). The reduction of unnecessary hospitalisations has the potential to not only improve patient outcomes, but also significantly lower healthcare costs and burden on hospital resources. Therefore, understanding the impact of modifiable environmental risk factors like pollen exposure on paediatric asthma readmissions will have direct relevance for paediatric asthma admissions and asthma overall.

1.3.3 Indoor environment

In contemporary high income societies like Australia, up to 90 percent of children's time is spent indoors (97). Mice, cockroaches, pets, dust mites, mould, cigarette smoke, endotoxin, and nitrogen dioxide have been found to be significant risk factors of childhood

asthma exacerbations (98). Reducing asthma morbidity and development is aided by indoor environmental management. As discussed above in section 1.2.1.1.1, pollen is another key risk factor for paediatric asthma exacerbations(34). There is the possibility for indoor risk factors to interact with pollen and amplify its negative effect on the respiratory health of children. It is plausible two allergens may increase the likelihood of airway inflammation and epithelium damage (99). Therefore, it is important to investigate the impact of pollen on readmissions in a poor indoor health environment.

1.4 Objectives

The aims of this doctoral project relate directly to the three topics of HAADs, readmissions and indoor environment and are summarised in four objectives.

1.4.1 Objective 1

For Objective 1 of this doctoral work, I used the Melbourne Air Pollen Children and Adolescent Health (MAPCAH) study to assess the role of pollen and fungal spores on two high asthma admission periods in Melbourne, Australia, from September 2009 to December 2011. To achieve this, I:

- identified high asthma admission days by using the normalised residuals from the entire time series of admissions during the two pollen seasons (October to December)
- 25 November 2010 and 30 October 2011 were identified as high asthma days.
- described the periods, based on the fact that the impacts of environmental factors are not always immediate.
- The autocorrelation function will be used to determine the number of days as high based on a moving average.
- statistically analysed the associations between aeroallergens (pollen and fungi) and admission periods.

Objective 1 was unique in that it had data for both pollen and fungal levels.

1.4.2 Objective 2

For Objective 2 of this doctoral work, I used all child hospital admissions for asthma in Victoria between the fiscal years ending 1997 to 2009 in the Victorian Admitted Episodes Dataset VAED), to comprehensively examine asthma-related hospitalisations across a

spectrum of geographical and climatic conditions, to identify the HAADs and high asthma readmission days (HARDs) within 28 days. To achieve this, I:

- identified the HAADs and HARDs using the Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) method (100).
- compared it with other methods (89) (45) used in the literature.

1.4.3 Objective 3

For Objective 3 of this doctoral work, I used all child hospital admissions for asthma in Victoria (1997 to 2009) in the VAED to study the association between grass pollen and paediatric asthma readmission. To achieve this, I:

- defined readmissions as subsequent admissions within 28 days of index admission discharge.
- statistically modelled the association between the grass pollen season and readmissions.
- statistically modelled the association between ambient grass pollen and readmissions.

In Chapter 3, no other data was available, such as fungal spores, so they were not considered.

1.4.4 Objective 4

For Objective 4 of this doctoral work, I used data from the Murdoch Children Research Institute (MCRI) collected between 1st September 2017 and 31st August 2018 to analyse the association of pollen and childhood asthma readmissions with indoor risk factors as effect modifiers. To achieve this, I:

- defined readmissions using different timeframes (within 28 days, within 3 months, within 1 year, and within pollen season)
- statistically analysed the association between ambient grass pollen and readmissions.
- stratified the models based on indoor risk factors.

In Chapter 4, no other data was available, such as fungal spores, so they were not considered.

1.5 Thesis overview

This thesis presents the original work that I carried out as described above to address the study objectives.

Chapter 1 outlines the rationale and objectives of my doctoral project and has a broad review of the literature on asthma aetiology.

Chapter 2 reviews the literature relevant to this project.

Chapter 3-6 have the results of the first to fourth objectives, respectively.

The methodology adopted and relevant discussions of Chapters 3, 4, 5 and 6 are presented in the respective chapters.

Chapter 7 has my overall conclusions, implications of findings and recommendations for future research.

2 Literature review

2.1 Introduction

The prevalence of allergic respiratory diseases, including asthma, has exhibited both a rise and subsequent plateau on a global scale (101, 102). During the pollen season, asthma places a substantial burden on the Australian public health system due to its significant economic costs (103). In addition to financial expenses, there are non-economic costs such as a loss to the well-being of individuals, their families, and caregivers (103). Climate change is expected to affect the range of allergenic species, as well as the timing, length, and intensity of pollen seasons. In addition, elevated levels of carbon dioxide (CO_2) may increase plant productivity and pollen production. Furthermore, higher seasonal rainfall can lead to increased vegetation growth and flowering, resulting in higher pollen abundance and potentially higher hay fever rates(104). However, it's important to note that climate change predictions in Australia suggest hotter and drier conditions, which might imply reduce pollen abundance in the future(105). Nonetheless, the data also suggests that during years of increased weather variability and storms, there could be substantial pollen exposures, even during periods of lower overall rainfall(106). Therefore, while increased rainfall may have a potential impact on increasing pollen health events during wetter years, the broader context of climate change and weather variability could lead to fluctuations in pollen levels and associated health effects. Fungal spores have also been found to play a role in triggering allergic asthma, and increased temperatures due to climate change may impact them as well (107). These factors may result in an increase in asthma exacerbations and hospital admissions. There are other potential effect modifiers of these associations and outcomes, such as repeat admissions during pollen seasons, that have yet to be addressed.

Based on a relatively high prevalence of childhood asthma in Australia and its associated burden(108), and due to the association between severity of symptoms among children and persistence of asthma into adult life (109), it is important to study the factors such as the environment that trigger childhood asthma outcomes such as admissions and readmissions. My research in this thesis will exclusively focus on admissions and readmissions among children and adolescents.

A global asthma epidemic affecting children is ongoing (2). The rate of asthma presentations in healthcare settings, such as emergency departments (EDs) or primary care clinics, can be calculated by determining the average attendance rate for a specific time period.

An asthma outbreak or epidemic occurs when attendance exceeds the normal rate. However, this term remains loosely defined and has rarely been quantified (110). It is crucial to identify triggers during periods when asthma exceeds its current rate.

Environmental risk factors, defined as elements or conditions in the environment that increases the likelihood of developing or exacerbating asthma, continue to be a major contributor to childhood asthma epidemic. Numerous Northern Hemisphere countries, including Canada, the United States, the United Kingdom, Mexico, Israel, Finland, Trinidad, and the West Indies, have recorded seasonal increases in asthma exacerbations necessitating hospitalisation. Australia and New Zealand have also noted similar seasonal patterns (111).

Australia and New Zealand have also reported similar cycles (112, 113). Consistent across countries, seasonal peaks in asthma-related hospital admissions were most pronounced in children, followed by younger adults and the elderly (114). Age group (by 5-year intervals) and geographic location were risk factors during peak times, with spring peaks usually attributed to aeroallergens (45). To ensure accuracy of detecting any true associations, it is necessary to consider other potential variables that may influence asthma admissions. Human rhinovirus (HRV) (115, 116), cigarette smoke exposure (117), indoor mold (118), in- house overcrowding (119), indoor air pollutants (120) (121), outdoor air pollutants (49), and weather conditions (122) are common factors that are recognised as important risk factors for childhood asthma admissions. Any potential confounders that are known to affect both pollen (the primary exposure) and asthma hospitalisations (the outcome) also need to be identified. To minimise bias and increase the accuracy of attributing an effect to a particular exposure, it is imperative to account for potential confounding factors in the study design and/or stratify by variables that are likely to be important in the pathway from exposure to outcome.

Meteorological variables, such as temperature, relative humidity (122) and air pollutants (123) are potential confounders of outdoor pollen exposure on asthma exacerbations. There may also be effect modification where the extent of the primary exposure's effect on the outcome will vary based on the third variable – the effect modifier. For example, sex and age may operate as potential effect modifiers, with hospitalisations for asthma being more frequent in boys throughout childhood, and in girls during adolescence (124).

To date, many studies have focused on admissions (115, 125) (120), but little on readmission (126, 127) for childhood asthma. Readmission rates are typically masked or diluted

in studies of asthma hospitalisations because the definition of readmission used in studies may vary (92). For example, some patients may be classified as having been hospitalised for a different condition even though asthma was a contributing factor (128). Additionally, the availability and quality of data sources used to calculate readmission rates can also affect the accuracy of the rates reported in studies(129). Studying asthma readmissions is important for improving the quality of care, reducing healthcare costs, enhancing patient outcomes, optimising resource allocation, and ultimately advancing public health and healthcare policy related to asthma management (130). Additionally, this subgroup may represent a more severe cohort, and gaining insights into their triggers and unique characteristics can inform better asthma management strategies. Many studies have assessed risk factors for asthma readmissions but not in the context of the environment. Some of these factors include age at admission (131-136), sex (131, 136), race/ethnicity (132, 134, 137), acute (131, 132, 138, 139) versus chronic asthma severity (58, 131, 136, 140), number of previous admissions (132, 138, 141, 142), socioeconomic status (137, 143), parental knowledge (136), and medication management (58, 131, 132, 136, 140, 141, 144-146).

Of these, age at admission, sex, race/ethnicity, severity of asthma, medication management, and parental knowledge were identified as factors contributing to higher risk of readmission. Prior hospitalisation for asthma has been demonstrated by several researchers to be a significant independent risk factor for readmission (147). Environmental risk factors such as seasons have only been evaluated in a small number of studies (124, 148-152). This chapter draws on published research literature to describe the available evidence on environmental risk factors, noting any gaps.

In this chapter, I define asthma, describe the different types of asthma, and outline the global and Australian trends in asthma prevalence. I also examine the negative impact of asthma on quality of life and the cost it imposes on society, with a specific focus on children. Despite a decline in overall asthma admission rates, children are still 2.8 times more likely to be admitted to hospitals than adults (153). I define asthma exacerbations, asthma emergency department (ED) use, admissions, the methods used for identifying high asthma admission days and asthma epidemics, and review the most common childhood asthma admissions triggers, both allergic and non-allergic. I explain how outdoor pollen can trigger asthma exacerbations and provide an overview of current understanding of allergic rhinitis. I briefly describe thunderstorm asthma and the impact of outdoor fungal spores on children with asthma. I examine the literature on pollen and other outdoor environmental risk factors for

childhood asthma readmissions. I consider potential confounding variables or interactions with other factors that can promote asthma exacerbation or airway inflammation. Finally, I highlight the current knowledge gaps that require attention.

2.2 Definition of Asthma

In terms of severity, onset, risk factors, triggers, treatment response, genetics, and natural history, asthma represents a heterogeneous set of clinical conditions (154). Often, it is difficult to differentiate asthma from other illnesses, such as reactive airway disease and bronchiolitis. Distinguishing features aid in differentiating asthma from other conditions. Asthmatic patients with bronchoconstriction typically exhibit wheezing, breathlessness, chest tightness, and coughing, responding well to treatment with intermittent exacerbations. In contrast, Chronic obstructive pulmonary disease (COPD) patients have a chronic cough, chronic sputum production, dyspnea, and effort limitations due to fixed airflow obstruction. COPD exacerbations worsen cough, expectoration, and dyspnea, necessitating antibiotics and systemic corticosteroids(155). The National Institutes of Health (NIH) (154) asthma guidelines from 1991, 1997, and 2007 state:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. The reversibility of airflow limitation may be incomplete in some patients with asthma.
>
> Asthma is a chronic inflammatory disease of the airways characterized by recurrent symptoms of variable airflow limitation (156).

Although a definition is available, diagnoses remain problematic as clinicians' diagnoses vary greatly (157). Diagnosing asthma in children under the age of 5 presents a unique set of challenges. Due to their limited ability to communicate symptoms effectively, young children may not express typical asthma complaints such as wheezing, chest tightness, or breathlessness

as clearly as older individuals. Additionally, their airways are naturally smaller, making it harder to distinguish between asthma-related symptoms and those caused by normal growth and development. These factors contribute to the complexity of diagnosing asthma in this age group, requiring careful evaluation, observation, and sometimes specialised tests to establish an accurate diagnosis. While spirometry is considered a valuable tool for diagnosing asthma, its use may be limited in children, especially those under the age of 5 (158). Typically, the discharge diagnosis is regarded as the most precise (159). In my study, an admission is considered asthma-related if the admission code indicates that asthma was the primary diagnosis.

2.3 Types of Asthma

Overreaction of the immune system to antigens (allergens) entering the body causes the airways to become inflamed, causing the air flow to become temporarily blocked, and the bronchial tubes to become hyper-responsive; this is what is known as allergic asthma. Pollen (160), home dust mites (161), cockroaches, pet dander (162), and fungal spores (38) are all recognised as common aetiological factors of allergic asthma. At least half of all asthma cases are thought to be allergic in nature (15). Allergic asthma often begins in childhood, and it is the leading cause of asthma in children (163). In contrast to allergic asthma, which is caused by allergens or an overactive Immunoglobulin E (IgE) response, non-allergic asthma is characterised by inflammation of the airways. Cold air due to weather conditions (122), exercising (164), obesity (165), inhaling tobacco smoke (166), taking non-steroidal anti-inflammatory drugs (NSAIDS) (167), breathing in air pollutants (168), being overweight (169), and being exposed to industrial and cleaning chemicals like solvents, cleaning products, dyes, aldehydes, and acrylates (170) are all possible non-allergic aetiological agents. Non-allergic asthma is caused by unclear processes (15) and typically does not manifest until maturity (171).

- Asthma includes a spectrum of diverse phenotypes that vary in appearance, aetiology, and pathophysiology. The risk factors for each asthma phenotype include genetic, environmental, and host variables. Although asthma in the family is prevalent, it is neither required nor sufficient for the development of asthma (172).
- Asthma can be divided into different types based on its pathophysiology. In children, asthma is defined by a T-helper cell type 2-dominant phenotype and reduced expression of innate immune genes. The involvement of regulatory T

cells (Tregs) is important in the development of childhood allergic asthma, although the extent of their involvement varies depending on the age of the children and the method of the study. Lee et al. (173) have shown a decrease in the number of Tregs in children with allergic airway disease, while others have reported an increase or decrease at different ages (174, 175). Treg dysfunction is also a significant factor in the development of asthma (176). Non-allergic asthma is characterized by elevated pro-inflammatory interleukin (IL) and inadequate suppression of certain cytokines by Tregs.

2.4 Trends in worldwide asthma prevalence

Prevalence and severity of asthma vary by age group, country, income, and region according to modelled data from the International Study of Asthma and Allergies in Childhood (ISAAC) Phases I (1993-95) and III (2001-03) and the Global Asthma Network (GAN) Phase I to determine patterns of change over nearly three decades (1993-2020) (177). Additionally, these variations in asthma prevalence extend to gender, with notable differences emerging across the life span. In childhood, it exhibits a higher incidence among boys. As children transition into adolescence, sensitisation patterns may shift, and with the onset of puberty, we may observe differences in asthma triggers, which can sometimes become more severe in girls and women (178).

Over the 27-year period (1993-2020), the prevalence of severe asthma symptoms among adolescents decreased by a 0.37 percentage point prevalence per decade (95% CI: -0.69 to -0.04), while the prevalence of ever having asthma increased by a 1.25 percentage point prevalence (95% CI: 0.67 to 1.83). This trend was also observed among children (0-19 years) –0·24 (–0·63 to 0·15) for severe asthma symptoms, and 0·56 (–0·13 to 1·24) for ever having asthma. Estimates of global asthma prevalence (across all ages) have been provided by the Global Burden of Disease (GBD) research. There has been a significant variance between GBD estimates of the global prevalence of asthma over time, with numbers ranging from 220.4 million in 2000 (179), 327.1 million in 2005 (180), 334.2 million in 2010 (11), 241.7 million in 2013 (181), 358.2 million in 2015 (182), 339.4 million in 2016 (183) and 272.7 million in 2017 (184).

While the prevalence of the condition remains relatively constant, the burden on both children and hospital systems is substantial, particularly in countries like Australia. This burden can manifest in the form of increased demand for hospital beds, longer hospital stays, and

higher healthcare costs, which can have significant impacts on the healthcare system and society. Thus, addressing this burden and finding effective treatments and preventative measures is crucial for ensuring the well-being of children and the sustainability of healthcare systems in affected regions.

2.5 Asthma in Australia

The prevalence of asthma in Australia is notably higher than other HICs (high income countries) such as the United States and Europe, with approximately 11% of the total population, or 2.7 million individuals, affected by the condition (185). This prevalence is similar for children between the ages of 0-14 years old, with the highest rate (15%) observed among boys 5-9years (108). As the top source of disease burden for the 5-14 age group and the tenth largest contributor to the overall burden of illness (186) (187), asthma is a significant health concern in Australia. With some of the highest asthma rates in the world (187), the impact of the condition is felt widely across the population and has important implications for public health policy and healthcare provision.

In Australia, presentations to emergency departments for asthma are reasonably frequent, and hospitalisations are required if not adequately managed at home. Severe asthma exacerbations often require medical attention, from primary care to emergency room visits and subsequent hospitalisation. Moreover, during peak seasons such as winter and pollen seasons, these admissions frequently occur. During peak pollen seasons or respiratory viral seasons, symptoms are exacerbated (188), causing parents to panic and take their children to the hospital. The hospital admission rate for children between the ages of 0 to 14 was markedly higher in 2020-21 at 225 per 100,000 individuals compared to the rate for individuals aged 15 and above, which was 68 per 100,000 individuals. Boys between the ages of 0 to 14 were 1.6 times more likely to be admitted to the hospital for asthma than girls in the same age group (189). Teenagers in the 15-18 age range tend to stay in the hospital longer (190). This could be because teenagers are in the process of transitioning from childhood to adulthood; they have unique differences in their airways and respiratory system that can affect their asthma management and recovery(191). It could also be due to a lack of adherence to treatment, psychological factors or co-existing conditions.

Additionally, recent thunderstorm asthma events (31) in Australia have further highlighted the impact of asthma on children, with hospitalisations and emergency department visits increasing during and after these events. This underscores the need for continued efforts

to address asthma as a public health concern, particularly among vulnerable populations such as children.

2.6 Asthma and quality of life

Asthma can greatly affect quality of life, with more severe symptoms of coughing, wheezing, and shortness of breath limiting physical and social activities, disrupting sleep patterns, and causing emotional distress. The need for regular medication, doctor visits, and monitoring can also be time-consuming and financially burdensome (192). The management of this condition generally proves effective for the majority of children, particularly when low doses of inhaled corticosteroids (ICS) are administered. These individuals experience good symptom control, with a reduced frequency of acute attacks. However, it is crucial to recognise that within this patient population, there exists a distinct subgroup that faces persistent challenges. Despite adhering to maximal recommended prescribed therapy, which may include high-dose ICS, long-acting beta2 agonists (LABA), and/or leukotriene receptor antagonists (LTRA), this subgroup remains symptomatic, experiences frequent exacerbations, and may even exhibit persistent airflow obstruction (193).

Exacerbations of asthma often necessitate pharmacological or medical intervention at the primary care, emergency room, or hospital level, and the condition has substantial impacts on the quality of life of people living with this condition. This includes affecting participation in activities of daily living (194, 195), impairing sleep (196, 197), disrupting school and work attendance (198), affecting weight and height development (199), and more (195). Caring for a child with severe asthma consumes a lot of energy, funds and time, compromises family privacy, isolates the family and negatively impacting their quality of life (200). Families are heavily burdened with managing symptoms, administering medication, trigger management, and medical follow-up (201). Additionally, asthma in childhood can impact mental health and wellbeing over the life course (202, 203).

Asthma was listed as the eighteenth leading cause of disability-adjusted life years (DALYs) lost among those aged 1 to 4 years, eighth among those aged 5 to 9, third among those aged 10 to 14, and twelfth among those aged 15 to 19 in the 1990 Global Burden of Disease research (15). In the 2010 Global Burden of Disease research, asthma was listed as the fourteenth leading cause of Years Lived with Disability (YLD) across all ages, and the thirteenth leading cause of YLD among non-communicable illnesses (204). Asthma was

among the top 10 causes DALYs among children and adolescents aged 5 to 14 in 2010, placing it at number 29 on the global DALY rankings (205).

2.7 Economic burden

In Australia, the average cost of an asthma-related visit to the emergency room is $443, a straightforward hospital admission is $2,591 (for about 1.5 hospital days), and a complex hospital admission is $5,393 (for approximately 3 hospital days) (187). In 2021, asthma was projected to cost Australia $28 billion, including $24.7 billion in lost productivity and early deaths, which equates to $11,740 per person with asthma (187). Indirect costs, such as lost productivity at work due to sick leave or carer's leave, and other expenses not reflected in health economic statistics, such as loss of work or school days, reduced job performance and decreased quality of life, also contribute to the economic burden of asthma. It is estimated that almost 2% of the national health budget is spent on asthma-related expenditures in countries with higher prevalence of asthma (206). These numbers demonstrate the devastating impact that asthma can have on an individual, their caregivers, and the community.

Direct hospital treatment (20%), prescription medications (50%) and out-of-hospital medical care (30%) were all anticipated to contribute to the $655 million (0.9% of total health spending) ascribed to asthma in Australia in 2008 and 2009 (207) and this is probably greater now. Additional costs to people, families, and caregivers arise due to decreased productivity in the workplace and unreimbursed out-of-pocket expenditures. Therefore, the Australian Government has designated asthma as a National Health Priority Area because of the severity and prevalence of the issue (208).

In the next section, I describe the risk factors that are most strongly associated with asthma exacerbations, emergency department use, and admissions in children and adolescents. I describe how they can be important factors on the pathway to asthma when I consider pollen exposure as the primary environmental trigger of asthma exacerbations. I have also described the methods most commonly used in identifying HAADs or asthma epidemics. I outline the key findings associated with respiratory viruses, fungal spores, and air pollutants. As pollen is the primary focus of this thesis, I provide an in-depth review of the research literature in a separate section.

2.8 Asthma exacerbation

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines an asthma exacerbation as an "episode of progressive increase in symptoms such as shortness of breath, cough, wheezing, or chest tightness, accompanied by decreases in expiratory airflow that can be quantified through measurement of lung function" (209). Furthermore, exacerbations are defined as an abrupt and severe loss of control that requires rapid therapy. Exacerbations of asthma continue to be a serious medical problem, and the frequency of asthma exacerbations is a major factor in determining asthma severity (210). They are a common reason for hospitalisation, especially among children and adolescents, where asthma control and management are challenging and identifying triggers can be difficult.

Asthma attacks in children can be triggered by a wide variety of reasons. Pollen concentrations in the air (in the range of 83–85 grains/m^3) and fungus spore densities in the environment are the two most common outdoor allergens (211-213). Indoor allergens including mice (214), cockroaches (215), pets (216), dust mites (217) and moulds (217) may also pose a risk. Those that are not allergens but are also important include rhinovirus (RV) infection and a lack of preventer use (218), extreme weather events like thunderstorms (45, 219-221), cigarette smoke exposure (including passive exposure) (222), non-steroidal anti-inflammatory drugs (NSAID) use (223), gaseous air pollutants (224), limited exercise (225), and obesity (226).

Children with mild to severe exacerbations with audible wheezing can move and speak in whole sentences or phrases while still taking deep breaths. In contrast, exacerbations can be so severe that a person has trouble speaking in whole words or even phrases, gasps for air, or has an oxygen saturation level of 90-94% on a pulse oximeter. There are several warning signs of a life-threatening exacerbation, including the patient seeming sleepy, tired, collapsing, not able to breathe, or having an oxygen saturation of 90% or below (227).

2.9 Asthma emergency department use

In Australia, one of the most frequent ED presentations in children is asthma (228). Most children with moderate to severe exacerbations are managed in ED settings. Environmental factors such as aeroallergens (34), weather conditions (229), air pollutants (230), and indoor allergens (231) have all been linked to asthma-related ED admissions among children. Other factors include prior ED use, age, frequent visits to GP, allergist visits (232), race, and income (233). Despite childhood asthma ED being an important outcome that

identifies children with high need of preventive care, my study did not consider ED use as an outcome. Instead, I have focussed on childhood asthma admissions and readmissions as outcomes for the reasons discussed in detail in the following sections.

2.10 Asthma admissions

When an asthma exacerbation is severe or life threatening, an asthmatic child may not respond to initial treatment with a short acting bronchodilator, such as salbutamol, and/or oxygen therapy (194). In these cases, urgent treatment in a hospital is required to prevent severe morbidity or fatality. These are the asthmatic cases that are the focus of Chapters 3 and 4 of this thesis.

2.11 Methods to identify high asthma admission days or asthma epidemic

In the medical literature, asthma epidemics are a rare occurrence and only occasionally mentioned. Some information about asthma epidemics is anecdotal, and a general theory has not yet been developed to explain their occurrence and causes. The following section details the frequently employed methods for identifying high asthma admission days (HAADs), as well as the methods utilised in the most widely acknowledged asthma epidemics, along with the limitations of each.

2.11.1 Using monthly average cut-offs

Salvaggio (83-86, 234) conducted a series of investigations into the New Orleans asthma epidemics and found that the authors used a specific cut-off to determine peak days (HAADs). They used the number of daily emergency room asthma admissions as a measure of asthma "epidemics." They initially set a cut-off of 35 to 50 daily admissions, depending on the monthly mean, to define an "epidemic" day. However, they found that clusters of high-admission days with a gradual rise and fall were more common than sharp peaks of over 100 admissions. Ultimately, the threshold used for defining "epidemic" days represented the number of daily admissions that separated the upper one-third from the lower two-thirds of all daily adult hospital emergency room asthma admission rates during the study's months. This cut-off excluded most of the clearly nonepidemic days (those with fewer than 40 daily admissions) while ensuring a sufficient number of high-admission days for meaningful statistical analysis. This study was conducted on emergency room for adults, which reflects a gap in the literature on hospital admissions, particularly for children. The size of the hospital

and the characteristics of its catchment area, which were not explicitly defined in the study, may have influenced these threshold values.

2.11.2 Using day of the week cut-off

Goldstein and colleagues (235) (236) created an epidemiological method to study the day-of-the-week effect in asthma ED admissions that would not be overly influenced by HAADs. This method uses weekly asthma-related ED admission data and ranks the daily number of ED visits from 1 to 7 within each week. the mean rank for each day of the week was estimated, followed by a test under the null hypothesis of no day-of-the-week effect.

2.11.3 Predicted mean-based method

Goldstein and Rausch (237) studied the emergency room admissions of three New York hospitals between 1969 and 1971. The series of the daily number of asthma emergency department admissions followed the Poisson distribution. Nonetheless, there was a handful of uncommon asthma days, based on deviations from the Poisson distribution. During a particular day, the number of asthma cases (Poisson distribution) compared with the parameter estimated by the mean number of cases, 15-day moving average. If the probability of having a particular number, or more was equal to or less than 0.05, it was considered an unusual day. A similar study (238) in Barcelona followed a similar method, but the chosen probability was 0.025. This study also considered ED admissions but not hospital admissions.

Newson et al. (89) in the UK informally defined an asthma epidemic as a situation where the residual from the log-linear model (adjusting for seasonality, time trend, and day of the week) exceeded 4 standard deviations from the predicted mean. This study was conducted on hospital admissions and included children (0-14 years). I have employed this method and labelled it as model-based method for comparison in Chapter 4 of my thesis.

2.11.4 Trimmed mean Q-Q plot method (TMQQ)

The first study that used this method in Australia was by Silver and colleagues (45). They identified (HAADs) by computing normalized residuals from the admissions time series over a period of 25 years. They began by subtracting a running trimmed mean from the original admissions time series and then dividing the result by a running trimmed standard deviation, which were both based only on the middle 50% of the data within a 31-day time frame. They classified a day as a HAAD if its normalized residual was at least 4.5 (i.e., 4.5 local standard

deviations above the local mean). This study was conducted on hospital admissions and included children (5-year intervals). I have also used this method for comparison in Chapter 4 of my thesis.

2.11.5 Other methods

Packe and Ayres (90) (1983) identified an intriguing asthma epidemic at the East Birmingham Hospital in Birmingham, UK. The authors do not explicitly define what they consider to be peak days. However, it seems that peak days are those on which there is a significant increase in the number of patients with acute asthma attending the hospitals, compared to the average number of daily emergency department attendances during that time period. Using an unclear methodology, Greenburg et al. (91) were the first to detect unusual increases in the frequency of emergency room admissions for asthma on a given day in New York. Their study revealed a significant pattern, during certain critical heat-required periods, there were statistically significant increases in asthma visits to hospitals.

2.11.6 Limitations of existing methods

The methodologies employed in the studies described above have significant drawbacks, particularly because they focused on emergency department (ED) visits (83-86, 234) (235) (236) (237) (91), rather than hospital admissions, and this choice of outcome measure can introduce biases and limitations in the interpretation of results. One potential limitation of using ED visits as the outcome measure is that it may not accurately capture the severity of the asthma exacerbation (239) or the true burden of the disease. Emergency department visits may include patients who have mild or moderate symptoms and are able to be treated and discharged without requiring admission to the hospital. Therefore, using ED visits alone as a measure of asthma morbidity may not fully capture the most severe cases of asthma exacerbations that lead to hospital admissions. Another potential limitation is that the decision to seek care in the ED can be influenced by factors such as insurance coverage, availability of primary care, and distance to the nearest hospital (209). These factors may be different for different patient groups and can introduce bias into the results if they are not considered. In contrast, hospital admissions are generally considered to be a more severe outcome measure and may be a better indicator of the burden of asthma in a population. Hospital admissions may also be less influenced by the aforementioned factors that can affect ED visits, as they are more likely to represent cases in which the asthma exacerbation is severe

enough to require inpatient care. Therefore, while studies using ED visits as the outcome measure can provide important information about asthma morbidity and health care utilisation, it is important to consider the limitations of this approach and to interpret the results in the context of the study design and population being studied.

Moreover, the mean and standard deviation used in the studies (235) (236) (45) (238) (237) (83-86, 234) are heavily influenced by outliers. This is especially true for the standard deviation, which is defined as the squared distance from the mean. Therefore, any definitions based on a mean and SD will tend to conceal outliers if they include outliers in their computation. Using a trimmed mean (45) is a well-known method for reducing the effect of outliers in the calculation of the mean. However, excluding 50% of the data runs the risk of over smoothing, severely limiting access to information in the data and, as a result, reducing the sensitivity to account for seasonality and time trend in a time series. The usage of 1.96, 4 or 4.5 SDs (83-86, 234) (45) (89) is not supported by any validation research to determine the effect of these definitions on the sensitivity or positive predictive value of HAAD classification. Ad-hoc methods (90) (91) cannot be replicated. In addition, the categorisation of HAADs by these approaches does not include any rigorous statistical testing. Therefore, in my study (Chapter 4), I utilised a robust statistical technique that has been shown to have excellent classification accuracy in other contexts. The approach is known as Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) (100). I have used this method to identify HAADs and high asthma readmission days (HARDs).

2.12 Studied risk factors for child and adolescent asthma outcomes – exacerbations and admissions

2.12.1 Respiratory viruses

It is not uncommon to contract a virus that affects the respiratory system, but in otherwise healthy people, the symptoms and long-term consequences are usually mild. Exacerbations of asthma in susceptible children can be triggered by infections, which initiate a complicated sequence of inflammatory processes in the airways (240). Human rhinovirus (HRV), respiratory syncytial virus (RSV), metapneumovirus, parainfluenza virus, and coronavirus are just a few of the many respiratory viruses linked to asthma exacerbations in children (241-243). However, human rhinovirus (HRV) has emerged as the primary aetiological component linked to asthma exacerbations. Allergic sensitisation may be an effect modifier in this association, leading to a greater risk among children (244), implying a possible

synergism between viral infection and exposure to allergens in sensitized children. Human rhinovirus (HRV) infections are responsible for more than 80% of children and adolescent asthma hospital admissions (245, 246). HRV is more prevalent in winter, it also circulates during spring and other seasons (241, 247). These spikes are often linked to the return of school-aged children after the winter vacation (248). Increased asthma exacerbations during the winter months have also been linked to respiratory syncytial virus (RSV) and influenza infections (241, 245).

In addition to the three genetically unique HRV species (HRV-A, HRV-B, and HRV-C), there are many subtypes within each of these species (247). HRV-A has 74 subtypes, HRV-B has 26, and HRV-C has around 50. It is hypothesised that HRV-C is responsible for significant asthma exacerbations in children (245), and that HRV-C infections have been linked to more asthma hospitalisations than other HRV species (249-252) since their detection around the year 2007 (253).

Rhinoviruses can be found all around the world and in all seasons of the year (254). This combined with exposure to pollen in the air during pollen season, potentially bring about immunological alterations in the lungs and elsewhere, and thus have an impact on the health of those exposed.

2.12.2 Ambient air pollutants

One possible environmental component that may have an impact on the genesis of asthma is exposure to ambient air pollution during early life and childhood. Children may be more vulnerable to the negative effects of air pollution, probably because they have a smaller capacity for the accumulation of inhaled particles in their nasal passages (255) or their higher ventilation rates (256). Additionally, they tend to breathe more frequently via their lips, which hinders nasal filtration and alters the temperature and humidity of the air that is inhaled. (257). Children are also more likely to be outdoors, and active compared to adults, which increases their exposure to background air pollution. A comprehensive review of 26 global studies revealed that children exposed to short-term increases in $PM_{2.5}$ by 10 $\mu g/m^3$ faced a 4.8% heightened risk of asthma-related emergency department visits and admissions. Notably, the impact was more pronounced in Europe and North America compared to Asia (258).

According to recent research, ambient air pollution may make asthma symptoms worse (259). For instance, a significant multi-centre study found that air pollution caused 15% of all occurrences of asthma symptoms (260). Whether air pollution also increases the risk for

developing asthma is less clear (261). Exposure to pollution have been linked with everyday symptoms (262), drug treatments (263), ED visits (264), and hospitalisations (265) (266-269) among children. Significant associations between asthma admissions and sulphur dioxide (SO_2) (266) (269) (268), nitrogen dioxide (NO_2) (267) (268) (269), PM_{10} (268) (269), and ozone (269) were observed in children under 14 years of age. Studies (49, 270) with children under 18 years found significant associations between both particulate pollutants (PM_{10} and $PM_{2.5}$) and gaseous pollutants (NO_2 and O_3) and admissions. In a study conducted in China from 2013 to 2016 (49), admissions in children under 6 years were associated with SO_2.

The relationship between pollen and childhood asthma admissions is complex and can be confounded by other environmental factors. Studies investigating the interaction between pollen and air pollutants have reported conflicting results. One study (268) (271) found no evidence of an interaction between pollens and air pollution, except for children's exposure to SO_2. and grass pollen. Another study (272) reported limited interaction between air pollutants and pollen in children, but the exposure to certain air pollutants and pollen was stronger in the cool season compared to the warm season. In addition, there is evidence (as discussed in the above paragraph) to suggest that air pollutants can independently impact childhood asthma admissions. It is therefore important to control for air pollutants when examining the effect of pollen on admissions, as failing to do so may lead to biased estimates of the true relationship. In recognition of this, air pollutants have been considered as a confounder in my research (Chapters 3 and 5).

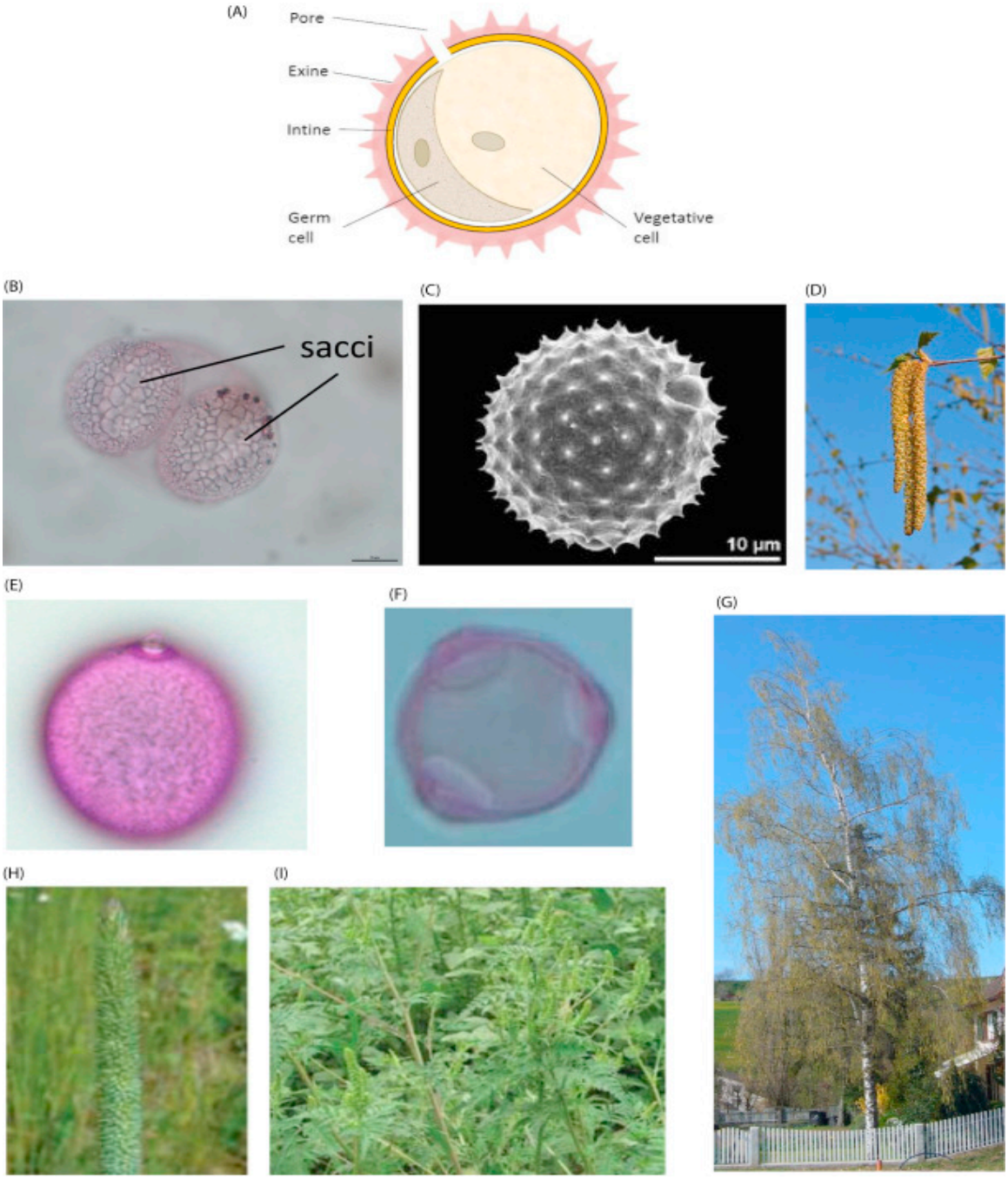
2.12.3 Pollen

The anther of flowering plants produces pollen, a biological structure that is a thin, whitish powdery mass composed of hundreds of pollen grains. These grains range in diameter from around 10 to 150 μm and contain the plant's genetic material. The basic function of pollen is to carry this material from the male reproductive cell to the female reproductive organ, where it is transferred via a pollen tube. The tube extends from the stigma, on the flower's surface, to the ovary, located around the base of the style (273).

Entomophilous pollen is pollen that is delivered from the anther to the stigma by insects, while anemophilous pollen is carried by the wind. Anemophilous pollens have a diameter of 10–50 μm, an aerodynamic surface, and a low density to facilitate wind movement. Pollen from gymnosperm trees in the Pinales group, such as stone pine trees (Pinus pinea),

may be relatively large (150 μm in diameter) because they have "wings" (bisaccate structures) that collect wind (274) (Figure. 1B).

Allergen-causing pollen is typically carried by the wind. Contrary to popular belief, it is formed from flowers that are green and not aesthetically pleasing, such as grass blossoms and birch tree catkins, as well as other weeds and trees. Grass, trees, and weeds may discharge vast quantities of pollen that are carried by the wind. The discharge of pollen from wind pollinated plants requires physical force to move the floral parts.



(A) Schematic representation of stylized pollen grain. (B) Bisaccate pine pollen grain showing two sacci. (C) Ragweed pollen grain visualized by scanning electron microscopy. Fuchsin stained grass pollen grain visualized by light microscopy. (D) Birch tree catkin (Dr Regula Gerhig, Federal Office of Meteorology and Climatology MeteoSwiss, Switzerland, 2019.) (E) Fuchsin stained grass pollen. (F) Fuchsin stained Birch tree pollen visualized by light microscopy. (G Birch tree (Dr Regula Gehrig). (G) Timothy grass inflourescence (Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology. 2014) (I) Ragweed. (Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology. 2014).)

Figure 1: Pollen allergen sources

2.12.3.1 Structure of pollen

The structure of a pollen grain includes an exine surface layer, which may be subdivided into layers with observable ornate structural elements such as spikes and roughness (Figure 1A). The intine, which protects the vascular and germ layers, is surrounded by the exine. Allergens can be found in the pollen, in the form of proteinaceous molecular components such as glycoproteins. The intine, exine layers, and cytoplasmic starch granules of the vegetative cells are potential harbouring grounds for allergens. Whole pollen cannot penetrate deeply into the lungs, but it can be ruptured due to ageing, mechanical friction, lightning activity within thunderstorm clouds, or swelling caused by water, thus releasing micron-sized sub-pollen particles that can reach the small airways beyond the pharynx (275). From the perspective of an allergy sufferer, a pollen grain is essentially a vector of allergen components. The pollen grain or the released allergen components make contact with the body's mucosal surfaces, such as the skin and the lining of the upper and lower airways (276).

2.12.3.2 Allergic rhinitis

Exposed individuals with a pre-existing clinical history of pollen hypersensitivity may develop a variety of symptoms and illnesses, including intermittent or seasonal allergic rhinitis (AR), often known as hay fever. Allergic rhinoconjunctivitis may be a more accurate name for this disorder, given the wide range of symptoms it causes, including those of the nose, throat, ears, and eyes. Acute rhinitis (temporary inflammation of the nasal passages), chronic rhinitis (persistent nasal inflammation that lasts for more than four weeks), itchy eyes, and watery eyes are all symptoms of AR (277).

2.12.3.2.1 Asthma and AR

Allergic rhinitis and asthma are related conditions in children. Children with AR are at an increased risk of developing asthma, and children with asthma are often also diagnosed with

AR. It is estimated that over 40% of children with asthma also have AR, and up to 80% of individuals with asthma have AR (278).

When AR is left untreated, it can contribute to the severity of asthma symptoms and increase the likelihood of asthma-related medical care, such as emergency department visits and hospitalizations. On the other hand, managing AR can reduce the severity of asthma and improve outcomes for children with both AR and asthma (279).

2.12.3.3 Biology of allergic pollen types

Different varieties of pollen have clinical significance in various parts of the world, depending on the planting and historical vegetation. For example, European plant species have been introduced to areas outside of Europe, with effects on local pollen production and distribution. According to a study by Ong et al (280), these introduced European plant species can have significant impacts on local pollen allergy patterns and the prevalence of pollen sensitivity in a given area such as Melbourne, Australia. The prevalence of pollen sensitivity varies considerably between geographic areas and human groups. Asthma can be triggered by high levels of pollen even if an individual is not sensitised to pollen (281). The allergen concentration of pollen, the route of exposure, and the time of day are all variables that may affect a certain person's reactions to pollen. Weeds, grasses, and trees are common sources of pollen allergens in both the Northern and Southern Hemispheres and will be discussed in detail in the next sections.

2.12.3.3.1 Grass

Grass pollen is the most well recognised and clinically significant source of outdoor allergens worldwide (282). During the European arrival period, native grasslands in Australia consisted of a mix of perennial warm- and cool-season grasses. In South Australia, tall, drought-tolerant warm-season grasses, primarily of the C4 summer-green variety, outperformed smaller cool-season grasses. Livestock quickly consumed these warm-season grasses, which are still scarce in today's landscape. They are well-suited to warmer, wetter growing seasons and drier cold seasons, like in the Kimberley region, where they dominate. On the other hand, C3 grasses are most prevalent in the south-eastern and southwestern corners of Australia, thriving in areas with high spring rainfall and milder temperatures (283). There are about 10,000 distinct species of grasses in the Poaceae family. There are six recognised subfamilies within this extremely vast botanical family, and a number of species within these subfamilies are known to generate allergenic pollen, including the Pooideae

subfamily of temperate grasses. There is a lot of knowledge about which species in this subfamily are allergenic, including the identification of several components of the allergens produced by these grasses. Kentucky bluegrass (*Poa pratensis*), orchard grass (*Dactylis glomerata*), perennial ryegrass (*Lolium perenne*), sweet vernal grass (*Anthoxanthum odoratum*), and Timothy grass are prime examples (23). Grass pollen is also important in non-temperate regions. Parts of Queensland, with its subtropical climate, are home to a range of grass species, including various species of subtropical Poaceae (282, 284). In Queensland it has been shown that grass pollen is a significant trigger for asthma in the area and that asthma exacerbations and hospitalisations may increase during the grass pollen season.

2.12.3.3.2 Tree pollens

Trees generate vast quantities of allergenic pollen. About 100 angiosperm (flowering) and gymnosperm (non-flowering) trees might cause allergen sensitisation in individuals with allergic sensitivities. The trees that produce allergic pollen belong to many distinct botanical orders: Fagales; Alder, Beech, Birch, Hazelnut, and Oak; Lamiales; Ash, Privet, Olive, Lilac; Proteales; Plane and Sycamore; and Pinales: Cupressaceae, Cypress, Japanese Cedar, and Juniper. The common white birch (*Betula verrucosa*) is one of the major allergenic tree pollen sources in Europe, particularly in the milder northern areas, including the Scandinavian countries. A single birch catkin can yield up to six million grains of pollen. A single birch tree may discharge about 5.5 billion pollen grains during one pollen season (285). In the Mediterranean, parts of southern Europe, North and South Africa, North and South America and Australia, clinically relevant tree pollens originate from olive and cypress trees (286). In cooler temperate climates of Northern and Central Europe, North America, East Asia and Northwest Africa, Birch, Alder and Hazel, are amongst the most clinically important tree pollen allergen sources (285). In the late winter and early spring, trees typically pollinate in Australia. The White Cypress (Murray) Pine is the only tree native to Australia that generates highly allergic pollen. South of the Tropic of Capricorn, it grows on the western plains and slopes of Eastern Australia through to Western Australia. It blooms from late July to the end of August. Early spring symptoms are usually attributed to Wattle trees but testing rarely show that Wattle pollen is the culprit. Numerous Casuarina or Australian Oak tree species release pollen all year long, which might result in AR symptoms at any time of the year (287). The most common tree pollens found in Sydney are from Casuarina, Eucalyptus, and Pinus species (288, 289).

2.12.3.3.3 Weed pollens

Weeds are plants that grow in unwanted locations and are considered undesirable as they compete with native or agriculturally grown plants for resources such as sunlight, water and nutrients. Several plant families possess allergenic pollen-producing species. Ragweeds (Short [Ambrosia artemisiifolia], Giant [A. trifida], and Western) are among the most invasive and clinically significant weed pollen producers (A. psilostachya). While each of these species is indigenous to the northern regions of the United States, they are now found across Southern United States, Western Europe, and now Central Europe. Invasions of ragweed have occurred in sections of the central and eastern coastal regions of Southern Australia, as well as in other locations. Other allergenic pollen sources in the Asteraceae family include Mugwort (Artemisia vulgaris), which is native to China, where its therapeutic benefits are acknowledged, and Feverfew (Tanacetum parthenium), whose leaves are skin irritants (290). Australia has been exposed to several weed species with highly allergenic pollen, including Pellitory weed, commonly known as asthma weed, which was imported from Italy in 1900 and primarily found in Sydney. The flowering plant known as Paterson's Curse (Echium plantagineum) was intentionally imported from England by Dr. Paterson in the 1800s. It has spread widely in rural areas of Australia and produces highly allergenic pollen. Imported pasture seed from the US brought ragweed and Parthenium weed, which have spread throughout Queensland and Northern New South Wales (287).

2.12.3.4 Pollen and childhood asthma admissions

Studying the association between pollen and childhood asthma admissions can help understand seasonal patterns of asthma and identify high-risk periods. Ambient grass and tree pollen were found to be signification risk factors for paediatric asthma hospital admissions, by two systematic reviews (291, 292).

In the review by Simunovic et al. (291), three studies (27) (293) (24) conducted on children assessed the association between asthma admissions and grass pollen. One study (27) in the US (sample size not reported) found no association between childhood admissions and pollen. At a lag of 0, an increase of 10 grains/m^3 after adjusting for other pollens resulted in a mean change of 1.8% (95% CI: -9.4, 14.5) for children aged 5-12 years and a mean change of 0.7% (95% CI: -7.4, 9.5) for children aged 1-17 years. A study in Spain (293) (sample size = 2609) found a positive correlation ($p < 0.00001$) between pollen counts and admissions. An Australian study (24) (sample size = 2098) conducted in 2018 found that an increase of 9

grains/m^3 in pollen concentration was associated with a significant increase in admissions, with an odds ratio of 1.037 (95% CI: 1.005, 1.070).

While examining asthma hospitalisations in 12 relevant studies, Shrestha et al. (292) noted a correlation between admissions and ambient grass and birch pollen. For every 10 grains/m^3 increase in grass pollen at lag 0 and birch pollen at lag 2 and lag 0–6, admissions for asthma increased by 3% [95% CI: 1%, 4%, degree of heterogeneity (I^2) = 0%; n = 2] and 0.85% (95% CI: 0.4%, 1.3%, I^2 = 0%; n = 2). In addition, a more recent study (294) in South Australia reported that tree pollen showed an incident rate ratio (IRR) of 1.17 (95% CI: 1.08, 1.28), p≤0.001 in August and, IRR of 1.23 (95% CI: 1.11, 1.37), p<0.001 for hospitalisations (0-17 years, n=22,114) in September.

Studies (294) (295) have also shown a significant association between weed pollen and childhood asthma admissions. A study (295) in the US found high correlations between asthma hospital admissions (0-14 years, n=17,902) and weed pollen (3-day lag) with a coefficient of r=.247. A study in South Australia also (294) found an increased risk of childhood asthma hospitalisations (0-17 years, n=22,114) with high weed pollen. Weed pollen showed borderline significance for hospitalisations in February (IRR 1.22; 95% CI: 1.00, 1.48), p=0.05 and significant increases in March (IRR 1.27; 95% CI: 1.05, 1.54), p=0.02, April (IRR 1.26; 95% CI: 1.03, 1.54), p=0.03, and May (IRR 1.16; 95% CI: 1.01, 1.33), p=0.04.

In all my results Chapters I have taken grass pollen as the main exposure variable, as it appears to be a significant trigger in Australia, especially in Melbourne. In addition, I have also considered tree and weed pollen in Chapter 3 of my thesis.

2.12.4 Thunderstorm asthma

While not the primary focus of my thesis, some of the data in Chapter 3 may overlap with periods where thunderstorm asthma (TA) may have been present. As such, I present relevant literature on this topic in this chapter.

A systematic review showed that grass pollen is a major cause of thunderstorm asthma (296). Acute bronchospasm that happens within minutes or hours of a thunderstorm or convergence line weather event (a band of rain and clouds that forms when winds from different directions meet) with or without lightning is what defines TA (297, 298). Thunderstorm Asthma can result in a severe asthma attack which can lead to emergency care and, in some cases, death (297, 299). It can cause a sudden increase in the number of people

who go to their doctor or hospital with breathing problems, which puts a lot of stress on health services. Mucus production, mucosal swelling, and IgE-mediated mast cell degranulation are signs of airway inflammation in TA. This is followed by an increase in sputum eosinophil cationic protein (ECP), sputum eosinophils, and IL-5-positive cells (300). Because TA causes changes like asthma, it has the same ICD code (J45, J45.0, J45.1, J45.8, J45.9, and J46) (301).

2.12.5 Seasonality and asthma

The seasonality of healthcare visits related to asthma is well established, with variations in the timing and severity of peaks among different age groups and regions. Winter peaks have been attributed to increases in respiratory virus infections in the population, while seasonal return to school effects have also been observed (302). However, several studies (45, 303) suggest that there may also be an increase in childhood asthma incidents in spring, which is connected to pollen exposure, including grass pollen, with or without thunderstorms.

Seasonality is an important factor to consider when examining the relationship between pollen exposure and asthma admissions, as the levels of pollen can vary throughout the year and may be more strongly associated with admissions during certain seasons. In Australia, the grass pollen season typically peaks in late spring and early summer (November to December), while the tree pollen season typically peaks in late winter and early spring (July to September). Regional differences in climate, plant species and local environmental conditions also effect the timing and severity of pollen seasons within Australia. For example, pollen seasons are typically more pronounced and long lasting in Southern, cooler regions, compared to Northern, tropical regions which have shorter, less intense pollen seasons. Grass pollen seasons in Australian cities differ in timing and duration. Melbourne peaks from October to December, Sydney in October and November, Adelaide stretches from September to February, Brisbane peaks from January to March, Canberra spans from July to February, Darwin is brief in May and June, and Hobart peaks between November and January (304). Additionally, seasonal fluctuations in weather patterns and air pollution levels can also impact the relationship between pollen exposure and asthma admissions (45). Therefore, it is important, and I have considered the seasonality of pollen exposure and other environmental factors when investigating the pathway from pollen exposure to admission in Chapter 3.

2.12.6 Outdoor fungal spores

In addition to pollen, it is important to consider fungal spores as a significant allergenic factor, given their potential risk to respiratory health (44). No prior study has evaluated the association between both pollen and fungal spores with HAADs (as discussed in introduction) during the pollen season. Fungi are effective dispersers of their reproductive spores, making them a common component of nearly every biome. More than 1.5 million different types of fungus have been proposed, but only around 10% have been named and documented (36). Their anatomy, physiology, and reproductive strategies all differ, making them everything but a unified group. Although most fungus are harmless, there are those that can cause illness in humans, animals, and plants (305).

2.12.6.1 Outdoor fungal spores and childhood asthma

The most common outdoor fungal species studied in ecological studies (306-309) assessing the fungal spores and hospitalisations for childhood and adolescent asthma are Alternaria and Cladosporium. Two studies were conducted in Australia, one among children 8-11 years (308) and one (309) among children 2-17 years. Other regions included the US (306) and Canada (307) with 0-18 and 0-14 year-old children respectively.

Despite the absence of a clear causal link, previous studies have indicated spikes in the number of airborne Alternaria species other fungal spores during thunderstorms (310) and during asthma epidemics (311), compared to normal levels. A study (312) suggests that epidemic thunderstorm-related asthma near the end of the grass pollen season may be most strongly linked to susceptibility to fungal spores, particularly Alternaria species. Aeroallergens such as pollen and fungal spores have been investigated for asthma hospitalisations among children and adolescents with asthma (27, 309). In 2006, Babin et al. conducted a study in the US (27) and found that a 1000 spores/m^3 increase in mold spores count was non-significantly associated with 1.1% (95% CI: -0.8, 3) and 2% (95% CI: -0.6, 4.6) for asthma-related admissions among 1-17 years and 5-12 years old children, respectively. However, results were only significant for weed pollen, with a 10 grains/ m^3 increase associated with 7.7% (95% CI: 0.7, 15.2) for 1-17 year-old and 10% (95% CI: 0.5, 20.5) for 5-12 year-old children. It should be noted that data on aeroallergens was collected only three days a week during the study period. Tham et al. (309) conducted a study in Australia that investigated the impact of outdoor fungi on childhood and adolescent asthma hospitalisations. The study controlled for pollen and other possible factors that could affect the results. The researchers found that exposure

to Alternaria (aOR 1.07; 95% CI: 1.03,1.11), Leptosphaeria (aOR 1.05; 95% CI: 1.02, 1.07), Coprinus (aOR 1.04; 95% CI: 1.01, 1.07), Drechslera (aOR 1.03; 95% CI: 1.00, 1.05), and total spores (aOR 1.05; 95% CI: 1.01, 1.09) was significantly linked to child asthma hospitalisations. The study also revealed that there were significant effects with some fungi up to three days later, including Alternaria, Leptosphaeria, Cladosporium, Sporormiella, Coprinus, and Drechslera.

Given the substantial link between aeroallergens (313) and the prevalence of symptoms during high-pollen days, I reasoned that exposure to fungal spores may be making the situation even worse. This is what I evaluated in my study (Chapter 3).

The following section focuses on readmissions, another important outcome that I have considered in my thesis.

2.13 Readmissions

Hospital readmissions, in general, quadruple the expense of inpatient care for children (314). Early readmissions (30 days after release) have been scrutinised as quality indicators and prospective criteria for reimbursement penalties. Late readmissions (>30 days), however, are significantly more prevalent in paediatric asthma (96, 315). These high asthma readmissions are worrisome considering that asthma is a disorder susceptible to ambulatory therapy for which prompt, adequate outpatient care might avert hospitalisation (316, 317). There is an urgent need to identify risk factors related to asthma readmissions so that personalised, evidence-based therapies may be given to children at the highest risk. Identifying risk factors that place patients at a higher risk for adverse asthma outcomes may considerably decrease asthma-related hospitalisations. Predictions have indicated that readmissions would continue to rise by 5% each year, with the greatest increase occurring among boys aged 2 to 5 years (318, 319). Therefore, I focus on readmissions, in my study, to better understand the pollen exposure burden on repeat admissions in children (Chapters 5 and 6).

2.13.1 Readmission within 28 days

My study focuses on 28-day readmissions. Evidence suggests that readmissions within 28 to 30 days following an admission are often due to uncontrolled asthma attacks and not responding treatment, indicating a more severe asthma episode (320).

Not all risk factors linked with 28-day asthma readmission have been well studied (321). Childhood readmissions within 28 days have been linked with season of presentation

(318) (150) (322). In Australia (318), among 2-18 year olds (sample size=2401 readmissions), winter had the highest seasonal peak (30.5%), followed by autumn (28.6%) and spring (24.6%) (p= 0.0005). The day of the week and month were strongly related to readmission patterns. In another study (322) on 2-18 year-olds, (sample size=not reported) in Michigan, US, it was determined that children who had been readmitted were more likely to have asthma index admissions in the summer due to hot weather conditions. In addition, patients were at a greater risk of readmission if they were discharged during summer. Similarly, another US study (150) among 5–18 year-olds reported that compared to winter, readmission rates for patients with an index hospitalisation were higher in summer or autumn.

In context to the grass pollen season, only one study (323) (sample size=2401) assessed the association with readmissions among 2–18 year-olds in Australia. A significant association was found between the grass pollen season and readmissions within 28 days, but only among males (p = 0.01). I have used grass pollen season in separate models as an exposure in my study (Chapter 5).

Air pollutants have also been linked with childhood asthma readmissions in the US, as shown in a study with a sample size of n=111 (150). Strong associations were identified for ozone and $PM_{2.5}$ even after controlling for other variables (length of stay, seasonal impact, type of insurance, sex, year, and ethnicity). Elevated $PM_{2.5}$ levels were strongly related with increased readmissions on the day of readmission and the previous day. When the model was adjusted for $PM_{2.5}$, however, ozone concentrations were only associated with readmission the day before and the day of readmission. Season-stratified models demonstrated positive associations between $PM_{2.5}$ and ozone, with readmissions during the warm season, but not during the cold season. Therefore, I have also considered air pollutants in the models that I have developed for my study (Chapter 5).

No study has assessed the impact of ambient pollen levels, known to be associated with admissions (as described in the section on pollen and childhood asthma admissions), on readmissions. However, repeated exposure to pollen can lead to repeat episodes of asthma exacerbations and increased hospitalisations. Therefore, in my study, I explore this association while controlling for air pollutants and weather variables (Chapter 5).

2.13.2 Readmission within other time frames

Readmission within other time frames is not the main outcome or focus of my study, therefore I briefly summarise below the factors studied by other researchers in relation to

readmission with other time frames such as 0.5 months and 12 months. Season (148) has been linked with readmission within 15-90 days (322), readmission within six months (148), and any readmissions over the study time period (324) (325). Traffic-related air pollution (TRAP) increased readmission within one year in one study(149), and any readmissions in another(152). Child Opportunity Index (a tool that measures the resources and opportunities available to children in different areas of the United States) and any readmissions (151), ozone and readmissions that occur 90 days or later (150) are the other associations studied. Studies have concluded that outdoor environmental exposures such as TRAP, ozone, $PM_{2.5}$, grass pollen, summer discharge, and an index admission that occurs in summer or autumn show varying levels of association with readmission rates in children with asthma, with the strongest associations seen in the 2 to 11 year-old age group, males, and Caucasian ethnicity.

Additional individual-level factors, such as a history of prematurity and complex chronic conditions like obesity, were identified as contributing to an elevated risk of readmissions. Furthermore, markers of disease severity, such as the length of stay (LOS) during the index admission, indicated their influence on readmission rates. In contrast, assessments of parental asthma knowledge, conducted in the absence of formal education programs, showed either negligible associations or no discernible links with readmission rates(326). Another study underscored the vital role of general practitioners in asthma management and the need for guideline-concordant care aligned with regular GP visits and self-management(327).

2.14. Indoor environment as an effect modifier in pollen exposure outcomes

When assessing the relationship between pollen and childhood asthma readmissions, the indoor environment could be considered as an important factor. A combination of exposures may increase the risk, while some exposures may have a negative interaction and potentially cancel each other out. The complex relationships between exposures require further investigation. Some of the sources of indoor air pollutants (Table1) and their possible interaction with pollen is briefly described below:

2.14.1 Indoor tobacco smoke

Environmental tobacco smoke has more than 4000 components, and more than 40 of them are known to cause cancer (328). The World Health Organization stated that about 700

million children, or about half of the world's children, have been exposed to tobacco smoke, mostly in their homes (329). Studies (58-63, 66, 321, 330-332) have suggested that exposure to second-hand smoke can increase the risk of childhood asthma readmissions in 30 days or one year.

Tobacco smoke exposure and asthma readmission within one year has been assessed in multiple studies (58, 61-63, 66, 330-332). One study found that more than three quarters of children who were readmitted in one year (79.5%) were exposed to tobacco smoke (61). Increase in odds of asthma readmission was found in four studies (61, 62, 330, 332) with OR ranging from 1.02 (66) to 2.27 (61); however, results were significant ($p<0.05$) only in one study (61). Another study (62) compared the risk of asthma readmission among a group who had more than 1 smoker in the home and a group who did not have the exposure, and found that the estimated risk ratio (RR) was 1.44 (95% CI: 0.87, 2.37).

Alshehri et al (2005) (147) reported that 36% of children were exposed to smoke with OR of asthma readmission within two months as 1.01 (95% CI: 0.34, 3.01). Smoking exposure and asthma readmission within 30 days was assessed in another study (321). The study reported non-significant results with OR 1.01 (95% CI: 0.34, 3.01) because they did not adjust for other important variables such as age, sex and socio-economic status. In a randomised controlled trial (59) with children (5-18 years), among the active group (defined as strategies for reducing exposure to allergens in the bedroom, which include covering the mattress, box springs, and pillows with special covers that prevent allergens from getting in, washing bed linens in hot water every week, replacing bedroom carpet with smooth flooring, and using a 3% tannic acid spray to treat the living room carpet) exposed to indoor smoking, 31% were readmitted due to asthma. The authors of the study (59) did not quantify or statistically analyse the difference in asthma readmission outcome.

Evidence has demonstrated that in children, exposure to tobacco smoke exacerbates hypersensitivity reactions to allergens (261). Children who are exposed to both second-hand smoke and pollen can be at increased risk of having asthma-related hospital readmissions compared to those exposed to only one of these risk factors. This is because concurrent exposures to factors that contribute to the exacerbation of asthma symptoms (as described in the studies above) can result in a cumulative effect on the airways, leading to increased asthma symptoms and a higher risk of hospital readmission. However, the extent to which parental smoking modifies the relationship between pollen and asthma admissions will depend on

several factors, including the severity and duration of exposure, the age of the child, and other underlying health conditions.

2.14.2 Pets

Pet hair, clothes, and indoor furniture can carry allergens like dander, urine and saliva for several months. Ingram et al. (333), who did a quantitative analysis of exposure to dog and cat allergens, found that a high prevalence of IgE antibodies to cat and dog allergens was linked to the presence of cat and/or dog allergens in the homes. Multiple studies (58-66, 334) have included pets as a potential exposure, with asthma readmissions as an outcome. The results are briefly described below:

2.14.2.1 Readmissions within 3-6 months

In Hayden and Perzanowski's (59) randomised control trial, 23 children aged 5-18 years, who had been admitted to hospital for asthma, were randomly allocated to an active (13 children) (described in section 2.14.1) or placebo (10 children) group. The authors reported a fall in allergen levels for the active group but did not report or statistically test the difference in allergen levels, including cat, between the placebo and active group. The authors did not quantify or statistically analyse the difference in asthma readmission outcome.

2.14.2.2 Readmissions within one year

Minkovitz (58) found that there were no differences (p=0.86) in the proportion of children who were exposed to pets and had multiple readmissions for asthma 6 (26%) compared to children who had single admissions 14 (28%). Similarly, Mersha et al (60) found 57.9% exposed to furry pets readmitted due to asthma and 52% not exposed readmitted, p=0.26. On the other hand, Youssef (61) reported that a higher proportion of readmitted children due to asthma were living in houses where birds or pets were kept (36.6%).

2.14.2.3 Readmission more than 12 months

A hospital-based case–control study (334) recruited 22 children readmitted for asthma and 22 controls not readmitted for asthma. Non-significant differences were found between case and controls for the presence of any pets adjusted OR 2.62 (95% CI: 0.51, 7.25), p=0.33, dog adjusted OR 1.63 (95% CI: 0.28, 9.44), p=0.58, and cat adjusted OR 1.84 (95% CI: 0.27,12.69), p=0.53.

Like exposure to second-hand tobacco smoke, exposure to both pet allergens and pollen can result in a cumulative effect. In my study, I have not included pets as an effect modifier due to the lack of available data on pet exposure (Chapter 6).

2.14.3 House dust mites

Most dust reservoirs, including mattresses, carpets, couches, draperies, soft toys, and clothes, contain dust mite allergens (335). The primary allergens are the immunostimulatory proteins found in dust mite faeces (336, 337). Mite allergens are mostly transported on big particles (diameter >10 m) and are typically undetectable in ambient air under normal settings (338). However, disruption of dust reservoirs, such as vacuuming or changing the bed, may aerosolize dust for up to 15 minutes and increase the quantity of allergens breathed (339).

Sporik et al. (67) reported that 83% of a group of 12 readmitted children due to asthma (readmitted within 6 months) and 32% of 60 non-readmitted children due to asthma were sensitized and exposed to more than 10 μg g-1 of House Dust Mites (HDM) (Der p1) in dust collected from the living room, bedroom or bedding ($p<0.001$). Another study (59) assessing asthma readmissions within 3-6 months reported a fall in allergen levels for the active group (as defined above in Section 2.14.1) compared to the placebo group. Elissa et al. (340) conducted a study on children under 14 years and found that 86% were exposed to dust in Group A (readmitted due to asthma within 1 year) and 36% in Group B (not readmitted); the difference was statistically significant $p=0.003$. Vicendese et al. (334), on the other hand, reported no difference in HDM levels between homes of readmitted and non-readmitted children due to asthma. Compared to homes that were vacuumed weekly or less often, vacuuming at least 2–3 times weekly was associated with a 15-fold increase in the odds of asthma readmission OR 15.7 (95% CI: 2.82, 87.2), $p=0.002$.

Carpets can trap and accumulate allergens, including pollen, dust mites, and pet dander, leading to increased exposure and exacerbation of asthma symptoms in children with asthma. Additionally, the presence of bacteria in carpets can also contribute to indoor air pollution, which can irritate the airways and increase airway inflammation, further exacerbating asthma symptoms. Therefore, the presence of carpets in the home environment can modify the relationship between pollen exposure and childhood asthma readmissions, with the effect being dependent on the type and quality of the carpet, as well as the level of maintenance and cleaning.

2.14.4 Cockroaches

Exposure to cockroaches has been associated with sensitisation and allergic respiratory symptoms (341). Studies (59, 60, 65, 331) have found a connection between exposure to cockroaches and readmission outcomes.

Auger et al. (331) conducted a prospective cohort study on 601 children aged 1-16 years. The outcome was asthma readmission within 12 months. Around 14.6% reported exposure to cockroaches. Adjusted hazard ratio computed was 0.82 but not statistically significant. Another study (60), with a similar asthma readmission timeframe, reported that 12.0% exposed to cockroaches were readmitted and 12.1% not exposed were readmitted but not statistically significant ($p>0.999$). Allergen levels including cockroaches were reduced in active group (as defined above in Section 2.14.1) compared to the placebo group in an RCT (59). However, no further analysis was conducted. Due to the mixed findings in the literature on cockroach exposure, it was not considered as an effect modifier in the analysis of this study (Chapter 6).

2.14.5 Mold and/or dampness

Mold-sensitive individuals' exposure to mold allergens is regarded as a significant risk factor for asthma severity and asthma exacerbations (342, 343). The taxonomic group Fungi Imperfecti of Ascomycetes, which includes Alternaria, Cladosporium, and Aspergillus species, is the most prevalent source of mould allergens (344).

A higher proportion of asthma readmitted within 12 months children were living in houses that were perceived as being damp (66.1%) (61). Mersha et al. (60) conducted a prospective cohort study of 695 Black and White children aged 1 to 16 years, with an asthma-related admission. The primary outcome was asthma readmission within 12 months. The indoor exposures included mould/mildew. They found equal proportion of readmissions in the exposed and non-exposed groups. Another study (65) on asthma readmissions within 12 months as an outcome and smoke, dogs and/or cats, mice, cockroaches, or mould as an exposure, reported OR= 0.99 (95% CI: 0.69, 1.43). However, no separate results for mould were present in the study.

The study by Vicendese and colleagues (334) included Cladosporium, yeast, Penicillium/Aspergillus or Alternaria spores as primary exposures. For every doubling of the concentration of colony forming units of airborne Cladosporium (per 28 L of air) in the

bedroom, there was over a 60% increase in the odds of readmission, with adjusted OR 1.68 (95% CI:1.04, 2.72), p=0.03. No significant results were obtained for Alternaria and Penicillium/Aspergillus.

In summary, there does not seem to be a specific exposure that is likely to be associated with asthma readmissions. Single exposures in asthma are typically polluted by further exposures (345). Each of them represents a complicated exposure, and interaction between all of these exposures is possible. For example, due to their inherent electrostatic qualities and porous surfaces, ambient inhalable particulate matter (PM) easily adheres to free airborne allergens generated by animal dander, dust mites, moulds, and pollens. In indoor areas where smoking is prevalent, tobacco smoke is the primary source of particulate matter (PM), and can account for 50–90% of the total indoor PM concentration (346). PM might interact with aeroallergens, hence causing airway sensitisation by modifying the allergenicity of airborne allergens. On the basis of these findings and the fact that little is known about the possible synergistic effect between poor indoor risk factors and allergens, specifically pollen, at the population level, studies are required to investigate the impact of pollen on hospital readmissions in the presence of poor indoor risk factors. I have addressed this research gap in Chapter 6 of my thesis.

In the next part, I will address other effect modifiers that may be important on the pathways between pollen exposure and childhood asthma outcomes. Additionally, I will also address the various confounders that may be important for relationship between pollen exposure and childhood asthma outcomes.

2.15 Potential effect modifiers and confounders of outdoor pollen

Asthma (347, 348) asthma exacerbations (349), and hospitalisations for asthma-related conditions (350) are all strongly associated with allergic sensitisation (350). Multiple studies have shown that children's sensitisation to aeroallergens may rise with time (351, 352). Individuals who are already sensitised to an allergen have an association between exposure to that allergen and a greater likelihood of severe asthma (67, 353).

Children with acute asthma attacks who had been sensitised and exposed to dust mites were more likely to be readmitted to hospital within a month, as described by Sporik et al (67). Together, these characteristics substantially increased the likelihood of needing medical attention in a hospital setting. Aeroallergens like fungus spores, pollen grains or animal dander tend to easily cling to the point of contact of ambient particulate air pollutants less than 10 um

in diameter. This is likely due to the fact that these pollutants have porous surfaces and electrostatic characteristics.

Particulate matter or gaseous pollutants can cause inflammation of the airways, making them more sensitive or hyperreactive. They can also interact with aeroallergens and change how allergenic they are. Damage to the mucosal lining of the airways and slowed mucociliary clearance may make it easier for inhaled allergens to reach the immune system. This link increases the risk of atopic sensitisation and worsening of symptoms in people who are already sensitive (354). Studies in a controlled lab setting have shown that air pollutants and aeroallergens act synergistically (355, 356). Also, changes in climatic conditions contributes to the amount and location of pollutants in the air and extends the time that allergenic pollens are in the air during certain seasons (357). In the same way, weather can directly affect asthma by affecting the airways or indirectly through allergens and pollution levels in the air (358). Therefore, it is important to control for possible effects of these variables and explore interactions and strata specific effects.

The objective of my doctoral research is to fill in the identified knowledge gaps in this literature review, with particular focus on the effects of outdoor pollen on child and adolescent asthma admissions, use of new robust method S-H-ESD in identifying HAADs and HARDs, effects of outdoor pollen in child and adolescent asthma readmissions with a focus on 28 days and synergistic effects of indoor risk factor and grass pollen on child and adolescent readmissions.

Table 1: Characteristics of the studies with indoor risk factors and readmissions as an outcome

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Minkovitz et al. (1999) (58) Baltimore, Maryland	Nested case-control study N=35	0-14 years old Mean + SD= 4.0±3.1 years	Repeated within one year.	Cigarette smoking Pets	More than half were exposed to cigarette smoking at home. There were no differences (p=0.19) in the proportion of children who were exposed to cigarette smoking and had multiple readmissions, 16 (49%) compared to children who had single admissions 46 (62%). There were no differences (p=0.86) in the proportion of children who were exposed to pets had multiple readmissions 6 (26%) compared to children who had single admissions 14 (28%).	No
Reznik (2006) (321) Bronx, New York	Matched case-control study Cases=152	Mean + SD (min-max) age=5.99 + 5.18 (0.20-20.30) years	The mean duration between the admission date of readmission and the discharge date of the index admission for cases was 15.8±8.5 days (range 0.0–30.0)	Cigarette exposure at home	Decreased the odds of readmission. OR= 0.81 (95% CI: 0.54–1.21), p value=0.306	No

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Hayden (1997) (59) Atlanta, USA	Randomised controlled trial. N= 25 (14 active and 11 placebo)	5 to 18 years old Mean (max-min) age Active group=9.8 (6-15) years Placebo group=8.6 (5-16) SD of age not reported	Percentage readmitted in the active group compared to % readmitted in the placebo group. PEF, FEV1 & MV were compared at three and six months	Indoor tobacco smoke Active: allergen-impermeable encasement of pillows, mattresses & box springs; hot wash bed linens or replace BR carpet with polished flooring; 3% tannic acid treatment of carpet. Placebo: permeable encasements; cold wash; water spray for carpet. BR & BG analysed for HDM, cockroach and cat	Indoor tobacco smoke: active=1. Placebo=1 31% of active & 20% of placebo group readmitted. Peak exploratory flow improved active group, $p<0.04$ and< 0.05. No change FEV1 & MV in active or placebo group. Allergen levels reduced in active group - levels not stated & no statistical analysis	No

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Sporik (1993) (67) UK	Case control N=72 Cases n=12 Controls n=60	All 1.5-15.5 years. Hospitalized for acute asthma six months prior. Mean, SD, min, and max age of readmitted group not reported.	Percentage readmitted in the preceding month.	HDM sens & expo > 10 µg g-1 Der p 1, LR, BR or BG Sampled from reservoir dust.	83% of exposed group compared to 32% of non-expo group readmitted $p < 0.001$.	No
Elissa (2019) (340) Alexandria, Egypt	Case-control study Group (A): readmitted within one year from first admission and Group (B): firstly admitted. N=50 in both groups	Mean + SD (min-max) age: Group A= 9.09+ 3.98 (4.5-13) years Group B= 8.65 + 4.01 (4-14) years	Percentage readmitted	Dust Odours	86% exposed to dust in group A and 36% in group B, p= 0.003. 18% reported odours in group A and 20% in group B, p=0.96	No

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Mersha (2021) (60) Cincinnati, USA	Prospective cohort study Readmitted within 12 months (n =134) Not readmitted within 12 months (n =561)	1-16 years Mean+ SD age: 6.28 + 4.03	Readmission within 12 months	Furry pets Cockroaches Rodents Carpets Mold/mildew Water leaks Cracks/holes in walls or ceilings Cotinine in serum >100 pg/mL	134 children (19.3%) were readmitted within 12 months. 57.9% exposed to furry pets readmitted and 52% not exposed readmitted, p=0.257. 12.0% exposed to cockroaches readmitted and 12.1% not exposed readmitted, p>0.999. 8.27% exposed to rodents readmitted and 8.12% not exposed readmitted, p>0.999. 27.1% exposed to carpets readmitted and 28.1% not exposed readmitted, p=0.895 15.9% exposed to mold readmitted and 15.8% not exposed readmitted, p>0.999. 26.3% exposed to water leaks readmitted and 23.8% not exposed readmitted, p-=0.625 31.3% exposed to cracks/holes in walls or ceilings readmitted and 21.6% not exposed readmitted, p-=0.026 Hardship was mediated by and indoor exposures that accounted for 9.0% of the total effect.	No

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Youssef (2005)(61) Egypt	Prospective case-control study N=112 readmitted (36.8%)	Mean ±SD (Min-Max) age: 1.75 + 1.25 (0.16-7.00) years	Within one year readmission	Ventilation of the household Dampness of the household Pets or birds in the household Smokers in the household	Bad ventilation was associated with a threefold increase in the risk of readmission (OR=3.03; 95%CI= 1.68, 5.49). More than three quarters of children who were readmitted (79.5%) were exposed to tobacco smoke. Presence of a smoker in the household increased the likelihood of readmission by 2.27 times (OR= 2.27; 95% CI= 1.28, 4.06). A higher proportion of readmitted children were living in houses that were perceived as being damp (66.1%) and where birds or pets were kept (36.6%)	No
Alshehri (2005) (147) Saudi Arabia	Longitudinal retrospective case–control study Cases=28 Controls=45	68% less than 4 years of age Mean, SD, min, and max age not reported.	Readmissions within two months	Exposure to smoke	36% had been exposed to smoke. OR=1.01 (0.34-3.01)	No
Henry (1995) (330) Australia	Prospective case-control study N=166 readmissions	1-15 years Mean age=5.8 years SD, min, and max age not reported.	Readmissions within one year	Any smoker in the home	Adjusted OR=1.26 (0.73-2.18)	Age, and severity
Auger (2015)(331) USA	Prospective observational cohort study N=135(22.5%) had been readmitted	Median age = 5 years	Readmissions within one year	Roaches Child's indoor smoke exposure.	Hazard ratio of readmission: Roaches- 0.82 (NS) Exposure to cigarette smoke: 0.83 (NS)	environmental exposures, medical home access, financial strain, and socioeconomic and demographic characteristics.

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Macarthur (1996) (62) Ontario, Canada	Cohort study N= 32 (47%) readmitted	Median age=3 years	Readmission within 12 months	> 1 smoker in home > 1 pet in home	Smoker, RR= 1.44 (0.87, 2.37) Pet, RR=0.66 (0.30, 1.47)	No
Wever-Hess (2001)(63) Netherlands	Prospective cohort study N=36 readmitted	Two age groups: 0-1 (27 readmitted) years and 2-4 years (9 readmitted).	Readmission within 12 months	Maternal smoking Smoking in household Pets present Damp housing	No significant differences present for the exposure variables between those admitted once and those readmitted.	No
Rodriguez-Martinez (2014) (64) Bogota, Colombia	Cohort Follow one year N= 101 n=36 children readmitted. n=65 children not readmitted	1-18 years Median (IQR) age= 5.5 (4.0–8.0) years	Bivariate analysis, % exposed comparing readmitted to non-readmitted. Multivariate analysis, outcome number of readmissions	Dog ownership previous 12 months Cat ownership previous 12 months Dog ownership previous 12 months	13.9% readmitted compared to 35.4% non-readmitted, p=0.02 8.3% readmitted compared to 4.6% non-readmitted, p=0.66 IRR 1.29 (0.45, 3.70), p=0.63	No age, no. oral steroids bursts, no. hospital admissions six months prior to study, maternal: allergic rhinitis; education level; depression score; asthma knowledge; smoking.

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Philips (2020)(65) Atlanta, USA	Retrospective cohort study N=152 readmitted	Age groups: 2–11 vs 12–18 years 2-11 years group= 128 (24.7%) readmitted 12-18 years group= 24 (25.5%) readmitted	Readmission within 12 months	Exposure to smoke, dogs and/or cats, mice, cockroaches, or mold	57 (30.6%) had the exposure and the outcome OR= 1.54 (1.05–2.27), p=0.03 Multivariate analysis: OR= 0.99 (0.69–1.43)	age; sex; race and/or ethnicity; language; ED visit in the previous year; asthma sick visit in the previous year; previous PICU admission; asthma severity; history of asthma comorbidity; controller medication prescribed at discharge; postdischarge visit scheduled; and index hospitalization APR-DRG severity of illness.
Visitsunthorn (2013) (66) Bangkok, Thailand	Retrospective case-control study I year readmission, N= 20 (26.3%) 1-3 months readmission=5 cases 3-6 months=8 cases 6-12 months= 7 cases	Age=0-3 years 3-6 years >6 years	Readmissions within 12 months	Household smoking Household pets	Smoking, OR=1.02 (0.36-2.83), P= 0.98 Pets, OR=1.88 (0.66-5.36), P=0.12	No

Year, country, (Citation)	Design N	Age	Outcome and summary measure	Indoor exposure	Results	Adjusted
Vicendese (2015)(334) Australia	Case–control study Cases, N=22 Control, N=22	2-17 years Mean + SD age of cases was 5.2 + 3.3 years. Mean + SD age of controls was 5.8 + 3.3 years.	Cases: at least two admissions within the study period (September 2009 to December 2011) Controls: who had only one admission	Total fungi Cladosporium Penicillium/Aspergillus Alternaria Yeast Vacuumed dust Pets Frequency of vacuuming Carpet Bedding Heating	Cladosporium (per 28 L of air) OR=1.68 (1.04–2.72), p=0.03 Yeast in the bedroom OR= 1.52, (0.99–2.34), P=0.05. Carpet OR= 4.07, (1.03–16.06), p=0.04 Compared with a feather doona, a synthetic doona was associated with a more than 14 times greater odds of readmission OR=14.6, (1.26–169.4), p¼0.03 Vacuuming at least 2–3 times weekly was associated with a 15-fold increase in the odds of readmission OR=15.7, (2.82–87.2), p=0.002	Age, sex, and human rhinovirus infection at admission (HRV)
Howrylak (2014) (332) USA	Prospective cohort study N= 103 (16.6)	1-16 years Mean + SD age = 6.43 + 4.02	Readmissions within 12 months	Caregiver report of any tobacco exposure detectable serum or salivary cotinine	Caregiver report of any tobacco exposure, adjusted OR=1.18 (: 0.79–1.89) Detectable serum or salivary cotinine, adjusted OR= 1.59 [1.02–2.48] and 2.35 [1.22–4.55], respectively	Age, sex, and race (categorized as white, African American, multiracial, or other, education, income, n asthma controller medication.

N=sample size, SD=Standard Deviation, min=minimum, max= maximum, IQR= interquartile range

3. The association between outdoor allergens – Pollen, fungal spore season and high asthma admission days in children and adolescents

3.1 Introduction

This chapter consists of a peer-reviewed published paper of original research to examine associations between grass pollen, and fungal spore exposures and high asthma admission periods among children and adolescents during the grass pollen seasons. This paper also examined potential effect modification by sensitisation to any aeroallergen status and sex.

Peak periods of hospital admissions due to asthma exacerbations can be triggered by high pollen (≥ 20 grains/m) days, especially during thunderstorm asthma events in the Southern Hemisphere (301). Fungal spores may also contribute to asthma exacerbations in children and adolescents (309). To date, there has been limited investigation into the individual effects of different types of aeroallergens on the occurrence of high asthma admission periods during pollen season in children and adolescents. Therefore, this chapter is distinctive in that it analyses each type of aeroallergen separately. It is important to study the individual effects of different types of aeroallergens because it will provide a better understanding of the specific triggers that contribute to asthma exacerbations in this population.

3.2 Research Question

What is the role of both pollen and fungal spores on the two High Asthma Admission Days (HAADs) that occurred during the peak grass pollen season (25/10/2010 & 30/11/2011) in Melbourne, Australia?

a. Are these associations modified by sex, and sensitisation to any aeroallergen?

3.3 Aim

To examine the association of both pollen and fungal spores on the two HAADs and explore effect modification by sex and atopy.

3.4 Ethics approval

This study was conducted using the subset of the data from Melbourne Air Pollen Children and Adolescent Health (MAPCAH), a longitudinal cohort study between September 2009 - December 2011. It has received ethics approval from Royal Children's Hospital (RCH) Ethics Committee and the La Trobe University Human Ethics Committee.

3.5 Contribution to knowledge

No study has previously investigated the impact of grass pollen and spores during high asthma admission periods during pollen season. The study shows that both grass pollen and fungal spores are important triggers during periods of high asthma admissions in pollen seasons, with a priming effect that increases the risk of hospital admission. Fungal spores on the same day were also associated with increased odds of admission, while grass pollen was not. If replicable, these findings can help predict and prepare for peak periods during grass pollen seasons.

3.6 Publication

A pre-print of this manuscript and supplementary data, as originally submitted, are included in this document.

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The association between outdoor allergens – Pollen, fungal spore season and high asthma admission days in children and adolescents

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Conflicts of interest

The authors declare there are no conflicts of interest.

Authorship statement

Mehak Batra, Don Vicendese, Katrina A Lambert, and Bircan Erbas conceived and designed the study. Mehak Batra and Don Vicendese analysed the data under the guidance of Katrina Lambert and Bircan Erbas. Mehak Batra prepared the manuscript under Bircan Erbas supervision. All authors did review and editing and finalising the manuscript.

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ABSTRACT

Periods when asthma admissions peaks have serious implications for asthma sufferers and hospitals. We assessed the association between aeroallergen exposure and childhood asthma peak periods during two grass pollen seasons using the Melbourne Air Pollen Children and Adolescent (MAPCAH) study conducted in Melbourne, Australia. Two peak periods were identified. Effect modifications by atopy, and sex were considered. All pollen 2 days prior was associated with increased odds of these peak periods. Same day fungal spores but not pollen was important. Grass at lag 2 was associated with increased odds 1.03 (95%CI 1.01, 1.05) as was the same day Alternaria 1.02 (1.00, 1.04) per spore/m^3 for boys. In addition to pollen, fungal spores particularly Alternaria may result in days of high exacerbations during pollen seasons. Further guidance is needed to better prepare families/carers with information about the increased risk of asthma attacks in children prior to pollen seasons.

Keywords: Environment; Adolescent health; pollen; Aeroallergen.

INTRODUCTION

Asthma is a chronic respiratory disease that sensitises the airways, which become inflamed when exposed to triggers. This inflammation results in chest tightness, cough, shortness of breath and wheezing, and sometimes leads to a 'flare-up' or attack, which can be a medical emergency (American Lung Association 2020). It affects 5-10% or estimated 23.4 million of the world's population including 7 million children (Morris 2020). Asthma places a severe burden on the public health system and economy with its total cost from both direct medical costs i.e. hospital admissions, the cost of pharmaceuticals and indirect costs i.e. time lost from work and/or premature deaths (Nunes et al. 2017). The underlying causes of asthma are still incompletely understood, although some triggers are environmental including pollen, fungi and extreme weather patterns such as thunderstorms asthma (TA) events (Asthma Australia 2019).

When peak periods in hospital admissions occur, they cause a huge and unexpected burden on the health care system, the patient and their care givers and family. Periods of high asthma admission days are defined as days with an unexpectedly high number of asthma admissions to hospitals based on varying thresholds (Silver et al. 2018). In the Southern Hemisphere, high asthma admission periods have occurred during TA events, which are defined as an asthma attack triggered by abrupt changes in environmental conditions caused by thunderstorm activity (Campbell et al. 2019). These usually occur during the pollen season when high pollen days are concurrent with thunderstorms and abrupt changes in weather conditions such as wind speed, temperature (Andrew et al. 2017) and relative humidity (Silver et al. 2018).

Melbourne has very high levels of grass pollen. A Burkard volumetric trap was used to monitor the atmosphere of Melbourne for pollen grains. Flowering plants and conifers, about twenty-two families, were identified in the pollen counts with 62% of these pollen grains belonging to trees, 20% to grasses and 9% to herbs and weedy plants. Grasses such as Ulmus and Cupressus had the most significant contribution to the pollen calendar. The pollen producing period of these plants spanned from end of June to end of February, accounting for 67% of the year. Introduced species such as perennial and annual rye grasses and canary grasses were the major contributors to grass pollen. These grasses are grown extensively as pasture grasses and the ryegrasses occur as weeds in wheat crops in Victoria (Ong et al. 1995-a). In Melbourne, exposure to grass pollen, notably that of the pasture grass perennial ryegrass, is the main cause of asthma from October to December (Haberle et al. 2014).

In separate high asthma periods, recorded in Australia (Marks et al. 2001) as well as other locations such as in the United Kingdom (UK), increased levels of grass pollen grains were found in the atmosphere (D'Amato et al. 2007). Higher levels of allergic sensitivity to ruptured ryegrass pollen starch granules has been detected in patients who experienced asthma during thunderstorms (Davies et al. 2017). Evidence for increased risk of emergency department presentations and hospital admissions during peak grass pollen seasons in children and adolescents has been demonstrated (Erbas B. et al. 2012; Erbas B. et al. 2018). As changing climatic conditions and longer intense pollen seasons are likely to result in similar events (Zhang et al. 2014; Ziska et al. 2019), it is important to better understand the factors that contribute to these high asthma periods especially in children and adolescents.

Fungal spores may also exacerbate asthma in children and adolescents as our own work suggests (Tham et al. 2016). In the atmosphere of Melbourne, Australia between October 1991 and December 1994, annual fungal spore counts, approximately half of which were identified as Cladosporium sp. and only about 1% Alternaria sp., varied widely from 1,106,037 in 1992 to 345,770 in 1994 (Mitakakis et al. 1997). Coupled with high pollen days and the high correlation between aeroallergens, it is possible that fungi exposure compounds the problem. But little has been done assessing both types of aeroallergens and their impact on high asthma admission periods in children and adolescents.

The Melbourne Air Pollen Children and Adolescent Health (MAPCAH) study recruited children and adolescents with incident asthma (Tham et al. 2016) during two peak periods of high asthma admissions (25/10/2010 & 30/11/2011) that occurred during the grass pollen seasons (Howden et al. 2011; Silver et al. 2018). Although not as severe as the 2016 TA event (Thien et al. 2018), these events still resulted in a large numbers of emergency calls, hospital attendances, and hospital admissions. Using the MAPCAH data we sought to assess the role of both pollen and fungal spores on these two events.

METHODS

Study design and Setting

This case-crossover analysis is a sub-study of the Melbourne Air Pollen Children and Adolescent Health (MAPCAH) study (Erbas Bircan 2013). The study was conducted in Melbourne, Victoria from September 2009 to December 2011 with daily asthma admissions (defined as ICD10 J45/46 codes) at The Royal Children's Hospital (RCH) aged 2 to 17 years. The total sample size considered for the study was 176 with a final 135 for case-cross over analysis. It excluded carers who couldn't participate due to language difficulties, children below

the age of 2 years and patients who did not live within the 50 kms of RCH. The MAPCAH study collected individual data on family history (family history of atopy and asthma), presence of atopy, eczema, hay fever (doctor diagnosed), and Human Rhinovirus (HRV) infection and daily incidence of airborne pollen and fungal spores during the study period.

The outcome variable: peak periods of high asthma admissions

To identify high asthma admission periods, we used the normalised residuals from the entire time series of admissions during the two pollen seasons. A running trimmed mean (averaging after removing the 1st and 99th percentile of the score) was subtracted from the original admissions time-series and then divided by a running trimmed standard deviation. Both trimmed statistics were based on a 7-lag day window (identified in the Partial correlation plots) (Silver et al. 2018). Another method, locally weighted scatterplot smoothing (LOWESS), was followed to confirm the results, which produced locally weighted means based on a one-week data bandwidth. We then isolated the dates whose LOWESS fits were 4 or more SD from their overall mean which is consistent with Silver et al. 2018. Using these methods, 25th November 2010 and 30th October 2011 were identified as high asthma days. As the impacts of environmental factors are not always immediate, it was important to identify preceding days that may be associated with the event. Likewise, days post event also needed to be considered to capture the delay in admissions. Assessing the autocorrelation function of daily admissions, we identified 2 days prior and 2 days post event as days associated with the high admission days. Therefore, our case period (outcome variable) was defined as the high admission days (25th November 2010 and 30th October 2011), 2 days prior and 2 days post these days.

Primary exposure variables

Using the guidelines of the World Allergy Organization (Abbas et al. 2012), a volumetric spore trap (Burkard, UK) was used to measure pollen (Grass, weed, and tree) and ambient fungal spores (Alternaria conidia, Cladosporium spores, and Smuts). The testing site is 20 m above ground levels on the roof top of a building located in central Melbourne. Daily 24-hour average pollen concentrations (grains/m3) were collected from a single Burkard volumetric trap (Burkard Manufacturing Co. Ltd., Rickmansworth, Hertfordshire, UK) during the MAPCAH study period.

Other variables

To assess individual atopic status, each participant underwent skin prick tests (SPTs). These SPTs were conducted with suitable controls for a panel of pollen [rye grass, seven grass mix (Phleum pratense, Dactylis glomerate, Poa pratensis, Agrostis gigantea, Festuca pratensis, Lolium, Anthoxanthum odoratum), birch, English plantain and ten tree mix (Alnus rugosa, Fraxinus Americana, Ulmus Americana, Fagus, Betula lenta, Acer saccharum, Carya ovata, Quercus alba, Populus alba, Platanus occidentalis), and fungal allergens (Alternaria conidia and Cladosporium spores)]. A skin reaction to one or more allergens with a size of at least 3 mm greater than the reaction to the negative control solution, was considered positive (The Australasian Society of Clinical Immunology and Allergy 2020). We grouped participants into age groups: 2-5, 6-12, or 13-17 years.

Outdoor daily levels of air pollutants and weather factors were also considered in the models. Particulate matter up to 2.5 μm in diameter ($PM_{2.5}$), relative humidity, maximum temperature, and the daily maximum 1-hour average nitrogen dioxide (NO_2) concentrations (parts per billion) were considered.

Statistical analysis

We used a bi-directional case-crossover approach to analyse the associations between aeroallergens and admission periods. This approach also controls for other confounding associated with the day of the week, monthly, seasonal, and long-term trends (Bateson and Schwartz 1999, 2001). Exposure and other environmental variables were available for both case and control days. Conditional logistic regression models were used to assess the association between same day and lagged pollen and fungi and asthma admissions in separate models. Models were adjusted for potential confounders such as pollutants and weather variables if they were statistically significant ($p<0.05$) or changed the estimated effect size of the primary exposure by 10%. Analyses were further stratified by, sex, and sensitisation to any aeroallergen to identify possible effect modification. All results are presented as odds ratios (OR) and 95% confidence intervals (CIs). All statistical analyses were performed using Stata IC 16. (StataCorp, College Station, Texas).

RESULTS

In 2010 and 2011, during the pollen season in Melbourne (1st October to 31st December) (Ong et al. 1995-b) there were 240 asthma admissions to The Royal Children's Hospital and of these 176 (73.3%) consented to participate in the MAPCAH study. In 2010, peak monthly admissions (79) occurred in November and on November 25th, of 10 admitted, 8 agreed to participate. Whereas in 2011, peak admissions (49) were in October and on

October 30th, there were 9 admissions and 5 agreed to participate. The majority were young boys. More than half of the participants were sensitized to any aeroallergen. During the 2010 pollen season, a minority were diagnosed with hay fever (20.6%) and those admitted during November, when the high asthma period occurred, were less likely to have a family history of asthma (27%) compared to those admitted during October (Table 1).

The pollen, fungal spores, pollutants and weather levels for both pollen seasons as median [25th percentile, 75th percentile], 2 days prior and on the high admission days are presented in Table 2. Alternaria 4 [18], Cladosporium 24 [6.5, 57], and Smuts 2 [0, 21.5] were considerably higher in 2010 compared to the 2011 pollen season. Except for Smuts and weed pollen (mainly Plantago, the plantains or fleaworts), all the aeroallergens were greater 2 days before than on the high admission days (25th November 2010 and 30th October 2011).

We constructed smooth plots between levels of daily aeroallergens and asthma hospital admissions to the Royal Children's hospital (Online supplementary Figures 1, 2, 3, 4, 5 and 6). For 2010, grass pollen was very high (>200 grains/m3) around 5 days (18th November) preceding the peak period (S1 Figure 1). Whereas in 2011, grass pollen was high 2 days prior to the high admission day or at the beginning of the period. However, tree pollen [mainly Cupressaceae (cypress) with smaller amounts of native Myrtaceae (eucalypt) pollen, as well as pollen from introduced northern hemisphere trees (Haberle et al 2014)] in both pollen season were highest around 11th October in 2010 (>1000 grains/m3) and 14th October in 2011 (>2000 grains/m3) (S2 Figure 2). Weed pollen (S3 Figure 3) recorded its highest counts both around 12th October (100 grains/m3) and 24th November (80-100 grains/m3) 2010. Cladosporium counts were highest around 15th October 2010 (S5 Figure 5). However, in 2011, Cladosporium median counts were low during the pollen season compared to 2010. Levels of Alternaria conidia were at their highest in Melbourne one day either side of high admission day that occurred on the 25th November 2010 (S4 Figure 4).

In unadjusted conditional logistic regression models, Alternaria (OR=1.04 per conidia/ m3 95%CI 1.03-1.04) and Cladosporium (OR=1.01 spores/m3 95%CI 1.00-1.02) were significantly associated with increased odds of asthma hospital admission during the high asthma period. Whereas grass pollen (OR=1.03 per grain/m3 95%CI 1.01-1.05), weed pollen (OR=1.05 per grain/m3 95%CI 1.03-1.07) and tree pollen (OR=1.00 per grain/m3 95% CI 1.000-1.001) were associated with increased odds at lag 2(Table 3).

In the adjusted analysis, Alternaria (OR=1.01 conidia/m3 95%CI 1.00-1.03) remained associated with asthma admissions during the high asthma period (p value = 0.031). In a fully

adjusted model, weed (OR=1.07 per count/m3 95%CI 1.00-1.01) and tree (OR=1.00 per count/ m3 95%CI 1.00-1.01) was also associated with asthma admissions at lag 2. Adding temperature and relative humidity to the adjusted models resulted in grass at lag 2 falling outside the set significance level (p value<0.09) (Table 3).

When stratified by sex, grass (OR=1.03 per grain/m3 95%CI 1.01-1.05) and weeds (OR=1.05 per grain/m3 95% .99-1.12) at lag 2 were associated with increased odds for boys. Same day Alternaria conidia was associated with increased odds in boys, but not girls in an adjusted model (OR=1.02 spores/m3 95%CI 1.00-1.04, p value=0.00) (Table 4).

DISCUSSION

Peak periods of asthma hospital admissions are a substantial burden on people with asthma and their care givers as they are unexpected. They are also a major burden on the health care system due to an emergency department visit and subsequent hospital admission. Using a method by Silvers et al (2018) that makes chance findings highly unlikely (< 4 in a million) we identified, two high asthma admission days that occurred on 25th November 2010, and 30th October 2011 during the grass pollen seasons. We considered a peak period as 2 days prior and 2 days post these days as evidenced by the autocorrelation plots. Although Silver and colleagues (Silver et al. 2018) found more days using their method during the same pollen periods as described here, they included both children and adults and used admission data from all public hospitals within greater Melbourne region which is a different sample included in our study.

Our findings suggested a 2-day lagged effect of both pollen and spores on child asthma admissions. Fungi, particularly Alternaria conidia (OR=1.017 per count/m3), were primarily implicated even-when adjusted for weather. Same day grass pollen was associated with child asthma hospital admission, but when adjusted for temperature and relative humidity, effects become statistically non-significant at the 0.05 level. However, grass and tree pollen at lag 2 were associated with increased odds of admissions. Boys were more susceptible than girls to grass pollen and Alternaria conidia.

Our findings are the first to suggest the importance of both grass pollen and spores during periods where risk of periods of high asthma admissions may occur. Previously, it was thought that pollen alone was a substantive trigger during the season, but we show here that pollen and fungi both with some lagged effects are associated for the same peak periods in children and adolescents. Although no lighting or thunderstorms occurred on identified high days and in line with previous work (Osborne et al. 2017), we have identified a lag 2-day grass

pollen effect but no same day effect. It is possible that pollen grains may have ruptured due to high relative humidity and although they are respirable, they are escaping detection due to their small size and hence their effects are not observed in the statistical models (Miguel et al. 2006).

Like a previous study (Newson et al. 2000) in the UK, higher airborne levels of fungal spores were also recorded during high asthma admission periods in Melbourne. Air pollution specifically $PM_{2.5}$ did not seem to have an impact on these associations observed during MAPCAH study in Melbourne. The role of fungi in TA events high asthma days have been documented internationally suggesting an association with fungal spores (such as Alternaria conidia, Cladosporium and Didymella species) (Anderson et al. 2001; Pulimood et al. 2007). Similarly, to a study from Canada (Dales et al. 2003), an increase in grass pollen counts could not explain the same day associations with emergency department visits but an increase in fungal spore counts might have been the underlying mechanism.

Children sensitized to aeroallergens may have been primed by extreme counts of daily grass pollen recorded in the beginning of November 2010 as the cumulative daily grass pollen concentrations generally remained high before the peak period. Furthermore, almost all (>75%) the participants admitted during this period were atopic. The lagged two-day effects of both pollen and fungal spores suggest a priming effect on susceptible populations. Repeated exposure of nasal tissues to a particular allergen may result in mucosal sensitivity (de Weger et al. 2011). Although a few studies [1, 2] have considered fungal spores in a limited way, our findings are the first to suggest strong effects of Alternaria conidia and Cladosporium in children and adolescents associated with the peak periods.

Aeroallergens, their timing, distribution, quantity, and potency are severely impacted by weather conditions. They also impact the distribution and severity of allergic disease (Reid and Gamble 2009). The role of high temperatures and humidity during the HAAD period can't be ruled out certainly given their synergistic properties with outdoor aeroallergen exposure. Both of these weather conditions have shown to be significantly associated with Cladosporium spore counts in a study conducted in Denver, Colorado (Katial et al. 1997). Also, indicated in a review (Reid and Gamble 2009) that although temperature and humidity can be strong predictors of mold concentrations, the effect varies by mold species and geography. Likewise, there are several other examples where regional weather patterns, such as increased temperature have led to enhanced pollen production (D'Amato et al. 2007). Further, it is predicted that pollen seasons might be extended globally due to climate change resulting in an increased risk of more frequent epidemic thunderstorm asthma events in the

future (D'Amato et al. 2016). However, in the present study adding meteorological variables did not significantly alter the relationships observed between aeroallergens and incidence of asthma (Héguy et al. 2008).

In our study, during periods where high asthma days occurred, child admissions were more likely to be male and in a younger age group. Consistent with other studies including our own, we found a higher odds of high asthma periods associated with grass pollen and some fungal spores for boys compared to girls (Shrestha et al. 2018).

This study has several strengths. A strength of the study is that additional data were collected from the admitted patients, including allergen sensitization tests and rhinovirus status. Our selection of a case-crossover design was appropriate for analysing time-variable exposures and the bi-directional selection of control periods allowed individual adjustment for seasonal and long-term trends. Although we are limited with the number of high asthma admissions that occur during grass pollen seasons by definition of the 4.0 SD which can be overly restrictive the case-crossover design enabled an increase in sample size as cases act as controls during control periods. This increased the statistical power to detect associations.

Children admitted to hospital for asthma are considered a group with severe asthma, so it is challenging to determine if these children would have been admitted for other reasons even if pollen and Alternaria were not to be found associated. The bidirectional design showed the risk was higher on those days. Of course, that doesn't mean there was zero risk on other days, but it was higher leading up to these days.

In summary, both pollen and fungal spores 2 days prior to a period of high asthma admissions seem to have a priming effect on susceptible children and adolescents that increases the risk of asthma hospital admission. Moreover, same day fungal spores were also associated with increased odds of admission, but grass pollen was not. This lack of association was possibly due to a sudden change in weather conditions resulting in the rupturing of pollen grains and hence went undetected. Studying environmental factors that may increase the risk of these high asthma periods provides better insights to not only predict the peak periods, but also to better prepare the health care system with early warning and mitigating the risk for the child. Public health programs need to increase awareness of ambient Alternaria and not just pollen during peak pollen seasons to ensure readiness of both populations at risk and its service providers.

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Table 1: Participant Characteristics for Pollen Seasons, 2010 and 2011

Year	**2010**			**2011**		
Months	October	November	December	October	November	December
No of admissions	28	79	42	49	40	2
No of participants	22 (78.6%)	64 (81%)	30 (71.4%)	30 (61.22%)	28 (70.00%)	2 (100%)
Sex						
Boys N (%)	13 (61.9%)	45(70.3%)	19(63.3%)	19(63.3%)	20(71.4%)	1(50%)
Girls N (%)	8 (38.1%)	19(26.7%)	11(36.7%)	11(36.7%)	8(28.6%)	1 (50%)
Age						
Mean+SD	5.2+ 2.7	5.8+ 3.4	6.1+ 4.0	5.4+ 3.1	4.6+ 3.1	3.5+ 0.7
Min	2	2	2	2	2	3
Max	12	15	16	15	12	4
Median	5	5	4	5	4	3.5
IQR (Interquartile range)	3	5.5	6	5	4	1
HRV status, N, Yes N (%)	21, 14 (66.7%)	64, 58 (75.00%)	30, 18 (60.00%)	30, 27 (90.00%)	28, 24 (85.71%)	2, 1 (50.00%)
Sensitive to any aeroallergen, N, Yes N (%),	21, 16 (76.19%)	64, 52 (81.25%)	30, 23 (76.67%)	30, 27 (90.00%)	28, 27 (96.43%)	2, 1 (50.00%)
Hay fever diagnosed, N, Yes N (%)	19, 3(15.79%)	43, 12(27.91%)	25, 3(12%)	28, 8(28.57%)	25, 3(12%)	2, 1 (50.00%)
Mother history of asthma, N, Yes N (%)	19, 8(42.11%)	63, 17(26.98%)	30, 6(20%)	28, 9(32.14%)	25, 6(24%)	2, 1 (50.00%)

Table 2: Aeroallergens for Pollen season 2010 & 2011

Aeroallergens and other Factors	Totals for pollen season Median [25percentile, 75th percentile]	2 days before High asthma day	High asthma admission day (25/11/2010)	Totals for pollen season Median [25percentile, 75th percentile]	2 days before High asthma day	High asthma admission day (30/10/2011)
Grass Pollen (grains/m3)	27.5 [7, 68]	112	34	20 [11, 51]	133	20
Tree pollen (grains/m3)	156 [85, 322.5]	614	216	134.5 [75, 246]	741	60
Weed Pollen (grains/m3)	5 [2, 14]	0	20	5 [2, 10]	4	5
Alternaria (counts)	4 [0,18]	70	53	3.5 [1, 9.5]	12	2
Cladosporium (counts)	24 [6.5, 57]	63	39	5.5 [0, 18.5]	74	0
Smuts (counts)	2 [0, 21.5]	1	30	0 [0, 0]	4	0
Max temp (°C)	22.8 [19, 25.5]	32.3	23.5	22.6 [19.95, 27]	26.4	17.4
PM Relative Humidity	45 [39, 57]	29	76	46 [34, 55]	46	72
PM2.5 µg/m3	3.5 [2.45, 5.05]	4.6	2.6	3.5 [2.8, 5.2]	-	-
NO2 ppb	8.15 [6.85, 10.05]	7.3	10.1	8.2 [6.3, 10.3]	7.6	3.5

Table 3: Associations between environmental data and asthma during high asthma periods

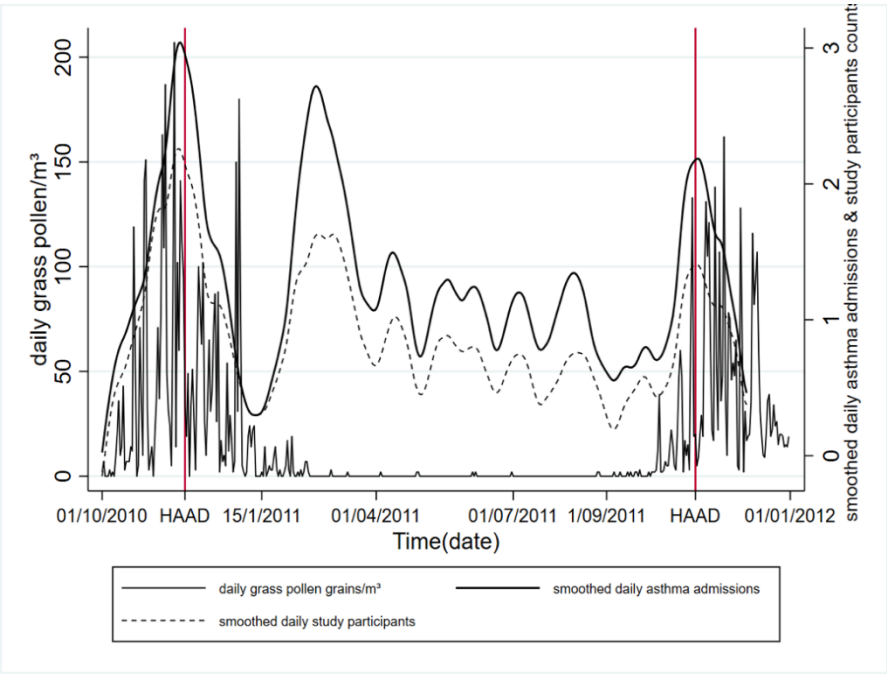
Environmental variables	N = 135 Unadjusted OR (95% CI) p value	N= 135 Adjusted Model OR (95% CI) p value
Grass	0.979 (.962- .996) 0.02	0.999 (.96-1.011) 0.07
Grass lag 2	1.031 (1.012-1.051) 0.00	1.017 (.999-1.035) 0.05
Tree	0.998 (.996-1.000) 0.08	0.995 (.991-.998) 0.01
Tree lag 2	1.000 (1.000-1.001) 0.04	1.000 (1.000-1.001) 0.03
Weed	1.148 (1.046-1.259) 0.00	1.125 (.982-1.289) 0.09
Weed lag 2	1.055 (1.033-1.078) <0.001	1.071 (1.006- 1.140) 0.03
Alternaria	1.040 (1.033-1.048) <0.001	1.017 (1.001-1.033) 0.03
Alternaria lag 2	0.989 (.976-1.003) 0.14	0.992 (.970-1.014) 0.49
Cladosporium	1.015 (1.006-1.025) 0.00	1.004 (.990-1.018) 0.49
Cladosporium lag 2	0.985 (.968-1.002) 0.09	0.984 (.956-1.012) 0.27
Smuts	1.030 (.988-1.073) 0.16	1.032 (.979-1.087) 0.24
Smuts lag 2	1.035 (.995-1.077) 0.08	.957 (.911-1.005) 0.08

In unadjusted models each aeroallergen is adjusted for its respective lagged variable and vice versa. Models are adjusted for Maximum temperature and Relative Humidity.

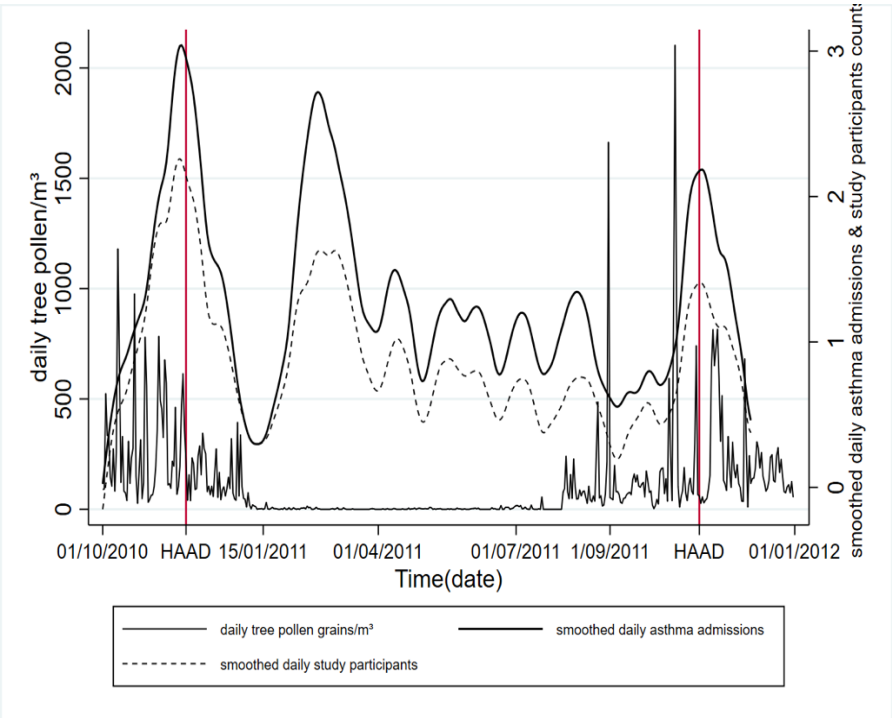
Table 4: Associations between environmental data and asthma during high asthma periods with models stratified by sex

Environmental variables	Boys, N = 93 Unadjusted OR (95% CI) p value	Girls, N=42 Unadjusted OR (95% CI) p value	Boys, N= 93 Adjusted OR (95% CI) p value	Girls, N = 42 Adjusted OR (95% CI) p value
Grass	0.965 (.949-.981) <0.001	0.994 (.973-1.015) 0.60	0.963 (.948-.979) <0.001	0.986 (.969-1.003) 0.11
Grass lag 2	1.050 (1.029-1.071) <0.001	1.015 (.993-1.037) 0.17	1.037 (1.017-1.058) <0.001	0.997 (.968-1.026) 0.86
Tree	0.997 (.994-.999) 0.01	0.999 (.998-1.000) 0.32	0.991 (.987-.996) 0.00	0.999 (.995-1.003) 0.77
Tree lag 2	1.000 (.999-1.001) 0.10	1.000 (.999-1.001) 0.25	1.001 (1.000-1.002) 0.02	1.001 (.999-1.002) 0.06
Weed	1.103 (.978-1.243) 0.10	1.260 (1.096-1.448) 0.00	1.087 (.941-1.255) 0.25	1.554 (1.119-2.158) 0.01
Weed lag 2	1.050 (1.027-1.073) <0.001	1.108 (.964-1.273) 0.14	1.058 (.997-1.122), 0.06	1.405 (1.051-1.877), 0.02
Alternaria	1.041 (1.031-1.051) <0.001	1.040 (1.030-1.050) <0.001	1.024 (1.008-1.040) 0.00	0.967 (.934-1.002) 0.07
Alternaria lag 2	0.989 (.974-1.005) 0.19	0.990 (.963-1.017) 0.47	0.998 (.977-1.021) 0.91	0.948 (.892-1.007) 0.09
Cladosporium	1.013 (1.003-1.023) 0.01	1.019 (.991-1.047) 0.17	1.005 (.992-1.019) 0.37	1.007 (.971-1.043) 0.70
Cladosporium lag 2	0.991 (.973-1.008) 0.31	0.964 (.941-.989) 0.01	0.994 (.970-1.018) 0.64	0.963 (.929-.999) 0.05
Smuts	1.038 (.994-1.084) 0.08	1.011 (.915-1.117) 0.83	1.045 (.986-1.107) 0.13	0.997 (.918-1.084) 0.96
Smuts lag 2	1.033 (.988-1.081) 0.14	1.047 (.952-1.152) 0.33	0.967 (.913-1.025) 0.26	0.955 (.869-1.049) 0.34

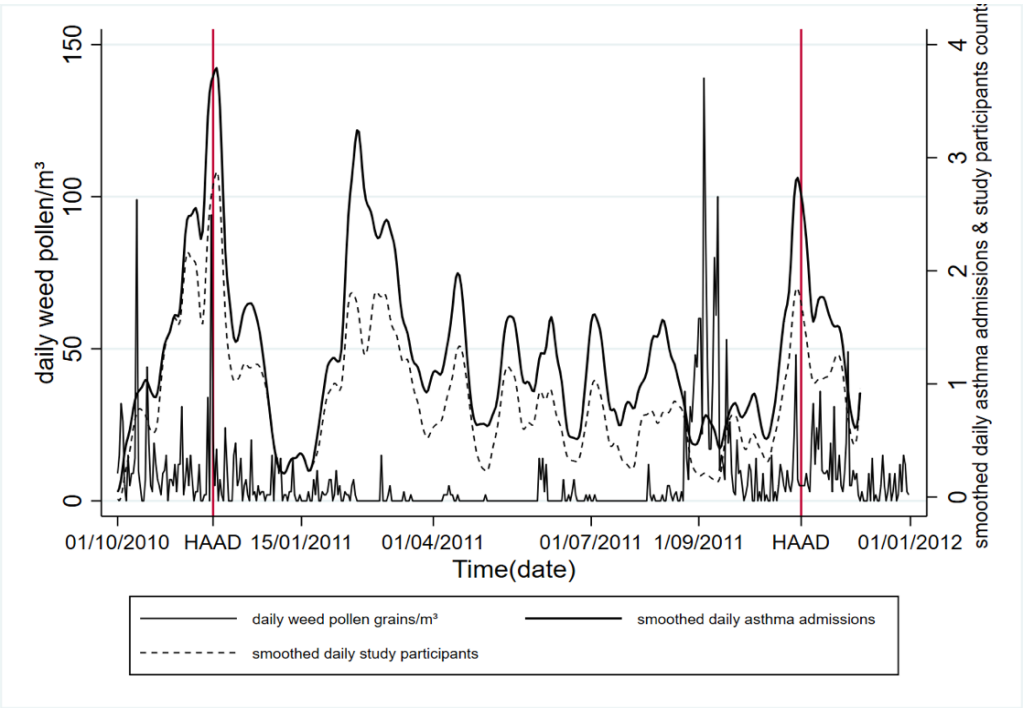
In unadjusted models each aeroallergen is adjusted for their respective lagged variable and vice versa. Models are adjusted for Maximum temperature and Relative Humidity.



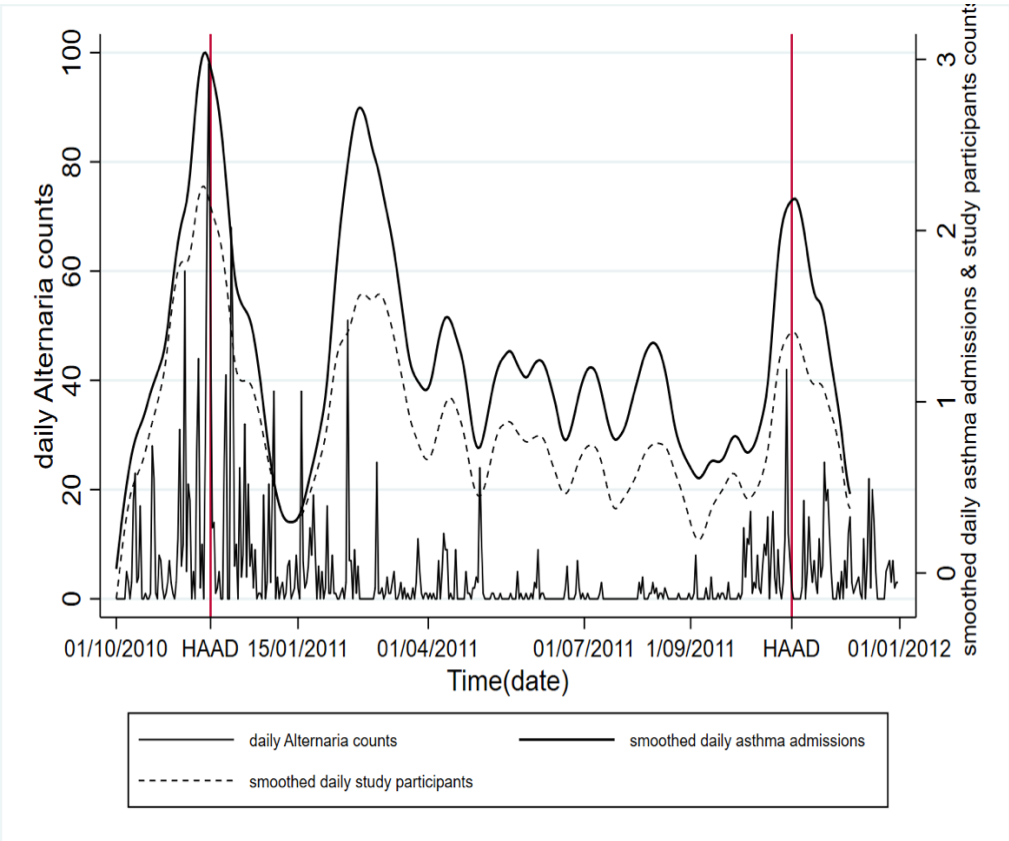
S1 Figure 1. Smoothed daily grass pollen counts and admissions, 2010 & 2011



S2 Figure 2: Smoothed daily tree pollen counts and admissions, 2010 & 2011



S3 Figure 3: Smoothed daily weed pollen counts and admissions, 2010 & 2011



S4 Figure 4: Smoothed daily Alternaria counts and admissions, 2010 & 2011

4. Asthma Hospital Admission and Readmission Spikes, Advancing Accurate Classification to Advance Understanding of Causes

4.1 Introduction

This chapter consists of a peer-reviewed published paper of original research that demonstrates the application of the Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) method, in identifying high asthma admission days (HAADs) and high asthma readmission days (HARDs). It also provides a comparison of this novel method with two existing methods documented in the literature (45, 359).

Previous studies have used various methods to detect HAADs, including smoothing methods (45), and time series statistical models (359). In my previous chapter, the smoothing method (45) was utilised for detecting HAADs. The method (45) involve assessing the magnitude of the residual against a predetermined threshold, typically based on the residual standard deviation. To date, there have been limited methods used to identify HAADs in childhood asthma admissions, and these methods have critical limitations. Therefore, this Chapter introduces the use of the S-H-ESD method (360) to identify HAADs and HARDs among children and adolescents.

4.2 Research Question

How effective is the S-H-ESD method in classifying HAADs and HARDs?

a. How does its performance compare to existing methods?

4.3 Aim

To introduce the S-H-ESD method, an easily applied robust statistical approach to classify HAADs and HARDs and compare it to the existing methods in the literature.

4.4 Ethics approval

The study received approval from the La Trobe University Human Research Ethics Committee (HEC18307).

4.5 Contribution to knowledge

In this paper a statistical method is demonstrated that I believe will assist in advancing research regarding days of unusually high asthma hospital admissions. To help understand factors that contribute to this phenomenon, an important component of respiratory critical

care, it is obviously important to accurately classify the days on which it may have occurred. As daily asthma admission is a time series, this is not a trivial exercise due to the confounding by seasonality and time trend. Several methods have been previously applied but have critical limitations and together may create inconsistencies in this area due to differences in definition. Furthermore, these methods have been formulated on an ad-hoc basis and are not within the evidential framework of statistical testing. The method I demonstrate is not difficult to apply and has the potential to systematise work in this area, which can enhance the synthesis of HAADs and thus add to its evidence base.

4.6 Publication

A pre-print of this manuscript and supplementary data (X Supplement), as originally submitted, are included in this document.

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Asthma hospital admission and readmission spikes, advancing accurate classification to advance understanding of causes.

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Conflicts of interest

The authors declare there are no conflicts of interest.

Authorship statement

Mehak Batra, Don Vicendese, and Bircan Erbas conceived and designed the study. Mehak Batra analysed the data under the guidance of Don Vicendese and Bircan Erbas. Mehak Batra prepared the manuscript under Bircan Erbas supervision. All authors did review and editing and finalising the manuscript.

ABSTRACT

Background: An important component of asthma care is understanding potential causes of high asthma admissions (HAADs) or readmissions (HARDs) with potential of risk mitigation. Crucial to this research is accurately distinguishing these events from background seasonal changes and time trends. To date, classification methods have been based on ad hoc and un-tested definitions which may hamper understanding causes of HAADs and HARDs due to misclassification. The aim of this article is to introduce an easily applied robust statistical approach, with high classification accuracy in other settings - the Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) method.

Methods: We demonstrate S-H-ESD on a time series between 1996 to 2009 of all daily paediatric asthma hospital admissions in Victoria, Australia.

Results: S-H-ESD clearly identified HAADs and HARDs without applying ad-hoc classification definitions, while appropriately accounting for seasonality and time trend. Importantly, it was done with statistical testing, providing evidence in support of their identification.

Conclusion: S-H-ESD is useful and statistically appropriate for accurate classification of HAADs and HARDS. It obviates ad-hoc approaches and presents as a means of systemizing their accurate classification and detection. This will strengthen synthesis and efficacy of research toward understanding causes of HAADs and HARDs for their risk mitigation.

INTRODUCTION

Prevalence of asthma exacerbation emergency department (ED) visits and then subsequent admission is still high among children and adolescents [1] and they create a substantial burden for children, their families, and the hospital system. Particularly, the increase in early readmission within 28 days [2], is dependent on factors that we are yet to identify fully. Environmental factors have been implicated with paediatric asthma ad-missions. Seasonality is an important marker of total environmental load or triggers, such as high pollen exposure and respiratory virus infections, which are associated with asthma hospital admissions [2-5].

Methodologically, in identifying high asthma admissions days (HAADs), we are undertaking the non-trivial task of detecting anomalous points in time series which are subject to seasonality, time trends and random variation. Accurate detection is important otherwise misclassification will distort any data signals regarding possible environmental or prognostic factors. With accuracy, methodological consistency is also required so as to be able to evaluate and synthesize evidence from different studies regarding HAADs and high asthma readmissions days (HARDs) in order to provide a stronger evidence base. Accuracy and consistency in identifying HAADs and HARDs increase the potential of detecting associated risk factors whose modification may lead to an attenuation of spikes in child asthma hospital admissions and the subsequent burden on the health system.

Anomalousness is based on the notion of occurrences that are unusual, unexpected, or, in statistical terms, extremal or outliers. That is, an unusually high spike in daily admissions time series. These terms capture anomalies on a global scale and inherent in them are ideas of distributional location and dispersion which informs the methods that have been employed to identify HAADs to date. Two studies applied a smoothing method to calculate a moving average, then used the magnitude of the residual (the difference between the average and the actual observed daily count) to determine if that day met the criterion of an HAAD. The criterion was relative to the residual standard deviation (SD) and if the residual was greater than a certain number of SDs, then that day was classified as an HAAD. One study applied a Fourier transform filter, as a way of determining the seasonally changing average and used an a priori chosen threshold of 1.96 SD [6], an a priori global (one size fits all) criterion. The second calculated a rolling average and SD based on a 25% trimmed mean, that is, only the middle 50% of the data were used, and applied a threshold of 4.5 SD that was chosen by inspecting residual quantile quantile (qq) plots to detect a critical departure point of the large residuals from the preceding ones [7]. The second method that has been employed in past

studies was model based, where a time series statistical model was applied to the data and, similarly to the previous method, the magnitude of the residual from the model predicted mean was assessed against the priori chosen threshold of 4 SDs from the mean [8]. As far as we can tell, these are the only methods that have been used for asthma admissions.

These approaches have some important limitations. The mean and SD are strongly affected by outliers. This is especially so for the SD due to its definition based on the squared distance from the mean. Hence, any definitions based on a mean and SD will tend to mask outliers when outliers are used in their calculation. Using a trimmed mean is a well-known method for reducing the effect of outliers in the calculation of the mean [9], however, excluding 50% of the data runs the risk of over smoothing, drastically restricting access to information in the data and therefore limiting sensitivity to account for sea-sonality and time trend in a time series. Furthermore, the use of 1.96, 4 or 4.5 SDs is not based on any validation testing to understand the impact of these definitions on sensitivity or positive predictive value in classifying HAADs. In addition, these methods do not include any formal statistical testing in regard to their classification of HAADs. They are based on the untested assertions that there are an unknown number of outliers, and they exist beyond a certain number of SDs from a sample or model predicted mean.

Anomalousness can also carry the idea of unusual or unexpected on a local scale. A high number of daily admissions for a particular time of the year may not be considered high in another, that is, it is important to account appropriately for seasonality. Similarly, a high day in one year may not be considered high in another and therefore it is also important to account for time trend. It has been shown that moving average techniques tend to filter out seasonal anomalies [10]. A time series statistical model with appropriate specification can adjust for seasonality and time trend. Time trend can be modelled both long term and short term, for example day of the week effects on hospital usage [11]. The limitation with model-based methods is that we are faced with model assumptions, choice, specification, and importantly, model capacity for capturing data trends. For example, in the model-based method discussed above, a log linear auto regressive statistical model was employed that accounted for seasonality and long-term time trend [8] but choices had to be made regarding log transformation and linear or non-linear specification for ex-ample. More importantly, this study made a choice of using 4 SDs as a threshold to classify HAADs. It may be asked, why not use 4.5 or 3.5? These values have not been tested regarding their sensitivity or specificity to detect HAADs.

There is a new method, published in 2017, that overcomes the critical limitations of current methods. It is termed the Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) method [10]. Validation testing of this method has shown it to be sensitive in detecting anomalous data observations both on a global and local scale, is model free and it incorporates statistical testing. Validation has shown it to have a sensitivity of about 96% and a positive predictive value (PPV) of 100% when it was applied with a statistically significant level of 0.05 in the setting of detecting anomalies in cloud infrastructure data [10]. Machine learning (ML) is in demand and has been widely used in respiratory studies, for example, COVID-19 [12,13] and COPD [14]. However, the method we put forward is straight forward to apply, does not require intensive resources and is easily understood and can be interpreted. Furthermore, our demonstrated method comes with robust statistical testing [15].

In this study, we demonstrate the use of S-H-ESD method, a novel approach, in the important task of detecting HAADs and HARDs. We also compare it to the methods mentioned above [7, 8].

MATERIALS AND METHODS

Design/Setting

We used all Victorian private and public hospitals data obtained from the Victorian Admitted Episodes Data set (VAED) and extracted daily counts of all hospital admissions for asthma from July 1st 1996 to June 30th 2009, 13 years or 4,748 days in total. Victoria is a state in Southeastern Australia. Only children (2-18 years) with primary admissions having with a principal diagnosis of asthma [ICD-9 codes (493) up to 1998 and ICD-10 codes (J45 or J46)] were included in the study. Readmissions were defined as a subsequent admission within 28 days of the index admission discharge [11]. The time series contained 53,156 admissions including 2,401 re-admissions [2].

The study was commenced after obtaining the ethics approval from La Trobe University Human Research Ethics Committee (HEC18307).

Statistical Method

We define robust in the usual statistical sense as being resistant to outliers in the calculation of location and spread.

We briefly describe the new method but supply more details in the supplement (See S1 Statistical Method - Details). The S-H-ESD method relies on robust measures of location and dispersion via the median and scaled median absolute deviation (MAD). Firstly, the time

series is decomposed into its trend and seasonal components using locally estimated scatterplot smoothing (STL) with an added weighting scheme to make it more robust and the residuals (the remainder) are extracted [16]. The residuals are passed to the Rosner Extreme Studentized Test (ESD) [17]. The ESD uses a statistical test based on the null hypothesis that there are no outliers against the alternative that there are up to k outliers, where k is chosen by the user. The level of statistical significance can be chosen as re-quired and is subject to Bonferroni correction based on the number of detected outliers. The test iterates through the data, removing the found anomaly for the next iteration. Choice of k can be adjusted until beyond which, no further outliers are detected and hence it is an exhaustive method. The ESD was initially formulated using the sample mean and SD and requires approximate normality as it refers to a t-distribution. Within S-H-ESD, the sample mean, and SD are replaced by the median and scaled MAD, robust measures of location and dispersion respectively [18, 19], and robustness is augmented by the use of a robust weighting scheme for extracting the residuals from the time series. This decom-position facilitates S.H.ESD to detect global and local anomalies and ensures that the re-siduals have a unimodal distribution which makes the choice of the ESD appropriate [10]. For further details regarding the metrics to evaluate this method, please refer to S1 Sta-tistical Method – Details.

We compare S-H-ESD to two other methods previously used for identifying days of unusually high asthma admissions.

1. Similarly, to the model-based approach by Newson et al. [8], we used a semi parametric general additive model (GAM) [20] to model mean asthma admission and readmission daily counts, adjusting for seasonality, time trend and day of week effect as done previously with these VAED data [11]. In line with Newson et al., we used the a priori definition of a residual being 4 SD from the model predicted mean as a threshold to identify HAADs and HARDs. We refer to this method as M.4SD, where M signifies model based.

2. We follow the example of Silvers et al. [7] and use a rolling 25% trimmed mean and SD then choose a threshold based on the inspection of residual qq plots. We refer to this method as TMQQ (trimmed mean qq plot).

We compare if the identified HAADs and HARDs are reasonable according to what may be expected from what is known about the seasonality and time trends of asthma admissions and readmissions in Victoria from our past research [2,11]. For time trend, we compare the number of HAADs and HARDs to pre and post 2002 as child asthma hospital readmissions reduced from 1997 to 2002 but showed an increasing trend to 2009 and

admissions reduced and then flattened out from about 2002. It would not be expected that HAADs and HARDs follow seasonality and time trends completely, by definition they are anomalous, but it would be expected that their likelihood would increase when more admissions occur, and it is well known that there is a strong seasonal aspect to child asthma hospital admissions. We present tables for the seasonality and time trend results. We also make comparisons of the days selected as HAADs and HARDs by the three methods in context of the time series themselves, for which we present graphical evidence. Our comparisons are basically descriptive although we did conduct some simulations, see File S2 in the Supplement. The S.H.ESD has already been subject to comprehensive validation testing for its application to cloud computing and we wish to compare methods used for the study of asthma hospital admissions as a way of alerting the asthma research community to this method. The methods were implemented with freeware R [21]. S.H.ESD was implemented via the AnomalyDetection library [22] and a statistical significance level of $p < 0.05$ was nominated in classifying HAADs and HARDs. The R libraries mgcv [23], ggplot2 [24] and stlplus [25] were used for the GAM model, graph plotting and time series decomposition, respectively. We also supply an R computer script for this method, see Supplement File S3.

RESULTS

Daily admission counts ranged between 0 and 51 (mean 11.3, SD 6.0). Daily readmission counts ranged between 0 and 5 (mean 0.5, SD 0.7) and only 15 (0.3%) and 2 (0.04%) days had daily readmissions of 4 and 5, respectively. See Figures S1 and S2 in the Supplement where we demonstrate STL decomposition [16] and which show the admissions and readmissions time series and their three components of time trend, seasonal fluctuation and the remainder (residuals). The seasonal and trend components have noticeable effects on both time series. As expected from our previous research, they show that the long-term time trend had been a decrease in admissions to about 2002 followed by a largely flat period but with a little oscillation and that readmissions also decreased to 2002 but was followed by an increasing trend to study period end [2,11].

In applying TMQQ, we found that the qq plots indicated thresholds of 10.2 and 7.5 SDs to identify HAADs and HARDs, respectively. The results of applying the three methods of S.H.ESD, M.4SD and TMQQ to all daily admissions and readmissions are displayed in Table 1 by month of occurrence to display their seasonality and Table 2 to describe time trends relative to pre and post 2002.

High Asthma Admission Days (HAADs)

S-H-ESD

17 days (0.4%) were classified as HAADs ($p < 0.05$) and they had between 33 and 51 daily admissions, see Figure 1. The most frequent month of occurrence was February (summer end and return to school) with 10 (59%), followed by May (autumn end) with 3 (18%). November (mid pollen season) had two HAADS. These months are consistent with seasonal peaks in child asthma admissions as shown from our previous research [2, 11]. Seven of the months, did not register any HAADs. This method detected more HAADs pre 2002 compared to post 2002 which reflects the long-term time trend in the data.

TMQQ

23 days (0.5%) were classified as HAADs and they had between 14 and 51 daily admissions, see Figure 1. The most frequent month of occurrence was February (summer end and return to school) with 20 (87%) followed by April, May and November with 1 (4%) each. These months are consistent with seasonal peaks in child asthma admissions. The remaining eight months did not have any days classified as HAADs. This method de-tected many less HAADs pre 2002 compared to post 2002, 26% compared to 74% re-spectively, which is not consistent with the long-term time trend in the data.

M.4SD

Seven days (0.2%) were classified as HAADs and they had between 28 and 51 daily admissions, see Figure 1. Four (57%) of the HAADs occurred in November (mid pollen season) followed by February (summer end) and March (autumn start) with 2 (29%) and 1 14%) respectively. Although they are small numbers, this distributional spread does not seem consistent with child asthma hospital admission in Victoria as a greater percentage is expected in autumn compared to spring [2]. Pre and post 2002 comparisons were consistent with known time trends.

High Asthma Readmission Days (HARDs)

S-H-ESD

In applying this method, we found that it failed for the detection of HARDs in our data set. It classified 39.4% of the readmissions as anomalous, many of which were daily counts of 1 or 2, a spurious result given the meaning of outlier. This was mainly due to the child asthma hospital readmission time series being a low count series with a range of 0-5, that is, highly discrete and was dominated by zero (60th percentile). If more than 50% of values are the same, then the MAD will equal zero and the method breaks down. We overcame this problem by adding smoothness using random noise from a uniform distribution between, but

not including, -0.5 and 0.5. Our simulation testing was based on the addition of smoothness. See Supplementary S2 for more details.

After the addition of smoothness, there were 25 days (0.5%) classified as HARDs ($p<0.05$) and they ranged between 3 and 5 daily readmissions, see Figure 2. All of the days with 4 and 5 readmissions (highest) and 8 of the days with 3 readmissions were classified as HARDs. The most frequent month of occurrence was August (winter end) with 7 (28%) followed by June (winter start) 6 (24%). These months are consistent with seasonal peaks in child asthma readmissions. All summer months and July (mid-winter) did not have any HARDs. More HARDS occurred post compared to pre 2002 which is consistent with long term time trend.

TMQQ

23 days (0.5) were classified as HARDs and they ranged between 2 and 5 daily re-admissions, see Figure 2. Only one of the two days with 5 readmissions and three of the 15 days with 4 readmissions were classified as HARDs. The months of most frequent occurrence were February (summer end and return to school), March and October (pollen season start) with 5 each (23%). February and October are not consistent with child asthma hospital readmission peaks in these data [11]. One HARD was classified for January when readmissions are historically very low. More HARDs were classified post 2002 but the difference compared to pre 2002 was close to an even split, 10 compared to 12, much less than the other two methods. This led us to consider this result not consistent with long term time trend.

M.4SD

18 days (0.4%) were classified as HARDs, and they ranged between 3 and 5 daily readmissions, see Figure 2. This method classified all the days with 4 or 5 readmissions and one of the days with three as a HARD. The most frequent month of occurrence was June (winter start) followed by March (autumn start) with 5 occurrences. These months are consistent with seasonal peaks in child asthma readmissions. Pre and post 2002 com-parisons were consistent with time trend.

These comparisons of results are summarized in Table

DISCUSSION

In this study we demonstrated the S-H-ESD method, an alternative robust technique to detect HAADs and HARDs and compared it to two previously used methods used for asthma admissions. We found more HAADs and HARDs after 2002, which possibly was due to instability in the admissions time series post 2002. That is, despite an overall lower number

of admissions compared to pre-2002, a higher number of anomalous days were identified. We showed how to extend S.H.ESD in the situation where the MAD equals zero. There were clear differences between the results obtained from the three methods. For HAADs, Figure 1 indicates that S.H.ESD classified the days that would be expected to be classified as HAADs indicating good sensitivity or low false negatives and had not classified days that would be expected not to be classified as HAADs (good PPV or low false positives). Whereas the TMQQ and M.4SD methods both missed some obviously high days (false negatives) and TMQQ classified many lower days, as low as 14 admis-sions, as HAADs (false positives). In the context of seasonality and time trend, comparing to other days close by, these low days classified by TMQQ could not be reasonably de-fended as HAADs as the mean admission count was 11.2. M.4SD did not seem to be prone to false positives as it mainly classified days with higher counts, 30 or above, but did classify two days with counts of 28 and 29 which are on the edge of credibility considering the many more days with higher counts. However, in context of the much lower counts in nearby days, these two days may be defensible. M.4SD had the lowest classification rate for HAADs, about half or less than the other two methods. It did not classify many of the high days that would be expected to be classified indicating a lower sensitivity (false negatives). From figure 1, it is interesting to note that there is little corroboration between the three methods. Of the 38 distinct days that were classified as HAADs by the three methods, only 3 days were chosen by all 3 methods and 3 days by two methods. S.H.ESD figured in all those corroborations indicating it likely had greater sensitivity than the other two methods.

For HARDs, Figure 2 indicates that S.H.ESD and M.4SD performed equally well. They both chose all the very high days of 4 or 5 readmissions and a few of the days with 3 readmissions but on which they corroborated on one of them only. In contrast, TMQQ classified only one of the two days with 5 readmissions and only 3 of the 15 days with 4 readmissions indicating a low sensitivity, or propensity for false negatives. TMQQ also chose 11 days with only two readmissions, which in context of this very low-count time series would be difficult to defend and indicated low PPV, a propensity for false positives.

TMQQ's difficulty with both the admission and readmission time series was likely due to a combination of its two main features. Its strong filtering mechanism of using only the middle 50% of the data to calculate a SD (moving) would have the effect of decreasing its magnitude because of reduced data variation. This increases the likelihood of false positives because distances from the mean would seem relatively larger in units of a smaller SD. It has also been shown that use of a moving average tends to hide seasonal anomalies and hence may

make TMQQ prone to false negatives [10]. TMQQ also has the limitation of an ad hoc choice of trimming width. It may be asked why choose 25%, why not 15%? It is not clear, what affect this might have on model sensitivity or PPV. We also found that choice of threshold criterion when assessing the residual qq plot could be subjective and difficult. It was not completely clear where to locate a critical departure point of the large residuals from the preceding ones [7].

M.4SD seemed to perform well with HARDs. This was likely due to the selection of 4 SD as the threshold criterion which happened to work well with the model we had chosen. The GAM we used was chosen because we understood its good performance in past research with these low count time series data [11]. However, this combination did not prove as serendipitous in the classification of HAADs as M.4SD seemed to be hampered by both false positives and false negatives. The limitation of M.4SD hinges on the need for model development, with all the choices that go with it, to account for data variation in order to make accurate predictions. After which, a choice of criterion for the number of SDs needs to be made in the presence of uncertainty about the effect on classification sensitivity and PPV.

In contrast, S.H.ESD was consistent in identifying HAADs and HARDs. From graphical evidence, it classified days as HAADs or HARDs that would be expected to be classified and did not classify days that would be expected not to be classified. The sea-sonality and time trends of the classified HAADs and HARDs, as best could be assessed with small numbers, also corresponded to the seasonality and time trends of the un-derlying asthma admissions and readmissions. The S.H.ESD method was able to classify HAADs and HARDs without imposing an a priori or ad-hoc definition of a high day as used by M.4SD or a data driven definition as done with TMQQ. In contrast to both TMQQ and M.4SD, S-H-ESD provided statistical evidence for the identification of HAADs and HARDs which the two other methods do not provide. S.H.ESD was easy to im-plement, as can be seen from the provided R computer code- see Supplement S3. The adding of smoothness, if required, is also straight forward to implement.

Although it worked well with our data, The developers of S.H.ESD felt its capacity to capture long term trend needed to be developed further [10]. This is important to minimise false positives and is the subject of further research. In saying that, it would be useful to test and validate our method in data sets from many different countries as S.H.ESD has the potential to standardise and synthesize similar research globally.

S.H.ESD presents as a suitable method to accurately identify HAADs and HARDs which would support research on these phenomena by reducing misclassification error due to false positives and false negatives. This is a crucial consideration for understanding the causes of HAADs and HARDs. If we seek to understand factors that are associated with high admission or readmission days, we must be as accurate as possible to identify them or we risk distorting any signal in the data because of misclassification. The application of different ad-hoc definitions for HAADs by different studies, makes comparison of study results difficult. Because of this, synthesis of study results in order to promote under-standing of causes of HAADs and HARDs is hindered. Because the S-H-ESD method works identically in any data set without any ad-hoc or a priori definitions for a HAAD or HARD, this source of heterogeneity between different studies would be removed which would also raise the potential of promoting their synthesis.

This study has the strength of using a comprehensive data set of two time series of 13 years in length with which to compare the three methods. The limitation of our study is that the basis of the comparisons was graphical and descriptive and was not based on simulated data sets with known outcomes. However, the S.H.ESD method has been in-ternally validated previously and shown to have a sensitivity and PPV of 96% and 100% respectively at the 0.05 level of statistical evidence [10]. The other two methods have never been tested in this way. Nevertheless, the aim of this article was to demonstrate the method, not to validate it.

CONCLUSIONS

The Seasonal Hybrid Extreme Studentized Deviate (S.H.ESD) method is easy to use and seems accurate in the identification of high asthma admission and readmission days. In contrast to other methods, S.H.ESD supplies appropriate statistical evidence for the identification of high admission days. Although we demonstrated the method on a paediatric asthma hospital admission data set, it can be applied also to adult asthma admissions or other time series in general.

S.H.ESD obviates the need for a priori classification criteria or ad hoc modelling and so promotes consistency and accuracy of research. It also presents as a means of sys-temizing the identification of days of high child asthma hospital admissions and read-missions. Consequently, this may have the benefit of opening up the potential of syn-thesizing research in this area from many groups across the globe. However, further study is required to corroborate the effectiveness of S.H.ESD for the accurate identification of days of high child asthma hospital admissions and readmissions.

Table 1. Number of days classified as high asthma admission (HAADs) and high asthma readmission (HARDs) daily counts with the three reviewed methods by month of occurrence over the 13 years of the study period

Month*	HAAD			HARD		
	S.H.ESD†	TMQQ‡	M.4SD⁋	S.H.ESD†	TMQQ‡	M.4SD⁋
December	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
January	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	1 (5.6%)
February	10 (59%)	20 (87%)	2 (29%)	0 (0%)	5 (22.7%)	0 (0%)
March	1 (6%)	0 (0%)	1 (14%)	5 (20%)	5 (22.7%)	5 (27.8%)
April	0 (0%)	1 (4%)	0 (0%)	1 (4%)	1 (4.5%)	1 (5.6%)
May	3 (18%)	1 (4%)	0 (0%)	2 (8%)	1 (4.5%)	1 (5.6%)
June	1 (6%)	0 (0%)	0 (0%)	6 (24%)	2 (9.1%)	6 (33.3%)
July	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)
August	0 (0%)	0 (0%)	0 (0%)	7 (28%)	1 (4.5%)	2 (11.1%)
September	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)	2 (11.1%)
October	0 (0%)	0 (0%)	0 (0%)	1 (4%)	5 (22.7%)	0 (0%)
November	2 (12%)	1 (4%)	4 (57%)	1 (4%)	0 (0%)	0 (0%)
Total	17 (101%)	23 (99%)	7 (100%)	25 (100%)	22 (99.7%)	18 (100.1%)
Total as % of 4,748 Days	0.4%	0.5%	0.2%	0.5%	0.5%	0.4%

* December is the start of summer. Pollen season starts October through to December. † Seasonal Hybrid Extreme Studentized Deviate test (see methods section). ‡ Using the method of a 25% trimmed mean (middle 50% of the data) and quantile quantile plots to choose the number of SD a positive residual is from the mean to define an unusually high count [7]. ⁋ 4 standard deviations for a model positive residual to be from the predicted mean as a priori definition of an unusually high count.

Table 2. Number of days classified as HAAD or HARD comparing study years pre and post 2002

Year	HAAD			HARD		
	S.H.ESD	TMQQ	M.4SD	S.H.ESD	TMQQ	M.4SD
<= 2002	10 (59%)	6 (26%)	5 (71%)	9 (36%)	10 (45%)	6 (33%)
> 2002	7 (41%)	17 (74%)	2 (29%)	16 (64%)	12 (55%)	12 (67%)
Total	17 (100%)	23 (100%)	7 (100%)	25 (100%)	22 (100%)	18 (100%)

In applying TMQQ, we found that the qq plots indicated thresholds of 10.2 and 7.5 SDs to identify HAADs and HARDs respectively. The results of applying the three methods of S.H.ESD, M.4SD and TMQQ to all daily admissions and readmissions are displayed in Table 1 by month of occurrence to display their seasonality and Table 2 to describe time trends relative to pre and post 2002.

Table 3. Summary of method consistency with seasonality, time trend and size of HAADs and HARDs

Year	HAAD			HARD		
	S.H.ESD	TMQQ	M.4SD	S.H.ESD	TMQQ	M.4SD
Seasonality	Yes	Yes	No	Yes	No	Yes
Time trend	Yes	No	Yes	Yes	No	Yes
Size	Yes	No	Yes	Yes	No	Yes

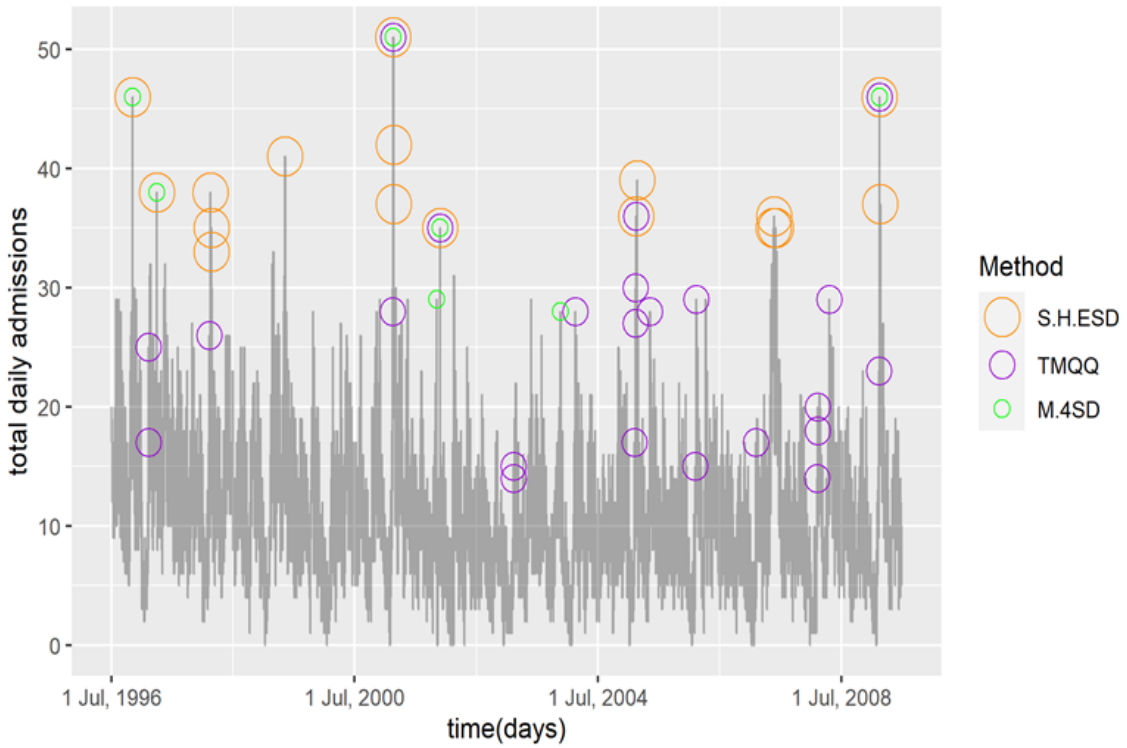

Figure 1. Time series of daily child asthma hospital admissions in Victoria with HAADs classified by the three compared methods

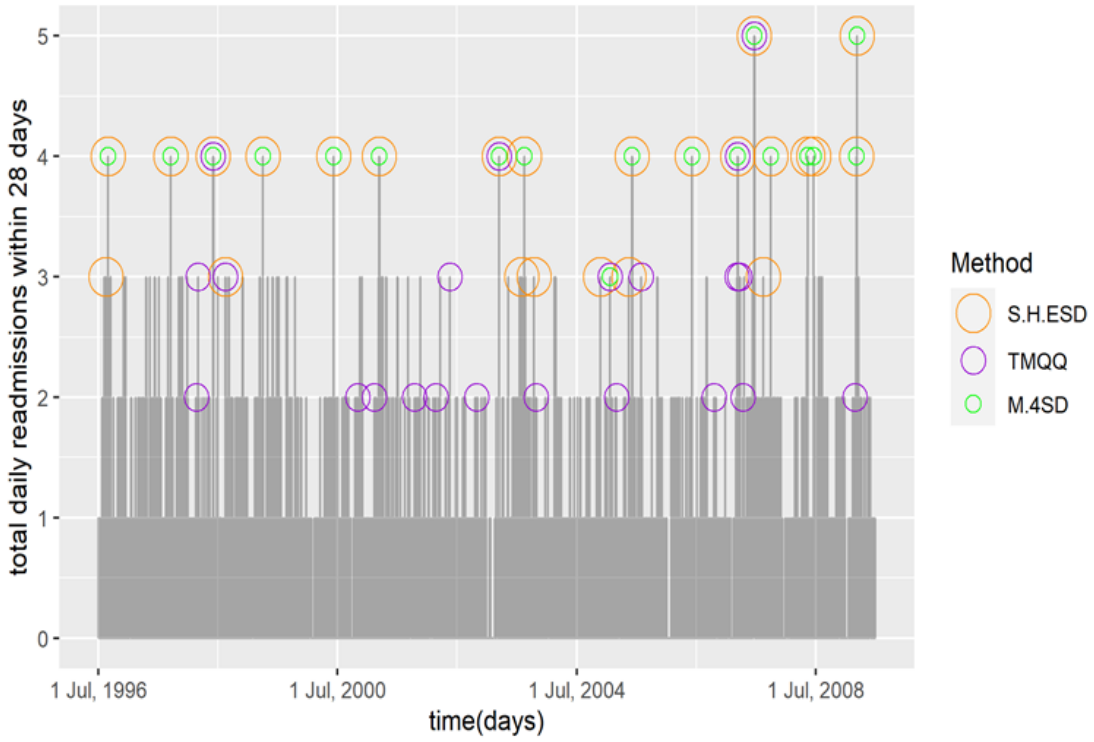

Figure 2. Time series of daily child asthma hospital readmissions within 28 days in Victoria with HARDs classified by the three compared methods

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X Supplement

S1: Statistical Method - Details

We define robust as being resistant to outliers in the calculation of location and spread. We outline the algorithm used for the S-H-ESD method but detail, including extensive test results, is provided here [1]. This method

1. Uses a robust method for time series decomposition based on Locally Weighted Scatterplot Smoothing (LOESS) [2] to extract the seasonal component and is referred to as Seasonal and Trend decomposition using LOESS (STL) [3]. STL is made more robust by including a further weighting scheme [1]. See Figures S1 and S2.

2. In developing S-H-ESD, it was found that PPV was improved by extracting the median of the time series in the place of the time trend [1].

3. After extracting the seasonal component and median, the residuals are passed to the Rosner Extreme Studentized Test (ESD) [4]. The ESD uses a statistical test based on the null hypothesis that there are no outliers against the alternative that there are up to k outliers, where k is chosen by the user. The level of significance for the test is controlled by a Bonferroni adjustment dependent on k. The test iterates through the data, removing the found anomaly for the next iteration. K can be adjusted until beyond which no further outliers are detected and hence it is an exhaustive method. Statistical significance levels can be chosen as required.

4. The ESD was initially formulated using the mean and standard deviation but within the S-H-ESD approach, they are replaced by the median and median absolute deviation (MAD), robust measures of location and dispersion respectively [5]. Furthermore, as the ESD was originally conceived as a test for outliers of a distribution that was approximately normal [4], the MAD is scaled by the 75th percentile of a standardized normal distribution, 1.4826, as a more robust estimate of dispersion irrespective of non-normality of the residuals [6].

S2: Adapting the method for high asthma readmissions days (HARDs)

In applying this method, we found that it failed for the detection of HARDs in our data set. It detected that 39.4% of the readmissions were anomalous, a completely untenable result. The readmissions time series is an example of a low count time series. It had a range of 0 to 5 and the 60th, 75th and 95th percentiles were 0,1 & 2 respectively. More details are

provided here [7]. Failure was due to a combination of the highly discrete nature of the time series due to its small range which was further dominated by zero. These factors combined to force over 98% of the time series residuals to be positive which gave the untenable result that 39.4% of the data were outliers, that is, basically all the non-zero readmission days.

To overcome this problem, we added random noise (jittered) from a uniform distribution between but not including -0.5 and 0.5 [U (-0.5, 0.5)]. Asymptotically, this has no effect on distribution on the mean of the readmissions time series 0.051, as the mean of two random variables is the sum of their means and the mean of a uniformly distributed variable between -0.5 and 0.5 is zero. The variance of the readmissions time series increases by the variance of U (-0.5, 0.5) which equals $^1/_{12}$, approximately equal to 0.083. The new variance is the sum of the variance of the non-jittered time series and $^1/_{12}$. It can be shown algebraically that this plays out to increase the standard deviation of the original time series relatively by approximately 5.5%. This was corroborated by simulation experiments (10,000) which indicated that from a SD of .74, the jittered readmissions time series has a SD of 0.792 ± 0.004. The simulation experiments also indicated that the median for the jittered data would be expected to be about 0.31 ± 0.01 and the MAD 0.72 ± 0.01. We considered this median a suitable measure of location for the readmission time series as the mean of 0.51 in the unsmoothed data was pulled a little to the right due to 90% of its distribution being either 0 or 1, 9.5% was 2 or 3 and 17 observations (< 0.05%) had values of 4 or 5. The MAD for the jittered data closely emulated the SD of the non-jittered readmissions indicating that, as a measure of spread, it was little affected by the jittering. As the S.H.ESD uses the median and MAD, this indicates the robustness of this method to accurately capture location and spread and that adding smoothness did not negatively impact it.

The methods were implemented with freeware R [8]. S.H.ESD was implemented via the AnomalyDetection library [9] and a statistical significance level of p = 0.05 was nominated in classifying HAADs and HARDs. The R libraries ggplot [10] and stlplus [11] were used for graph plotting and times series decomposition respectively.

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5. Grass pollen exposure is associated with higher readmission rates for paediatric asthma

5.1 Introduction

This Chapter consists of a peer-reviewed published paper of original research that examine the association between grass pollen and childhood asthma readmission within 28 days. The paper also assesses effect modification by age and sex of the participants.

A significant proportion of available paediatric health-care resources is used by childhood asthma-related readmissions, turning them into a major challenge for primary healthcare expenditure in the public health system (92). Many studies (361-363), including my research (Chapter 3), have been undertaken to understand the factors that trigger asthma exacerbations requiring admissions. Only a handful of studies (364) have explored the risk factors of asthma readmission rates. Furthermore, very few studies (324, 365) have investigated the impact of outdoor environment risk factors, mainly air pollutants associated with asthma readmission rates. No study has been undertaken to estimate the impact of outdoor aeroallergens such as grass pollen and fungal spores on readmission rates. Therefore, the purpose of this study is to evaluate the effect of grass pollen on childhood asthma readmissions. Due to insufficient data, however, the study was unable to examine the impact of fungal spores.

5.2 Research Question

What is the role of pollen on readmissions (within 28 days) in children and adolescents?

a. Are these associations modified by age and sex of the participants?

b. Are there lag effects?

5.3 Aim

To examine the association between grass pollen and paediatric asthma readmissions within 28 days.

5.4 Ethics approval

The study was granted ethical approval from both the La Trobe University Human Research Ethics Committee and the Victoria State Government Department of Health.

5.5 Contribution to knowledge

The findings of my study provide new insights into the risk factors associated with childhood asthma readmissions. Specifically, the study highlights the role of outdoor aeroallergens such as grass pollen in increasing the likelihood of preventable early childhood asthma readmissions. By identifying this risk factor, the study adds to the existing body of knowledge on the environmental factors that contribute to childhood asthma exacerbations. Moreover, the finding that younger children with severe or poorly controlled asthma are at increased risk of readmissions highlights the importance of early intervention and targeted therapies for these high-risk patients. If the findings of my research are replicable, they could have important implications for healthcare policy and asthma management strategies.

5.6 Publication

A pre-print of this manuscript and supplementary data, as originally submitted, are included in this document.

Batra M, Dharmage SC, Newbigin E, Tang M, Abramson MJ, Erbas B, et al. Grass pollen exposure is associated with higher readmission rates for paediatric asthma. Pediatric Allergy and Immunology. 2022; 33: e13880.

Grass pollen exposure is associated with higher readmission rates for paediatric asthma

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CONFLICT OF INTEREST

Michael J Abramson holds investigator-initiated grants for unrelated research from Pfizer, Boehringer-Ingelheim, Sanofi and GSK. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. Shyamali C Dharmage holds investigator-initiated grants for unrelated research from Sanofi and GSK. The other authors have no conflict of interests to declare.

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ABSTRACT

Background: Paediatric asthma hospital readmission is a burden on the individual and costly for Australian hospitals. Grass pollen's role, a known trigger for asthma admissions, is unexamined in readmissions. We examined the association between grass pollen and paediatric asthma readmission.

Methods: The Victorian Admitted Episodes Dataset was used to identify all primary admissions with a principal diagnosis of asthma in children aged 2-18 years between 1997 and 2009. Readmissions were defined as subsequent admissions within 28 days of index admission discharge. Generalized additive models were used to assess associations between readmission, grass pollen season and daily grass pollen counts, lagged and cumulative. Models were further stratified by sex and age group.

Results: Mean daily readmission was higher during grass pollen season than other times of the year, incidence rate ratio (IRR) 1.44 (95%CI, 1.03, 2.02) and for children aged 2-5 years, IRR 1.99 (1.26, 3.14). Same day grass pollen was non-linearly associated with daily readmission for the 13-18 age group between 110-to-256 grains m -3, $p<0.01$. Lag 2 grass pollen was non-linearly associated with daily readmissions overall ($p=0.03$), boys ($p=0.01$) and younger age groups 2-5 ($p=0.02$) and 6-12 ($p<0.001$).

Conclusions: Grass pollen exposure was associated with higher readmission rates for paediatric asthma. Treatment plans prior to discharge could be implemented to reduce the likelihood of readmission by younger children during the pollen season.

Keywords: Adolescent health; Children; Environment; pollen; Asthma; readmissions; season.

INTRODUCTION

Asthma is a major public health concern with increases in global prevalence, and asthma related morbidity and mortality among children, documented over the past 4 decades.[1]Asthma remains one of the most frequent reasons for hospital admission amongst children.[2] An unplanned and potentially prevantable admission to the hospital following a discharge from the hospital after an index admission is classified as an avoidable hospital readmission. Globally and in Australia, asthma hospital readmissions attract unbalanced allocation of resources and funding from healthcare systems.[3] The factors that increase the likelihood of asthma readmission remain poorly understood.

Most studies[4] of risk factors for repeat admissions have mainly focused on behavioural and lifestyle, asthma characteristics and family history of asthma or allergic diseases. Indoor environmental factors such as exposure to allergens or pollution and home characteristics have also been associated with readmissions.

Grass pollen[5], an outdoor aerollaergen, is a known risk factor for primary asthma admission, and leads to inadequate asthma control, indicating the plausability of an association with asthma readmissions. Lagged and cumulative effects of pollen on child hospital asthma admissions have been assessed by previous studies.[5,6]The response to environmental factors may be delayed or accumulate over 1-3 days.[7] This phenomenon represents a "priming" effect.[8] However, we are not aware of any previous study examining both lagged and cumulative effects of pollen on paediatric asthma readmissions.

Given this major gap, this study aimed to examine the association in Victoria, Australia, between grass pollen and repeat paediatric admissions within 28 days using linked hospital data in Victoria, Australia between 1997-2009.

METHODS

Study design and population

All asthma re-admissions from Victorian private and public hospitals were analysed using data from the Victorian Admitted Episodes Dataset (VAED) for the period 1st July 1997– 30th June 2009, with a total of 4383 days observed. Age, sex, admission, and separation dates at admission were extracted. Only primary admissions with a principal diagnosis of asthma, ICD-9 code 493 up to 1998 and ICD-10 codes (J45 or J46) for children 2-18 years of age were included in the present study. The total sample size consisted of 48,068 admissions. A probabilistic linkage algorithm was used to identify all admissions for a particular child. All

children were deidentified. Readmissions for the present study were defined as a subsequent admission within 28 days[9] of the discharge date of the index admission.

We obtained ethics approval for study from La Trobe University Human Research Ethics Committee and the Department of Health. Individual written consent of parents was not required.

Exposure variable

Daily 24-hour average pollen concentrations (grains m^{-3}) were collected using a Burkard volumetric trap located at the Parkville campus of the University of Melbourne as described previously. [10] Sampling was from October to December each year, coinciding with the peak grass pollen season.[11] For other months, it was assumed that the daily grass pollen count was zero.[12]

Other variables

Daily weather data were obtained from The Bureau of Metrology from 9 stations[13] between 1997-2009. The average daily values of all meteorological variables, such as maximum and minimum air temperatures (24 hours after 9 am [local time] in degrees Celsius) and relative humidity were used. Values of relative humidity (%) for 3 hourly observations were first averaged for each day. All the averages of each station were averaged to make one overall average.

Hourly data on air pollutants were obtained from the Environment Protection Authority Victoria (EPA)[14] from 13 monitoring sites. The average daily values from all the sites of pollutants, ozone (O_3) and particulate matter up to 10 μm (PM_{10}) were considered. All the averages of each monitoring site were averaged to make one daily average. The daily weather and EPA data were mapped to the corresponding day of hospital admission.

Statistical methods

To describe the seasonality of the readmission time series, we decomposed it into its seasonal, time trend and random components using locally estimated smoothing with an added weighting scheme to make it more robust. The seasonal component was extracted and plotted with a 14-day moving average overlaid. Means and percentiles were estimated for daily asthma re-admissions, pollutants, meteorological variables, and grass pollen levels. The outcome variable was daily asthma readmission, a low count time series assumed to follow a Poisson distribution.[3] We tested a negative binomial distribution, but it had a poorer fit compared to a Poisson distribution. We investigated the association between daily readmissions and daily

pollen counts at lags 0 to 3, and cumulative lags of 3 and 7 days, and whether association varied by age group or sex. We also aimed to examine the association between daily readmission and pollen season, when in separate models, pollen season was entered as a binary variable in place of daily pollen counts. It is difficult to precisely define when the pollen season starts or finishes. Furthermore, the likely complex impact of climate change on the start and duration of pollen seasons across Australia is unknown, but subject to ongoing study.[15,16] However, it is well established that peak pollen season generally occurs between October to December in Victoria.[12,15,16] Therefore, we used peak pollen season for the present study to define pollen season as October to December. We built the statistical models starting with the unadjusted associations, followed by the adjusted models.

To aid interpretation, pollen variables were transformed to a base 2 log scale where a unit increase represented a doubling of the pollen concentrations on the original scale.[17] As it was likely that cumulative and lagged grass pollen, meteorological and pollutant variables and time variables did not necessarily have a linear fit with readmission counts, we therefore used semi-parametric Poisson generalized additive models (GAM)[18] The results from the final adjusted models are presented.

As part of model development, we assessed the fit of several models based on lagged grass pollen and 3 (lags 0-3) and 7 (lags 0-7)-day cumulative grass pollen using likelihood ratio tests or the Akaike information criterion (AIC) as appropriate.[19] Maximum temperature, relative humidity, O_3 and PM_{10} were considered as potential confounders. Models were further stratified by sex and age. Age was categorized as 2-5 years, 6-12 years, or 13-18 years. The GAMs were fitted and graphed using the mgcv and mgcViz libraries respectively in R.[20] The analyses were exploratory but based on results from our previous studies of child asthma admissions and readmissions. [9,21]We knew that for admissions, pollen exposure was important, so we hypothesized a similar association for readmissions. Hence, we started with an a priori hypothesis in order to build a parsimonious model that fitted the data best, in order to elucidate any association between ambient pollen exposure and readmission. Consequently, no adjustments were performed for multiple comparisons given these comparisons were a priori decided and they are related to the same research question of whether pollen levels are related to readmissions. Data preparation was done with Stata 16.0 (Statacorp, College Station, TX, USA). The level of statistical significance was set at 0.05.

RESULTS

A total of 47,456 children aged 2-18 years, 28,598 (60.2%) males and 18,858 females, were admitted to hospital for asthma between 1997 and 2009. Across the whole study period, 2,152 of these admissions (4.53%) were followed by an asthma readmission within 28 days of discharge. Mean (SD) daily re-admissions were highest among the 2–5-year age group at 0.26 (0.52) and for boys overall at 0.27 (0.54) (Supplementary Table 1). During peak pollen season, mean daily readmissions were above the overall mean (Figure 1).

Daily grass pollen concentrations during the pollen season ranged between 0 and 356 grains m^{-3} (Table 1). Spearman correlations between daily grass pollen counts and environmental factors during the study period are presented in Supplementary Figure 1.

Association between grass pollen season and readmissions

Our model (Table 2) showed that grass pollen season was associated with mean daily readmission rates, which were 1.44 times higher than outside pollen season (95% CI = 1.03, 2.02). Models stratified by sex showed that the association between mean daily readmission rates and daily pollen concentrations were similar for boys and girls. When we refitted the grass pollen season models stratified by age group, we observed an association between grass pollen season and daily readmission rates in the youngest age group (2-5 years) with IRR (incidence rate ratio) = 1.99, 95% CI (1.26, 3.14).

Association between daily grass pollen concentration and daily readmission rates

Lag 2 daily pollen concentrations, model results showed a significant non-linear association with all daily readmissions (Supplementary Figure S3) and across all sex and age strata except for 13-18 years old children (Table 3). Weak evidence for an association between the mean daily readmission rate and grass pollen at lag 0 only at concentrations above approximately 128 grains/m^3 (Supplementary Figure S2) was observed. For lag 0, there was an effect of grass pollen counts on daily readmission rates overall (Table 3) and the association between daily readmissions and grass pollen concentration was significant for the 13–18-year age group (Figure 2).

Cumulative pollen values over 4 days were significantly associated with daily readmissions only for the 6-12 years age group (Table 3 and Supplementary Figure S4).

DISCUSSION

Studies[4] of readmissions differ in temporal windows, with readmissions considered within 2,[22] 3,[23] 6 months,[24] to a maximum of 10 years.[25] Many studies tend to focus on readmission within 12 months.[26,27] However this does not allow identification of environmental

causes, because 12 months overlap different seasonal risk factors such as pollen and/or viral infections. Only a few studies have assessed readmissions defined as within 28 days of an index separation,[9] even though there is evidence that 28 days is a good interval to use to assess whether a subsequent admission is related to the previous one.[28] In our study, mean daily asthma readmission rates within 28 days were statistically significantly higher during the grass pollen season in Melbourne (October to December) compared to the rest of the year. Furthermore, daily readmissions were observed to increase 2 days after grass pollen exposure. The impact of lag 2 pollen on readmissions varied by age group with younger children (<13 years) being at greater risk. Older children and adolescents seemed to be impacted more by ambient grass pollen concentrations on the same day of admission.

Similar to hospital admissions,[5] grass pollen season was associated with readmissions and for younger children. Impact of pollen seasons[3] or allergenicity of ragweed [29] has been assessed by some other studies; however, they were not directly comparable with our finding. The association between asthma readmissions and daily pollen on lag day 2, seemed to be mainly driven by younger children (<13 years of age). This would be consistent with a "priming" effect of grass pollen on readmissions. Younger children have different respiratory physiology and function compared to older children. Younger children may have better ability to accommodate / tolerate airway compromise and thus, it takes longer for them to present with symptoms following pollen increase compared to older children, who have more bronchial hyperresponsiveness (BHR) and present with symptoms sooner. Also, the likelihood of readmission could be higher in younger children with a history of allergies or hay fever due to their impaired immune response, however we did not have individual level data. Cumulative exposure over 3 days was also important in 6-12 years old children. Lack of adherence to prescribed regular preventer treatment and possibly the presence of more severe asthma in this age group[6] could be a possible explanation for this effect. Increased susceptibility to environmental triggers due to poorer adherence is likely to result in residual airway inflammation in this age group.

Same day pollen impacted on all children, but more so in older children. The association for all readmissions showed a qualitatively similar association but the evidence was not as strong. This could have been due to the relative magnitude of the change in mean daily readmission being smaller for all readmissions. A plausible biological pathway that could explain older children/adolescents' reaction to same day pollen vs 2 days later, may be due to the greater likelihood of concomitant allergic rhinitis which leads to increased airway hyper-responsiveness (AHR). Once inflammation leads to AHR, it takes a couple of days for

symptoms to manifest. Adolescents might also be more likely to have poor asthma control leading to underlying airway inflammation. The 13–18-year age group is more likely to understand triggers and the need to adhere to preventive measures i.e., medications and/or limiting exposure to a minimum when the levels are extreme. This might be the reason for the observed decline at pollen concentrations higher than the levels associated with an increased rate of readmission (Figure 2).

The impact of grass pollen at lag 2 on mean daily readmission showed a linearly increasing association above about 110 grains /m^3 for all readmissions (Supplement, Figure S3). Therefore, our findings are consistent with the generally accepted definition of extreme pollen days i.e., >100 grass pollen grains/m^3. This is potentially important for asthmatic patients, as well as the medical services that are likely to manage these patients. Further studies of readmissions are needed to confirm or replicate our findings.

Season as a predictor has also been documented,[30] with early readmissions (within 2 weeks of discharge) occurring most often during spring. However, these studies were not directly comparable, as our focus was only the grass pollen season which, along with respiratory viruses[31] increases the risk of asthma exacerbations. It remains a possibility that child and adolescent asthma are caused by different types of pollen across different geographic locations. Also, climate change impacts are likely to be complex and location dependent. In contrast to the Northern Hemisphere, impacts are not yet clear in Australia due to inconsistent monitoring resulting in insufficient data. [16] In this study, we are building on our previous work with a more detailed analysis of the association between pollen season and child asthma hospital readmissions. We aim to follow this up with more recent data that would also include recent thunderstorm asthma events and for which we have currently applied for ethical approval.

The possibility that local variations in pollen levels, pollen types and pollen combinations across areas affecting child and adolescent asthma ED presentations should also be considered in such studies.

A strength of this analysis was the inclusion of data from the VAED, a large comprehensive data base including all paediatric asthma admissions from Victorian public and private acute hospitals for 1997–2009. The length of the study period and sample size provided sufficient power to detect meaningful associations with childhood asthma readmissions. To allow for potential non-linearity in model specification, a generalised additive model was fitted.

However, some limitations should be considered when interpreting the results. During the study period, no grass pollen data were collected outside of peak pollen season, but daily

concentrations were likely to then be very low.[12] The average length, dates and duration of the pollen season for any particular site, may often vary from one year to the next. Rainfall, temperature, and other meteorological parameters influence pollen season timing and duration, as well as day to day variations in pollen concentrations. As also will synoptic and larger-scale climate fluctuations such as the El Niño Southern Oscillation.[15] Melbourne usually witnesses its peak grass pollen season between October to December. [12,15] It may trigger symptoms of hay fever and allergic asthma in susceptible individuals, when there is a sufficient ambient concentration of pollen.[32]Hence, the importance of establishing any increased risk of readmission during this period.

Another limitation is that we did not have data on individual patients' sensitization, viral infections, hay fever, or second-hand smoking, which could be considered as important modifying factors. However, we had a time series of aggregated daily counts and, although important, individual data could not be incorporated. Furthermore, our models imply that all children experienced identical exposures to ambient grass pollen and therefore our analyses may be subject to misclassification bias. [7] Therefore, this study does not have sufficient evidence to conclude a causal association. Nevertheless, this result, along with other findings that accounted for these factors. [7] indicate that the hypothesis of an association between readmission and ambient pollen concentrations is plausible.

Nonetheless, our findings have important implications regarding repeated child asthma admissions and pollen exposure among younger children. There is a need to target interventions for children with severe or under controlled asthma, prior to the pollen season. Communication of interventions at the time of hospital discharge has been shown to be associated with reduction in hospital readmissions and improved treatment adherence and patient satisfaction.[33] This study also highlighted the importance of monitoring daily readmission counts. Therefore, the health system needs to include systematic monitoring of daily counts to understand associated aetiological factors. Maintaining the effectiveness of care, whilst transitioning from hospitals to community, along with follow ups targeting children who are at a higher risk of readmission, are also important. Stronger links between the health system and community, possibly through asthma education could result in the availability of appropriate care for asthma management in the community for the mitigation of environmental triggers and use of asthma controller devices. These measures may prevent repeated hospitalisations and reduce readmissions for asthma in young children.

AUTHOR CONTRIBUTION

MB, DV, BE designed the study, analysed the data and wrote the manuscript. All the authors critically revised the manuscript. All authors have read and approved the final manuscript.

IMPACT STATEMENT

Grass pollen increases the likelihood of preventable early childhood asthma readmissions. Younger children with severe or poorly controlled asthma could be referred for preventive therapies before the grass pollen season, to reduce the likelihood of a repeat admission.

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Table 1: Grass pollen and environmental factors, 1997-2009

Weather variables	Mean (SD)	Minimum	25%	Median	75%	90%	Maximum
Maximum temperature (oC)	19.69 (6.09)	7.99	14.92	18.67	23.12	28.48	46.31
Minimum temperature (oC)	11.68 (4.14)	0.30	8.70	11.50	14.40	17.10	26.70
Relative humidity (%)	69.91(10.91)	21.01	63.5	70.72	77.36	83.23	96.37
Pollutants							
Ozone (ppm)	13.89 (5.99)	0.39	9.59	13.52	17.60	21.62	45.01
PM10 (µg/m3)	18.24 (10.26)	3.36	12.53	16.34	21.68	27.85	306.02
Grass pollen (only pollen season (October-December) (grains/m3)	38.13 (0.14)	0	6	19	48	98	356
Cumulative grass pollen (0-3)	148 (141)	1	46	98	214	353	784
Cumulative grass pollen (0-7)	275 (233)	3	104	207.5	399	606	1225

Table 2: Summary of the GAM models showing the incidence rate ratios (95%CI) for mean number of daily readmissions rates, comparing grass pollen season to outside of pollen season

	Time + day of the year +day of the week	Time + day of the year + day of the week + maximum temperature	Time + day of the year + day of the week + maximum temperature +PM10	Time + day of the year + day of the week + maximum temperature +PM10 +relative humidity	Time + day of the year + day of the week + maximum temperature +PM10 +relative humidity +Ozone
All	1.44 (1.03, 2.02) *	1.43 (1.02, 2.00) *	1.43 (1.02, 2.00) *	1.44 (1.03, 2.02) *	1.44 (1.03, 2.02) *
Stratified by gender					
Males	1.51 (0.96, 2.38)	1.51 (0.96, 2.38)	1.51 (0.96, 2.38)	1.51 (0.96, 2.38)	1.53 (0.97, 2.40)
Females	1.51 (0.93, 2.46)	1.51 (0.93, 2.46)	1.32 (0.81, 2.14)	1.51 (0.93, 2.44)	1.31 (0.81, 2.13)
Stratified by age-group					
2-5 years	2.01 (1.27, 3.17) **	2.01 (1.27, 3.15) **	2.00 (1.27, 3.15) **	2.01 (1.27, 3.17) **	1.99 (1.26, 3.14) **
6-12 years	1.48 (0.78, 2.8)	1.46 (0.77, 2.78)	1.47 (0.77, 2.79)	1.48 (0.78, 2.79)	1.47 (0.78, 2.79)
13-18 years	0.6 (0.29, 1.22)	0.6 (0.29, 1.21)	0.59 (0.29, 1.21)	0.59 (0.29, 1.21)	0.6 (0.29, 1.23)

P value: * ≤ 0.05, **≤0.01, statistically significant

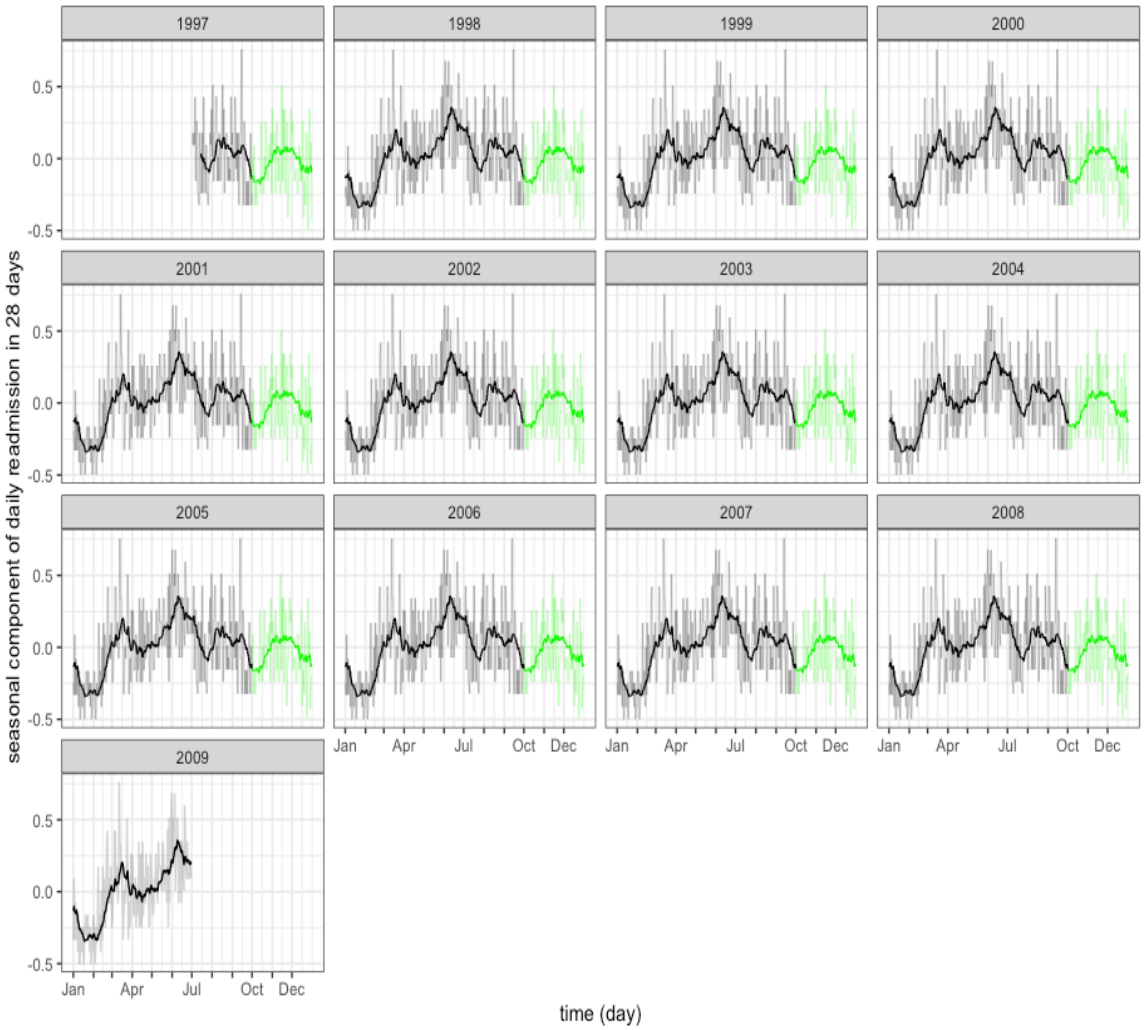
Table 3: Summary of the GAMs with pollen counts per cubic metre showing p values for the smooth fits

Pollen values	All	Males	Females	2-5 years	6-12 years	13-18 years
Lag 0	0.07	0.17	0.29	1.00	0.12	<0.01**
Lag1	0.49	0.42	0.98	0.45	0.37	0.11
Lag2	<0.01**	0.01*	0.01*	0.02*	<0.001***	0.28
Lag3	0.18	0.87	0.11	0.75	0.34	0.52
Cumulative (0-3)	0.41	0.18	0.29	0.64	0.05*	0.27
Cumulative (0-7)	1.00	0.41	0.79	0.32	0.12	0.51

Models were adjusted for Time +dow + maximum temperature +PM_{10} +relative humidity +Ozone.
P value: ≤ 0.05, statistically significant.

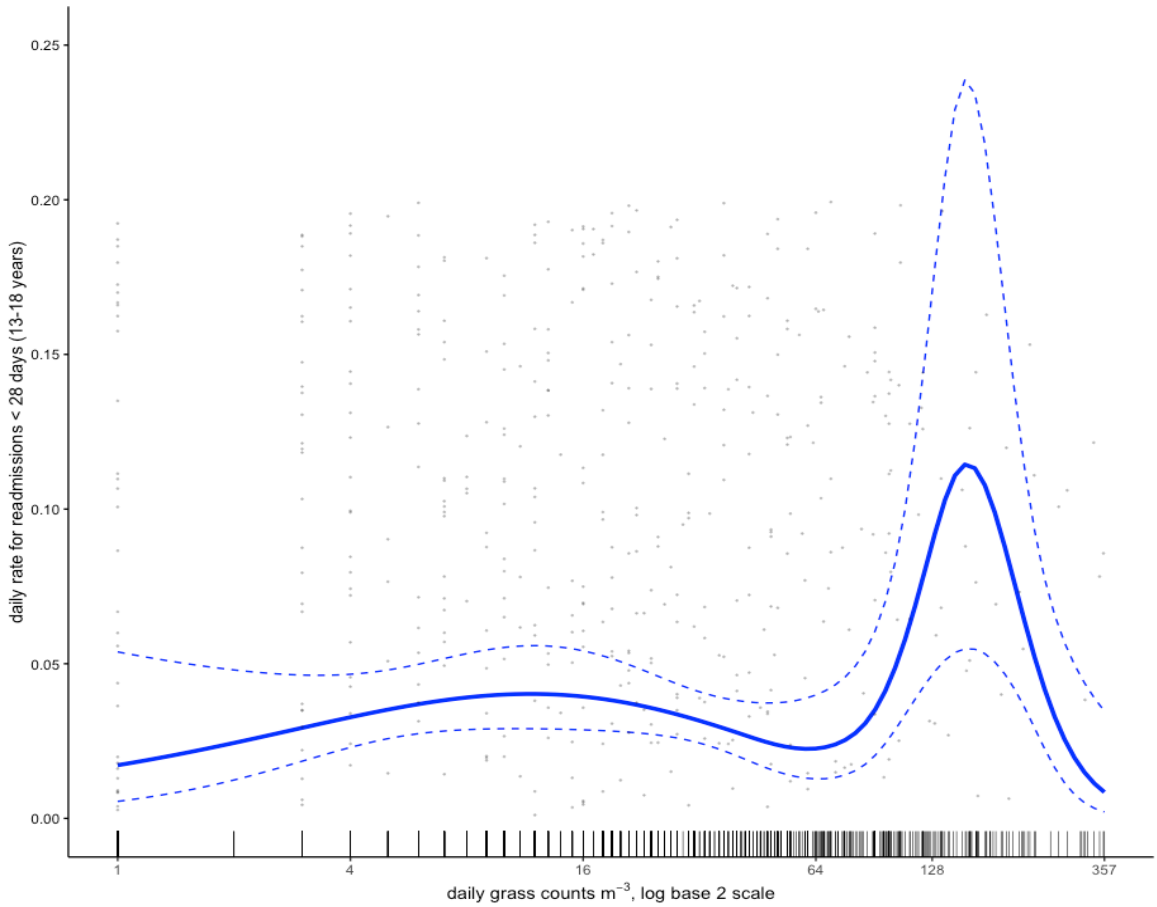
Table S1: Summary statistics, 1997-2009

Variable	Mean (SD)	Minimum	25%	Median	75%	90%	Maximum
All Re-admissions	0.49 (0.72)	0	0	0	1	1	5
Male Re-admissions	0.27 (0.54)	0	0	0	0	1	4
Female Re-admissions	0.21 (0.46)	0	0	0	0	1	3
2-5 years Re- admissions	0.26 (0.52)	0	0	0	0	1	4
6-12 years Re-admissions	0.14 (0.38)	0	0	0	0	1	4
13-18 years Re-admissions	0.07 (0.28)	0	0	0	0	0	2



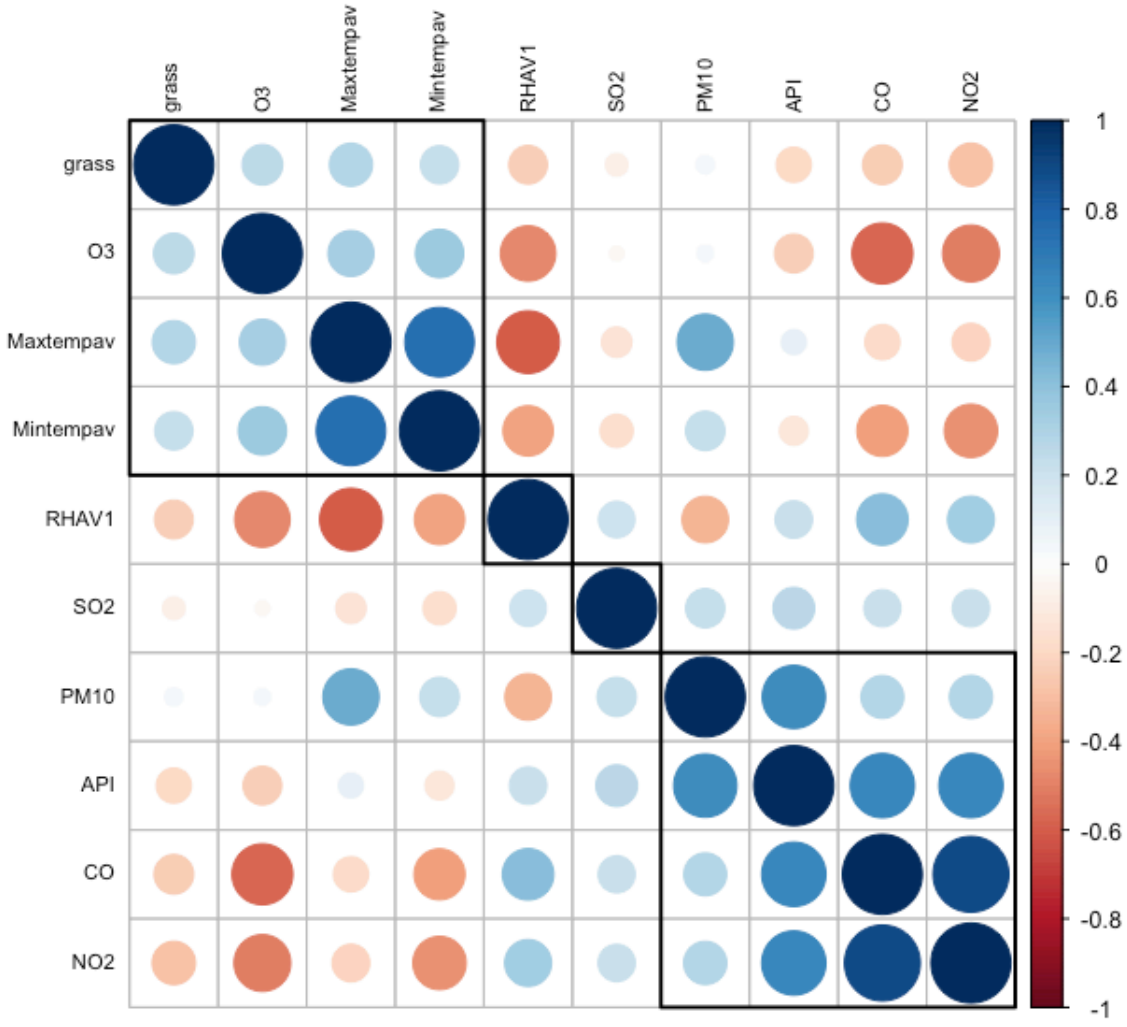
*0 represents the overall mean and therefore positive values indicate greater and negative values indicate lesser, than overall mean daily readmissions.

Figure 1: Time series decomposition of daily child asthma readmissions with the seasonality component extracted and mean centred* with an overlaid 14 day moving average. The green sections indicate the months of October to December, the definition of the peak pollen season.



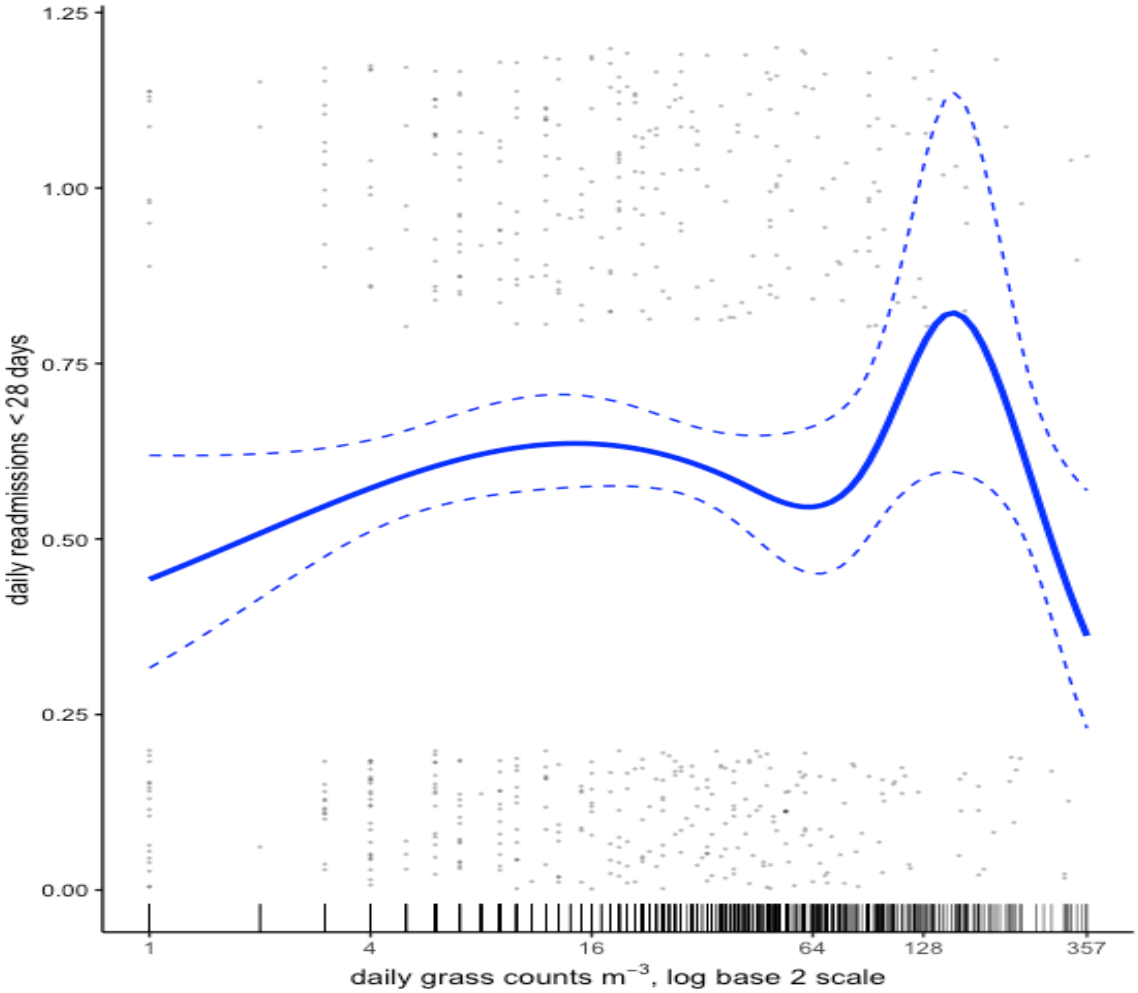
The vertical Y axis in the above graph has been truncated for clarity.

Figure 2: Impact of grass pollen at lag0 on readmissions among children 13-18 years old. P value=0.008 for smooth fit. Blue dotted lines represent the 95% confidence interval.



RHAVI=Average Relative Humidity, API= Airborne particle index, CO= Carbon Monoxide, NO_2= Nitrogen dioxide, O_3= Ozone, PM_{10}= Particulate matter up to 10 µm, and SO_2= Sulphur dioxide. Diameter of the circle indicates the size of the correlation, e.g., the full diagonal circles have diameter 1. The colour indicates positive or negative correlation.

Figure S1: Spearman Correlation coefficients between daily levels grass and environmental factors from 1997-2009



The vertical Y axis in the above graph has been truncated for clarity.

Figure S2: Impact of grass pollen at lag0 on all readmissions. P value=0.07 for smooth fit. Blue dotted lines represent the 95% confidence interval.

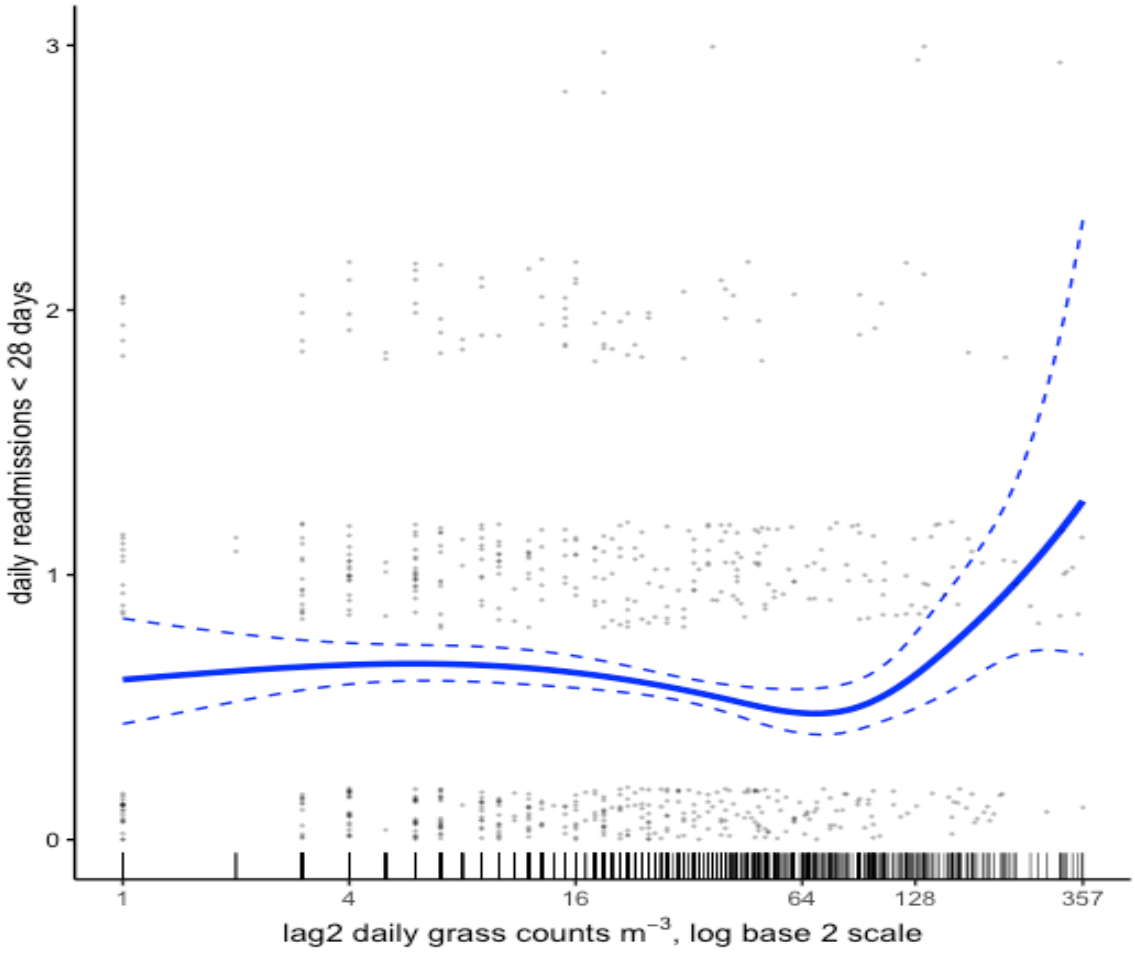
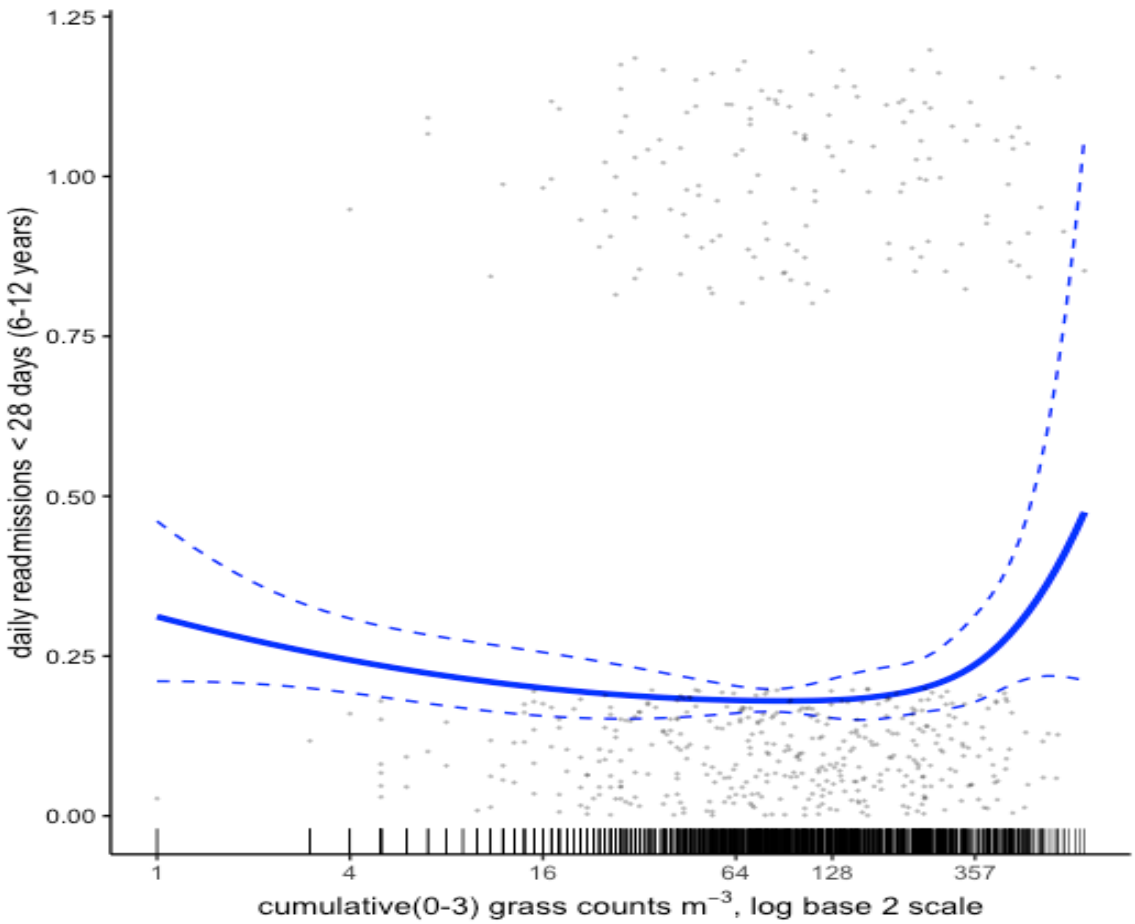


Figure S3: Impact of grass pollen at lag2 on all readmissions. P value=0.003 for smooth fit. Blue dotted lines represent the 95% confidence interval.



The vertical Y axis in the above graph has been truncated for clarity.

Figure S4: Impact of cumulative grass pollen (0-3) on readmissions among children 6-12 years old. P value=0.05 for smooth fit. Blue dotted lines represent the 95% confidence interval.

6. Does the indoor environment modify the association between grass pollen exposure and asthma readmission?

This is an original research thesis and result chapter. It extends on the Research Questions addressed in number 3 and will be published after the submission of this doctoral thesis.

6.1 Introduction

People tend to spend more than 75% of their time indoors, and thus, it is essential to comprehend the role that indoor settings play in asthma outcomes (366). Indoor environmental exposures associated with asthma outcomes include allergens (e.g., dust mites and cockroach allergens) and air pollution (e.g., moisture, tobacco smoke, dust, and chemicals) (367). In later life, allergic sensitisation is a strong predictor of disease persistence, with studies indicating that most asthmatic schoolchildren are sensitised to at least one indoor allergen (368-370). A study found that 91% of hospitalised asthmatic children were sensitised to at least one indoor allergen (371). Sufficient evidence has accumulated to deem indoor air pollutants, including dust, dust mites, and moisture (372, 373), as associated with paediatric asthma exacerbations. Causal relationships between exposures to pollutants and allergens and the subsequent development of asthma have been demonstrated most strongly for dust mite allergens (374).

Two studies assessed the relationship between indoor air quality and hospital childhood asthma readmissions. Howrylak et al. (332) considered tobacco use in an indoor setting with identifiable serum or salivary cotinine biomarkers, and Vicendese et al. (68) found higher levels of fungi and yeast in children's bedrooms to be associated with an increased risk of readmissions. The latter study also found that carpeted floors in a child's bedroom, and a high frequency of vacuuming, daily or 2/3 times per week, compared to weekly or less often at home, were significantly associated with increased odds of readmissions for paediatric asthma (68). Although vacuuming is intended to remove allergens, it was proposed that frequent vacuuming might accelerate the dispersion of allergens into the air and alter spore size distribution, enabling deeper penetration of the lung. It has also been suggested that parents, concerned for their asthmatic children, may be vacuuming more frequently, which could introduce reverse causation.

As shown in Chapter 3, asthma exacerbations are influenced by numerous additional factors, such as pollen. The potential exists for indoor air allergens and pollution, primarily from parental smoking, to interact with pollen and synergistically increasing the adverse effects of pollen on children's respiratory health (375). This combination of two allergens can potentially increase the chances of enhanced levels of airway inflammation and epithelial damage (99). Since inflammation plays a central role in asthmatic pathophysiology (376), simultaneous exposure to multiple allergens has sustained effects (377); I hypothesized that concurrent exposure to indoor risk factors could enhance the impact of pollen on childhood asthma readmissions.

Moreover, to better assess the potential impact of pollen on respiratory health in the presence of poor indoor environment, it is necessary to understand not only the interactions or combined effects but also to elucidate any effect of pollen on an asthma outcome in different strata of an indoor risk factors. To the best of my knowledge, no study has examined the association of pollen and childhood asthma readmissions with indoor risk factors as effect modifiers. As discussed in Chapter 5, this doctoral study analysed the association between ambient grass pollen and childhood asthma readmissions within 28 days. As discussed in Chapter 5, my study found that childhood asthma readmissions were significantly increased with pollen exposure. In this chapter, I aim to assess the statistical evidence for the hypothesis that indoor risk factors will enhance and/or modify the impact of pollen on childhood asthma readmissions. I will do this by using another data set, obtained from Murdoch Children's Research Institute (MCRI), to consider indoor environment factors such as parental smoking exposure, carpeted rooms, signs of mold, water dampness, and the presence of unusual smells.

6.2 Methods

6.2.1 Study design and population

This prospective case-control study is a secondary analysis of the Asthma Re-admission Study, a multicentre cohort study conducted by the MCRI on children, aged 3 to 18 years, admitted to the Royal Children's Hospital, The Northern Hospital or University Hospital Geelong between 1st September 2017 and 31st August 2018, with a discharge diagnosis of asthma or wheeze. Primary caregivers of identified children were sent a study information letter and given an opportunity to decline further contact by MCRI. If further contact was not declined, the research team contacted the primary caregiver via phone for recruitment. Once consent was given and participants enrolled in the study, the caregiver completed a short survey, which was captured using Research Electronic Data Capture

(REDCap). The Murdoch Children's Research Institute provided primary caregivers with the option of enrolling and participating via the phone or online. During the short survey, caregivers were asked if their child had a regular general practitioner (GP) and, if they did, to identify them via name, practice name and address. The GPs were mailed an Information Letter for the study and a hard copy of the 17-item survey (Supp B) with an option to complete it online or via email.

6.2.2 Data Sources

In the MCRI study, all participants completed a short 12-item survey via phone or online (Supp A), and all nominated GPs were sent a 17-tem survey to complete. The research team for the study reviewed the Electronic Medical Record (EMR) of each participant manually, using a 41-item standardised data collection form to extract relevant information from the index admission (Supp C). Electronic medical record data were captured using Research Electronic Data Capture (REDCap). The Murdoch Children's Research Institute's two primary reviewers cross-checked a random sample(N=10) from each site to estimate inter-rater reliability. A 91% agreement was reported across all three sites, with similar percentage agreement at each location. Participant records were linked the with the Victorian Admitted Episodes Dataset (VAED) and Victorian Emergency Minimum Dataset (VEMD) using the child's name, date of birth, sex and Medicare number. The linkage was completed by the Centre for Victorian Data Linkage (CVDL). These data capture hospital admission or ED presentation to any Victorian public hospital.

6.2.3 Definitions

6.2.3.1 Exposure

Pollen exposure data was measured daily between October 2017and January 2018 using a Burkard volumetric spore trap located at the Earth Sciences Building inside the University of Melbourne precinct. In compliance with pollen monitoring standards (378), the trap was placed on the rooftop which was 15 metres above the ground. An adhesive surface of the trap collected airborne grass pollen, which was later identified and measured daily with a light microscope. The daily average grass pollen counts was expressed in terms of number of pollen grains per m^3. The peak grass pollen season in Melbourne is between October to December, but pollen may be detectable from August to January (379). However, to trigger symptoms of hay fever and allergic asthma in most susceptible individuals, there needs to be a sufficient ambient concentration of pollen (380). Ambient grass pollen concentrations begin

to rise in October and peak between November and December. Therefore, days outside this period were assumed to have a zero daily grass pollen count (380). For the present study, pollen season is defined as October to December.

Indoor environmental variables: Parental interviews recorded:

Smoking exposure: "Is the child exposed to cigarette smoke in the home? If the parent smokes outside the home and not inside or near the child, it was counted as 'yes'",

Carpeting: "Is the child's room carpeted?"

Presence of unusual smells: "Are there any unusual smells inside the home (moldy, musty, damp, earthy or of chemical)?"

Water in the home: "Are there any signs of mold, water damage or condensation in the home that are bigger than an A4 piece of paper?".

6.2.3.2 Outcome

Any Readmission within 28 days: cases were defined as those that had a subsequent admission (asthma or wheeze) within 28 days (124) of the index admission's discharge date, whereas controls had no readmissions within 28 days.

Any readmissions within 3 months: cases were defined as those that had a subsequent admission (asthma or wheeze) within 3 months of the discharge date of the index admission, whereas controls had no readmissions within the study period.

Any readmissions: cases were defined as those that had a subsequent admission (asthma or wheeze) within one year of the discharge date of the index admission, whereas controls had no readmissions within the study period.

Any readmissions within pollen season: cases were defined as those that had a subsequent admission (asthma or wheeze) within the pollen season, irrespective of the index admission date, whereas controls had no readmissions within the pollen season.

6.2.4 Potential confounders/adjustment variables

Patient age, sex, previous admissions, previous emergency admissions, prior inhaled corticosteroids, prior history of an intensive care unit (ICU), length of stay at index admission, and admission to ICU at the index admission were used as confounders (381).

6.2.5 Effect modifiers

Considering the above-stated hypothesis, to assess the interactive effect of indoor air pollutants and pollen on readmissions, models were stratified based on indoor air pollutant status.

6.2.6 Statistical analysis

Logistic regression was used to analyse the association between pollen exposure and outcomes. The model was adjusted for potential confounders and other variables. Corresponding 95% confidence intervals were used with adjusted odd ratios in presenting the results. Exposures and all other variables were considered statistically significant if the p-value was less than 0.05 and other variables were included if there was a change in the estimated effect size of pollen exposure by at least 10%. Interaction analyses were conducted with indoor air pollutants, and strata specific odds ratio (OR) and 95% confidence interval (CI) will be presented. Due to the power for interaction being lower than the non-interaction analysis, if p-value for the interaction was less than 0.1, it will be deemed as significant. All analyses in this Chapter were performed with Stata, Version 14.2 (Stata Corp, Texas, TX, USA).

6.2.7 Ethical approval

Ethical approval for the Asthma Re-admission Study was granted by the Murdoch Children's Research Institute (HREC 38295).

6.3 Results

The characteristics of the study participants are shown in Table 1 of this chapter. There were 767 index admissions, with mean age 6.1 years (SD= 3.1 years). Of the total admissions, 62.8 % were females. There was a total of 65 (8.5%) participants who reported exposure to cigarette smoking at home. The majority of the participants, 505 (65.8%), had carpeted rooms. Only a few, 47(6.1%), reported the presence of unusual smells at home. There was a total of 299 (39.0%) readmissions (Table 2). Of the total readmissions, 56 (18.7%) had readmission due to asthma or wheeze within 28 days, which represented 7.3% of the total admissions. Within 3 months, 121 (15.8%) participants had one or more readmissions. About 112 (14.6%) of the children had a readmission within pollen season, which represented 40.5% of all readmissions.

6.3.1 Association between pollen exposure and readmission outcomes

Readmissions within 28 days or any readmission were not associated with grass exposure. The odds of readmission within 28 days compared to no readmission within 28 days was the same for the pollen exposure OR 1.00 (95% CI: 0.98, 1.01), p=0.89. The odds were similar for readmissions within 3 months compared to no readmissions within 3 months OR 0.99 (95% CI: 0.98, 1.00). Pollen exposure during the pollen season was associated with an increased odd of readmission OR 1.04 per 1 grain/m^3 increase (95% CI: 1.04, 1.06), p<0.001 (Table 3). The adjusted estimated pollen effects were similar to the crude estimates for all the outcomes except for any readmissions (Table 4). In the adjusted model, the odds of any readmission were significantly greater in the presence of pollen during the pollen season aOR 1.01 (95% CI: 1.00, 1.02), p=0.02.

6.3.2 Association between all the exposures and outcomes.

Readmission within 28 days: Smoking exposure at home OR 1.32 (95% CI: 0.54, 3.24), p=0.53, and signs of mold and/or water damage OR 1.18 (95% CI: 0.44, 3.17), p=0.74 increased the odds of readmission but did not reach statistical significance. On the other hand, the presence of carpet in the room and unusual smells were protective (Table 5). Similar results were obtained for the adjusted model (Table 6).

Any readmissions: Daily pollen counts OR 1.01 (95% CI: 0.99, 1.01), carpeted room OR 1.10 (95% CI: 0.81, 1.50), and signs of mold and/or water damage OR 1.09 (95% CI: 0.65, 1.85) non-significantly increased the odds in the unadjusted models (Table 5). However, in the adjusted model, only pollen exposure was statistically significant and increased the odds aOR 1.01 (95% CI: 1.00, 1.02), p = 0.02 (Table 6).

Any readmissions within 3 months: Compared to other home environment exposures, smoking exposure at home and signs of mold and/or water damage increased odds of readmission but with inadequate statistical evidence, aOR 1.49 (95% CI 0.75, 2.91), p=0.25, aOR 1.07 (95% CI 0.53, 2.18), p=0.84, respectively. (Table 6).

Any readmissions within pollen season: For every unit increase in the concentration of pollen, there was an approximate 5% increase in the odds of any readmission within a pollen season aOR 1.05 (95% CI 1.04, 1.05), p=<0.001.

6.3.3 Association between pollen exposure and each outcome stratified by the home environment variables

Any readmission within 28 days and any readmissions within 3 months were not associated with grass pollen exposure in the models stratified by smoking exposure at home, carpeted room, unusual smells, and signs of mold and/or water damage. However, for any readmissions, when stratified by carpet status, readmission was 1.01 times more likely to occur with a unit increase in grass pollen concentrations among participants with a carpeted room OR=1.01 (95% CI: 1.00, 1.01), p=0.03. Grass pollen exposure was significantly associated with any readmissions within pollen season, irrespective of the home environment variables (Table 7). All the home environment variables had no interaction effect with pollen exposure (Table 8).

Table 1: Characteristics of asthma re-admission study participants

Variable	No (%)
Total admissions	767
Age, Mean (SD)	6.1 (3.1)
Sex	
Males	482 (62.8)
Females	285 (37.2)
Child exposed to cigarette smoke	
Yes	65(8.5)
No	702 (91.5)
Child room carpeted	
Yes	505 (65.8)
No	262 (34.2)
Presence of unusual smells	
Yes	47(6.1)
No	720 (93.9)
Signs of mould and/or water damage	
Yes	76 (9.9)
No	690 (90.1)
Grass pollen during the pollen season, Mean (SD)	33.6 (22.3)

Table 2. Readmission outcome variables 1/09/2017-30/08/2018

Outcome variables			No (%)
Any readmissions within 28 days	Cases	Readmissions within 28 days	56 (7.3)
	Controls	No readmission within 28 days	711 (92.7)
Any readmissions	Cases	Any readmissions	299 (39.0)
	Controls	No readmissions	468 (61.0)
Any readmissions within 3 months	Cases	Any readmissions within 3 months	121 (15.8)
	Controls	No readmissions within 3 months	646 (84.2)
Any readmissions within the pollen season	Cases	Any Readmission within pollen season	112 (14.6)
	Controls	No readmissions within pollen season	655 (85.4)

Table 3. Crude association between pollen exposure and each outcome

Outcome variables	N	OR (95% CI)	p
Any readmissions within 28 days	766	1.00 (0.98, 1.01)	0.98
Any readmissions	766	1.00 (0.99, 1.01)	0.11
Any readmissions within 3 months	766	0.99 (0.98, 1.00)	0.10
Any readmissions within pollen season	766	1.04 (1.04, 1.06)	0.00

Table 4. Adjusted association between pollen exposure and each outcome

Outcome variables	N	aOR (95% CI)	p
Any readmissions within 28 days	766	1.00 (0.98, 1.02)	0.82
Any readmissions	766	1.01(1.00, 1.02)	0.02
Any readmissions within 3 months	766	0.99 (0.98, 1.00)	0.26
Any readmissions within pollen season	766	1.05 (1.04, 1.06)	0.00

Notes: adjusted for patient age, sex, previous admissions, previous emergency admissions, prior inhaled corticosteroids, prior history of an intensive care unit (ICU), length of stay at index admission, and admission to ICU at the index admission.

Table 5. Crude association between each exposure and outcome (N=765)

Exposure	Outcome							
	Any readmissions within 28 days		Any readmissions		Any readmissions within 3 months		Any readmissions within pollen season	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Pollen exposure	1.00 (0.98, 1.01)	0.98	1.01 (0.99, 1.01)	0.11	0.99 (0.98, 1.00)	0.09	1.05 (1.04, 1.06)	0.00
Smoking exposure at home	1.32 (0.54, 3.24)	0.53	0.84 (0.49, 1.44)	0.54	1.35 (0.71, 2.58)	0.35	0.77 (0.33, 1.83)	0.56
Carpeted room	0.79 (0.45, 1.38)	0.41	1.10 (0.81, 1.50)	0.53	0.81 (0.54, 1.22)	0.32	1.25 (0.77, 2.04)	0.36
Unusual smells	0.25 (0.03, 1.93)	0.18	0.87 (0.44, 1.69)	0.68	0.94 (0.38, 2.31)	0.90	0.67 (0.23, 1.92)	0.46
Signs of mold and/or water damage	1.18 (0.44, 3.17)	0.74	1.09 (0.65, 1.85)	0.73	1.02 (0.51, 2.05)	0.95	1.55 (0.71, 3.39)	0.28

All the exposures were mutually adjusted to each other.

Table 6. Adjusted association with each exposure and outcome (N=765)

Exposure	Outcome							
	Any readmissions within 28 days		Any readmissions		Any readmissions within 3 months		Any readmissions within pollen season	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Pollen exposure	1.00 (0.98, 1.02)	0.80	1.01 (1.00, 1.02)	0.02	0.99 (0.98, 1.00)	0.26	1.05 (1.04, 1.06)	0.00
Smoking exposure at home	1.35 (0.53, 3.42)	0.52	0.90 (0.51, 1.58)	0.71	1.49 (0.75, 2.91)	0.25	0.78 (0.31, 1.99)	0.61
Carpeted room	0.81 (0.45, 1.43)	0.47	1.13 (0.81, 1.56)	0.75	0.78 (0.51, 1.18)	0.24	1.33 (0.80, 2.20)	0.25
Unusual smells	0.19 (0.02, 1.64)	0.13	0.83 (0.42, 1.56)	0.61	0.77 (0.30, 1.97)	0.59	0.77 (0.27, 2.18)	0.62
Signs of mold and/or water damage	1.25 (0.44, 3.42)	0.66	1.05 (0.65, 1.82)	0.83	1.07 (0.53, 2.18)	0.84	1.43 (0.63, 3.24)	0.38

Notes: adjusted for patient age, sex, previous admissions, previous emergency admissions, prior inhaled corticosteroids, prior history of an intensive care unit (ICU), length of stay at index admission, and admission to ICU at the index admission. All the exposures were mutually adjusted to each other

Table 7. Adjusted association between pollen exposure and each outcome, stratified by home environment variables

Exposure	Outcome							
	Any readmissions within 28 days		Any readmissions		Any readmissions within 3 months		Any readmissions within pollen season	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Smoking status								
Yes	1.00 (0.96, 1.04)	0.83	1.01 (0.99, 1.05)	0.17	0.99 (0.95, 1.03)	0.63	1.06 (1.02, 1.10)	<0.001
No	1.00 (0.98, 1.01)	0.97	1.01 (0.99, 1.01)	0.07	0.99 (0.98, 1.00)	0.25	1.05 (1.04, 1.06)	<0.001
Room carpeted								
Yes	1.00 (0.98, 1.02)	0.69	1.01 (1.00, 1.01)	0.03	0.99 (0.98, 1.01)	0.66	1.05 (1.04, 1.06)	<0.001
No	0.99 (0.97, 1.02)	0.68	1.00 (0.99, 1.01)	0.66	0.98 (0.96, 1.00)	0.09	1.05 (1.03, 1.06)	<0.001
Unusual smells								
Yes	-		0.98 (0.95, 1.02)	0.42	-	-	1.04 (0.99, 1.09)	0.09
No	1.00 (0.98, 1.01)	0.82	1.00 (1.00, 1.01)	0.02	0.99 (0.98, 1.00)	0.35	1.05 (1.04, 1.06)	<0.001
Signs of mould, water dam								
Yes	0.86 (0.58, 1.28)	0.47	0.99 (0.97, 1.03)	0.94	0.86 (0.66, 1.11)	0.25	1.04 (1.01, 1.08)	0.01
No	1.00 (0.98, 1.02)	0.68	1.00 (1.00, 1.01)	0.03	0.99 (0.98, 1.01)	0.43	1.05 (1.04, 1.06)	<0.001
Presence of one indoor variable								
Yes	0.98 (0.95, 1.03)	0.57	1.00 (0.98, 1.02)	0.45	0.96 (0.92, 0.99)	0.92	1.04 (1.03, 1.07)	<0.001
No	1.00 (0.98, 1.02)	0.68	1.00 (0.99, 1.01)	0.05	0.99 (0.98, 1.01)	0.80	1.05 (1.04, 1.06)	<0.001

Note: adjusted for patient age and sex

Table 8. Interaction between pollen exposure and home environment variables (N=766)

Outcome	Yes smoking at home OR (95% CI)	No smoking at home OR (95% CI)	p-value for interaction
Any readmissions within 28 days	1.01 (0.98, 1.01)	0.99 (0.86, 1.05)	0.66
Any readmissions	1.01 (0.99, 1.03)	1.01 (0.99, 1.01)	0.53
Any readmissions within 3 months	0.98 (0.98, 1.00)	0.99 (0.98, 1.00)	0.93
Any readmissions within pollen season	1.05 (1.02, 1.07)	1.04 (1.04, 1.06)	0.58

Outcome	Yes, Carpeted room OR (95% CI)	No, Carpeted room OR (95% CI)	p-value for interaction
Any readmissions within 28 days	1.00 (0.98, 1.02)	1.00 (0.97, 1.02)	0.59
Any readmissions	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)	0.27
Any readmissions within 3 months	1.00 (0.98, 1.01)	0.98 (0.98, 1.01)	0.23
Any readmissions within pollen season	1.05 (1.04, 1.06)	1.04 (1.03, 1.08)	0.24

Outcome	Yes, Unusual smells	No, Unusual smells	p-value for interaction
Any readmissions within 28 days	-	1.00 (0.98, 1.02)	-
Any readmissions	0.99 (0.96, 1.02)	1.01 (1.00, 1.02)	0.37
Any readmissions within 3 months	-	0.99 (0.98, 1.00)	-
Any readmissions within pollen season	1.04 (1.01, 1.07)	1.05 (1.04, 1.06)	0.60

Outcome	Yes, Signs of mold and/or water damage	No, Signs of mold and/or water damage	p-value for interaction
Any readmissions within 28 days	0.86 (0.55, 1.35)	1.00 (0.99, 1.02)	0.49
Any readmissions	1.00 (0.98, 1.03)	1.01 (1.00, 1.02)	0.51
Any readmissions within 3 months	0.87 (0.67, 1.13)	0.99 (0.98, 1.00)	0.28
Any readmissions within pollen season	1.05 (1.02, 1.07)	1.05 (1.04, 1.06)	0.43

Outcome	Yes, Presence of one indoor variable	No, Presence of one indoor variable	p-value for interaction
Any readmissions within 28 days	0.99 (0.96, 1.03)	1.00 (0.98, 1.02)	0.95
Any readmissions	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	0.98
Any readmissions within 3 months	0.97 (0.94, 1.00)	0.99 (0.98, 1.01)	0.06
Any readmissions within pollen season	1.05 (1.03, 1.07)	1.05 (1.04, 1.06)	0.99

Note: adjusted for patient age and sex

6.4 Discussion

Globally, children and adolescents continue to be at risk as asthma remains improperly managed, resulting in high hospital readmissions (124). Useful insights, concerning patterns in the occurrence and medical care for acute asthma in children can be gained by examining these hospital readmissions (382). This study has considered three distinct readmission time periods i.e., within 28 days, 3 months, and 12 months. It was found that 39% and 7.3 % of 767 children were readmitted to the hospital for asthma or wheeze within 1 year and 28 days respectively.

6.4.1 Association between pollen exposure and readmission outcomes

The very nature of the role of aeroallergens in causing sensitisation and subsequent disease development remains ambiguous despite substantial evidence linking aeroallergens and allergic diseases (383). In contrast to a previous study (124), my study found that grass pollen increased the likelihood of readmissions within 1 year. However, due to the difference in time periods for both studies, and the absence of actual pollen data values in the previous study(124), the direct comparisons cannot be relied upon. Further, the lack of any clear association between grass pollen and asthma readmission within 28 days is inconsistent with my previous findings during my doctoral research (384). Thus, this finding should be interpreted with caution until it is replicated in another large study population, as an association with childhood asthma readmissions may be underestimated (34).

6.4.2 Association between all the exposures and outcomes.

This study also sought to identify whether the indoor environment in which children live was associated with readmissions for paediatric asthma independent of grass pollen.

This study supports previous study findings that the prevention of smoking within indoor environment may be effective in decreasing hospital readmissions within 28 days and 3 months in children with asthma. Asthma admissions, irrespective of multiple and single admission groups, were found to be related to the number of parents who smoked in the home (385). Paediatric asthma recurrence was found to have parental smoking and overcrowding of bedrooms as risk factors in a study by Huss et al (386). In a US study (332) among 619 children, caregiver reports of tobacco exposure was not associated with readmission to hospital within a year, but detectable serum or salivary cotinine was associated with a 60% increased risk of readmission. In my study, the point estimate for smoking exposure at home i.e., odds ratio 1.35, despite it being not statistically significant, raises the possibility of an important effect. This insignificant finding could be due to social desirability bias to underreport tobacco

exposure and may have underestimated the risk and low number of participants in the study when stratified(387). Therefore, there is a possibility of further exploration by repeating the study using serum or salivary cotinine biomarkers (387) which could provide a more reliable estimate.

Water damage and subsequent development of mold is another vital factor that impacts the indoor environments. Poorly managed moisture responsible for mold has been linked to childhood asthma (68, 388, 389). This study found that signs of mold, and/or water damage increases the odds of readmission irrespective of the timeframe, but these estimated effects were not statistically significant. The connection between mold and asthma, however, is complicated and not fully understood. The lack of association between readmission outcomes and unusual smells in my study may reflect a bias toward underreporting as we have relied on parents self-reported information.

6.4.3 Association between pollen exposure and each outcome stratified by the home environment variables

The results demonstrated that all poor indoor environmental factors considered did not impact the risk of childhood asthma readmissions due to pollen. The models stratified by home environment variables did not show any significant association in the current study. This could be attributed to a smaller sample size due to stratification and thus, this finding warrants further exploration to confirm the association. Longitudinal studies with large sample size, or statistical power estimation taking into consideration the design effect of stratification, are crucial to ensure that such a study is scientifically valid, beneficial and cost-effective (390).

6.4.4 Strengths and limitations

The strengths of this study have been the inclusion of detailed information on respiratory health history and indoor environmental risk factors. Additionally, associations with multiple outcomes with different readmission timeframes and daily actual pollen values were used to assess the associations. On the other hand, small sample size, has been a key limitation. We understand that the presence of recall bias (self-reported information on home environment variables) and recall error can push the estimates towards null (391) because of potential underreporting and/or missing information. Although no grass pollen data was available outside of pollen season, the values were likely to be zero or close to zero. Further, lack of information on outdoor air pollutants and discharge history (392), both of which are important potential variables, could be considered as an important limiting factor.

6.5 Conclusion

The findings of this study have implications for the care of asthmatic children, despite study limitations. A cohort of children with poor indoor environment, specifically exposure to smoking at home, was found to have increased asthma readmission occurrences, indicating a target population for disease prevention. In developing management strategies for caregivers, the study suggests that information on target population's indoor environment is likely to assist care providers in establishing asthma triggering risk factors. Care providers may evaluate the key indoor environmental exposures that are known to trigger asthma symptoms and exacerbations, including the sources of indoor air pollution such as smokers in the home, use of gas stoves and appliances, and the presence of mold in the home. The ability to modify indoor environments makes addressing indoor air pollution an attractive target for disease prevention. Based on knowledge of the sources and underlying characteristics of the exposure (393), strategies including source removal, source control, and other mitigation strategies can be devised to address potentially relevant indoor exposure.

7. Synthesis

7.1 Introduction

As discussed in the literature review (Chapter 2), there has been a rise followed by a plateau in allergic respiratory diseases, particularly asthma, on a global scale. The rise and plateau in asthma prevalence are influenced by multiple factors. While genetics play a role, the rapid increase in recent decades suggests that environmental factors are the primary drivers behind this phenomenon. The 'hygiene hypothesis' and shifts in lifestyle may offer explanations for the initial rise in asthma cases. Additionally, anthropogenic climate change has emerged as a proposed contributor to the ongoing high asthma rates worldwide. Interestingly, certain regions exhibit a leveling off or even a decline in asthma prevalence, which could be attributed to genetic factors reaching a limit and changes in childcare practices(102). In the Southern Hemisphere, grass pollen has been recognised as an important aeroallergen, capable of triggering serious asthma symptoms (45). Changing climatic conditions can have a significant impact on pollen dispersion and concentration, as well as the duration and intensity of the pollen season. These changes can exacerbate the severity of seasonal allergies and asthma symptoms, particularly in children, who may be more sensitive to pollen exposure (394). This may result in an increase in asthma exacerbations, hospital admissions, and readmissions. This doctoral research studied high asthma admission periods and readmissions to gain a deeper understanding of pollen's role in asthma exacerbations among children and adolescents.

In the next section I summarise the results of each chapter separately.

7.2 Summary of findings

The specific objectives of my research were:

1. To assess the role of pollen and fungal spores on two high asthma admission periods from September 2009 to December 2011.
2. To identify high asthma admission days (HAADs) and high asthma readmission days (HARDs) within 28 days and compare it with existing methods (89) (45).
3. To study the association between grass pollen and asthma *readmissions* (*within 28 days*) in children and adolescents.
4. To analyse the association of pollen and childhood asthma readmissions with indoor risk factors as effect modifiers.

7.2.1 Role of pollen and fungal spores in high asthma admission periods

A sub-study of the Melbourne air pollen children and adolescent health (MAPCAH) cohort was conducted to answer Objective 1. The study collected individual data and daily airborne pollen and fungal levels. The normalised residuals of the asthma admission time series during the 2010 and 2011 pollen seasons were used to identify high admission periods. The running trimmed mean and standard deviation, based on a 7-day window, were used to determine the high admission days. The results were confirmed using a locally weighted scatterplot smoothing method, and 25 November 2010 and 30 October 2011 were identified as high asthma admission days during this period. The study considered two days prior to, and two days post the high admission days as the case period. The primary exposure variables were pollen (grass, weed, and tree). I also considered other aeroallergens such as ambient fungal spores (Alternaria conidia, Cladosporium spores, and Smuts) as exposures. The bi-directional case-crossover approach was used to analyse the association between aeroallergens and admission periods, while controlling for confounders such as air pollutants.

In 2010 and 2011, during the pollen season, there were 240 asthma admissions to The Royal Children's Hospital. Of these, 176 (73.3%) participated in the MAPCAH study. In 2010, the peak monthly admissions occurred in November and, of the 10 admitted on November 25th, eight agreed to participate. In 2011, the peak admissions were in October and, of the nine admissions on October 30th, five agreed to participate.

In the adjusted analysis, same day Alternaria conidia (spores/m^3) OR 1.01 (95% CI: 1.00, 1.03), p= 0.031 and grass pollen (per count/m^3) OR 1.017 (95% CI: 0.999, 1.035), p = 0.05 at lag 2 were associated with higher odds of asthma admissions. In the analysis stratified by sex, the results showed that grass OR 1.03 per grain/m^3 (95% CI: 1.01, 1.05) and weed OR 1.05 per grain/m^3 (95% CI: 0.99, 1.12) were associated with higher odds of asthma admission for boys at lag 2. Alternaria conidia on the same day was linked to higher odds for boys only in the adjusted model OR = 1.02 spores/m^3 (95% CI: 1.00, 1.04), p=<0.001.

The study found a 2-day lagged effect of both pollen and fungal spores on child asthma admissions, suggesting a priming effect on susceptible populations. Repeated exposure of nasal tissues to a particular allergen may result in mucosal sensitivity and lagged effects, which suggests a priming effect on susceptible populations (395). Boys were more susceptible than girls to grass pollen and Alternaria conidia. The differences in lung structure and function

between boys and girls may play a role in the higher incidence of asthma-related hospital admissions for boys at an early age (396). Air pollution and weather conditions did not significantly impact the relationship. Further research and analysis would be needed to determine the reasons for this finding.

Previous studies (27, 293) indicated the significance of both pollen and fungal spores as triggers for high asthma admission in children and adolescents. Nevertheless, the relationship between these allergens and high asthma admission days remains unexplored, making our results unique. This aspect of the study was published in International Journal of Environmental Health Research. DOI: 10.1080/09603123.2021.1885633.

7.2.2 Identification of HAADs and HARDs

To answer Research Question 2, I utilised data from the Victorian admitted episodes dataset (VAED) to analyse hospital admissions for asthma from 1 July 1996 to 30 June 2009. Only children who had a principal diagnosis of asthma, identified by specific International Classification of Diseases (ICD) codes were included in the study. Readmissions were defined as a subsequent admission within 28 days of the index admission discharge. The time series included 53,156 admissions, including 2,401 re-admissions.

The Seasonal Hybrid Extreme Studentized Deviate (S-H-ESD) (360) method that uses robust measures of location and dispersion through median and scaled median absolute deviation. The data were time series and decomposed into its time and seasonal components using locally estimated scatterplot smoothing. The residuals were then extracted and passed through the Rosner Extreme Studentized Test, a statistical test that determines if there are any outliers in the data. The test iterates through the data, removing any detected anomalies. In this method, the sample mean, and standard deviation were replaced by the median and scaled Median Absolute Deviation (MAD) for improved robustness; the residuals had a unimodal distribution which made the use of the Extreme Studentized Deviate (ESD) appropriate. The method in the study was also compared with two previously used methods i.e., Model 4 Standard Deviation (M.4SD)(89) and Trimmed Mean Quantile Quantile plot (TMQQ)(45).

The number of daily hospital admissions for asthma ranged from 0 to 51 and daily readmissions ranged from 0 to 5. Only 0.3% of days had 4 daily readmissions, and 0.04% of days had 5 daily readmissions. S-H-ESD identified 17 days (0.4%) as HAADs with 33 to 51 admissions, TMQQ identified 23 days (0.5%) with 14 to51 admissions, and M.4SD identified 7 days (0.2%) with 28 to 51 admissions. With S-H-ESD, 25 days (0.5%) were classified as

HARDs with daily readmissions ranging from 3 to 5 ($p < 0.05$). TMQQ classified 23 days (0.5%) as HARDs with daily readmissions from 2 to 5 and M.4SD categorised 18 days (0.4%) as HARDs with daily readmissions from 3 to 5.

The results of this chapter showed that S-H-ESD had a better performance in detecting HAADs and HARDs, with greater sensitivity and fewer false positives or false negatives, compared to the other two methods. The M.4SD method performed well in detecting HARDs but had limitations in detecting HAADs. The TMQQ method struggled with both HAADs and HARDs, and its performance was influenced by its features and choice of threshold criterion. The S-H-ESD method performed consistently and effectively without requiring an a priori or ad-hoc definition of high days.

This is the first application of the S-H-ESD method for the identification of HAADs and HARDs. Further investigation is necessary to validate the findings of our study. The findings from this part of my research were published in Diagnostics journal. DOI: 10.3390/diagnostics12102445

7.2.3 Role of pollen in asthma readmissions within 28 days

To address Research Question 3, I used the same dataset as in Objective 2, except for the data from 1996, which was excluded due to the unavailability of pollen data. In this chapter, the outcome was readmissions that were characterised in the same manner as in Chapter 5, as a subsequent admission occurring within 28 days of the discharge date from the first admission (323). The primary exposure variable in the study was daily pollen counts in Melbourne, Australia, which were sampled from October to December annually to coincide with the peak grass pollen season. It was assumed that the daily grass pollen count is close to zero during the remaining months (380). The peak pollen season, which was defined as the period from October to December, was another exposure considered. Generalised additive models (GAMs)(397) were used to assess the association between pollen season, actual pollen counts and readmissions within 28 days. Lagged and cumulative effects of pollen were also studied. Daily weather and pollution data were considered as confounding variables. An examination of effect modification by age and sex was conducted.

During the entire study period, 4.53% (2152 readmissions) of these cases resulted in an asthma readmission within 28 days of discharge. The highest daily mean readmissions (with

SD) were observed in the 2 to 5-year age group at 0.26 (0.52) and for boys overall at 0.27 (0.54).

During the peak pollen season, the mean daily readmissions were above the overall mean. The models I fitted demonstrated that there was an association between the grass pollen season and mean daily readmission rates, which were 1.44 times higher during the pollen season compared to outside of it (95% CI: 1.03, 2.02), $p \leq 0.05$. The analysis stratified by sex showed that the association between mean daily readmission rates and daily pollen concentrations was similar for boys and girls. When I analysed the models further by age group, I found that in the youngest group (2-5 years), there was an association between the grass pollen season and daily readmission rates, with an incidence rate ratio of 1.99 (95% CI = 1.26, 3.14, $p<0.01$).

The results of the lag 2 daily pollen concentrations and the model indicated a significant nonlinear association with all daily readmissions for all sex and age groups except for children aged 13-18. There was weak evidence for an association between the mean daily readmission rate and grass pollen at lag 0, only at concentrations above 128 grains/m^3. For lag 0, there was a significant impact of grass pollen counts on daily readmission rates overall, and the association between daily readmissions and grass pollen concentration was significant for the 13–18-year age group.

The results indicated that same day exposure to grass pollen counts had an impact on readmission rates for all children, with a stronger effect seen in older children (13-18 years). This might be because older children/adolescents spend more time outdoors, which could contribute to greater exposure to pollen. The association between asthma readmissions and daily pollen on the second day after exposure seemed to mainly impact younger children. This could be due to a "priming" effect of grass pollen on readmissions. Younger children have different respiratory physiology and function compared to older children and may be able to tolerate airway changes better, so it takes them longer to show symptoms after increased pollen exposure (398). However, older children have more bronchial hyperresponsiveness and show symptoms sooner.

This study is the first to examine the relationship between pollen and readmissions, so comparisons were limited. In summary, while the association between seasonal pollen exposure and asthma readmissions may not be surprising, this study provides valuable insights into the timing, and age-related variations of this association. The findings from this analysis were published in Pediatric Allergy and Immunology. DOI: 10.1111/pai.13880.

7.2.4 Indoor environment as an effect modifier for pollen associations with asthma readmissions

To address Research Question 4, I utilised the data from the Asthma Re-admission Study, which was a cohort study that was carried out by the Murdoch Children's Research Institute (MCRI) between 1 September 2017 and 31 August 2018. The data was obtained through a standardised questionnaire, with additional details being obtained by linking the participant records with the Victorian Admitted Episodes Dataset (VAED) and Victorian Emergency Minimum Dataset (VEMD) using the child's name, date of birth, sex, and Medicare number. Grass pollen was considered as primary exposure variable, and daily counts were available from October to December (peak grass pollen season in Melbourne, Australia); days outside of the detectable period were assumed to have a daily grass pollen count of zero. The outcomes for the study were readmission within 28 days, readmission within 3 months, readmission within 1 year, readmission within pollen season. The indoor variables i.e., smoking exposure at home by parents, carpeted rooms, unusual smells, and water leakage were considered as possible effect modifiers.

During the study period there was a total of 299 (39.0%) readmissions of which 56 (18.7%) were due to asthma or wheezing within 28 days, representing7.3% of the total admissions. Within three months, 121 (15.8%) children had one or more readmissions. About 112 (14.6%) of the children had a readmission within the pollen season, which represents 40.5% of all readmissions. The exposure to pollen during the pollen season was associated with an increased likelihood of readmission with odds of 1.04 (95% CI: 1.04, 1.06), $p<0.001$ per grain/m^3 increase. The adjusted estimates showed a significant increase in the odds of any readmission during the pollen season aOR 1.01 (95% CI: 1.00, 1.02), $p=0.02$.

Grass pollen exposure was significantly associated with readmission within the pollen season OR 1.05 (95% CI: 1.04, 1.06), $p<0.001$, after adjusting for the effect of home environment variables. Actual grass pollen concentrations were not linked to readmission within 28 days or 3 months in the main model nor when stratified by smoking exposure at home, carpeted rooms, unusual smells, and signs of mold and/or water damage. However, any readmission within one year was 1.01 times more likely to occur with a unit increase in grass pollen concentrations, among participants with a carpeted room OR 1.01 (95% CI: 1.00, 1.01), $p=0.03$. Smoking exposure at home increased non-significantly the odds of readmission within 28 days, and within 3 months after controlling models for pollen or other indoor risk factors.

No interaction effects between home environment variables and pollen exposure were observed.

In this study, grass pollen increases the odds of readmissions within one year, which contradicts a previous study (124). It is, however, not possible to compare the two studies directly because of differences in time frames and the lack of actual pollen data values in the previous study (124). Further, the result of my study indicates that there might be an association between smoking exposure at home and the risk of an outcome, even though it was not statistically significant. Additionally, this result may not be reliable due to possible underreporting of tobacco exposure by parents who were biased towards presenting themselves in a socially desirable manner. To address this limitation, future studies could consider using biomarkers such as serum or salivary cotinine to provide a more reliable estimate of tobacco exposure (399). The risk associated with smoking can be more accurately assessed and better understood through the use of these biomarkers.

The results of my study highlight the complex relationship between childhood asthma readmission and various factors such as poor indoor environment and pollen exposure. While the results suggest that indoor environmental factors did not have a statistically significant impact, some estimated effects were contributing to the increase risk of asthma readmission, it is important to note that the results were limited by the sample size, which was further reduced due to the stratification process. This means that there is a need for further exploration of this topic, particularly through more extensive and scientifically rigorous research.

7.3 Methodological strengths and limitations

The strengths and limitations of the methodology described in Chapters 3,4,5 and 6 will be discussed in this section.

7.3.1 Study design and sample size

The first Research Question was addressed through the Melbourne Air Pollen Children and Adolescent Health study, which was conducted from September 2009 to December 2011. We used a bi-directional case-crossover design as it is suitable for the evaluation of transient short-term exposures, such as pollen, other allergens, air pollutants, or weather changes, on the risk for individuals of short onset events, such as hospitalisation (42). It gives a high temporal resolution that is difficult to achieve with other study designs (400). It controls for time-invariant individual risk factors (e.g., age, sex, genetics) by comparing the exposed individual to themselves, reducing the potential for confounding (400). However, the

limitation that needs to be considered in the design is that individual risk factors associated with childhood and adolescent asthma, such as lifestyle factors, would need to remain stable over time. If this assumption is not met, the results may be biased (401).

The second and third Research Questions were answered using the VAED dataset. It provided data on children over 13 years, which allowed longitudinal analysis of asthma hospitalisations and readmission outcomes. Moreover, it resulted in a large sample size, which, at a given statistical level, increased the potential of detecting associations with repeat hospitalisations, as discussed in Chapter 5. As it was a comprehensive database that encompassed all childhood asthma hospitalisations from both public and private hospitals, it enabled the comparison of the three methods (S-H-ESD, TMQQ, M.4SD) in Chapter 4. However, the accuracy and completeness of the data in the VAED may be limited by the quality of data collection and reporting processes in the hospitals, and the lack of detailed information on some factors that are important for asthma research, such as socioeconomic status(402), and lifestyle factors(403). In Chapter 4, the absence of individual-level data is not a significant concern, as the focus was primarily on introducing the method. Although I assessed population level rather than individual level associations in Chapter 5, it is possible that residual confounding might have occurred, which will be further discussed in Section 7.3.5.

To answer my fourth question, I used a case control study design where I deemed the cases as children readmitted within 28 days, readmitted within 3 months, readmitted within 1 year, and readmitted within pollen season. Controls are children not readmitted within 28 days, not readmitted within 3 months, not readmitted within 1 year, and not readmitted within pollen season. A case control design is useful when the number of participants with the outcome is small (404), such as for this study, where there were only 56 children who were readmitted within 28 days. This resulted in a case control ratio of approximately 1:12.5. As the cases and controls were from the same study base and given the small number of cases, this improved the statistical precision of the analyses (405). The design also allowed me to examine multiple risk factors such as pollen levels, smoking exposure at home, carpeted rooms, unusual smells, and signs of mold and/or water damage for the outcomes. Data on participants' indoor environments were collected using a standardised questionnaire; this ensured that all participants were asked the same questions in the same way, which can reduce the risk of measurement error (406). However, it is a well-known fact that every study design has its own limitations and drawbacks. Due to the small number of readmissions within 28 days in this study (n = 56), it was highly possible that some associations might not have been detected,

especially when I undertook stratification of the models by indoor variables. However, there was also the possibility of no associations. The questionnaire utilised to gather information regarding indoor variables, such as exposure to smoking at home and typical odours at home, might have been susceptible to social desirability bias.

7.3.2 Statistical analysis

A thorough statistical analysis has been employed throughout the study, as described in all my results chapters

For Research Question 1, the first step was to identify the HAAD periods using the method employed in Silver et al's (45) study. The method had some advantages such as its use of normalized residuals to identify HAADs, which helps to account for fluctuations in the data and thus avoiding false positives (407). The 31-day time frame used in the analysis helps to reduce the impact of long-term trends on the results. Additionally, the use of a threshold of 4.5 standard deviations above the local mean provides a clear criterion for identifying HAADs. However, limitations exist, and these include the use of the mean and standard deviations which are highly impacted by impacted by outliers and trimming 50% of the data raises the risk of over smoothing, which can restrict access to information in the data, limiting sensitivity to detect seasonal trends in time series (see Literature Review Chapter 2). Furthermore, using 4.5 standard deviations as a cut-off is not supported by any validation research and its effect on the sensitivity or positive predictive value of HAAD classification is unknown. The second step in the analysis was the application of bi-directional case-crossover analysis that used regression models (408) to estimate the effects of aeroallergens on periods of HAAD and allowed the adjustment for potential confounders and other variables.

For Research Question 2, a new approach was introduced to address the limitations of existing methods in classifying HAADs. The advantages of this new method were the use of robust measures for determining the central tendency and spread of the data, specifically the median and the median absolute deviation. The robustness of the method was strengthened by the implementation of a robust weighting technique in calculating the residuals from the time series while allowing for long-term and seasonal trends. The application of the ESD test also provided statistical evidence at the 0.05 level and did not rely on ad hoc cut-offs such as 4.5 standard deviations from the mean for the residuals. Moreover, the effectiveness of the S.H.ESD method had been previously validated and found to have a high sensitivity and positive predictive value (PPV) of 96% and 100% respectively, based on statistical evidence at a significance level of 0.05 (24).

The third Research Question was addressed using Generalised Additive Models (GAMs). GAMs offer a significant advantage in being able to model both linear and non-linear relationships between pollen and readmissions within 28 days (as described in Chapter 5). They allow for a better fit of the model compared to a solely linear specification, particularly when the relationship between the variables is complex, as was the case (409). To evaluate model fit, information criteria such as the Akaike Information Criterion (AIC) were employed. Akaike Information Criterion measures the quality of each model's fit to the data, with lower AIC values indicating better empirical support for the model. Akaike Information Criterion values were used to compare the models detailed in Chapter 5.

7.3.3 Pollen and pollen season exposure ascertainment

Based on evidence from 1995 by Ong et al (380), and more recent work by Beggs et al. (410), grass pollen season (Chapters 3, 5, and 6) was defined as being from October to December. Although there may be ambient pollen in September and January, these months were not included in the definition of grass pollen season, in order to disregard extremely low, clinically irrelevant pollen counts leading up to the start and following the end of clinically important ambient pollen concentrations (410). Pollen counting in Victoria, Australia, is conducted by the School of Botany (now Biosciences) at The University of Melbourne, from where the Ong et al. (380) study originated. Since the late 1990s until the present time, ambient pollen concentrations have been recorded almost exclusively between October to December. There were just two years, between September 2009 to December 2011, in this 30+ year timeframe when ambient pollen concentrations were recorded continuously in Victoria, the data of which was used in this study, as described in Chapter 3. The data indicated that January pollen levels were low (2010 mean 3.6, median 2; 2011 mean 8.1 and median 3) compared with October (2010 mean 63.1, median 32; 2011 mean 24.0, median 15), November (2010 mean 60.2, median 34; 2011 mean 71.4, median 57) and December (2010 mean 45.5, median 47; 2011 mean 17, median 17) in the same years (Chapter 3).

There may, indeed, be low levels of ambient grass pollen in January, as noted in some studies (32, 380, 411). Ong et al's (380) study showed that both major and minor grass pollen peaks almost always occurred in October, November, or December, except for just one season in 1990 where the peak occurred in early January. In all other years, January grass pollen levels were very low (380). Importantly, Ong et al. (380) further observed that November and December typically accounted for between 74%-95% (mean 81%) of total seasonal grass pollen counts (380), except for the 1976-77 years when these months accounted for only 58%

of the total count, and December-January accounted for 75%. Ong et al. put this down to unusual meteorological conditions. I also conducted a sensitivity analysis in which the pollen season was extended to include January, which showed that the association between daily readmissions and pollen season was lost; IRR 0.86 (95%CI 0.61, 1.21), p = 0.38 (Chapter 5). However, this result was affected by misclassification bias because January was characterised by low grass pollen concentrations and, as just discussed, January also had the lowest daily readmissions of the year (see Chapter 5, Figure 1). This meant that the January data dominated the association between pollen season and daily readmissions in October to December, which I knew was not the case (see Chapter 5, Figure 1). It was for the same reasons that I did not include September, even though September may also have some grass pollen counts. For example, in September 2009 (as observed in Chapter 3), the highest recorded grass pollen count was 14, with a mean of 1.8 and a median of 0. In 2010, the maximum grass pollen count was 5 with a mean of 0.2 and a median of 0. In 2011, the maximum grass pollen count was 3 with a mean of 0.6 and a median of 0. Ong et al. (380) showed that some concentrations in September were similar to some of those in January. In Melbourne, plane trees tend to flower in late winter to early spring, typically from August to October. However, the exact timing can vary from year to year and may be influenced by factors like temperature and weather patterns (379). Haberle et al (379), using MAPCAH pollen data collected between September 2009 and December 2011, reported that the months from February to September in Melbourne, Victoria, would correspond to the timeframe in which the 10% of the total annual pollen count was collected on the trapping surface. Except for the period between September 2009 and December 2011, over which the MAPCAH study ran, recent grass pollen distributions, including any impacts of climate change, outside of October-December in Victoria are not well understood/documented. There has been calls for more consistent monitoring of pollen right across Australia which would resolve this problem (88).

Another limitation to consider is the lack of pollen data at the individual level in my research. Pollen data collected at a population level may not accurately reflect the exposure of children to specific types of pollen. This can lead to misinformed conclusions about the relationship between specific types of pollen and asthma outcomes. As pollen levels can vary greatly within a small area, averaging the data at a population level because of a lack of understanding of the spatial distribution of pollen and its association with childhood asthma admissions and readmissions, can mask these differences. Also, averaging the pollen data at a population level can make it more difficult to establish cause-and-effect relationships between pollen exposure and asthma outcomes. This is because individual factors such as genetics,

lifestyle, and environmental exposures can confound the relationship between pollen and asthma. It would be ideal to precisely evaluate each child's exposure to pollen when examining the connection between pollen exposure and health outcomes, as this would reduce exposure and spatial misclassifications, and thus decrease the potential for bias or attribution errors. However, this may be difficult to do at a population health level. In environmental epidemiology, a person's exposure to outdoor factors, such as pollen, is typically estimated from monitoring stations (412).

In Melbourne, pollen counting is typically performed using a device known as a Burkard Volumetric Spore Trap, or Burkard trap in short. The Burkard trap collects air samples and deposits pollen onto a microscope slide, which is then stained and examined under a microscope to count the number of pollen grains present. The number of pollen grains is then used to calculate a pollen concentration, which is expressed in grains per cubic meter of air. Pollen monitoring stations in Melbourne use this method to monitor the levels of different types of pollen in the air, and this information is used to estimate individual exposure to pollen and to provide public health warnings about high pollen days. In my research, the method of assigning exposure by using a single daily measurement of pollen concentration from one pollen monitoring station could have resulted in a non-differential misclassification bias due to the factors mentioned in above paragraph. The release and distribution of pollen can be affected by local weather conditions, making daily averages unreliable. Additionally, the placement of the monitoring station and wind direction can affect the accuracy of the measurement. Contradicting these limitations, research has shown that using data that from a single monitoring station provides a practical estimation within a 30-kilometer radius (413) and be a good proxy for inhaled dose, especially in areas where local emissions are not a factor (412). In saying that, a study (414) analysed and reported that, when the levels of pollen grains are low, multiple sampling sites may be necessary to understand their distribution within a town, if that information is important. However, if the grass pollen count is relatively high, then only one site may be sufficient to detect effects.

7.3.4 Definition of asthma hospitalisation

In Chapter 3 of this thesis, asthma hospitalisation is defined as an admission for asthma with a primary diagnosis code of J45 in accordance with the International Classification of Disease, 10th Revision (ICD-10-AM) (415). Most international studies have used either ICD-9 codes (271, 416-418), ICD-10 codes (419), or a combination of both ICD-9 and ICD-10 codes (420) to define asthma hospitalisation based on clinical coding in databases. However,

in Chapters 4, 5, and 6, ICD-9 code 493 was used up to 1998, and ICD-10 codes (J45 or J46) were used thereafter. This is due to the overlap of the study time frame and the transition to the updated ICD-10 coding system. There is no difference between ICD-10 and ICD-10-AM codes when it comes to diagnosing asthma.

The benefit of utilising validated hospitalisation diagnosis codes is that it ensures all asthma admissions are accounted for, as this is a critical database for hospital funding. However, there may have been some misclassification of diagnoses, which would have been non-differential. I excluded children under two years to minimise the risk of misdiagnosis bias, as accurately diagnosing asthma in this age group can be masked by effects of wheezing and/or respiratory viruses, and therefore challenging. Asthma is more accurately diagnosed in children aged six years or older, as they are better able to communicate their symptoms and perform lung function tests. This is because asthma symptoms can overlap with those of other respiratory conditions, and young children may not be able to express their symptoms clearly or consistently (421).

7.3.5 Residual confounding and effect modification

Individual level data such as a park variable (grass outside your home or residence in front of a park) and lifestyle factors (going to a park or engaging in outdoor exercise when pollen levels are high) can be confounding factors to consider when examining the relationship between pollen and childhood asthma admissions (Research Question 1). By considering individual level data, researchers can better control for these confounding factors and obtain more informative results. However, the main strength of case-crossover analysis used in Chapter 1 is that the individual level data is not necessarily required. This is because the case-crossover design uses the same individual as their own control, eliminating the need to control for individual level differences (422). By comparing within individuals, the effects of unknown time-invariant confounders are controlled for.

The main limitation in the analysis presented in Chapter 5, which examined the association between pollen and readmissions within 28 days, is the absence of individual data on patient-level factors, such as exposure to other types of pollen, sensitisation, viral infections, hay fever, and second-hand smoking. These factors could be considered as important confounders and/or modifying factors in the relationship between pollen exposure and readmissions (423). Despite this limitation, my study used a time series of aggregated daily counts, which allowed for the examination of patterns in the data over time. However, this method does not allow for the inclusion of individual-level data, which would provide a more

comprehensive understanding of the relationship between pollen exposure and asthma readmissions.

7.3.6 Generalisability

The results of a case-crossover study of Research Question 1 are only generalisable to populations with similar characteristics as the study participants. The generalisability of this study is also limited by the fact that it was conducted in Melbourne, Australia and may not be applicable to other regions with different climates and allergens. For example, the types of grasses that produce pollen and the levels of exposure to them can vary widely depending on the location (23, 379). Similarly, the levels of fungal spores in the air can also vary based on the climate and geography of a region (424). Patterns of sensitisation are a complex interplay between environmental and genetic influences, but environmental influences may have the stronger hand (425). A child's sensitivity to specific pollen or fungi is determined by the geographical distribution of these allergens (309, 426). Nevertheless, the fact that grass pollen is the most widespread group of pollen allergens globally (427) makes the study highly relevant and capable of being applied to other settings.

Another factor that can limit the generalisability of the findings in Chapter 3 is that the study only considered the association between aeroallergen exposure and childhood asthma peak periods during two grass pollen seasons and may not be applicable to other seasons. The impact of aeroallergen exposure on childhood asthma admissions during other seasons has been studied (27, 293) but more studies are needed to better understand these associations in other seasons.

The method S-H-ESD described in Chapter 4 for the classification of high asthma admission days has high accuracy and can be applied in other settings to accurately identify and distinguish these events, making it a useful tool for asthma research and care. However, the VAED used in Chapters 4 and 5 is limited to data from Victoria, Australia, and may not be representative of asthma hospitalisations and readmissions in other regions or countries. Chapter 4 is mainly focused on introducing the method, so the issue of the results' generalizability is not a concern. It is important to note this limitation for Chapter 5 and to consider the potential impact on the conclusions drawn from the study when interpreting the results.

A key limitation of the study described in Chapter 5 is its small sample size, which restricts its generalisability to the general population. The small size was due to the short

duration of the study and the outcome, i.e., readmissions within 28 days, which was approximately 7%. Despite this, a significant amount of information was collected on various confounders and individual-level data, making the study a valuable starting point for generating hypotheses worthy of future investigation.

7.4 Implications and recommendations

The section on implications is divided into three subheadings: research, practice, and policy.

7.4.1 Research implications and recommendations:

The findings of Research Question 1 emphasise the critical importance of raising awareness about the impact of exposure to grass pollen and fungal spores on hospital admissions in children with asthma. Supporting initiatives aimed at increasing public understanding of aeroallergen exposure as a significant problem can potentially lead to a reduction in asthma-related hospital admissions during pollen seasons. While intervention studies (428) have mainly focused on reducing exposure during periods of high risk, such as thunderstorms, their strategies can also be applied throughout the year. For instance, daily monitoring of pollen and fungal spore levels and providing warnings to individuals with asthma can be effective in reducing exposure during thunderstorm periods and high asthma admission days. However, this monitoring may not be widely disseminated to all at-risk groups, including culturally and linguistically diverse (CALD) and socially disadvantaged populations, which may limit the effectiveness of these interventions. Therefore, future research could explore effective ways to disseminate these interventions to these groups. Similarly, allergen-specific immunotherapy or pharmacotherapy can be effective in reducing the impact of grass pollen and fungal spores on asthma. To maximize the benefit from these treatments, which are typically limited to individuals with hay fever and severe asthma, it is imperative to continue involving healthcare professionals, such as General Practitioners through their professional body, The Royal Australian College of General Practitioners (RACGP) (429), in discussions on how to better prepare patients with asthma for the pollen season. This could include identifying children who may benefit from these interventions, ensuring timely access to medications and therapy, and developing personalised management plans to optimise asthma control during the pollen season.

The results from the analysis of hospital admissions for asthma (HAAD) on 25 November 2010 suggest that the storm front that reached Melbourne the previous evening

was not the only factor contributing to the spike in admissions (430). The significant association between aeroallergens and hospital admissions highlights the importance of considering airborne allergens as a potential factor in future asthma epidemic events. In the light of these findings and the growing concern over the impacts of climate change, it is increasingly important to consider the role of aeroallergens, air pollution, and other potential factors in the occurrence of asthma epidemics. Climate change is expected to worsen air quality and increase the frequency and severity of extreme weather events, both of which can exacerbate the negative effects of aeroallergens and air pollution on respiratory health (431). Additionally, climate change may also lead to changes in plant growth and distribution, which could alter the types and levels of aeroallergens present in the environment (431). Given these potential impacts, it is critical that future studies investigate the complex interplay between climate change, aeroallergens, and air pollution in the occurrence of asthma epidemics. By better understanding these relationships, we can develop more effective strategies for preventing and managing asthma and other respiratory diseases in the face of climate change.

Research Question 2 highlights the need for further refinement of methods to identify hospital admissions and readmissions in children with asthma. This opens up the potential of developing predictive models for HAADs and HARDs. Relying on the accuracy of the SHESD method to accurately classify HAADs and HARDs, models can be developed and trained to predict future high pollen days. Suitable covariates on which to base a predictive model would need to be identified and the model could be developed using standard statistical approaches, machine learning techniques (e.g., random forest, neural networks), or a combination ensemble method. The model would need to be internally and externally validated using model metrics based on area under the receiver operator curve, calibration, and decision curve analysis (432-434). This predictive model has the potential to provide early warnings for medical systems to allocate extra resources, if required.

The implications of Research Question 3 are not limited to the need for developing treatments that consider exposure to grass pollen in children with asthma. They also highlight the importance of collecting more data on repeat admissions to assess the synergies between environmental exposures and asthma outcomes. Additionally, future studies could focus on extending these findings to other regions, as the effects of environmental factors on asthma outcomes may vary depending on geographic location. By doing so, we can gain a more comprehensive understanding of the underlying mechanisms and potential interventions for reducing the impact of environmental factors on asthma outcomes. Moreover, the 2-day lag effect observed in this study suggests the need for more research to fully understand the

mechanisms underlying the two-day effect and to determine the extent to which priming plays a role, which could inform the development of new treatment strategies for asthma.

The findings related to Research Question 4 adds to the understanding of how assessing indoor factors as an effect modifier aids in better understanding the contribution of outdoor pollen as a trigger for asthma admission/repeat admission in children. This could lead to a more comprehensive understanding of the impact of environmental factors on asthma in children, and the development of treatments that target indoor environmental factors, to reduce the incidence of asthma exacerbations in children.

7.4.2 Practice implications and recommendations

The current results are not sufficient to make specific practice recommendations because further research with more extensive methodologies is required to validate them. Nevertheless, these findings have important practical implications for healthcare providers and children with asthma. Providers, including hospitals and healthcare professionals, should be aware of peak grass pollen seasons and the potential impact of fungal spores on asthma. This information can be used to educate parents and children about proactive measures, such as avoiding outdoor activities during high-risk periods, and keeping windows closed, to manage their symptoms during these times. Emphasising the importance of health literacy before pollen seasons can also help parents be more proactive in managing their children's asthma. Hospitals could incorporate this knowledge into their monitoring systems to flag potential peak periods and take appropriate proactive measures to support patients and families.

The use of S-H-ESD to detect HAADs and HARDs is a novel approach used in my research. While further research and validation are needed to establish the reliability and accuracy of the approach, the potential of S-H-ESD to inform health care providers' understanding of asthma admissions and readmissions patterns could have a significant impact on clinical decision-making and patient management strategies. This information could help providers identify high-risk periods and possible triggers for asthma exacerbations, allowing for more effective and specific preventative measures and personalised treatment plans. By improving asthma control and reducing the frequency of hospitalisations, providers can ultimately enhance the quality of life of patients with asthma.

To reduce the risk of paediatric asthma readmissions during the grass pollen season, healthcare providers could proactively identify and target families at high risk of repeat admissions. This can be achieved by utilising research that has already developed a risk profile,

and working with their GPs to ensure that these families are identified and given personalised treatment plans before the pollen season begins. Providers should also encourage parent/carer/guardian to monitor pollen forecasts and adjust their behaviours accordingly. By targeting high-risk families early, healthcare providers can help prevent asthma exacerbations and reduce the burden of readmissions on patients and their families.

7.4.3 Policy implications and recommendations

While the evidence in this thesis provides a foundational understanding, specific policy recommendations require further research and data analysis for comprehensiveness and actionability. Nevertheless, my research offers valuable insights for policy development in mitigating asthma triggers in children. Policymakers should continue to prioritise the monitoring and management of airborne allergens such as grass pollen and fungal spores (435), which can help allocate resources effectively, and implement strategies to reduce asthma-related hospital admissions. Efforts by government departments, such as the Department of Health (DoH) to address this issue should be supported and expanded where necessary. The results of the research also suggest that policymakers should target interventions to high-risk populations and prioritise funding for research into the relationship between grass pollen exposure and paediatric asthma readmissions.

Additionally, policies should be developed to incentivise families and households, especially those under the social housing scheme, to improve the indoor environment for asthmatic children. This could involve local government working together with these families to provide resources and education on reducing indoor air pollution, as well as financial support for necessary changes. Some government agencies and organisations have already implemented programs and initiatives aimed at improving indoor air quality and reducing exposure to environmental pollutants for all individuals, including children with asthma (436). These programs may include funding for research, education and awareness campaigns, and technical assistance for families and households to make necessary changes to improve indoor air quality.

The goal of these policies should be to reduce exposure that is likely to trigger the occurrence and severity of asthma attacks in children and improve their overall health outcomes. It is important for policymakers to prioritise research in this area to continue to advance our understanding of the impact of indoor air pollution on asthmatic children, especially during pollen periods and inform future policy decisions.

8. Conclusion

At the start of my doctoral research, I thoroughly analysed the available evidence for the associations between grass pollen in the outdoor environment and hospitalisations and readmissions for asthma in children and adolescents. I then carried out four studies using three different sets of data to study the relationships between outdoor pollen exposure and asthma hospitalisations during peak pollen season, and readmissions. I also analysed how certain risk factors and asthma triggers may modify these effects.

In summary I found the following regarding child/adolescent asthma outcomes:

- There was limited understanding of the contributions of outdoor grass pollen and fungal spores to high asthma admissions periods during peak pollen season.
- There was a need for a robust statistical technique that has excellent classification accuracy in classifying high asthma admission days (HAADs) and high asthma readmission days (HARDs).
- There was limited understanding of the contributions of outdoor grass pollen on asthma readmissions.
- The role of pollen on readmissions with indoor risk factors as effect modifiers has yet to be explored.
- Grass pollen and outdoor fungal spores, particularly Alternaria, were associated with child and adolescent asthma hospitalisation.
    - Same day Alternaria significantly associated with asthma admissions.
    - Grass pollen at lag 2 significantly associated with asthma admissions.
    - For boys, grass pollen and weed pollen at lag 2 were associated with higher odds of asthma admission.
    - Same day Alternaria conidia was linked to higher odds of admissions for boys.
- The Seasonal Hybrid Extreme Studentised Deviate (S-H-ESD) method had a better performance in identifying HAADs and HARDs, with higher sensitivity and fewer false positives or negatives when compared to the Trimmed Mean Quantile Quantile plot (TMQQ) and Model 4 Standard Deviation (M.4SD) methods.
- There was an association between grass pollen season, ambient grass pollen and mean daily readmission rates.

- Mean daily readmission rates were higher during pollen season compared to outside pollen season.
- The analysis, stratified by sex, showed that the relationship between average daily readmission rates and pollen season was similar for both boys and girls.
- The analysis, stratified by age group, showed that there was an association between average daily readmission rates and pollen season only in the younger age group.
- Daily pollen concentrations at lag 2 showed associations for children in age groups 2-5 years, and 6-12 years, and not for adolescents13-18 years.
- Same day pollen concentrations significantly increased readmissions among older children (13-18 years).

- Some indoor risk factors such as carpeted room and smoking exposure at home may modify the association between outdoor grass pollen and childhood asthma readmissions.
  - During the pollen season, exposure to actual ambient pollen concentrations was related to higher odds of readmission.
  - In the models that were stratified by smoking exposure at home, presence of carpet, unusual odours, signs of mold and water damage, exposure to grass pollen was not associated with readmission within 28 days or three months.
  - Among children who had a carpeted room, any readmission within one year was associated with grass pollen concentrations.

In conclusion, my doctoral research has filled important gaps in our understanding of exposure to outdoor pollen and asthma hospitalisations and readmissions in children and adolescents. The study found a significant association between high asthma admission days in Melbourne and exposure to both grass pollen and Alternaria conidia during peak grass pollen season. The S-H-ESD method was identified as having better performance in detecting high admission days and readmission days. Furthermore, the study found that childhood asthma readmissions within 28 days were higher during peak grass pollen season, and increased with cumulative exposure, particularly for younger children. The relationship between hospital readmissions, with different time frames for asthma and pollen exposure, was also explored, with the results showing that grass pollen increased the likelihood of readmissions within a year. However, there was limited power to detect any effect modification by indoor risk factors.

Further research with large study samples, over longer periods of time with improved exposure assessment methods, and inclusion of important individual information that relate to admissions and readmissions, are needed to see if my findings can be replicated. Although questionnaires have been utilised to assess indoor risk factors, future research needs to focus on improving the standardisation of exposure assessment by incorporating actual measurements for mold, dampness, and other potential indoor asthma triggers.. Grass pollen is one of the most prevalent airborne allergens and has a significant impact on respiratory health, particularly for children with allergies or asthma. While it is not possible to control the presence of grass pollen in the air, it is important to understand how its effects on respiratory health can be attenuated or prevented to benefit public health.

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Appendix 1: Supp A- Caregiver Survey

Caregiver Short Interview

1. Caregiver's date of birth

_____

2. Caregiver sex

◯ Female
◯ Male
◯ Other

2a. Please specify caregiver sex

_____

3. Number of caregivers in the household?

_____

4. Number of children in the household?

_____

5a. *Optional* Last year's household income before tax?

_____

5b. *OR* If they prefer to respond in income brackets:

◯ Less than $20,000
◯ $20,001 to $40, 000
◯ $40,001 to $60,000
◯ $60,001 to $80,000
◯ $80,001 to $100,000
◯ $100,001 to $120,000
◯ $120,001 to $140,000
◯ $140,001 to $160,000
◯ More than $160,001

5c. *OPTIONAL* Does the caregiver receive government support payments? (i.e., Centrelink payments)

◯ Yes ◯ No

5d. *OPTIONAL* Does the caregiver have a Government concession or healthcare card?

◯ Yes ◯ No

6. Caregiver highest level of education

Please note, if a caregiver has a diploma select 'Certificate 1-4'

◯ Primary School
◯ High School (Secondary Certificate of Education)
◯ Certificate 1-4
◯ Undergraduate Degree
◯ Post Graduate Degree

7. Caregiver relationship to the child

◯ Mother
◯ Father
◯ Grandparent
◯ Aunt/Uncle
◯ Sibling
◯ Legal Guardian

8. Is the child exposed to cigarette smoke in the home?

Please note, if the participant says the parent smokes outside the home and not inside or near the child we are counting this as 'yes'

◯ Yes
◯ No

9. Is 's room carpeted?

◯ Yes
◯ No

10. Are there any unusual smells inside the home (mouldy, musty, damp, earthy or chemical)?

If the participant indicates the mould is in very small amounts or is only around for small periods of time please mark as no

◯ Yes
◯ No

11. Are there any signs of mould, water damage or condensation in the home that are bigger than an A4 piece of paper?

◯ Yes
◯ No

Patient (child's) GP

12. Does the child have a regular GP?

◯ Yes
◯ No

12a. Regular GP Type

◯ Unknown (no GP info)
◯ GP
◯ GP Practice

12b. Does the caregiver give permission for the MCRI research team to contact the child's regular GP?

◯ Yes
◯ No

12c. GP Title

◯ Mr
◯ Miss
◯ Ms
◯ Dr
◯ A Prof
◯ Prof

12d. GP first name	_____
12e. GP last name	_____
12f. GP Address Line 1/Name of GP Practice	_____
12g. GP Address Line 2/GP Practice Street Address	_____
12h. GP Practice City/Suburb	_____
12i. GP Practice State	◯ VIC ◯ TAS ◯ NSW ◯ SA ◯ QLD ◯ WA ◯ NT ◯ ACT
12j. GP Practice Post Code	_____

Appendix 2: Supp B- GP Survey

GP Survey

1. What is your gender?

- ○ Female
- ○ Male
- ○ Other (please specify)

1.1 Please specify your gender

_____

2. How many years have you been working as a general practitioner?

- ○ Less than 6 years
- ○ 6-15 years
- ○ More than 15 years

3. Have you ever had formal paediatric health care training outside of your FRACGP (or equivalent)?

- ○ Yes
- ○ No

3.1 Please specify the type of formal paediatric health care training you completed outside your FRACGP (or equivalent).

4. Approximately, how many children (0-18 years) do you see per week?

- ○ Less than 11
- ○ 11 to 20
- ○ More than 20

5. What proportion of children (0-18 years) do you bulk bill?

- ○ All
- ○ Some
- ○ Only children covered by health care card/concession card (or equivalent)
- ○ None

The next set of questions asks about your usual care of children aged less than 18 years with asthma.

6. Do you look after children with asthma in your practice?

- ○ Yes
- ○ No

7. Can you say why you do not look after children with asthma? (Tick all the apply)

- ☐ I prefer to send all children with asthma to a specialist
- ☐ Parents of children with asthma ask me for a referral to a specialist
- ☐ Other (please specify)

7.1 Please specify

	Not at all confident	Not very confident	Somewhat Confident	Very Confident	Extremely confident
8. How confident do you feel looking after children with well controlled asthma?	○	○	○	○	○
9. How confident do you feel looking after children with poorly controlled asthma (i.e. with symptoms in between asthma attacks)?	○	○	○	○	○
10. How confident do you feel looking after children post discharge from hospital with asthma?	○	○	○	○	○

11. Do you use any of these asthma guidelines in your practice? (Tick all that apply)

☐ Health-Pathways
☐ The Royal Children's Hospital clinical practice guidelines
☐ UK NICE guideline
☐ Other (please specify)

11.1 Please specify the other guidelines you use

12. How often do you ask a parent if their child has an asthma management plan?

○ Never
○ About 1/4 of the time
○ About 1/2 the time
○ About 3/4 of the time
○ All the time

13. If the child does not have an asthma management plan, do you provide one at least once?

○ Yes, to all children with asthma
○ Only to children needing regular medications
○ No, this is the responsibility of hospitals and specialists

14. If a child with known asthma is coughing and wheezing on most days, what is your usual management? (Tick all that apply)

☐ Refer to a specialist
☐ Start or increase dose of inhaled corticosteroids
☐ Increase dose of Salbutamol (Ventolin)
☐ Review the diagnosis
☐ Check adherence to medications and inhaler techniques
☐ Trial a course of antibiotics
☐ Reduce/avoidance of cigarette smoke and other environmental exposures
☐ Manage co-morbid allergic rhinitis and food allergies
☐ Start Monteleukast (Singulair)

15. What is your usual follow-up practice for children with asthma?

○ Book in regular follow-up for all children with asthma
○ Book in regular follow-up for children with persistent asthma or poorly controlled asthma only
○ Follow-ups are booked by families when needed
○ Others (please specify)

15.1 Please specify the other follow-up practices you use

16. What is your usual follow-up practice after a child is admitted to hospital for asthma? (Tick all that apply)

- ☐ Contact the family to make an appointment
- ☐ Leave it to the family to make an appointment
- ☐ I do not always know when the child has been in hospital for asthma

17. How can you, as a GP, help to keep children with asthma out of hospital?

Appendix 3: Supp C - Electronic Medical Record Data Collection Form

Demographics

1. Does the family require an interpreter for medical appointments?

- ○ Yes
- ○ No
- ○ Not Recorded

2. Birth gestation

- ○ >= 37 weeks (term)
- ○ 32-36 weeks (moderate to late preterm)
- ○ 28-31 weeks (very preterm)
- ○ < =27 weeks (extremely preterm)
- ○ Not recorded

3. Weight at index admission (in kg)

_____

4. Height at index admission (in cm)

_____

History of asthma severity

5. Year of asthma diagnosis (preferred)

If year/age of diagnosis cannot be found, please note year of first hospital encounter for asthma or wheeze

_____

6. Has the child previously been admitted to the Index hospital for asthma or wheeze?
Excluding ED & ED SSU presentations

- ○ Yes- Asthma
- ○ Yes- Wheeze
- ○ Yes- Asthma and Wheeze
- ○ Neither

6a. How many times in the 12 months prior to index admission has the child been admitted to hospital for asthma?
Excluding ED & ED SSU

_____

6b. How many times in the 12 months prior to index admission has the child been admitted to hospital for wheeze?
Excluding ED & ED SSU

_____

7a. How many times in the 12 months prior to index admission has the child presented to ED (including ED SSU stay) for asthma?

_____

8. Has the child ever been admitted to ICU for asthma or wheeze?

◯ Yes- Asthma
◯ Yes- Wheeze
◯ Yes- Asthma and Wheeze
◯ Neither

8a. How many times has the child has been admitted to ICU for asthma?

8b. How many times has the child has been admitted to ICU for wheeze?

9. What is the child's usual asthma treatment prior to admission? (Tick all that apply)

(Please note. This does not include medications provided in the hours before the admission. It does not include medications used to manage the exacerbation of symptoms for which they have presented to hospital)

☐ Nothing
☐ Inhaled corticosteroids (Flixotide, Alvesco, Pulmicort, Flixonase, Qvar, Beclometasone)
☐ Combination corticosteroid & reliever (Seretide, Symbicort, Flutiform)
☐ Oral Monteleukast (Singulair)
☐ Oral corticosteriods (Predmix >7 days)
☐ Biologics - Omalizumab (Xolair), Mepolizumab (Nucala), Reslizumab (Cinqair), Bneralizumab (Fasrena), Dupilumab (Dupixent)
☐ Medication - Salbutamol (Ventolin) as required
☐ Other
☐ Not recorded

9a. Please specify what other treatment the child was on prior to admission

9b. Where was the child's usual treatment noted?
Please tick all that apply

☐ Index admission file
☐ ED notes
☐ Follow-up appointment
☐ Previous encounter (in the last 12-months)

10. Does the child have allergies or allergic illnesses?
(E.g., eczema, allergic rhinitis/hayfever)

◯ Yes
◯ No
◯ Not recorded

10a. What allergic illnesses does the child have?

☐ Eczema
☐ Allergic rhinitis (Hayfever)
☐ Food allergies
☐ Grass allergy
☐ Pollen allergy
☐ Other allergy

10b. Please specify other allergies:

10c. Was the status of the child's allergy management noted in the notes of the index admission?

e.g., did the clinician note if the hayfever was well controlled or under control at the index admisison

◯ Yes
◯ No

11. Does the child experience any other chronic comorbidities?
(E.g., heart disease, diabetes)

◯ Yes
◯ No
◯ Not recorded

11a. What comorbidities does the child have? (Please list)

12. Does the child's medical record indicate that they experience, or may experience, anxiety?

I.e., their diagnosis is not definitively asthma, rather that their symptoms may be symptomatic of anxiety
OR when you search anxiety in the EMR, clinician notes suggest the child may experience anxiety.

◯ Yes
◯ No
◯ Not recorded

Asthma Control (before the current exacerbation)

13. Does the child usually (in the last 3 months) experience day time asthma symptoms?
(E.g., wheeze, cough, shortness of breath)

◯ Yes
◯ No
◯ Not recorded

13a. How many days of the week is the child having daytime symptoms?

◯ 1
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ Not recorded

13b. Where was the child's usual day times symptoms noted?
Please tick all that apply

☐ Index admission file
☐ ED notes
☐ Follow-up appointment
☐ Previous encounter (in the last 3-months)

14. Does the child usually (in the last 3 months) experience any limitation of activities due to their asthma?
(E.g., restricted participation in sport)

◯ Yes
◯ No
◯ Not recorded

14a. Where was the child's limitations noted?
Please tick all that apply

☐ Index admission file
☐ ED notes
☐ Follow-up appointment
☐ Previous encounter (in the last 3-months)

15. Does the child usually (in the last 3 months) experience asthma symptoms during the night (nocturnal symptoms)?
(E.g., Cough, wheeze, need Salbutamol/Ventolin, night time awakening from asthma symptoms)

◯ Yes
◯ No
◯ Not recorded

15a. How many nights a week is the child having nocturnal symptoms/ awakenings?

◯ 1
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ Not recorded

15b. Where was the child's night symptoms noted?
Please tick all that apply

☐ Index admission file
☐ ED notes
☐ Follow-up appointment
☐ Previous encounter (in the last 3-months)

16. Does the child usually (in the last 3 months) need Salbutamol (i.e., Ventolin, Asmol) to manage their symptoms?

◯ Yes
◯ No
◯ Not recorded

16a. On average how many days per week is the Salbutamol (Ventolin, Asmol) required?

◯ < 1 a week
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ Multiple times a day
◯ Not recorded

16b. Where was the child's Salbutamol (Ventolin) use noted?
Please tick all that apply

☐ Index admission file
☐ ED notes
☐ Follow-up appointment
☐ Previous encounter (in the last 3-months)

17. Has the child ever had a lung function test?

Find it in RCH EPIC- Results Review- FEV1

◯ Yes
◯ No
◯ Unknown

17a. Date of lung function test most recent to index admission:

_____

17b. FEV 1 - Pre %Pred Result:
See pre FEV value highlighted outlined in organge (highlighted in yellow and outlined in orange is the value we are after)

_____

17c. Lung function FEV 1 pre % result categorised:

◯ ?80% predicted or personal best ?80 %
◯ 60-79% predicted or personal best 75-80%
◯ < 60% predicted or personal best < 75%
◯ Not recorded

17d. FEV 1 - Post %Pred Result:

See pre FEV value highlighted outlined in red (highlighted in yellow and outlined in red is the value we are after). It is likley this field will be empty unless the child had a low Pre FEV result. The post FEV result is the childs lung fuction score post recieving Ventolin.

_____

18. Did the CLINICIAN note in the index admission that the child responded or was responding to Salbutamol (Ventolin)?

◯ Yes
◯ No
◯ Not recorded

19. In the notes of the Index Admission, was it documented whether the child has severe, persistent or poorly controlled asthma?

◯ Yes
◯ No
◯ Not recorded

20. In the index admission or follow-up notes was it documents by a CLINICIAN that the child had a diagnosis or impression of asthma (not including wheeze)?

Please note, if there is a diagnosis of wheeze or viral wheeze the answer is no

◯ Yes
◯ No
◯ Not recorded

20a. Where was the asthma diagnosis noted? (please tick all that apply)

☐ Index Admission
☐ Follow-up Appointment

---

21. Has the child experienced asthma exacerbations or episodes in the 12 months prior to Index Admission? An exacerbation or episode is an increase in medications or symptoms (cough, limitation of activities, wheeze) compared to usual/baseline.†

◯ Yes
◯ No
◯ Not recorded

21a. Number of exacerbations in 12 months prior to Index Admission

_____

21b. OR number of exacerbations in the last 3-months

_____

21c. How often are the exacerbations on average?

◯ < = 6 weeks in between exacerbations
◯ >7 weeks in between exacerbations
◯ Persistent symptoms
◯ Not recorded

Hospital management of asthma for index admission

22. Did the child present to a GP clinic before presenting to hospital?

◯ Yes
◯ No
◯ Not recorded

---

23. Was Salbutamol (Ventolin) given prior to the index hospital admission (or ED presentation) to manage symptoms of exacerbation?

◯ Yes
◯ No
◯ Not recorded

23a. How often was Ventolin given? (the shortest interval)

◯ < 1 hour between doses
◯ between => 1 and < 3 hours
◯ between => 3 and < 4 hours
◯ =< 4 hours between doses
◯ Not recorded

23b. How much Ventolin was given? (the largest quantity)

◯ 2 puffs
◯ 3-6 puffs
◯ 7-12 puffs
◯ >12 puffs
◯ Not recorded

23c. Did the child receive Ventolin via a nebuliser (neb) before presenting to the hospital?

◯ Yes
◯ No
◯ Not Recorded

---

24. Was Prednisolone (Pred/Predmix) given at before hospital presentation (at home or at GP)?

◯ Yes
◯ No
◯ Not recorded

24a. Answer 1 of the next 2 questions, depending on the information provided:

How much Prednisolone was given in mg?

_____

24b. OR
How many tablets of Pred was taken before presenting to hospital?

_____

24c. OR
How many doses (days) of Pred was taken before presenting to hospital?

_____

---

25. Did the child present to the ED before being admitted?

If the child's Index Admission type is ED to SSU or ED to Admissions, that indicates a Yes to this question.†

◯ Yes
◯ No
◯ Unknown

25a. Was the child admitted to ED SSU during the index admission (ED SSU is considered more than 4 hours in ED)?

◯ Yes
◯ No
◯ Unknown

25b. What treatment did the child received in ED and/or ED SSU?

☐ Oxygen
☐ High flow nasal cannulae
☐ Inhaled Salbutamol (Ventolin)
☐ Inhaled Ipratropium (Atrovent, Atrovent Nebulising Solution, Ipratropium bromide)
☐ Oral Prednisolone (Pred, Predmix, Panafcort)
☐ Oral Dexamethasone
☐ IV Methylprednisolone
☐ IV Aminophylline
☐ IV Magnesium Sulphate
☐ IV Salbutamol
☐ Antibiotics (e.g. Penicillin, Ceftriaxone, Flucloxacillin, Roxithromycin, Azithromycin)

26. Did the child get admitted to hospital during the index admission (please note ED SSU does not constitute an admission to hospital)?

◯ Yes
◯ No
◯ Unknown

26a. What treatment did the child received during their inpatient stay?

☐ Oxygen
☐ High flow nasal cannulae
☐ Inhaled Salbutamol (Ventolin)
☐ Inhaled Ipratropium (Atrovent, Atrovent Nebulising Solution, Ipratropium bromide)
☐ Oral Prednisolone (Pred, Predmix, Panafcort)
☐ Oral Dexamethasone
☐ IV Methylprednisolone
☐ IV Aminophylline
☐ IV Magnesium Sulphate
☐ IV Salbutamol
☐ Antibiotics (e.g. Penicillin, Ceftriaxone, Flucloxacillin, Roxithromycin, Azithromycin)

27. What ward was the child discharged from?

◯ ED SSU
◯ Gen Med SSU (RCH)
◯ P SSU (NH & BH)
◯ Other inpatient ward
◯ Other

27a. Please specify the discharge destination:

_____

28. Were there any scans or tests ordered during the Index Admission?

☐ None
☐ Blood Test/full blood count/blood gas
☐ X-ray
☐ Other
☐ Unknown

28a. Other scan or test

29. Was the child admitted to ICU during this admission?

◯ Yes
◯ No

30. Was the child prescribed inhaled corticosteroids (e.g Flixotide, Seretide, Alvesco) at discharge?

◯ Yes
◯ Already on inhaled corticosteroids
◯ No
◯ Not recorded

30a. Which inhaled corticosteriod was prescribed?

◯ Flixotide
◯ Seretide
◯ Alvesco
◯ Pulmicort
◯ Symbicourt
◯ Other
◯ Not recorded

30b. Please specify other inhaled corticosteroid

_____

30c. What is the total dose of inhaled corticosteriod each day in micrograms?

_____

31. In the index admission or follow-up notes was it documented by a CLINICIAN that the child should cease taking a previously prescribed preventer?
If the clinician is just changing the preventer brand or type this is to be marked as 'No', we are interested in cases where clincians have advised children who were previously on a preventer to stop taking a preventer all together.

◯ Yes
◯ No
◯ Not recorded

32. Was the child prescribed Monteleukast (e.g. Singulair) at discharge?

◯ Yes
◯ No
◯ Not recorded

32a. What is the total dose of Monteleukast per day in mg?

_____

33. Was the child prescribed oral corticosteriods (Predmix, Prednisolone, Dexamethasone) on discharge?

◯ Yes
◯ Told to take but not prescribed as already has at home
◯ No
◯ Not recorded

33a. For how many days was the oral corticosteriod prescribed for after discharge?

_____

34. Was the child prescribed antibiotics at discharge to treat a respiratory (e.g., lungs, airways) or asthma/wheeze-related illness?

Please note, if the antibiotics were for prescribed to treat an illness that is unrelated to the asthma/respiratory function (e.g., infected wound), please click No.

◯ Yes
◯ No
◯ Not recorded

34a. For how many days were the antibiotics prescribed?

_____

35. Did the child get medication in-hand when discharged?

◯ Yes
◯ No
◯ Not recorded

35a. Which medications were provided in-hand?

☐ Inhaled Corticosteroids (Flixotide, Seretide, Alvesco, Pulmicort, Symbicort)
☐ Oral Corticosteriods (Prednisolone, Dexamethasone)
☐ Monteleukast (Singulair)
☐ Salbutamol (Ventolin)
☐ Spacer +/- mask
☐ Other
☐ Not recorded

35b. Which other medication(s) was provided in-hand?

_____

35c. How many days worth of medication was provided in hand?

_____

36. Length of stay (days)

_____

37. Asthma Plan Provision

◯ Yes
◯ Already has plan/ plan already provided
◯ No
◯ Not recorded

37a. How do you know asthma plan was provided?

◯ Criteria Led Discharge
◯ Clinical Notes
◯ Other

38. Was asthma education given?

◯ Yes
◯ No
◯ Not recorded

38a. How do you know they received asthma education?

◯ Criteria Led Discharge
◯ Clinician Notes
◯ Other

39. Was the child's asthma medication technique reviewed?
E.g. did the clinician or nurse note that they reviewed the child's spacer and or puffer technique

◯ Yes
◯ No
◯ Not recorded

39a. How do you know their asthma medication technique was reviewed?

◯ Criteria Led Discharge
◯ Clinician Notes
◯ Other

40. Was follow-up organised following discharge?

◯ Yes
◯ No
◯ Not recorded