
# ASSESSING THE ROLE OF TEMPERATURE AND AIR POLLUTION IN EXACERBATING CHILDHOOD ASTHMA IN CAPE TOWN, SOUTH AFRICA

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**(PHKTSH006)**

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# DECLARATION

I, Tshepo Kingsley Phakisi, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Mr. Tshepo Kingsley Phakisi 13 February 2022

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# ABSTRACT

Childhood asthma is one of the most common chronic diseases worldwide, including in South Africa. There has been substantial evidence on the role of air pollution in asthma exacerbation but limited research on the role of climate change and how the interaction between climate change and air pollution is affecting childhood asthma, specifically in low and middle-income countries (LMICs). Temperature changes can be used as an effect of climate change to investigate the association between climate change, air pollution and childhood asthma. This study, therefore, used a case study approach aimed at examining the interaction between air pollution and temperature in exacerbating childhood asthma focusing on clinical data obtained from Red Cross War Memorial Children's Hospital, air quality data (City of Cape Town) and temperature data (South African Weather Services) for Cape Town, South Africa for three study years (2009, 2014 and 2019).

The protocol (Part A) of the mini dissertation describes childhood asthma literature globally and in LMICs and specifically in South Africa. It also discusses the increasing incidences and prevalence of the disease and possible causes such as air pollution and climate change. Furthermore, it discusses the vulnerability of children to the exposure of interest, being air pollution ($PM_{2.5}$, $PM_{10}$, $NO_2$ and $O_3$) and climate change (i.e., temperature). Subsequently, the development of air quality standards is discussed, specifically concerning whether they consider the specific children's vulnerability to exposures. The protocol then describes the study population and methodologies for conducting this study.

The journal ready article (Part B) presents the findings of the study. Spearman's correlation was used to measure the degree of association between temperature variables and air pollutants. The results indicated that diurnal temperature was associated with PM2.5 ($r=0.579$: $p<0.01$) and PM10 ($r=0.505$: $p<0.01$). A Poisson regression analysis was applied to evaluate the relationship between asthma exacerbation with air pollutants and temperature variables. In a univariate analysis there was a statistically significant relationship between asthma exacerbation and diurnal temperature for 2019, IRR=0.98 (95% CI,0.97 – 0.99) $p<0.05$, maximum temperature 2014, IRR=0.99(95% CI, 0.98 - 1.00) $p<0.05$ and for 2019, IRR=0.98(95% CI, 0.97 - 0.99) $p<0.01$, average temperature 2014, IRR=0.99(95% CI, 0.98 - 1.00) $p<0.05$ and for 2019, IRR=0.98(95% CI, 0.97 - 0.99) $p<0.01$. Using a multivariate analysis there

was no significant relationship between childhood asthma exacerbation and air pollutants ($PM_{10}$, $NO_2$ and $O_3$) except for $PM_{2.5}$ IRR=0.12(95% CI, 0.01 - 0.81) $p<0.05$. Diurnal temperature statistically significant childhood asthma predictor for 2009, IRR=1.02(95% CI, 1.00 - 1.05) $p<0.05$ and for 2014, IRR=0.97(95% CI, 0.96 - 0.99) $p<0.01$. Temperature increase, therefore, seems to be related to asthma exacerbation. More research is needed on the relationship between diurnal temperature, childhood asthma, and air pollutants to inform adaptation strategies. The findings of this study are important for the development of climate change and health adaptation and prevention strategies in South Africa, particularly in relation to heat adaptation. These findings are also relevant for the development of air quality guidelines and guidelines to address children, as the most vulnerable population to environmental health exposures.

The appendices (Part C) present the analyses that were not included in the protocol (Part A) and article (Part B). These also include documents relating to the study such as ethics approval and permission to conduct research by different entities.

**Keywords:** Climate change; Temperature; Air pollution; Childhood asthma; low-and middle-income countries, Heat adaptation.

# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| $CO_2$ | Carbon Dioxide |
| CO | Carbon Monoxide |
| COPD | Chronic Obstructive Pulmonary Disease |
| CI | Confidence Interval |
| COCT | City of Cape Town |
| DALYS | Disease Measured by Disability-Adjusted Life Years |
| GINA | Global Initiative for Asthma |
| GHGS | Greenhouse Gases |
| HIC | High-Income Countries |
| ICD CODE 10 | The International Classification of Diseases 10th Revision Codes in Parentheses |
| ISAAC | International Study of Asthma and Allergies in Childhood |
| LMICS | Low-and Middle-Income Countries |
| NAAQS | South African National Ambient Air Quality Standards |
| $NO_2$ | Nitrogen Dioxide |
| NCDS | Non-Communicable Diseases |
| $O_3$ | Ozone |
| PM | Particulate Matter |
| RXH | Red Cross War Memorial Children's Hospital |
| SAWS | South African Weather Services |
| $SO_2$ | Sulphur Dioxide |
| WHO | World Health Organization |

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# PART A: PROTOCOL

# 1. Introduction

## 1.1. Introduction and Problem Statement

### 1.1.1 Introduction

Climate change often referred to as global warming, is a major threat to all living organisms and particularly the health of children (UNICEF South Africa, 2011; Landrigan et al., 2018). It disturbs the ecosystem from maintaining equilibrium, caused by decades of anthropogenic activities, such as the burning of fossil fuels which release greenhouse gases into the atmosphere (Von Schneidemesser et al., 2015). This warming causes effects such as extreme weather events, increased temperature, frequent and prolonged droughts, floods, heatwaves and storms and sea-level rise (Portier et al., 2010). As these climatic changes occur, environmental and human health effects are observed McCarthy, Best & Betts, 2010; WHO WMO, 2012). These effects impact the population's health and well-being, especially vulnerable groups such as children, with a variety of direct and indirect effects (Wright & Norval, 2014). These effects of climate change led to further implications on children's developmental pathways, educational development and compromising of health and nutrition.

The direct effect of climate change includes increased pollen allergens caused by an increase in carbon dioxide ($CO_2$) levels through the promotion of plant growth (Fann et al., 2016). Whereas the indirect effect includes increased concentrations of air pollutants such as ozone due to an increase in temperature and wind distribution (Von Schneidemesser et al., 2015). Ebi & Paulson (2007)'s report for UNICEF on climate ma and children illustrated these impacts on child health using available literature at the time (see figure 1 below). These impacts result in the prevalence, incidence and exacerbation of non-communicable diseases (NCD's) in children (Bradshaw et al., 2011; Wright & Norval, 2014). These observations depict how both direct and indirect climate change effects significantly impact child health.

Non-communicable diseases (NCDs) in South Africa are on the rise since 2005, reaching epidemic proportions, together with an increase in communicable diseases (Statistics South Africa, 2014). These trends have been attributed to aging populations, urban nutrition transition, low-quality healthcare, unequal access to healthcare services affecting mostly the urban poor and rural populations (Mayosi et al., 2009). More recently, research has indicated that many NCDs are climate sensitive. In 2004, NCDs accounted for 28% of the country's total burden of diseases measured by disability-adjusted life years (DALYs). Therefore, evidence suggests climate change effects as one of the drivers for the increase in these NCDs (Mayosi et al., 2009).

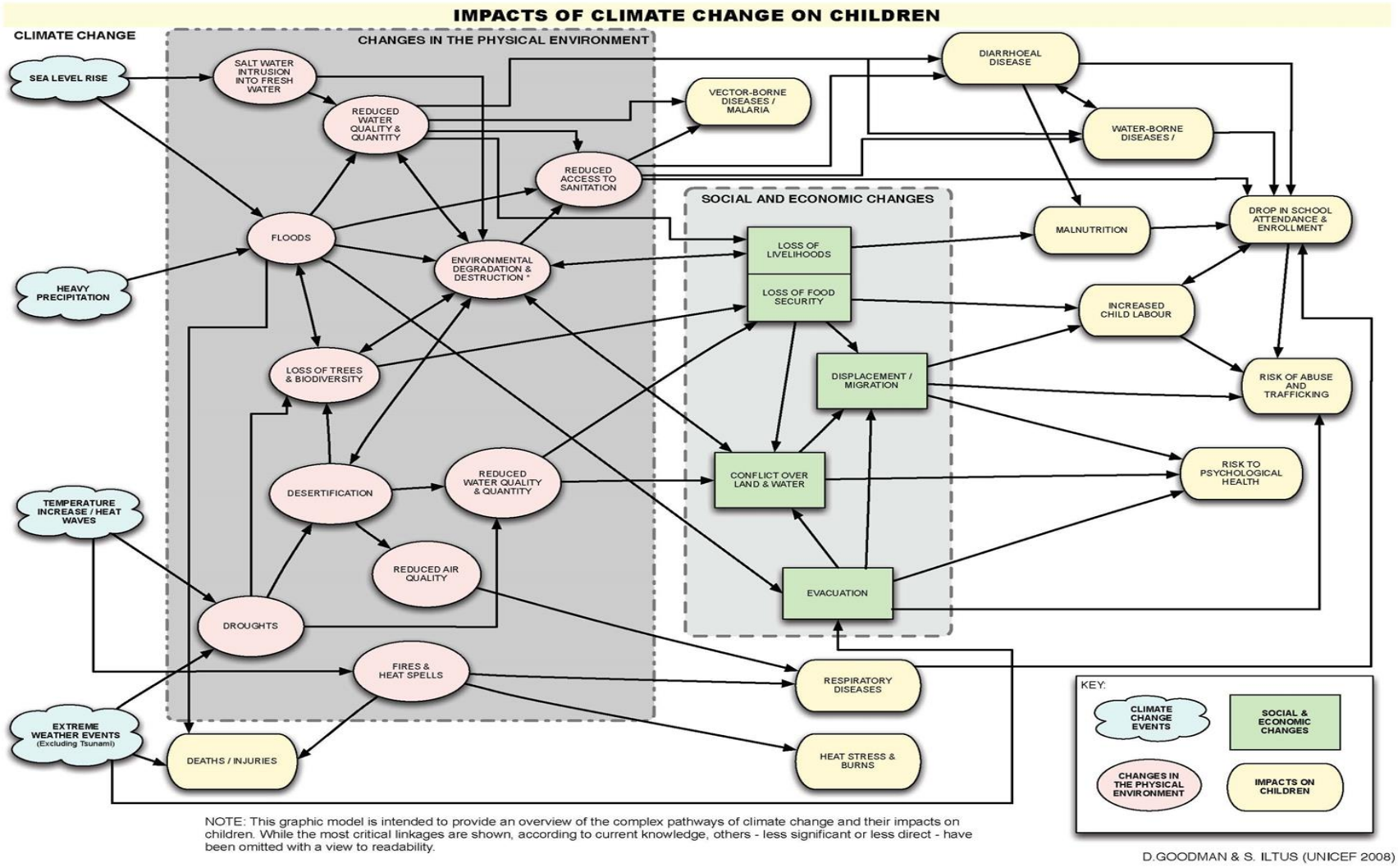


**Figure 1. Climate Change Impacts on Children's Health and Well-being**

(Source: Ebi & Paulson 2007)

This burden places South Africa in the highest-burden quintile; higher than most developed countries, with HIV/AIDS being one of the reasons for such an increase in the burden of NCD's (Mayosi et al., 2009). Common NCD's in South Africa include cardiovascular diseases, diabetes, cancers, mental illness, chronic obstructive pulmonary disease (COPD) and asthma for children (De Wet & Frade, 2018; StatsSA, 2018). These diseases affect mostly the poor and vulnerable, especially children, as access to healthcare is limited and the environmental health risks are increasing (Chetty, 2009; Mayosi et al., 2009; Bradshaw et al., 2011; Viviers & van Zyl-Smit, 2015).

In South Africa, Asthma and COPD are the leading respiratory diseases, together with occupational lung disease (Mayosi et al., 2009; Viviers & van Zyl-Smit, 2015). The International Classification of Diseases 10$^{th}$ Revision Code (ICD code 10) is a system code developed by the World Health Organization (WHO) to code health conditions into internationally accepted codes. Using the ICD code 10 enables easy patient diagnosis and coding, thus, easier to track. Chronic lower respiratory diseases are translated into codes J40-J47, here we find asthma and COPD, the two major contributors to mortality under the chronic lower respiratory diseases. In 2015, of the 3% fatalities attributed to chronic lower respiratory disease, COPD and asthma contributes 83% of deaths (Statistics South Africa, 2018). Asthma and status asthmaticus, a condition of a repeated asthma attack without pause, coded as J45 and J46 respectively, under chronic lower respiratory diseases, contributed 22% and 5.6% deaths respectively and together accounts for 28% of deaths by chronic lower respiratory disease for both adults and children (Statistics South Africa, 2018). Stats SA report like many other studies did not report on children aged 5 to 14 years but rather include this age grouping into either child aged 1 -14 years or into the adolescent ages. This creates a disparity in understanding the top 10 diseases of that age group which is the interest of this paper (Wet & Odimegwu, 2013; StatsSA, 2018). The Stats SA report indicated the role of asthma and COPD among South Africa's burden of diseases. Although the statistics are not disaggregated for children, it illustrated that childhood mortality in high-income countries (HICs) is lower compared to children from low-and-middle-income countries (LMICs) (Ferrante & La Grutta, 2018). Since climate change plays a role in increased respiratory health-related problems, this research, therefore, focused on the impact of climate change by investigating the association of temperature and air pollution with exacerbating childhood asthma in Cape Town of Western Cape Province South Africa.

### 1.1.2 Problem Statement

Over recent decades, the prevalence and severity of asthma have seen an enormous increase for both children and adults globally (Ferrante & La Grutta, 2018). The increase is mainly observed in LMICs when compared to the HICs, where the prevalence is reported to have plateau in certain populations

(Rodriguez et al., 2017; Chen et al., 2021). According to the Global Initiative for Asthma (GINA)'s 2018 report, there are currently 339 million people diagnosed with asthma globally (Asher I, Haahtela T, Selroos O, 2018; Masekela et al., 2018). This increase is mostly observed in LMICs as compared to HIC, where the prevalence and severity of asthma seem to have stabilised (Ferrante & La Grutta, 2018; Masekela et al., 2018). These observations have challenged previous beliefs that asthma is a disease of HICs. This indicates that HICs due to developmental spectrum, diseases declined because of behavioural changes and access to resources that led to improved interventions necessary for disease prevention strategies for managing asthma prevalence and severity in comparison to many LMICs (Levin & Weinberg, 2011; Ferrante & La Grutta, 2018). Current asthma prevalence and increase in severity are too rapid to be attributed to just genetic predisposition. Therefore, environmental factors, such as changes in weather, pollen and increased environmental pollution from industrialisation need to be assessed, particularly air pollution in LMICs (Thompson, Matamale & Kharidza, 2012; Rother, H. A., Wijesekerab, S., & Wardb, 2019). In the past LMICs were plagued with lack of resource which resulted in misdiagnosis, loss to follow-ups, unavailability of essential drugs and inadequate health system that rendered ineffective to control and manage asthma from diagnosis to treatment (Baard et al., 2021). However, countries have been developing and strengthening their health system, which enhanced awareness, monitoring and diagnostic practices of the disease, these had a massive impact on the increased prevalence currently observed(Ferrante & la Grutta, 2018; Enilari & Sinha, 2019; Baard et al., 2021). It is also noteworthy to indicate the role of data reporting by countries through the GINA, this initiative collate data from epidemiological studies conducted in different countries. This has thoroughly improved data reporting as more epidemiological research is undertaken (Asher I, Haahtela T, Selroos O, 2018; Masekela et al., 2018).

Similar to HICs in the past, LMICs pursuit of economic development through industrialisation, a process synonymous with an increase in environmental pollution, has led to diseases associated with increased environmental health risk which tends to increase in low-income households. It is important to note that most LMICs do not have enough industries to significantly impact greenhouse gas (GHGs) emissions, except China, India, Brazil and South Africa (Olhoff & Christensen, 2018). The environmental impacts of the era of industrialisation do not only affect human health but also is a concern for the impact on climate change, thus, leading to increased temperature variability. There is daily, monthly and yearly temperature change due to an increase in mean and variance or both (Michaels et al., 1998; Folland, Karl & Jim Salinger, 2002; Cox et al., 2020). The related increase of GHGs in the atmosphere leads to anthropogenic climate change and air pollution which are widely considered major modern public health concerns (Von Schneidemesser et al., 2015).

Globally, asthma is ranked 14th on the list of the burden of disease and in the top 10 of DALYs among 5 – 14-year-olds (Olaniyan et al., 2017; Ferrante & La Grutta, 2018). In South Africa, asthma is currently the most common NCD affecting children, thus, impacting their health and well-being, especially in urban areas such as Cape Town (Levin & Weinberg, 2011)(Redfern, Westwood & Donald, 2016); (Masekela et al., 2018).

Many studies have reported the increased relationship between air pollution and asthma, either by exacerbation of asthma symptoms or increase in asthma prevalence (Nriagu et al., 1999; Adetoun, Briggs & Hansell, 2013; R N Naidoo, T G Robins, S Batterman, G Mentz, 2013; Mohammad et al., 2014; Olaniyan, T. A., Dalvie, M. A., & Jeebhay, 2015). This increase could also be attributed to the modern anthropogenic climate change impacts such as temperature. The relationship between climate change and air pollution is a complicated one, through meteorological variables climate affects air quality by emission, transport, dispersion, chemical transformation and deposition of pollution (Orru, Ebi & Forsberg, 2017). In a systematic review investigating the relationship between temperature and childhood asthma exacerbations, the study found that 14 of the 23 studies included in the review reported an inverse relationship between childhood asthma exacerbations and ambient temperature, as temperature decreased, exacerbations increased whereas nine studies investigating hot weather and observed increased attacks during hot weather. The other three studies reported a relation between diurnal temperature (temperature difference) and asthma exacerbations however the remaining two studies reported no relation between temperature and asthma exacerbation (Shoraka et al., 2019). In a time-stratified case-crossover study conducted in China, the study found a U shape relationship between temperature and asthma. The results indicated a non-linear association between ambient temperature and adult asthma hospitalisations, most of the cases were observed in the temperature of moderate to cold with the young and vulnerable populations experiencing the disease burden (Chen et al., 2022). Air pollution will likely have the most severe impact on vulnerable populations, which includes those who are immuno-compromised (meaning those with immune diseases such as HIV/AIDS), pregnant women, the elderly, children and those living in poverty (Manisalidis et al., 2020). Recent studies also reported how the association between climate change and air pollution is further increasing the burden of disease around the world, especially in LMICs, threatening vulnerable populations, especially children (Jassal, 2014). Childhood asthma is on the rise, and it is largely attributed to host, lifestyle and environmental factors. Environmental degradation such as in particular climate change and poor air quality being more prevalent in LMICs whereas host factors such as obesity, tobacco smoke, vitamin D deficiency, antibiotics, chronic psychological stress, viral and bacterial infections being more prevalent in upper-middle to HICs (Puranik et al., 2017).

## 1.2. Literature Review

### 1.2.1. Childhood Asthma

Asthma is a chronic non-communicable respiratory disease characterised by inflammation of the airway and bronchial hyper-responsiveness (Jeebhay & Quirce, 2007; Cruz, Stelmach & Ponte, 2017). Genetic predisposition and environmental exposures, such as indoor and outdoor air pollution, pollen, and climatic weather conditions are most likely contributing factors to the asthma prevalence, phenotype and severity (D'Amato et al., 2010; Cruz, Stelmach & Ponte, 2017; WHO (World Health Organization), 2017). The prevalence of asthma is defined as the number of cases within a population at a time and severity being the exacerbation of the disease (D'Amato et al., 2010; Cruz, Stelmach & Ponte, 2017; WHO (World Health Organization), 2017).

Patients with asthma can either be diagnosed with intermittent asthma, where they experience symptoms after a long time and when symptoms return. It lasts from a few hours to a week, or patients are diagnosed with persistent asthma, where symptoms are incessantly present (Aït-Khaled & Enarson, 2006; NHLBI, 2007). Patients diagnosed with persistent asthma are classified either into mild, moderate or severe asthma which classification is determined by the degree of severity of the disease (Aït-Khaled & Enarson, 2006; NHLBI, 2007).

Mild and persistent asthma patients present symptoms of increased episodes of shortness of breath, coughing, wheezing and in some cases chest tightness but not as frequent as moderate, with symptoms occurring daily and severe persistent asthma symptoms are consistently occurring as it is easily triggered, especially at night (Aït-Khaled & Enarson, 2006; Chetty, 2009). Without treatment, asthma severity will progress to the last stage of severe asthma, which results in uncontrolled asthma requiring prompt treatment to prevent hospitalisation or death from frequent severe attacks (Jeebhay & Quirce, 2007; Kling et al., 2013).

These asthmatic incidences affect not only the public health aspects (e.g. disease burden on health systems and strained medical resources) but also socio-economic factors (e.g. medication and treatment costs) resulting in incurred individual costs, household and public healthcare service cost in terms of loss of capital (Mayosi et al., 2009; Zar & Lalloo, 2013). Another social impact, particularly related to children, is the loss of school days as a result of absenteeism from schools which can lead to low performance in school (Cruz, Stelmach & Ponte, 2017). Capital loss affects both the government and patients, through the treatment of the disease. Money meant for food and other utilities are used for healthcare costs (Zar & Lalloo, 2013). Childhood asthma is not just a burden on those diagnosed but on the society as a whole and this is a clear indication that those without capital, regarded as most vulnerable, suffer the most from the disease.

### 1.2.2. Asthma and childhood asthma prevalence

In a global landmark asthma epidemiological study conducted by the International Study of Asthma and Allergies in Childhood (ISAAC), consisting of three phases; phase I was conducted from 1992 to 1996 and surveyed asthma symptoms' prevalence and allergic diseases among children worldwide (Ellwood et al., 2005; Lee et al., 2007), while phase II (1998 to 2004), investigated the contribution to the risk and the protective factors in the observed differences in Phase I. Phase III repeated phase I to draw a comparison, of which the results showed the variation in global asthma symptom prevalence. Generally, high asthma prevalence was observed in English-speaking countries and Latin America. Comparatively, it was higher in Western Europe compared to lower prevalence in Eastern Europe, Africa and Asia (Beasley, 1998).

In phase III of the study, countries that reported low prevalence in the first phase then reported an increased prevalence, these were countries classified under the LMICs category (Pearce et al., 2007). The increase in childhood asthma prevalence could be attributed to increasing in industrialisation leading to greater environmental pollution. Although HICs had reported higher asthma symptoms' prevalence than LMICs, South Africa reported a high prevalence of more than 20% relative to other LMICs (Pearce et al., 2007).

The study was reported on participants experiencing symptoms such as wheezing, coughing or chest tightness as the underlying cause of chronic airway inflammation which obstructs airflow (Aït-Khaled et al., 2007; Pearce et al., 2007; Global Initiative for Asthma, 2014). Phase III of the study illustrated a change with LMICs experiencing low prevalence which is on an increase but is also accompanied by greater severity of asthma (Pearce et al., 2007). This study supported the much-publicised illustration that childhood asthma prevalence is on the rise in LMICs in recent years.

Childhood asthma occurs in 14% of children on the global burden of disease (Pearce et al., 2007; To et al., 2012), ranking number 14 on the disability-adjusted life years (DALYs) globally. The Global Initiative for Asthma (GINA) report estimates that in the years between 2011 and 2014, about 235 million to 334 million people had asthma (Global Initiative for Asthma, 2014). According to the World Health Organization (WHO), respiratory diseases which include asthma and COPD account for 3.9 million deaths per year globally (WHO, 2009). In 2016, 9 % of child mortality is attributable to household and ambient air pollution globally(World Health Organization, 2018). Air pollution is one of the major causes of childhood asthma.

South Africa's childhood asthma prevalence was at 20,3% in Cape Town and 18% in Polokwane for children aged 13 to 14 years old according to the ISAAC phase III study for the year 2005. Phase III in

comparison to phase I, indicated an increase in asthma prevalence among children aged 13-14 years old, with prevalence for phase I being 16% in Cape Town (Pearce & Douwes, 2006; Asher I, Haahtela T, Selroos O, 2018). As Asthma prevalence increased, the severity also increased, in phase III, it was reported that half of the children who had asthma, were diagnosed with severe asthma. The prevalence for children aged 6-7 years old in Polokwane was 11,2% and 5,7% of those had severe asthma symptoms (Asher I, Haahtela T, Selroos O, 2018). This solidifies Ferrante and La Grutta's (2018) findings that even though severe asthma was more common in HIC, but LMIC had higher rates of severe asthma among children.

### 1.2.3. Childhood Asthma Burden of Disease in Africa

In Africa, the asthma incidence rate ranged from 10% to 20% for the year 2004, accounting for approximately 50 million people living with asthma globally for the year, with South Africa reporting the highest prevalence in the continent. In South Africa, asthma as a cause of death ranks fourth among 5 to 34-year-olds globally (Jeebhay & Quirce, 2007; Global Initiative for Asthma, 2014; Yakubovich, Cluver & Gie, 2016). South Africa reported the highest prevalence over other African countries. This could be attributed to the availability of data due to better reporting and patient access to the health system relative to other African countries (Jeebhay & Quirce, 2007). There is a need to improve access to healthcare in Africa as Asthma remains one of the most undetected and untreated diseases.

In systematic analysis, comparing asthma prevalence in Africa in the years 1990, 2000, and 2010 utilising cross-sectional population-based studies to provide asthma prevalence as listed in Table 1, The results showed that there was an increase by over 20 million cases of asthma per decade (Adeloye et al., 2013). However, the conclusions of this study by Adeloye et al. (2013) are not a true reflection of the asthma prevalence in the African continent, since the available data mostly came from studies conducted in South Africa and Nigeria (eleven and eight studies, respectively) with fewer (less than five) studies from other African countries. A recently published paper on the environmental risk factors for asthma in 13-14-year-old African children using the ISAAC III to calculate the prevalence and severity, indicated that asthma prevalence within the age group is at 12.8% (CI 12.4 – 13.2), while asthma severity was 8.7% (CI 8.4-8.0) using the ISAAC III (Ayuk, Ramjith & Zar, 2018).

The African continent has inequitable access to the public healthcare system, which makes it difficult to obtain accurate data on disease prevalence. South Africa is industrialised, and the public health system caters for both rich and poor, although not equally, but it allows researchers to investigate data collected, providing a more accurate comparison with other countries on the same scale in terms of origin, culture, and development. These asthma increases are consistent with the changing African

continent environments such as the increased urbanisation, which is accompanied by the adoption of western lifestyles and the ageing populations accompanied by increased NCD (Wjst & Boakye, 2007; Samoli et al., 2011).

**Table 1. Asthma prevalence in Africa in the years 1990, 2000, and 2010 Adeloye *et al.*, 2013)**

| | **Asthma among children under the age of 15 years** | **Asthma among people aged 15 to 45 years** | **Total African population with asthma** |
|---|---|---|---|
| **1990** | 34.1 million | 64.9 million | 74.4 million |
| **2000** | 41.3 million | 82.4 million | 94.8 million |
| **2010** | 49.7 million | 102.9 million | 119.3 million |

In an African cross-sectional study on asthma prevalence focused on the prevalence of the disease from 1990 to 2010, the reported crude prevalence of asthma for 2000, was higher among urban than rural residents and are mostly attributed to increased ambient air pollution contributed by the industrialisation of the urbanised environment including the increased traffic (Jeebhay & Quirce, 2007). Earlier studies exploring asthma prevalence in rural areas reported low prevalence compared to urban areas in African countries (Van Niekerk et al., 1979; Weinberg, 2000). A comparative study by Van Niekerk was conducted in rural areas of the Former-Transkei (Eastern Cape Province) and urban Cape Town (Western Cape Province) assessing asthma prevalence in 695 and 671 African Xhosa children (aged 6 to 9 years), respectively. The study showed a difference of 3.03% between urban areas (reporting a prevalence of 3.17%) and rural areas with a prevalence of 0.14% (Van Niekerk et al., 1979; Weinberg, 2000). The further children lived away from urban areas, the less likely they were to develop asthma disease.

The results of the study were also supported by a review by Weinberg (2000) 's analysis of African studies based on childhood asthma and urbanisation. The analysis compared the urban high-income, urban low-income and rural communities from Zimbabwe, Ghana and Kenya (Van Niekerk et al., 1979; Weinberg, 2000). The results concurred with the South African study, that high-income urban communities had a higher prevalence of childhood asthma followed by the low-income communities and then the lowest prevalence being those in rural areas (Van Niekerk et al., 1979; Weinberg, 2000). The impact of industrialisation on the burden of the disease is evident in the differences in the prevalence of asthma in urban and rural areas. Urbanisation is linked with industrialisation, thus, altering the existing relationship between human health and the environment. Environmental degradation is known to give rise to chronic respiratory diseases such as asthma.

These environmental degradation in urban areas are introduced by industrialisation, which is accompanied by pollution-related incidences such as industrial and vehicle emissions. While rural populations are rarely exposed to these types of pollution, they are mostly exposed to indoor air pollution such as burning of wood for cooking and warming up, and agricultural pollution resulting from the spraying of pesticides (Van Niekerk et al., 1979; Weinberg, 2000).

### 1.2.4. Asthma Triggers

The allergic and non-allergic triggers of asthma are of importance to understanding the epidemiology. Asthma is known to be caused predominantly by a genetic predisposition and/or environmental factors. Environmental factors include allergens and air pollution, with the latter being of most significance, as it is currently being declared as a global health threat affecting everyone, but most importantly the vulnerable (World Health Organization, 2018; Landrigan et al., 2019).

Within the domain of allergic asthma triggers, there are two categories: indoor and outdoor triggers, outdoors includes pollen and seasonal asthma (Gautier & Charpin, 2017). Indoor triggers are indoor air pollution, moulds, dust mites, cockroaches and rodents and others including pets such as dogs and cats (McCarty & Ferguson, 2014; Gautier & Charpin, 2017). Children are mostly known to spend a large portion of their day indoors, be it at schools, day care and home afterwards, the significance of indoor triggers are highlighted by those aspects.

The non-allergic asthma triggers are also classified into indoor and outdoor, these include viral infections, smoking and second-hand smoking, climatic conditions such as cold and hot weather, thunderstorms and occupational exposures as previously mentioned, air pollution is an important trigger, but it can be found both indoor and outdoor. Indoor (i.e. household) air pollution predominantly results from polluting fuel technologies of cooking, lighting and heating (World Health Organization, 2018). Outdoor (i.e. ambient) air pollution predominantly results from burning fossil fuels, industrial processes, agricultural practices and more natural processes such as wildfires, dust storms and volcanic eruptions (Gautier & Charpin, 2017).

### 1.2.5. Impacts of Environmental Exposures on Childhood Asthma Prevalence and Severity

In the year 2000, South African deaths attributed to four environmental risk factors were 24 000 which accounted for 4.6% of all deaths. These environmental risks include indoor and outdoor air pollution, unsafe water and lead exposure (Norman et al., 2010). The overall burden of disease due to environmental risks is 3.7% of the total disease burden in the country (Department of Health, 2009; Mathee & Wright, 2014). For children under age 5 years, environmental risks accounted for 10.8%

with the burden of disease estimated at 9.7% for children. Children are different from adults because they are constantly developing as they grow, they breathe more, eat more and drink more in proportion to their weight and they are unaware of the risks to their health (Norman et al., 2010).

A systematic review investigating the association between environmental health exposures and childhood asthma exacerbation and control in children with the mean age of 9 years, the review found the association between environmental health exposure and childhood asthma exacerbation (Dick et al., 2014). The association was at an odds ratio of 2 – 3 for environmental tobacco smoke, allergens, unflued heaters and poor air quality with a modest magnitude effect. It is important to note that the paper published by Dick et al., (2014) only include 27 studies in the review, which were published before 2013. One of the papers reviewed, in the case of air pollution, using a three pollutant model ($PM_{2.5}$, $NO_2$ and $SO_2$) with exposure to a higher concentration of outdoor $NO_2$ was associated with increased asthma symptoms such as coughing and wheezing at a 95% confidence interval (CI) of OR 1.2, (95% CI 1.0 -1.5), with increased exposure to both $NO_2$ and $PM_{2.5}$ reduces the forced expiratory volume in 1s ($FEV_1$)by 0.5% to 1% thus indictive of airways obstructiveness (Dick et al., 2014). Adaeze et al., (2018) reaffirmed the findings in her paper on investigating environmental factors associated with asthma and severity in African children aged 13 – 14 years old. Using a population-based cross-sectional study method in 10 centres, where the ISAAC took place in the continent and administered written and environmental questionnaires. The environmental exposures that were evaluated were physical exercise, television watching, various biomass and environmental tobacco smoke exposure, consumption of paracetamol, large family sizes and having pets in the home. Maternal smoking, open fires, electric heating were associated with asthma prevalence whereas having cats, monthly intake of paracetamol, frequent exercise and maternal smoking were associated with severe asthma. Of noteworthy is the fact that the study depended on participants being truthful and being able to recall, as they utilised self-administered questionnaires (Ayuk, Ramjith & Zar, 2018).

### 1.2.6 Impacts of Air pollution on Asthma

Air pollution poses a major hazard to global public health, with the increasing burden of disease. In 2012 more than 3.7 million deaths were attributed to the deteriorated ambient air quality (Tibbetts, 2015; Brauer et al., 2016). Indoor and outdoor air pollution is the leading environmental health risk, responsible for the death of about 7 million people in the year 2012, compared to other environmental health risks factors such as malaria and malnutrition of children under 5, which accounts for 4 million and 3.1 million deaths respectively, (Tibbetts, 2015; Brauer et al., 2016). According to WHO, in the year 2016 ambient air pollution caused 4.2 million premature deaths, with almost 300 000 of them occurring among children under five years (World Health Organization, 2018). This makes deteriorated

air quality a major environmental health risk factor and a leading environmental cause of premature deaths globally (Akhtar & Palagiano, 2018; (World Health Organization, 2018).

#### 1.2.6.1 Criteria pollutants

Criteria pollutants are pollutants that are considered as being of public health importance, for which ambient concentration standards have been set. These include nitrogen dioxide, particulate matter, ground-level ozone, carbon monoxide and sulphur dioxide. These standards are set at the ambient air quality limits to ensure air quality management that is tolerable to human health. Most of the research into the health impacts of outdoor air pollutants, especially respiratory diseases such as asthma, depicts an association between asthma and exposure to most criteria pollutants (Ierodiakonou et al., 2016; Ding et al., 2017) (World Health Organization, 2006). The major problem with these limits is that they have been developed for adults and therefore, may not be adequate to protect children.

WHO provides countries with management strategies regarding the levels of pollution. These guidelines are considered tolerable for public health exposures but most importantly, they are considered too strict for countries to adopt in the development of their tailored standards. These guidelines are seen, to deter economic development. Although the choice of air quality standard is impacted by various factors, most are economically driven with public health concerns being of less significance. Table 2 below, is a comparison of ambient air quality standards of different countries. South Africa's ambient air quality standards compared with the WHO, United States of America, European Union, United Kingdom and Brazil, South African partners in the Brazil Russia India China and South Africa (BRICS) emerging economies (National Environmental Research Institute of Denmark, 2004; David R Boyd, 2006).

**Table 2. Table of country specific criteria pollutants and standards**

| **South Africa's NAAQS comparison with WHO and other country specific criteria air quality standards** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Criteria pollutants** | **Average period** | **WHO and Country specific threshold concentration (µg/m$^3$)** | | | | | |
| | | **South Africa's NAAQS** | **WHO AQG** | **Brazil AAQS** | **European Union AQFD** | **United Kingdom** | **United States of America NAAQS** |
| **Sulphur Dioxide ($SO_2$)** | 10 minutes | 500 | 500 | | | | |
| | 1 hour | 350 | | | 350 | 350 | 214 |
| | 24 hours | 125 | 20 | 80 | 125 | 125 | |
| | 1 year | 50 | | | | | |
| | | | | | | 266 (15 min) | |
| | 1 hour | 30 | | | | | |
| | 8 hours | 10 | | | 10 | 10 | 10 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Carbon Monoxide (CO)** | | | | | | | |
| **Nitrogen Dioxide ($NO_2$)** | 1 hour | 200 | 200 | 320 | 200 | 200 | |
| | 1 year | 40 | 40 | 100 | | 40 | |
| | | | | | | | |
| **Ozone ($O_3$)** | 8 hours | 120 | 100 | | 120 | | 160.7 |
| | | | | | | | |
| **Particulate matter ($PM_{10}$)** | 24 hours | 75 | 50 | 150 | 50 | 50 | 150 |
| | 1 year | 40 | 20 | 60 | 40 | 40 | |
| | | | | | | | |
| **Particulate matter ($PM_{2.5}$)** | 24 hours | 40 | 25 | 150 | 25 | | 35 |
| | 1 year | 15 | 10 | 50 | 20 | 25 | 12 |
| | | | | | | | |
| **Benzene ($C_6H_6$)** | 1 year | 5 | | | 5 | 16.25 | |
| | | | | | | | |
| **Lead (Pb)** | 1 year | 0.5 | | 0.5 | 0.5 | 0.25 | 0.5 |
| | | | | | | | |

In the above table 2, all countries' standards are more than the WHO guidelines (Radaideh & Shatnawi, 2015). The guidelines are set to influence public health policies that improve air quality and thus protect children's health (Landrigan et al., 2018). The WHO recommended guidelines are based on evaluations of current scientific research evidence related to the impact of air pollutant emission levels on human health. WHO recommended guidelines with a set of different interim targets for each criteria pollutant. The interim targets are the proposed incremental steps targeted towards reducing air pollution, especially in highly polluted areas. The goal of the interim targets is to reduce the risk of acute and chronic human health effects of air pollution (World Health Organization, 2006). The countries use these guidelines and, in some cases, the interim target to draw up their country specific ambient air quality standards. When drafting the standards, countries are expected to consider sustainable development pillars which are economic development, social and health impact along with environmental considerations. The purpose of this exercise is to ensure development is not derailed by health and environmental consideration, and that poverty is alleviated (World Health Organization, 2006). It is important that in consideration of these air quality standards, a policy document is drafted to benefit the vulnerable, especially children's health and well-being.

1.2.6.2 Particulate matter

One of the major pollutants affecting child health is particulate matter, it is a mixture of solid and liquid particles suspended in the atmosphere, these particles consist of dust, pollen, ash, fumes and mists and aerosols. These are a group of the most harmful type of air pollutants due to their mass and

compositions (World Health Organization, 2006; Global Asthma Network, 2014). The size is mostly less than 10 aerodynamic diameters, due to their properties, the particles are enabled for easy dispersion in the air and deposition within the respiratory system (McCormack et al., 2011). Currently, the particle diameters being measured under the South African national ambient air quality standard and for regulatory purposes are defined as $PM_{10}$ and $PM_{2.5}$ using their size for identification, $PM_{10}$ are particles aerodynamic diameters less than 10 micrometre and $PM_{2.5}$ are particles of aerodynamic diameters less or equal to 2.5 micrometre (Department of Environmental Affairs, 2009). The smaller the size of the particle, the greater the dangers of causing harm to human health (WHO, 2003; World Health Organization, 2006).

These particles are derived from anthropogenic and natural sources, they are directly and indirectly emitted into the atmosphere as primary and secondary pollutants (World Health Organization, 2006). Secondary pollutants result from the combination of different primary pollutants (World Health Organization, 2006). In the City of Cape Town, these sources include wildfires resulting from drought, releasing smoke and $CO_2$. Other pollutants result from informally controlled fires due to the burning of wood by informal food traders, for home heating, burning of waste and windblown dust from unpaved roads in denuded areas. The commonly controlled fires within households are wood-burning and the use of paraffin leading to human-induced pollution (Western Cape Provincial Government, 2015).

Particulate matter is one air pollutant that is mostly associated with the exacerbating of existing human health effects such as asthma (Lin et al., 2002; WHO, 2003). A time-series analysis, conducted in Toronto, investigated the association of particulate matter of the size between 10 and 2.5 ($PM_{10-2.5}$) aerodynamic diameter with asthma hospitalisation in children (Lin et al., 2002; WHO, 2003). There was a significant association observed between $PM_{10-2.5}$ and asthma hospitalisation but there was no association for other particulate matter fractions size (Lin et al., 2002; WHO, 2003). According to Burnett (1999), $PM_{10-2.5}$ are stronger predictors for asthma hospitalisation, whereas $PM_{2.5}$ is a strong predictor of respiratory infections (Lin et al., 2002). However, there is evidence that support $PM_{2.5}$ as strong predictor for asthma, in a systematic review and meta-analysis study investigating the impact of $PM_{2.5}$ on emergency department visit, $PM_{2.5}$ was concluded to have an adverse effect after a short-term exposure (Lin et al., 2002; WHO, 2003). South African standards for $PM_{2.5}$ and $PM_{10}$ are not tailored for children, thus, putting their lives at risk of conditions such as asthma.

#### 1.2.6.3 Ozone

Ozone is more intertwined with climate change than most of the criteria air pollutants. There are two types of ozone in the atmosphere, one present as a layer that protects the earth from radiation and

the other as ground-level ozone or tropospheric ozone. The latter is a toxic reactive oxidant pollutant gas that is highly dangerous (Von Schneidemesser et al., 2015). Tropospheric ozone is a secondary pollutant formed through an interaction of chemical pollutants such as nitrogen oxides ($NO_x$), volatile organic compounds (VOCs), methane and $CO_2$ in the presence of sunlight (Von Schneidemesser et al., 2015). This means the pollutant is not emitted directly from a specific source but result from the chemical interaction between primary pollutants and temperature (World Health Organization, 2006b; Chen et al., 2015).

This air pollutant is associated with a variety of health effects which include worsening asthma symptoms in patients (Wright et al., 2011; Naidoo et al., 2013). In a Taiwanese study investigating the effect of PM2.5 and ozone on lung function in non-asthmatic children, the combined effects showed a reduction in lung function, whereas ozone alone resulted in decreasing mid-expiratory flow in children related to asthma (Chetty, 2009; McCarty & Ferguson, 2014). Short-term exposure to ozone has also been associated with childhood asthma and the development of asthma (Chen et al., 2015). It is expected that asthma incidences are enhanced by exposure to ozone, thus, increasing the prevalence rate of childhood asthma.

#### 1.2.6.4 Sulphur dioxide

Sulphur dioxide ($SO_2$) belongs to the sulphur oxide ($SO_X$) group. $SO_2$ is classified under a criteria pollutant and is mostly found in higher concentrations compared to other $SO_X$ gases. $SO_2$ is emitted into the atmosphere due to fossil fuel burning from mostly industries such as power plants and mineral processing. Emission of this pollutant contributes to increased concentrations leading to the formation of other $SO_X$ gases such as $SO_3$. $SO_2$ is known to affect human health especially the respiratory system and has resulted in childhood asthma hospital admissions (Sunyer et al., 2003; Lin et al., 2004).

#### 1.2.6.5 Nitrogen dioxide

Nitrogen dioxide ($NO_2$) is grouped under extremely reactive gases called nitrogen oxide (NOx). The NOx is known to chemically react with other pollutants in the presence of sunlight resulting in $O_3$ (ozone). Unlike $O_3$, $NO_2$ is a primary pollutant and therefore, directly emitted from a source as a result of common anthropogenic activities such as fossil fuel combustion (Von Schneidemesser et al., 2015). Sources of these pollutants are associated with transport, industries and residential heating and cooking. This criteria pollutant is also known to irritate the respiratory system when inhaled at high concentrations. Short-term exposure to $NO_2$ effects includes asthma symptom exacerbation and long-term exposure to increased concentrations is associated with the development of full-blown asthma

(Takenoue et al., 2012; Héroux et al., 2015). Children are most vulnerable to these pollutants while playing outside, commuting to and from school and while at school.

#### 1.2.6.6 Carbon monoxide

Carbon monoxide (CO) is a primary pollutant emitted directly from sources related to both anthropogenic and natural activities. Major anthropogenic sources include transportation and biomass burning due to incomplete combustion. CO is known to react with $NO_X$ and other forms of pollutants. CO is a lethal pollutant, especially when exposed to high concentrations and can lead to asphyxiation resulting in death (Von Schneidemesser et al., 2015). Exposure to lower concentrations may result in headaches, vomiting and nausea and other health effects. CO is known to increase asthma attacks and increase hospital admissions in children (Evans et al., 2014).

### 1.2.7 Climate Change and Air Pollution

#### 1.2.7.1 Anthropogenic climate change

Climate change is referred to as "a systematic change in the long-term state of the atmosphere over multiple decades or longer" (Myhre et al., 2013). It is caused by decades of increasing GHGs such as in atmospheric $CO_2$ (Myhre et al., 2013) due to natural and anthropogenic sources. In South Africa, these sources are found in urban and rural areas. Urban sources include industries, transportation, and coal-fired energy, whereas the rural sources are cooking and heating up using wood fires, and agricultural practices. Anthropogenic climate change is referred to as climate change induced by human activities resulting in air pollution and contributing to an increase in GHGs emissions (Myhre et al., 2013). Air pollution, relates to the Industrial Revolution and the release of large amounts of GHGs into the atmosphere, thus, destabilising the global climate system (Akhtar & Palagiano, 2018).

Air pollution and climate change are interrelated. They emanate from similar sources and are interdependent as climate change results in favourable conditions for air pollution as concentration increases (Von Schneidemesser et al., 2015). Therefore, air pollution and climate change drivers can be reduced using the same mitigating strategies (Ramanathan & Feng, 2009).

#### 1.2.7.2 Effects of climate change on air pollution

Air quality is affected by both air pollutants and climate effects, with the latter referring to meteorological changes such as weather patterns and conditions (Von Schneidemesser et al., 2015). Weather conditions are location specific and include temperature, cloudiness, precipitation, humidity and wind speed and direction. These weather conditions are modified by climate change, particularly climate variation in return, weather conditions affect the air quality by enhancing the pollutants properties, dispersion and concentrations (Fann et al., 2016).

The influence of changes in weather conditions on air quality is well documented (Chou et al., 2010; D'Amato et al., 2015; Fann et al., 2016). The study conducted in India investigated the influence of temperature, relative humidity, and seasonal variations on ambient air quality for the following criteria pollutants: SO2, NOx, respirable suspended particulate matter (RSPM), and total suspended particulate matter (SPM). Meteorological variables such as temperature may affect air quality in several ways. It may affect the concentration of air pollution through the severity and frequency of the episodes. Ozone is formed during the photochemical reaction, a process that occurs in the presence of bright sun and high temperatures by VOCs and (NOx. These pollutants are emitted into the atmosphere from both natural and anthropogenic sources (Anenberg et al., 2020; Lu et al., 2022). The regression analysis was used in different seasons where $SO_2$ and NOx were negatively correlated in summer and positively correlated with temperature during the post-monsoon season. There was a positive correlation between temperature and RSPM, and SPM in all seasons except for the post-monsoon season. The role of the temperature of ambient air pollutants concentration can be observed. The study could not find any correlation with other meteorological conditions (Soriano et al., 2017). Meteorological conditions such as wind pattern, precipitation frequency, relative humidity, and temperature affect air pollution concentration and dispersion (Pan et al., 2020).

#### 1.2.7.3 Temperature and childhood asthma

As indicated in the literature above, meteorological conditions were widely proven to be associated with the deterioration of air quality, which is known to exacerbate asthma (Hervás et al., 2015). The role of temperature in the formation of $O_3$ is documented. Most studies focused their attention on temperature as an effect modifier and not as exposure of interest when assessing childhood asthma exacerbations (Sousa, Alvim-Ferraz & Martins, 2013). In recent years researchers were studying the association of temperature on childhood asthma exacerbations and their findings indicate that the relationship between temperature and asthma is U-shaped, this is supported by earlier studies that included air pollution and meteorology (Farkhondeh, Samarghandian & Azimi-Nezhad, 2018; Shoraka et al., 2019).

A Chinese ecological study was conducted for the years 2008 to 2017 in shanghai city using the Poisson generalized linear regression model combined with a distributed lag nonlinear model in examining effects of meteorological factors (temperature, air pressure, humidity, wind speed) on childhood asthma exacerbations. The authors had a maximum of 28-day lag for a whole year and a 5-day lag for the winter season. It was found that these factors were significantly associated with childhood asthma exacerbation and that the seasons were identified to be the effect modifiers (Hu, Cheng, et al., 2020). Another Chinese study, a time-series assessing the relationship between temperature variation between neighbouring (TVN) days and hospital visits for childhood asthma in China, used the same

methods as the ecological study. TVN and childhood asthma hospital visits were found to be significantly correlated, both girls and boys experiencing the greatest effect 5 and 3 lag days respectively and, 1 and 5 lag days for children aged <5 and ->5 – 14 years respectively (Li et al., 2016). In the earlier ecological study, it was also observed that children <5 years visited the hospital for asthma exacerbations more compared to older children and with boys experiencing more effect overall (Hu, Cheng, et al., 2020). Most studies of temperature and childhood asthma relationship in LMICs were conducted in China (Guo et al., 2012; Lam et al., 2016; Li et al., 2016; Hu, Cheng, et al., 2020; Hu, Xu, et al., 2020; Wei et al., 2020).

### 1.2.8 Gaps in the literature

Numerous studies are focusing on the impact of air pollution and child health globally, with the inclusion of South Africa (Oecd, 2013; World Health Organization, 2016; Landrigan et al., 2018). These studies explored the relationship between air pollution and the burden of childhood respiratory diseases, particularly asthma, including the type of air pollution and how it contributed to the asthma diagnosis (Kistnasamy et al., 2008; Olaniyan, T. A., Dalvie, M. A., & Jeebhay, 2015; Olaniyan et al., 2017). Despite the well-defined association between air pollution and the risk of childhood asthma, there have not been any South African studies that researched childhood asthma exacerbation due to the effect of temperature and air pollution. From the literature, it was proven that climate change and air pollution are linked. Despite some efforts to reduce air pollution sources, there hasn't been much success in improving air quality thus GHG emitted into the atmosphere results in climate change and extreme weather events such as temperature variability (Liao & Chang, 2014; Ebi, Campbell-Lendrum & Wyns, 2018). Poor air quality is associated with childhood asthma, which is on the increase in recent years (Ostro et al., 2001; Olaniyan et al., 2016; Ding et al., 2017b). This study seeks to understand the impact of temperature and air pollution in contributing to childhood asthma exacerbation, and possible prevalence and incidence.

# 2 Research Aim, Hypothesis, Objectives

## 2.1 Research Aim

This study aims to determine whether temperature variables exacerbate the relationship between air pollution (i.e., $PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$) and childhood asthma incidences in Cape Town, South Africa.

## 2.2 Hypothesis

Between the years 2009 and 2019, there has been an increase in childhood asthma incidences in Cape Town, South Africa. It is argued that this increase is exacerbated by the deterioration of air quality due

to the influence of temperature on air pollution. Therefore, we hypothesise that temperature and air pollution is associated with in house hospital treatment for childhood asthma.

## 2.3 Objectives

The objectives for achieving the study aim are:

- To determine which City of Cape Town air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$) concentration levels are linked with childhood asthma cases admitted at Red Cross War Memorial Children's hospital.
- To investigate ambient temperature and air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$) associated with childhood asthma cases in the City of Cape Town for children treated at Red Cross War Memorial Children's hospital.

**Table 3. Data Required to Meet Objectives**

| **Objectives** | **Data Required (Jan 2009 – Dec-2019)** | **Sources** |
|---|---|---|
| • To determine which City of Cape Town air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$) concentration levels are associated with childhood asthma cases admitted at Red Cross War Memorial Children's hospital. | Ambient air quality data ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$),<br>childhood asthma-related hospital admissions data<br>Such as:<br>• Asthma ICD-10 coding.<br>• Date of birth of the patient.<br>• Gender.<br>• Residential area.<br>• Second hand-smoking history.<br>• Treatment date. | City of Cape Town (Air quality data),<br>Western Cape Provincial Department of Health - Red Cross Hospital (Patient File) |
| • To investigate ambient temperature and air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$) associated with childhood asthma cases in the City of Cape Town. | Ambient air quality data ($PM_{2.5}$, $PM_{10}$, $NO_2$, $O_3$),<br>Childhood asthma-related hospital admissions data<br>Such as:<br>• Asthma ICD-10 coding.<br>• Date of birth of the patient.<br>• Gender.<br>• Residential area.<br>• Second hand-smoking history.<br>• Treatment date. | City of Cape Town (Air quality data),<br>Western Cape Provincial Department of Health - Red Cross Hospital (Patient File),<br>South African Weather Services |

| | | |
|---|---|---|
| | • Ambient temperature:<br>• Minimum,<br>• Maximum and,<br>• Average temperature | |

# 3 Methods

## 3.1. Study Design

A time series regression study design will be conducted between the years 2009 to 2019, analysing secondary data. This study will focus on childhood asthma prevalence among patients admitted to the Red Cross War Memorial Children's Hospital (RXH), using data obtained from the Western Cape Department of Health's information database. The information to be collected includes patient admission data and residential area which will be measured by corresponding correlation coefficients with the ambient air pollution data obtained from the City of Cape Town. The air quality data will include these criteria pollutants $PM_{2.5,}$ $PM_{10}$, $NO_{2,}$ $O_3$ concentration levels with the exclusion of $SO_2$, CO as these are well researched international and in South Africa. Ambient temperature data will be from the South African Weather Service. In this study, the exposures are temperature and air pollution levels, and the outcome of interest is hospital visits for childhood asthma exacerbations.

## 3.2. Study Population and Sampling

Red Cross Children's War Memorial hospital is a referral hospital catering for children under the age of 13 years old. The data to be reviewed will be for all children patients treated for asthma at the RXH from January 2009 to December 2019. The eligible age group for this study is between 6 – 13 years old; this is because it is difficult to diagnose children under six years old for asthma (Guo et al., 2019). Asthma cases will be utilised as a proxy for exacerbation of childhood asthma incidences. paediatric asthmatic patients' visits will be regarded as individual cases, regardless of a patient having multiple visits.

Exclusion criteria

The following are exclusion criteria for this study:

- Other respiratory diseases such as tuberculosis, COPD, etc. except for Asthma
- Patients younger than 6 years old
- Patients not treated at the RXH

### 3.2.1. Study Location

The study location is Cape Town, Western Cape Province, South Africa. The city is bounded by the Atlantic Ocean, and it is one of the most urbanised areas in the country. The metropolitan area has a total population of 3,740,026 million people (Statistics South Africa, 2012). It is industrialised with industries such as oil refineries, airports, and harbour. The area is characterised by dry summer conditions and mild winter seasons and the rain occurs mostly during winter seasons (Western Cape Provincial Government, 2015b).

## 3.3. Data Collection

To attribute air pollutants and temperature to childhood asthma, the following three main approaches to data collection must be followed.

### 3.3.1. Childhood asthma data

Childhood asthma data will be collected from the Provincial Department of Health's information database for patients treated at RXH. This data will be extracted using the ICD code 10 of asthma conditions. Should the data not provide a clear asthma diagnosis, asthma medication prescription will be used to determine or confirm asthma diagnosis, as per Appendix A. Each visit will be regarded as an individual case regardless of the same patient being treated multiple times. By treating hospital visits as individual cases, we quantify asthma exacerbation with the resultant exposures. The data to be collected from the patient case information using the patient data capture form (Appendix B), includes demographics such as age, address, gender, ethnicity and cases of second-hand smoking and asthma case-related information such as the date of treatment visits.

### 3.3.2. Air pollution data

The City of Cape Town has 14 air quality monitoring stations. These stations are in areas where there is a high risk of air pollution due to the proximity of the air pollution source. Air pollution data from all stations will be collected from the City of Cape Town's database and extracted into air quality data capture form (Appendix C), the data will be from the year 2009 to 2019. Air pollution data to be collected include daily averages of $PM_{2.5}$ $\mu g/m^3$, $PM_{10}$ $\mu g/m^3$, $NO_2$ $\mu g/m^3$ and $O_3$ $\mu g/m^3$.

### 3.3.3. Meteorological data

Meteorological data will be obtained from the South Africa Weather Services. The data to be collected are ambient temperatures (°C) for a period of 10 years, from January 2009 to December 2019. This data will be extracted into the Meteorological data capture form (Appendix D).

Asthma, air pollutants and ambient temperature data will be collected from different independent sources, such as South African Weather Services (ambient temperature data). No ethical approval is needed for temperature data, City of Cape Town Health (Air Pollution data) and Red Cross Hospital

(Health – Asthma data). This data will be categorised according to table 4 of the variables for analysis. SPSS 2015 version will be used for further analysis of the data.

## 3.4. Data Analysis

The study will focus on using meteorological and environmental factors in identifying childhood asthma exacerbations. This will include correlating ambient temperature for the last decade with the air pollution levels of the individual pollutants such as $PM_{2.5,}$ $PM_{10}$, $O_3$, and $NO_2$. These will be correlated with data collected on asthma treatment for children using a poisons regression analysis. The regression analysis studies are extensively used in the field of environmental epidemiology, more especially in assessing short-term exposures to environmental pollutants such as air pollution, meteorological variables and specific health effects or hospital admissions (Krishnan., 2013).

All data collected will be entered into SPSS statistical analysis software. The data will be cleaned, before analysis, to identify missing variables. As this is a mini-dissertation, three endpoints within 10 years (2009-2019) will be selected for analysis, these are 2009, 2014 and, 2019. Data will be converted and analysed using the following methods:

- Data will be analysed according to the objectives of the study.
- Descriptive analysis to be used to assess the distribution of the age, sex, and characteristics of the visits such as the date (year, month, and day), season and day of the week of the patient at the time of the visit.
- Using spearman's correlation coefficient to investigate the relationship between temperature variables and air pollutants.
- Poisson regression analysis to be conducted for analysing the relationship between daily childhood asthma treatment visits, air pollutants data as well as ambient temperature data. It will be done by using univariate and multivariate analysis.

Table 4 depicts how data will be categorised into different types of variables for collection and analysis.

**Table 4. Type of variables**

| Variable name | Variable | Type of variable |
|---|---|---|
| **Health data** | | |
| Year 1-10 | January 2009 – December 2019 | Categorical data |
| Admission month 1-12 | January to December | Categorical |
| Season 1-4 | Summer<br>Autumn<br>Winter<br>Spring | Categorical |
| Age | | Numerical |

| | | |
|---|---|---|
| Age group 1 – 3 | <5; 5 – 8, 9 – 13 | Categorical |
| Gender | Male and Female | Categorical |
| Education 1 – 5 | Day-care, Pre-School, Primary School and Secondary, Not Schooling | Categorical |
| Second-hand smoking 1 – 3 | Yes, No or Do not know | Categorical |
| **Meteorological data - Temperatures (°C)** | | |
| Temperature | Minimum Temperature | Numerical |
| | Average Temperature | Numerical |
| | Diurnal Temperature | Numerical |
| | Maximum Temperature | Numerical |
| **Air pollution data** | | |
| Particulate Matter 2.5 | $PM_{2.5}$ µg/$m^3$ | Numerical |
| Particulate Matter 10 | $PM_{10}$ µg/$m^3$ | Numerical |
| Nitrogen Dioxide | $NO_2$ µg/$m^3$ | Numerical |
| Ozone | $O_3$ µg/$m^3$. | Numerical |

### 3.4.1. Validity and Reliability of Measurements

The climate, air pollution and health data used in this study are regarded valid and reliable as they were captured, cleaned, and reviewed from various independent sources (South African Weather Services, City of Cape Town Health and Red Cross Hospital). There is a possibility of some Information bias due to missing variables such as age, sex, ethnicity, and address and in dealing with this problem, any missing information shall be reported as such in the discussion of findings.

## 3.5. Limitations

Due to time constraints as this is a mini dissertation, the study would be limited to observing only the three types of air pollutants ($PM_{2.5,}$ $PM_{10}$, $NO_2$ µg/$m^3$ and $O_3$ µg/$m^3$) and one climate factor (temperature) for childhood asthma exacerbation analysis. These pollutants – $SO_2$ and CO), will not be part of the study, including these other climate factors (wind speed & direction, precipitation, and humidity). There are possible confounders that will be excluded such as indoor air quality, and the role played by pollen in the asthma incidences. Added to that there is also a lack of data regarding individual-level exposure data for air pollutants and air temperature. The other limitation of the study is attribution. Asthma has been on the increase for several years and there are difficulties in the degree to which the change can be attributed to climate change. Only retrospective data will be collected from one children's tertiary hospital in the City of Cape Town; thus, restrictions exist in comparison. However, the analysis that will be provided in this research will give insights into potential associations and whether there is a need to collect this type of data consistently for prevention and adaptation planning.

# 4. Ethical Considerations

Ethics approval will be obtained from the UCT Faculty of Health Sciences, Human Research Ethics Committee, the Western Cape Provincial Department of Health for RXH data and the City of Cape Town.

## 4.1. Privacy/Confidentiality

There will be no actual patient contact or patient identifiers used in the study. Only the principal investigator and supervisors will have access to patient information obtained from the dataset and this information will be strictly confidential. Each patient will be assigned a unique study number as an identifier and all the records linking individual patients to the data will be stored at the school of public health and family medicine, division of environmental health under lock and key. The information will be kept there for a maximum period of 5 years. Patient names and addresses will not be included in the publication of the study.

## 4.2. Benefits

The findings of the study are expected to contribute to current gaps in the knowledge of the role of temperature and air pollution in exacerbating childhood asthma. Furthermore, the study will contribute to public health interventions aimed at reducing childhood asthma due to temperature and air pollution. The study findings will be beneficial for policy initiatives including South Africa's climate change and health adaptation strategies. We hope that the findings will lead to better exposure risk awareness and policy changes, including the review of current limits set out for criteria air pollutants.

## 4.3. Consent

There is no consent required from the study participants since this is secondary data analysis. The approval to conduct research will be obtained from the University of Cape Town's faculty of health sciences human research ethics committee. Furthermore, permission to analyse the patients' records will be obtained from the RXH research committee. Permission for access to temperature records and air quality records will be obtained from the South African Weather Services and The City of Cape Town research committee, respectively.

## 4.4. Foreseeable Harm

The study poses no foreseeable harm as secondary data analysis will be conducted.

## 4.5. Vulnerable Participants

The study will utilise case review data from the RXH. The participant data is from children below the age of 13 years old for 10 years. Since this research is based on secondary data analysis and the study requires no participants, there will be no vulnerable participants included directly.

# 5. Logistics and Time schedule

The study is allocated the timeline indicated in the table below.

**Table 5. Study timeline**

| Items | May 2020 | June 2020 | July 2020 | Aug 2020 | Sept 2020 | Oct 2020 | Nov 2020 | Dec 2020 | Jan 2021 | Feb 2021 | March 2021 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Proposal | | | | | | | | | | | |
| UCT Ethics approval | | | | | | | | | | | |
| CCT Health Ethics | | | | | | | | | | | |
| WC Health Ethics | | | | | | | | | | | |
| Data collection | | | | | | | | | | | |
| Data analysis | | | | | | | | | | | |
| Article drafts to supervisors | | | | | | | | | | | |
| Full Thesis drafts, Turnitin and submission | | | | | | | | | | | |

This dissertation will take 5 months to complete and is scheduled to be handed in by the March 2021 deadline as indicated in table 5.

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# PART B: JOURNAL READY ARTICLE

Part B: Journal "Ready" Manuscript

(For Journal of Environmental Research and Public Health)

(Refer to Appendix K: for guidelines for publication in the journal of environmental research and public health)

# Assessing the Role of Temperature and Air Pollution in Exacerbating Childhood Asthma in Cape Town, South Africa

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**Abstract:** This study was aimed at examining the interaction between air pollution and climate change, using temperature as a direct impact of climate change for the years 2009, 2014, and 2019. This was done by evaluating the relationship between temperature (maximum, minimum, and diurnal) and air pollution ($PM_{2.5}$, $PM_{10}$, $NO_2$, and $O_3$) in childhood asthma exacerbations using hospital data from Red Cross War Memorial Children's Hospital. Air quality data from all the 14 monitoring stations in Cape Town including temperature data were collected for the same period. Spearman's correlation was applied to measure the degree of association between temperature and air pollutants. Poisson's regression was used to evaluate the relationship between asthma exacerbations and, air pollutants and temperature variables. A total of 7753 asthma cases were included in the study. Asthma exacerbations in the autumn, winter and spring seasons were significantly higher than in the summer across all the years. There was a statistically significant relationship between asthma exacerbations and diurnal temperature (2019), maximum temperature (2014 and 2019), average temperature (2014 and 2019). The diurnal temperature was associated with $PM_{2.5}$ and $PM_{10}$. There was no significant relationship between asthma exacerbations and air pollutants ($PM_{10}$, $NO_2$, and $O_3$). Temperature increase appeared to be related to asthma exacerbation. The urgent fulfilment of the Paris Agreement is mandatory to avoid climate breakdown and detrimental health effects. Although this study provides data to inform current adaptation strategies, more research on the relationship between temperature, air pollutants, and childhood asthma is needed to include other provinces within South Africa.

**Keywords**: Childhood Asthma; Climate change; Temperature; Air pollution; Low-and middle-income countries; heat adaptation.

## 1. Introduction

Global and regional climate change is a long-term shift caused primarily by the emission of greenhouse gases into the atmosphere by natural and anthropogenic sources, with the latter is through the burning of fossil fuels [1]. This process not only contributes to climate change but also decreased air quality. The World Health Organization has described climate change as the biggest threat to public health in the 21st century. It has an impact on the social and environmental determinants of health such as clean drinking water, good air quality, food security, and adequate shelter. [2]. It is estimated that about 23% of all deaths can be attributed to environmental determinants of health [3].

Air pollution was shown to have adverse effects on health, including respiratory diseases such as asthma [3–5]. The impact of air pollution on child and adult asthma has been extensively studied and understood [4,6,7]. Yet, how climate change exacerbates asthma incidences is still poorly understood, especially for vulnerable groups such as children [8].

Asthma is a common chronic respiratory disease characterized by swelling of the airway and hypersensitivity of the lungs [9,10]. It is a complex heterogeneous disease due to its epidemiology, aetiology ranging from host risk factors (e.g., sex, age, and genetic predisposition), environmental health risks (e.g., pollen, indoor, and outdoor air pollution), and climatic weather conditions (e.g., temperature) [11]. These are the risk factors that influence the prevalence, phenotype, and severity of asthma in children [12].

Over the last few decades, asthma has been on the rise and this was observed through the rapid increase in prevalence, severity, and exacerbations of both adult and childhood asthma globally [13]. Asthma exacerbation also referred to as asthma attack, is due to a decrease in airflow caused by inflamed airways [13–16]. Asthma affects more than 300 million people worldwide, making it one of the most important diseases in children and adults [17]. In 2018 asthma was ranked 28$^{th}$ and 16$^{th}$ in the global estimates of the leading burden of disease and caused of years lived with disability respectively [18,19]. In children aged 5 – 14 years, asthma is ranked 14$^{th}$ on the global burden of disease and is in the top ten on the disability-adjusted life years. The increasing incidences of childhood asthma are also being observed in LMICs such as South Africa, where it was estimated that 20% of children aged 13 – 14 years old have asthma [19,20].

The increase in asthma prevalence appears to be too rapid to be attributed to just genetic and commonly researched environmental triggers such as seasonality, pollen, and air pollution in both children and adults [11,18]. Climate change impacts on childhood asthma prevalence and exacerbation are not well established but they are considered an effect modifier for exacerbating existing health problems [21,22]. Using temperature as a direct effect of climate change, can, directly and indirectly, impact childhood

asthma. Asthma is affected through air pollution by controlling the movement, concentration, and reaction of air pollutants that people are exposed to [23,24].

Climate change and air pollution are known to affect children suffering from asthma disproportionately as compared to adults [3,8]. This is due to their developing bodies, which are at a greater risk than adults to have short- and long-term effects from exposure to these environmental health factors [25]. In South Africa, the most studied population for air pollution and respiratory diseases are adults compared to children and particularly not childhood asthma [26,27]. Olaniyan and colleagues' study is aimed to understand the role of Cape Town in South Africa's air pollution and climate change in childhood asthma using ambient temperature as an indicator in explaining the increasing childhood asthma exacerbations [28,29]. The findings from the research presented in this article could contribute to the updating of air quality policies, adaptation strategies, and heat-health action plans aimed at protecting children from harmful air pollution and temperature exposure levels.

## 2. Materials and Methods

### *1. Study Design*

For assessing the role of temperature and air pollution in exacerbating childhood asthma among patients treated for asthma at the Red Cross War Memorial Children's Hospital (RXH), we utilised a time series regression study design. Data reviewed from RXH medical records were then analysed with corresponding temperature and air pollution data from the CoCPT.

### *2. Childhood Asthma Data*

Asthma data was collected from RXH which is a referral hospital for children in the Western Cape. Referral areas for the hospital include Klipfontein sub-district, Mitchells Plain sub-district, Rosebank, Mowbray, Rondebosch, and Salt River (Figure 1). Children who were inpatients and outpatients at the RXH with an asthma diagnosis were included in the study. Inpatients were defined as being admitted to the hospital for asthma treatment. Whereas outpatients were children treated for asthma without hospital admission. Asthma was classified by using the International Classification of Diseases Codes (ICD-10 Code) J45.0 to J45.998. Asthma cases were reviewed for three different years, that is from 2009, 2014, and 2019. These years were selected to provide a snapshot analysis over ten years with 2014 the midpoint of the study timeframe. RXH data was extracted from the hospital information system Clinicom ™, a data source providing Patient Master Index functionality which is widely used in the Western Cape Province. The data collected include patient names, age, address, ethnicity, gender, treatment or admission date, ICD-10 Codes, and descriptive diagnosis. A total of 15 811 patient visits data was reviewed for the study period. The inclusion criteria for this study were patients between the ages of 6 and 13 years who must reside in the City of Cape Town (CoCPT) at the time of capture. A

total of 7 753 patient visits (49.0%) met the study criteria, while 8 058 patient visits (51.0%) were excluded for not meeting the inclusion criteria (patients under 6, and over 13 years old and those who reside in another town). Of the 7 753 incidences of asthma cases included in the study, the majority were outpatients with only 409 (5.3%) being admitted as inpatients.

**Figure 2. City of Cape Town 's Air Quality Monitoring Stations Network**


*3. Air Quality and Temperature Data*

For the three study years (2009, 2014, and 2019), we collected the daily air quality data from six of the 14 CoCPT air quality monitoring stations (Figure 1) linked to the study patient's addresses. The four air pollutants known to affect asthma, based on evidence from the literature, were collected. These were: Ozone ($O_3$), Nitrogen Dioxide ($NO_2$), Particulate Matter with a diameter equal to or less than 10 ($PM_{10}$), and Particulate Matter with a diameter equal to or less than 2.5 ($PM_{2.5}$) [30,31]. Since the CoCPT only started to measure $PM_{2.5}$ in 2019, the data were not available for 2009 and 2014. A 24-hour average was calculated for $PM_{2.5}$ and $PM_{10}$. For $NO_2$, the highest one-hour reading for the day was selected for analysis, and for $O_3$ 8 hours running average was calculated. The calculations were conducted per the South African National Ambient Air Quality Standards (NAAQS) [32,33].

Daily temperature data from the Cape Town stations were assembled from the South African Weather Services (SAWS) for the years 2009, 2014, and 2019. Temperature data collected were from January to December of each study year including minimum and maximum daily temperatures. We calculated

the daily average and diurnal temperatures from daily maximum and minimum temperatures. Diurnal temperature is the variation between the daily maximum and minimum temperature. The two datasets were used to match with the hospital childhood asthma data.

*4. Statistical Analysis*

The following demographic variables were analysed: gender, age, air quality monitoring station, type of asthma, and seasons of the asthma hospital visits. Due to the lack of good air quality data, a snapshot approach was used to analyse the relationship between the three study variables. Spearman's correlation coefficient analysis was utilised to assess the association between daily air quality and temperature variables. Poisson's regression analysis was carried out for assessing the association of temperature and air pollution in exacerbating childhood asthma treated at RXH. For each of the air pollutants, a new variable was created by dividing the air pollutant reading by 10 units. Models assessing the relationship between city-wide temperature and all childhood asthma cases treated at RXH were statistically significant and had a good fit in terms of the Pearson's Chi-Squared value and the omnibus test having a p-valve $< 0.05$. The regression models for the selected study years that included air pollution did not have the goodness of fit and had an insignificant omnibus test thus indicating an insignificant association of a p-value $>0.05$. These analyses were performed using IBM SPSS Statistics 27 tool.

*5. Ethics*

Ethical approval for the study was granted by the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee HREC Ref: 677/2020. Permission to conduct the study was obtained from the City of Cape Town (Ref: 28110) and Red Cross War Memorial Children's Hospital (RXH: RCC251/WC_202011_025).

## 3. Results

*Demographic and health characteristics of study participants*

Table 1 outlines the participant's sociodemographic characteristics. We observed a 10% and 5% increase in 2014 and 2019 respectively of asthma cases treated at the RXH from 2009. Of the 7 753 patient visits, 4 411 (56.8%) were male patients and 3 342 (43.0%) were female. The number of patient visits by age was 4 809 (62.0%) for the 6 – 9 years old and 2863 (37.0%) for the 10 – 13 years old. The number of the asthma cases treated at RXH grouped per air quality monitoring station was 4 370 (56.3%) for those from Athlone, 2 157 (27.8%) for those from Khayelitsha, and the remaining monitoring stations accounting for 1 187 (15.3%). Of all paediatric asthma cases treated at RXH by diagnostic type as per the ICD 10 (Table A1.), most cases were due to predominantly allergic asthma 4 113 (53.0%) and unspecified asthma 3 604 (46.4%). For predominantly allergic asthma, there was a consistent increase

compared to 2009 for the study years; 12.5% in 2014 and 2% in 2019. Unspecified Asthma had a decline by 3% in 2014 and increased by 3.5% in 2019 compared to 2009. In terms of the total number of paediatric asthma exacerbations treated at RXH per season, there were 2 089 (26.9%) in summer, 1 972 (25.4%) in autumn, 2 086 (26.9%) in winter, and 1 606 (20.7%) in spring.

**Table 1. Demographic characteristics of child asthma patients treated at RXH - 2009, 2014, and 2019 (N = 7753)**

| | *2009 (n=1953)* | | *2014 (n=2701)* | | *2019 (n=3099)* | |
|---|---|---|---|---|---|---|
| | **Frequency** | **%** | **Frequency** | **%** | **Frequency** | **%** |
| *Type of admission* | | | | | | |
| *Inpatient* | 95 | 5 | 129 | 5 | 185 | 6 |
| *Outpatient* | 1858 | 95 | 2572 | 95 | 2914 | 94 |
| | | | | | | |
| *Gender* | | | | | | |
| *Male* | 1113 | 57 | 1506 | 56 | 1792 | 58 |
| *Female* | 840 | 43 | 1195 | 44 | 1306 | 42 |
| | | | | | | |
| *Age* | | | | | | |
| *Group (6 - 9)* | 1211 | 62 | 1736 | 64 | 1943 | 63 |
| *Group (10 - 13)* | 742 | 38 | 965 | 36 | 1156 | 37 |
| | | | | | | |
| *Area of residence* | | | | | | |
| *Athlone* | 1020 | 52 | 1352 | 51 | 1998 | 65 |
| *Khayelitsha* | 607 | 31 | 896 | 33 | 654 | 21 |
| *City Hall* | 89 | 5 | 126 | 5 | 100 | 3 |
| *Other* | 237 | 12 | 301 | 11 | 334 | 11 |
| | | | | | | |
| *Types of asthma* | | | | | | |
| *Predominantly Allergic asthma* | 703 | 36 | 1635 | 61 | 1775 | 57 |
| *Nonallergic asthma* | 14 | 1 | 10 | 0 | 9 | 0 |
| *Mixed asthma* | 0 | 0 | 1 | 0 | 2 | 0 |
| *Asthma. unspecified* | 1236 | 63 | 1055 | 39 | 1313 | 42 |
| | | | | | | |
| *Season of the year* | | | | | | |
| *Summer* | 537 | 27 | 707 | 26 | 845 | 27 |
| *Autumn* | 521 | 27 | 677 | 25 | 774 | 25 |
| *Winter* | 514 | 26 | 725 | 27 | 847 | 27 |
| *Spring* | 381 | 20 | 592 | 22 | 633 | 20 |

**Seasons**: Summer (December, January, and February), Autumn (March, April, and May), Winter (June, July, and August) and, Spring (September, October, and November).

*Air quality data and childhood asthma exacerbations*

The air quality was of varied standard and usability Table 2. Below for the 14 monitoring stations reviewed, only eight had some data available for the study years that was usable. For example,

Khayelitsha has $PM_{10}$ in 2009, Goodwood has $PM_{10}$ in 2014, and City Hall has $NO_2$ in 2014. For the year 2019, adequate data was only available for Tableview for $PM_{2.5}$, $PM_{10}$, and $NO_2$. Interestingly for $O_3$, only Atlantis had data available for 2009.

**Table 2. Air quality data usability received from the City of Cape Town**

| Air quality monitoring station | O3 | | | NO2 | | | PM2.5 | | | PM10 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | 2014 | 2019 | 2009 | 2014 | 2019 | 2009 | 2014 | 2019 | 2009 | 2014 | 2019 |
| Atlantis | - | - | ✓ | - | × | - | - | - | - | - | - | - |
| Athlone | - | - | - | - | - | - | - | - | - | - | - | - |
| City Hall | - | - | - | - | ✓ | - | - | - | - | - | - | - |
| Plattekloof | - | × | × | - | × | × | - | - | - | - | × | ✓ |
| Goodwood | × | × | × | - | ✓ | - | - | - | - | ✓ | ✓ | × |
| Khayelitsha | - | - | - | - | × | - | - | - | ✓ | ✓ | × | × |
| Bothasig | - | - | - | - | ✓ | - | - | - | - | - | - | - |
| Tableview | - | - | - | - | ✓ | ✓ | - | - | ✓ | - | × | ✓ |
| Molteno | - | ✓ | × | - | - | - | - | - | - | - | - | - |
| Foreshore | - | - | - | - | - | - | - | - | × | - | × | × |
| Bellville | - | - | - | - | - | - | - | - | - | - | × | - |
| Summerset West | - | - | - | - | - | - | - | - | - | - | - | - |
| Wallacedene | - | - | × | - | - | - | - | - | - | - | × | - |

*Legends: × = Data received and not usable (no readings/too many gaps)
- = Data not received
✓ = Data received and usable (there were gaps but was usable)

Table 3 and Table 4 links patients to the corresponding air quality monitoring stations for gender and age, respectively. Most asthma patients treated at RXH were from around the Athlone and Khayelitsha air quality monitoring stations for both inpatients and outpatients. Over the three study years, asthma patients treated at RXH linked to Athlone air quality monitoring station increased over time for both inpatient (2.8%) and outpatients (53.6%). Males had more cases in the outpatient cases compared to the females who had more inpatient cases for the three-year study (Table 3) and in the inpatient group, females had more cases compared to males for the three years of study. Age group 6 – 9 years olds had more cases in both the outpatients and inpatients groups than the 10 – 13 years olds (Table 4). Overall Athlone had more patients but due to lack of air quality data from the Athlone air quality monitoring station (Table 2), the patients from the station could not be included in the analysis of the air quality and asthma resulting in a major limitation to the study.

**Table 3. Frequencies of asthma exacerbations per monitoring station for patients treated at RXH by gender (N= 7753)**

| Air Quality monitoring station | Outpatients | | | | | | | | | | | | Inpatients | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | | | | 2014 | | | | 2019 | | | | 2009 | | | | 2014 | | | | 2019 | | | |
| | Male | | Female | | Male | | Female | | Male | | Female | | Male | | Female | | Male | | Female | | Male | | Female | |
| | n | % | n | % | n | % | n | % | N | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Athlone** | 585 | 54.5 | 391 | 49.8 | 775 | 53.5 | 522 | 46.4 | 1093 | 64.1 | 790 | 65.3 | 18 | 45.0 | 26 | 47.3 | 26 | 44.8 | 29 | 40.8 | 50 | 57.5 | 65 | 67.0 |
| **Atlantis** | 0 | 0.0 | 0 | 0.0 | 18 | 1.2 | 27 | 2.4 | 22 | 1.3 | 9 | 0.7 | 0 | 0.0 | 0 | 0.0 | 1 | 1.7 | 14 | 19.7 | 0 | 0.0 | 0 | 0.0 |
| **Bellville** | 32 | 3.0 | 30 | 3.8 | 28 | 1.9 | 18 | 1.6 | 42 | 2.5 | 13 | 1.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Bothasig** | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Cape Point** | 0 | 0.0 | 0 | 0.0 | 6 | 0.4 | 8 | 0.7 | 19 | 1.1 | 18 | 1.5 | 1 | 2.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 4.6 | 0 | 0.0 |
| **City Hall** | 48 | 4.5 | 31 | 3.9 | 58 | 4.0 | 58 | 5.2 | 63 | 3.7 | 28 | 2.3 | 4 | 10.0 | 6 | 10.9 | 4 | 6.9 | 6 | 8.5 | 4 | 4.6 | 5 | 5.2 |
| **Foreshore** | 5 | 0.5 | 14 | 1.8 | 1 | 0.1 | 9 | 0.8 | 19 | 1.1 | 4 | 0.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Goodwood** | 25 | 2.3 | 25 | 3.2 | 23 | 1.6 | 32 | 2.8 | 26 | 1.5 | 19 | 1.6 | 1 | 2.5 | 0 | 0.0 | 2 | 3.4 | 6 | 8.5 | 2 | 2.3 | 1 | 1.0 |
| **Khayelitsha** | 339 | 31.6 | 236 | 30.1 | 446 | 30.8 | 421 | 37.5 | 339 | 19.9 | 276 | 22.8 | 14 | 35.0 | 18 | 32.7 | 17 | 29.3 | 12 | 16.9 | 19 | 21.8 | 19 | 19.6 |
| **Maitland** | 32 | 3.0 | 39 | 5.0 | 55 | 3.8 | 26 | 2.3 | 39 | 2.3 | 32 | 2.6 | 2 | 5.0 | 4 | 7.3 | 5 | 8.6 | 3 | 4.2 | 4 | 4.6 | 5 | 5.2 |
| **Molteno** | 0 | 0.0 | 2 | 0.3 | 7 | 0.5 | 0 | 0.0 | 14 | 0.8 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 0 | 0.0 |
| **Somerset-West** | 0 | 0.0 | 3 | 0.4 | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Tableview** | 7 | 0.7 | 9 | 1.1 | 29 | 2.0 | 3 | 0.3 | 22 | 1.3 | 13 | 1.1 | 0 | 0.0 | 1 | 1.8 | 3 | 5.2 | 0 | 0.0 | 2 | 2.3 | 2 | 2.1 |
| **Wallacedene** | 0 | 0.0 | 4 | 0.5 | 2 | 0.1 | 0 | 0.0 | 6 | 0.4 | 6 | 0.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 1.4 | 0 | 0.0 | 0 | 0.0 |
| **Total** | 1073 | 100 | 785 | 100 | 1448 | 100 | 1124 | 100 | 1705 | 100 | 1209 | 100 | 40 | 100 | 55 | 100 | 58 | 100 | 71 | 100 | 87 | 100 | 97 | 100 |

**Table 4. Frequencies of asthma exacerbations per monitoring station for patients treated at RXH by age group (N= 7753)**

| Air Quality monitoring station | Outpatients | | | | | | | | | | | | Inpatients | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2009 | | | | 2014 | | | | 2019 | | | | 2009 | | | | 2014 | | | | 2019 | | | |
| | Age group (6 - 9) | | Age group (10 - 13) | | Age group (6 - 9) | | Age group (10 - 13) | | Age group (6 - 9) | | Age group (10 - 13) | | Age group (6 - 9) | | Age group (10 - 13) | | Age group (6 - 9) | | Age group (10 - 13) | | Age group (6 - 9) | | Age group (10 - 13) | |
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Athlone** | 585 | 51.3 | 391 | 54.5 | 818 | 49.9 | 479 | 51.3 | 1218 | 67.7 | 665 | 59.7 | 31 | 44.3 | 13 | 52 | 34 | 35.1 | 21 | 65.6 | 89 | 62.2 | 26 | 61.9 |
| **Atlantis** | 0 | 0.0 | 0 | 0.0 | 30 | 1.8 | 15 | 1.6 | 14 | 0.8 | 17 | 1.5 | 0 | 0.0 | 0 | 0.0 | 14 | 14.4 | 1 | 3.1 | 0 | 0.0 | 0 | 0.0 |
| **Bellville-South** | 31 | 2.7 | 31 | 4.3 | 34 | 2.1 | 12 | 1.3 | 34 | 1.9 | 21 | 1.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Bothasig** | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Cape Point** | 0 | 0.0 | 0 | 0.0 | 6 | 0.4 | 8 | 0.9 | 28 | 1.6 | 9 | 0.8 | 1 | 1.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 2.8 | 0 | 0.0 |
| **City Hall** | 63 | 5.5 | 16 | 2.2 | 75 | 4.6 | 41 | 4.4 | 76 | 4.2 | 15 | 1.3 | 9 | 12.9 | 1 | 4.0 | 9 | 9.3 | 1 | 3.1 | 8 | 5.6 | 1 | 2.4 |
| **Foreshore** | 9 | 0.8 | 10 | 1.4 | 1 | 0.1 | 9 | 1.0 | 5 | 0.3 | 18 | 1.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Goodwood** | 28 | 2.5 | 22 | 3.1 | 39 | 2.4 | 16 | 1.7 | 23 | 1.3 | 22 | 2.0 | 1 | 1.4 | 0 | 0.0 | 8 | 8.2 | 0 | 0.0 | 2 | 1.4 | 1 | 2.4 |
| **Khayelitsha** | 369 | 32.3 | 206 | 28.7 | 552 | 33.7 | 315 | 33.8 | 313 | 17.4 | 302 | 27.1 | 22 | 31.4 | 10 | 40 | 24 | 24.7 | 5 | 15.6 | 26 | 18.2 | 13 | 31 |
| **Maitland** | 43 | 3.8 | 28 | 3.9 | 55 | 3.4 | 26 | 2.8 | 56 | 3.1 | 15 | 1.3 | 5 | 7.1 | 1 | 4.0 | 5 | 5.2 | 3 | 9.4 | 9 | 6.3 | 0 | 0.0 |
| **Molteno** | 2 | 0.2 | 0 | 0.0 | 7 | 0.4 | 0 | 0.0 | 5 | 0.3 | 10 | 0.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 1.4 | 0 | 0.0 |
| **Somerset-West** | 0 | 0.0 | 3 | 0.4 | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Tableview** | 6 | 0.5 | 10 | 1.4 | 20 | 1.2 | 12 | 1.3 | 23 | 1.3 | 12 | 1.1 | 1 | 1.4 | 0 | 0.0 | 2 | 2.1 | 1 | 3.1 | 3 | 2.1 | 1 | 2.4 |
| **Wallacedene** | 4 | 0.4 | 0 | 0.0 | 2 | 0.1 | 0 | 0.0 | 4 | 0.2 | 8 | 0.7 | 0 | 0.0 | 0 | 0.0 | 1 | 1.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Total** | 1141 | 100 | 717 | 100 | 1639 | 100 | 933 | 100 | 1800 | 100 | 1114 | 100 | 70 | 100 | 25 | 100 | 97 | 100 | 32 | 100 | 143 | 100 | 42 | 100 |

*Temperature variables and air pollutants*

We observed that there were no significant disparities between the different years of study for temperature and air pollutants (Table 5). For maximum yearly temperature means for the years 2009, 2014, and 2019 there were 22.79 (SD 4.63), 22.88 (SD 4.78), and 22.61 (SD 4.36) respectively in degree Celsius. Minimum yearly temperature means for the years 2009, 2014 and, 2019 we observed 12.53 (SD 3.97), 12.60 (SD 4.32) and, 12.49 (SD 3.75) respectively in degree Celsius.

**Table 5. Summary statistics for temperature and air pollutants for the years 2009, 2014, and 2019.**

| Environmental determinants | 2009 | 2014 | 2019 | All Years |
|---|---|---|---|---|
| | Mean (IQR), SD | Mean (IQR), SD | Mean (IQR), SD | Mean (IQR), SD |
| **Daily temperature measures** | | | | |
| **Maximum Temperature °C** | 22.77 (19.10 - 25.85), 4.76 | 22.87 (18.70 - 26.00), 4.77 | 22.61 (19.20 - 25.50), 4.36 | 22.75 (19.10 - 25.80), 4.63 |
| **Minimum Temperature °C** | 12.50 (9.70 - 15.30), 3.82 | 12.60 (9.70 - 15.90), 4.32 | 12.48 (9.90 - 15.60), 3.75 | 12.53 (9.80 - 15.60), 3.97 |
| **Daily Average Temperature °C** | 17.64 (14.60 - 20.40), 3.79 | 17.74 (14.56 - 20.73), 17.74 | 17.55 (14.66 - 20.33), 3.61 | 17.64 (14.60 - 20.52), 3.84 |
| **Diurnal Temperature °C** | 10.27 (7.20 - 12.70), 4.10 | 10.28 (7.40 - 12.40), 3.92 | 10.13 (7.60 - 11.80), 3.71 | 10.24 (7.40 - 12.30), 3.92 |
| **Daily Air Pollution concentrations** | | | | |
| **24hour average Khayelitsha AQM Site $PM_{10}$ ug/$m^3$** | 44.67 (28.52 - 55.97), 23.25 | | | |
| **24hour average Goodwood AQM Site $PM_{10}$ ug/$m^3$** | | 26.79 (17.87 - 32.90), 11.40 | | |
| **Daily highest City Hall AQM site $NO_2$ ug/$m^3$** | | 13.52 (00 - 25.00), 15.16 | | |
| **24hour average Tableview AQM Site $PM_{2.5}$ ug/$m^3$** | | | 8.14 (5.41 - 9.72), 4.42 | |
| **24hour average Tableview AQM Site $PM_{10}$ ug/$m^3$** | | | 19.77 (14.26 - 22.77), 8.27 | |
| **Daily highest Tableview AQM site $NO_2$ ug/$m^3$** | | | 14.85 (10.0 - 20.0), 9.19 | |
| **8-hour average Atlantis AQM Site $O_3$ ug/$m^3$** | | | 45.37 (34.0 - 55.71), 14.85 | |

With regards to air pollutants levels, the $PM_{10}$ levels at the Khayelitsha station in 2009 had a mean of 44.68 (SD 23.5) thus indicating a large variation in the air quality data received from the city. There were six exceedances recorded for Khayelitsha $PM_{10}$ in 2009. Although not comparable, Goodwood $PM_{10}$ for the year 2014 had a mean of 26.79 (SD 11.41) and a range of 59.89 with no exceedances. 2019 $PM_{10}$ at Tableview had a mean of 19.77 (SD 8.28) and a range of 55.54 and no exceedance recorded. 2019

$PM_{2.5}$ at Tableview had a mean of 8.14 (SD 4.42) and a range of 45.55 for the entire year 2019. Tableview had only one exceedance for $PM_{2.5}$.

For $NO_2$ at City Hall in 2014, it had a mean of 13.52 (SD 15.16) and a range of 76.00 with no exceedances recorded for the year. In 2019 at Tableview, $NO_2$ had a mean of 14.85 (SD 9.19) and a range of 113.00. For $O_3$, only Atlantis was analysed for the year 2019. The mean value was 45.37 (SD 14.85) and a range of 114.50 was recorded. Atlantis had two exceedances for $O_3$ in 2019. The exceedances were measured against the South African National Ambient Air Quality Standards (NAAQS).

*Association between air pollutants and temperature variables*

As per Table 6, a statistically significant positive strong correlation analysis was observed between $PM_{2.5}$ and $PM_{10}$ ($r = 0.790$, $p < 0.01$). There was a statistically significant positive moderate correlation between $PM_{2.5}$ and diurnal temperature ($r = 0.57$, $p < 0.01$). Diurnal temperature was moderately correlated with PM10 and maximum temperature ($r = 0.50$, $p < 0.01$) and ($r = 0.51$, $p < 0.01$) respectively. $NO_2$ was not significantly correlated with any variable in Tableview but at City Hall in 2014, there was a very weak significant correlation between NO2 and maximum, minimum, and average temperature Table A5.

**Table 6. Spearman's correlation coefficients between daily air pollutants and temperature variables in the Tableview, Cape Town for the year 2019.**

| | *$PM_{2.5}$ ug/m³* | *$NO_2$ ug/m³* | *$PM_{10}$ ug/m³* | *Maximum Temperature* | *Minimum Temperature* | *Average Temperature* | *Diurnal Temperature* |
|---|---|---|---|---|---|---|---|
| *$PM_{2.5}$ ug/m³* | 1 | | | | | | |
| *$NO_2$ ug/m³* | -0.108* | 1 | | | | | |
| *$PM_{10}$ ug/m³* | 0.790** | -0.095 | 1 | | | | |
| *Maximum Temperature °C* | 0.293** | -0.057 | 0.283** | 1 | | | |
| *Minimum Temperature °C* | -0.179** | -0.049 | -0.145** | 0.629** | 1 | | |
| *Average Temperature °C* | 0.079 | -0.060 | 0.094 | 0.913** | 0.878** | 1 | |
| *Diurnal Temperature °C* | 0.579** | -0.007 | 0.505** | 0.518** | -0.269** | 0.166** | 1 |

*P < 0.05 ** P < 0.01

*Association between childhood asthma and temperature variables*

In Table 7, in the year 2009, none of the analysed temperature variables was statistically significant predictors of childhood asthma exacerbations in the city for children treated at the RXH. However, maximum, and average temperature in 2014 were significant predictors for several patients treated for childhood asthma exacerbations at RXH. The incidence rate ratio (IRR) for asthma cases treated at RXH due to these two-temperature variables was 0.99 for both maximum and average temperature variables. For every one-unit increase in the predictor variables (maximum and average temperature), the incidence rate ratio (the number of asthma cases treated at RXH) increased by a factor of 0.99 for both variables. The other significant results were observed in 2019, maximum temperature (IRR = 0.98, CI 0.97 – 0.99, $p < 0.01$), average temperature (IRR = 0.99, CI 0.97 – 0.99, $p < 0.01$), and diurnal temperature (IRR = 0.98, CI 0.97 – 0.99, $p < 0.05$). For every one-unit increase in the predictor variables (average, diurnal, and maximum temperature), the incidence rate ratio (the number of asthma cases treated at RXH) increased by a factor of 0.99, 0.99, and 0.98 respectively.

**Table 7. Poisson's regression (Univariate) analysis: risk of asthma exacerbation due to temperature variables.**

| | **2009 (N=1953)** | | | | **2014 (N=2701)** | | | | **2019 (N=3099)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **IRR** | **95% CI** | | **Sig.** | **IRR** | **95% CI** | | **Sig.** | **IRR** | **95% CI** | | **Sig.** |
| **MAXIMUM TEMPERATURE** | 1.01 | 0.91 | 1.13 | 0.75 | 0.99 | 0.98 | 1.00 | 0.04* | 0.98 | 0.98 | 0.99 | 0.00** |
| **MINIMUM TEMPERATURE** | 0.93 | 0.81 | 1.07 | 0.34 | 0.99 | 0.98 | 1.00 | 0.13 | 0.99 | 0.98 | 1.00 | 0.27 |
| **AVERAGE TEMPERATURE** | 0.98 | 0.85 | 1.12 | 0.77 | 0.99 | 0.98 | 1.00 | 0.05* | 0.98 | 0.97 | 0.99 | 0.01** |
| **DIURNAL TEMPERATURE** | 1.08 | 0.95 | 1.22 | 0.21 | 0.99 | 0.98 | 1.00 | 0.46 | 0.98 | 0.97 | 0.99 | 0.02* |

*P < 0.05 ** P < 0.01

**Table 8. Multivariate regression analysis: Risk of asthma exacerbations for the different suburbs from 2009 to 2019.**

| | 2009 (n= 606) Khayelitsha | | | | 2014 (n= 63) Goodwood | | | | 2014 (n= 126) City Hall | | | | 2019 (n= 31) Atlantis | | | | 2019 (n= 39) Tableview | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **IR** | **95% CI** | | **Sig.** | **IR** | **95% CI** | | **Sig.** | **IR** | **95% CI** | | **Sig.** | **IR** | **95% CI** | | **Sig.** | **IR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.52 | 1.19 | 1.93 | 0.00** | 1.63 | 0.68 | 3.92 | 0.26 | 0.91 | 0.76 | 1.10 | 0.35 | 1.00 | 0.92 | 1.09 | 0.90 | 3.38 | 1.15 | 9.88 | 0.02* |
| **Winter** | 1.46 | 1.14 | 1.86 | 0.00** | 1.87 | 0.78 | 4.49 | 0.15 | 1.19 | 0.99 | 1.43 | 0.05* | 1.02 | 0.94 | 1.12 | 0.54 | 3.20 | 1.11 | 9.24 | 0.03* |
| **Spring** | 1.37 | 1.07 | 1.76 | 0.01** | 1.12 | 0.44 | 2.87 | 0.80 | 0.97 | 0.81 | 1.17 | 0.80 | 1.07 | 0.98 | 1.17 | 0.09 | 1.44 | 0.47 | 4.42 | 0.52 |
| **Summer** | 1 | . | . | . | 1 | . | . | . | 1 | . | . | . | 1 | . | . | . | 1 | . | . | . |
| **$PM_{2.5}$ ug/m³** | | | | | | | | | | | | | | | | | 0.12 | 0.01 | 0.81 | 0.03* |
| **$PM_{10}$ ug/m³** | 0.98 | 0.94 | 1.03 | 0.55 | 0.82 | 0.58 | 1.14 | 0.24 | | | | | | | | | 1.89 | 0.90 | 3.94 | 0.09 |
| **$NO_2$ ug/m³** | | | | | | | | | 1.01 | 0.97 | 1.06 | 0.42 | | | | | 0.77 | 0.54 | 1.11 | 0.17 |
| **$O_3$ ug/m³** | | | | | | | | | | | | | 1.00 | 0.97 | 1.02 | 0.96 | | | | |
| **Diurnal Temperature** | 1.02 | 1.00 | 1.05 | 0.03* | 1.04 | 0.95 | 1.13 | 0.34 | 0.97 | 0.96 | 0.99 | 0.00** | 0.99 | 0.98 | 1.00 | 0.08 | 1.07 | 0.97 | 1.18 | 0.17 |

*P < 0.05 ** P < 0.01

Overall, for Table 8, the only air pollutant that was statistically significant to the outcome of interest is $PM_{2.5}$ ug/m³ for the year 2019 in Tableview, however this negative relationship cannot be real and is due to the small sample size and therefore the results were not presented. In 2009 at Khayelitsha, the risk of childhood asthma exacerbations was significantly higher in the autumn, winter, and spring compared to the summer. For 2014 at City Hall (winter only), for 2019 at Atlantis (Spring only), and 2019 at Tableview (Autumn and winter), the incidence rates ratio of asthma exacerbations was significantly higher than for the summer months with the spring months. For Diurnal temperature, the incidence rate of childhood asthma exacerbation was 2%. In 2014 at City Hall, the diurnal temperature was significantly associated with reduced incidents of childhood asthma exacerbation for children treated at RXH. The incidence rate ratio for asthma exacerbations treated at RXH was significantly higher in autumn, winter, and spring compared to summer.

## 4. Discussion

In this study, we analysed the air pollutants $PM_{2.5}$, $PM_{10}$, $NO_2$, and $O_3$ and temperature variables; daily maximum, minimum, average; and diurnal temperature with child asthma exacerbations treated at RXH. Several global studies support the notion that air pollution and temperature are significantly associated with childhood asthma exacerbations [7,34–39]. In our findings, there was no statistically significant association between childhood asthma exacerbations and air pollutants $PM_{10}$, $NO_2$, and $O_3$., However, there was a statistically significant negative result with PM2.5with childhood asthma. These results are questionable as literature has proven on many occasions that PM2.5 having adverse impacts on asthma exacerbations and more particularly in children [50–54]. The reason for the significant result could be due to the small sample size from Tableview, n = 29 patients for Tableview for the year 2019. In terms of temperature, the diurnal temperature was a consistent predictor for childhood asthma exacerbation treated at RXH, along with seasonality.

Since the year 2009, asthma cases treated at the RXH have been on the rise. Our findings thus support the current research literature that childhood asthma is increasing globally and particularly in LMICs [19,27,40]. For this study, the increase was observed in cases and not rates as it was not correlated to the entire population, but asthma cases treated at RXH. Overall, of the children treated for asthma at the RXH, 56.9% were male. Although fewer females were treated during the same period, of the inpatients, females had a higher admission rate of 54.5%, similar results were observed in other studies [41,42]. This finding supports the results of a review that found increased childhood asthma prevalence in males compared to their female counterparts [15,18]. Males have smaller airway diameters, increased allergic inflammations, and higher serum IgE levels than females [43]. Denlinger et al also found that there is no gender disparity in childhood asthma hospitalization due to exacerbations. A review by Fuseini and Newcomb, however, discovered that boys are twice as likely as girls to be hospitalised for asthma exacerbation [44]. The high incidences of asthma in males are set to switch to females during pubertal development [44]. These findings suggest that sex is a significant risk factor for childhood asthma exacerbations, it predisposes children differently depending on their age.

There is sufficient evidence of seasonal influence on asthma exacerbations in recent years [21,45–49]. This was also one of the main findings of this study, we found in all univariates and multivariate analyses that asthma exacerbations occurred more in the autumn, winter, and spring seasons when compared to the summer season. These results were also observed in a cross-sectional study conducted in Taiwan 2004 using the ISAAC participants aged 6 to 15 years old and examining the relationship between indoor environmental factors and seasonal childhood asthma [45]. Using multivariate logistic regression, Han and colleagues found that asthma prevalence was high in winter and at the lowest

point in the summer and the analysis took to account various environmental factors and individual susceptibility [45].

The results also showed a positive correlation between air pollutants and temperature variables. Diurnal temperature is an important predictor of air pollutants $PM_{10}$ and $PM_{2.5}$ but not for $O_3$ and $NO_2$. Similar findings were observed in an Australian time-series study investigating the relationship between diurnal temperature and childhood asthma exacerbations [42]. Xu and colleagues observed that diurnal temperature was significantly associated with $PM_{10}$, $O_3$, and $NO_2$. In our research, there was, unfortunately, a lack of good air quality monitoring data available in Cape Town.

In analysing the CoCPT's air quality data, it evident that air monitoring and data archiving were of inadequate quality. As indicated in Table 2, there were only a few monitoring stations that we received data from, which was acceptable for analysis. Most of the children identified in this study with asthma, based on the address in their files, fell into the catchment area for the Athlone air quality station (Table 3 and Table 4). Yet, the city was unable to provide data from this station, thus negatively affecting the study in meeting its aims and objectives. There were previous studies that conducted research using the air quality data from the city, but the method focused on assessing all the available data from different stations using the assumption that all participants were exposed at the same level regardless of where the pollutant was measured in relation to where the participant resided [27]. The current study method is crucial for understanding environmental exposure among patients in the same residential area. This type of epidemiological research is key to driving policy change to protect vulnerable populations such as children.

*Limitations of the study*

The study could not reproduce the results observed in other studies over the years, mainly due to inadequate air quality data received from the city. This caused a major limitation to the study and most patient data 56% were not utilised in the analysis of air quality and asthma. To understand how air pollution affects child health, it is essential to have good air quality data that would include the air pollution type, source, and concentration to which children are commonly exposed [55–57]. In a 2010 report by the Western Cape Province, Data inadequacy was highlighted as an issue impeding the province's ability to comprehensively assess air quality. The entity's unwillingness to share data and poor data recording contributed to the inadequacy [58]. Although the City of Cape Town now uses the requirements of the US EPA (Environmental Protection Agency) ambient air quality monitoring methods, ISO/IEC17025:2005 standards and SANAS TR07-03 to ensure air pollution quality assurance and control protocols are in place [58,59]. The National state of air quality report highlighted the CoCPT

as having most of the stations having low data recovery and this is also supported by the 2018 Provincial air quality report [60,61]. Air quality and temperature measurements were for a population level, and we used the assumption that children living around an air quality monitoring station experience the same exposure levels [62]. This method does not provide the individual exposure level. Another limitation was the lack of the exact data on which patients were seen due to emergency asthma attacks and which were due to an appointment system as utilised at the different clinics at the hospital, leading to sampling bias.

The health data received from the hospital did not have information on second-hand smoking. This is one of the important risk factors for respiratory diseases, especially asthma. Globally, it is estimated that over 40% of children are exposed to tobacco smoke [62]. Smoking is estimated to be on the rise and more especially in LMICs [63,64]. The data on second-hand smoking would have provided the study rich information in efforts to control for confounding factors associated with the risk factor.

Future research should focus on the impact climate change and air pollution have on child health, particularly in Africa. The research should be a city-wide study that would include data from all the healthcare centres in Cape Town. In eliminating the measurement bias, personal monitoring devices could be applied to determine exposure to air pollutants using more robust statistical analysis such as time series and spatial temporal analytics, as the study lacked more of these sophisticated analytical tools to better link meteorological variables and air pollution to health outcomes [62, 65, 66].

## 5. Conclusion

In this study, we found significant associations between childhood asthma exacerbations and diurnal, average, and maximum temperature. However, there were no significant associations between childhood asthma exacerbations and air pollutants ($PM_{10}$, $O_3$, and $NO_2$). There was a significant association observed between childhood asthma exacerbations and seasonality. The diurnal temperature was an important predictor for $PM_{2.5}$ and $PM_{10}$ and the health department must be aware of the risk diurnal temperature poses on child health. Early warning systems should be put in place to predict any spikes in temperature for better prevention strategies. The findings illustrate a need for children's respiratory health to be addressed in sub-national and national climate change adaptation and mitigation strategies. More data is needed for further study and replication of the finding to increase knowledge on individual child exposure to temperature and air pollutants. In the age of the Anthropocene and a climate crisis, long-term data on air pollutants must be rigorously collected and made officially available in South Africa and Cape Town. Our study highlights that the fulfilment of the Paris Agreement of avoiding further temperature increases is mandatory for protecting the health of all, as well as future generations.

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# PART C: APPENDICES

# Appendix A: Asthma Patient Medication.

Medication list of drugs used for patients presenting with asthma symptoms. This medication list of medication will be used to assist with information bias for patients whose diagnosis is not written, if the drug used appears on the list, the patient had presented with an asthma attack.

**Table A 1. Asthma Patient Medication List**

| FS_Detail | FS_Group |
|---|---|
| ADRENALINE 1 in 1000 Injection | MEDICINE RESPIRATORY |
| ADRENALINE 1 in 1000 Injection | MEDICINE RESPIRATORY |
| AMINOPHYLLINE 250 mg in 10mL Injection | MEDICINE RESPIRATORY |
| AMINOPHYLLINE 250 mg in 10mL Injection | MEDICINE RESPIRATORY |
| BECLOMETHASONE AQUEOUS 50 micrograms per metered dose Nasal Spray | MEDICINE RESPIRATORY |
| BECLOMETHASONE AQUEOUS 50 micrograms per metered dose Nasal Spray | MEDICINE RESPIRATORY |
| BECLOMETHASONE DIPROPIONATE 100 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| BECLOMETHASONE DIPROPIONATE 200 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| BUDESONIDE 100 micrograms per metered dose Inhaler+Spacer | MEDICINE RESPIRATORY |
| BUDESONIDE 100 micrograms per metered dose Inhaler+Spacer | MEDICINE RESPIRATORY |
| BUDESONIDE 200 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| BUDESONIDE 200 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| BUDESONIDE AQUEOUS 100 micrograms Nasal Spray | MEDICINE RESPIRATORY |
| CETIRIZINE DIHYDROCHLORIDE 10 mg Tablets | MEDICINE RESPIRATORY |
| CETIRIZINE DIHYDROCHLORIDE 10 mg Tablets | MEDICINE RESPIRATORY |
| CHLORPHENIRAMINE MALEATE 2 mg in 5mL Syrup | MEDICINE RESPIRATORY |
| CHLORPHENIRAMINE MALEATE 2 mg in 5mL Syrup | MEDICINE RESPIRATORY |
| CHLORPHENIRAMINE MALEATE 4 mg Tablets | MEDICINE RESPIRATORY |
| CHLORPHENIRAMINE MALEATE 4 mg Tablets | MEDICINE RESPIRATORY |
| FORMOTEROL 12 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| FORMOTEROL 12 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| IPRATROPIUM BROMIDE (ATROVENT 0.5) 500 micrograms in 2mL Nebules | MEDICINE RESPIRATORY |
| IPRATROPIUM BROMIDE (ATROVENT 0.5) 500 micrograms in 2mL Nebules | MEDICINE RESPIRATORY |
| IPRATROPIUM BROMIDE 20mcg / SALBUTAMOL 100mcg (COMBIVENT) Inhaler | MEDICINE RESPIRATORY |

| | |
|---|---|
| IPRATROPIUM BROMIDE 40 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| IPRATROPIUM BROMIDE 40 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| MESNA (MISTABRON) 600 mg in 3mL Inhalation | MEDICINE RESPIRATORY |
| MONTELUKAST SODIUM 10 mg Film Coated Tablets | MEDICINE RESPIRATORY |
| MONTELUKAST SODIUM 10 mg Film Coated Tablets | MEDICINE RESPIRATORY |
| MONTELUKAST SODIUM 5 mg Chewable Tablets | MEDICINE RESPIRATORY |
| MONTELUKAST SODIUM 5 mg Chewable Tablets | MEDICINE RESPIRATORY |
| OXYMETAZOLINE 0.025 % Nasal Drops | MEDICINE RESPIRATORY |
| OXYMETAZOLINE 0.025 % Nasal Drops | MEDICINE RESPIRATORY |
| OXYMETAZOLINE 0.05 % Nasal Drops | MEDICINE RESPIRATORY |
| OXYMETAZOLINE 0.05 % Nasal Drops | MEDICINE RESPIRATORY |
| PENTOXIFYLLINE 400 mg Tablets | MEDICINE RESPIRATORY |
| PORACTANT ALFA 120 mg in 1.5mL Lung Surfactant | MEDICINE RESPIRATORY |
| PORACTANT ALFA 120 mg in 1.5mL Lung Surfactant | MEDICINE RESPIRATORY |
| PORACTANT ALFA 240 mg in 3mL Lung Surfactant | MEDICINE RESPIRATORY |
| PORACTANT ALFA 240 mg in 3mL Lung Surfactant | MEDICINE RESPIRATORY |
| PROMETHAZINE 10 mg Tablets | MEDICINE RESPIRATORY |
| PROMETHAZINE 10 mg Tablets | MEDICINE RESPIRATORY |
| PROMETHAZINE 25 mg Tablets | MEDICINE RESPIRATORY |
| PROMETHAZINE 25 mg Tablets | MEDICINE RESPIRATORY |
| PROMETHAZINE 50 mg in 2mL Injection | MEDICINE RESPIRATORY |
| PROMETHAZINE 50 mg in 2mL Injection | MEDICINE RESPIRATORY |
| SALBUTAMOL 100 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| SALBUTAMOL 100 micrograms per metered dose Inhaler | MEDICINE RESPIRATORY |
| SALBUTAMOL 2 mg in 5mL Syrup | MEDICINE RESPIRATORY |
| SALBUTAMOL 2 mg in 5mL Syrup | MEDICINE RESPIRATORY |
| SALBUTAMOL 4 mg Tablets | MEDICINE RESPIRATORY |
| SALBUTAMOL 4 mg Tablets | MEDICINE RESPIRATORY |
| SALBUTAMOL 5 mg in 1mL Nebuliser Solution | MEDICINE RESPIRATORY |
| SALBUTAMOL 5 mg in 1mL Nebuliser Solution | MEDICINE RESPIRATORY |
| SALBUTAMOL 5 mg in 5mL Injection | MEDICINE RESPIRATORY |
| SALBUTAMOL 5 mg in 5mL Injection | MEDICINE RESPIRATORY |
| SALBUTAMOL 500micrograms in 1ml Injection | MEDICINE RESPIRATORY |
| SALBUTAMOL 500micrograms in 1ml Injection | MEDICINE RESPIRATORY |
| SALMETEROL 25/FLUTICASONE 125 micrograms per metered inhalation Inhaler | MEDICINE RESPIRATORY |
| SALMETEROL 25/FLUTICASONE 125 micrograms per metered inhalation Inhaler | MEDICINE RESPIRATORY |

| | |
|---|---|
| SALMETEROL 25/FLUTICASONE 250 micrograms per metered inhalation Inhaler | MEDICINE RESPIRATORY |
| SALMETEROL 50/FLUTICASONE 250 micrograms per metered inhalation Accuhaler | MEDICINE RESPIRATORY |
| SALMETEROL 50/FLUTICASONE 250 micrograms per metered inhalation Accuhaler | MEDICINE RESPIRATORY |
| SALMETEROL XINAFOATE 25 micrograms per metered inhalation Inhaler | MEDICINE RESPIRATORY |
| SODIUM BICARBONATE 2% Nose Drops | MEDICINE RESPIRATORY |
| SPACER (AEROCHAMBER) Spacer | MEDICINE RESPIRATORY |
| SPACER (AEROCHAMBER) INFANT Spacer | MEDICINE RESPIRATORY |
| SPACER (AEROCHAMBER) INFANT & MASK Spacer | MEDICINE RESPIRATORY |
| SPACER (ZERO STAT V) Inhaler | MEDICINE RESPIRATORY |
| SPACER (ZERO STAT V) + BABY MASK Inhaler | MEDICINE RESPIRATORY |
| SPACER (ZERO STAT V) + BABY MASK Inhaler | MEDICINE RESPIRATORY |
| SPACER (ZERO STAT) Inhaler | MEDICINE RESPIRATORY |
| SPACER (ZERO STAT) Inhaler | MEDICINE RESPIRATORY |
| SURFACTANT (TOTAL PHOSPHOLIPIDS) (N) 200 mg Injection | MEDICINE RESPIRATORY |
| SURFACTANT (TOTAL PHOSPHOLIPIDS) (N) 200 mg Injection | MEDICINE RESPIRATORY |
| SURFACTANT (TOTAL PHOSPHOLIPIDS) 200 mg Injection | MEDICINE RESPIRATORY |
| SURFACTANT TOTAL PHOSPHOLIPIDS 100 mg Injection | MEDICINE RESPIRATORY |
| THEOPHYLLIN ANHYDROUS (L.A.) 200 mg Tablets | MEDICINE RESPIRATORY |
| THEOPHYLLIN ANHYDROUS (L.A.) 200 mg Tablets | MEDICINE RESPIRATORY |
| THEOPHYLLIN ANHYDROUS (L.A.) 300 mg Tablets | MEDICINE RESPIRATORY |
| THEOPHYLLIN ANHYDROUS (L.A.) 300 mg Tablets | MEDICINE RESPIRATORY |
| THEOPHYLLINE (NUELIN) 25 mg in 5mL Alcohol Free Syrup | MEDICINE RESPIRATORY |
| THEOPHYLLINE (NUELIN) 25 mg in 5mL Alcohol Free Syrup | MEDICINE RESPIRATORY |
| TRIMEPRAZINE TARTATE (6MG/1ML) (S5) 30 mg in 5mL Syrup | MEDICINE RESPIRATORY |
| TRIMEPRAZINE TARTATE (6MG/1ML) (S5) 30 mg in 5mL Syrup | MEDICINE RESPIRATORY |

# Appendix B: Patient Data Capture Form

Patient data sheet for capturing patient information for each observation.

**Table A 2. Patient Data Capture Form**

| Study No. | Date of Birth | Age | Gender | Residential Area | Asthma ICD-10 coding | Treatment Date | Second-hand smoking history |
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# Appendix C: Air Quality Data Capture Form

**Air quality data sheet for capturing $PM_{2.5}$, $NO_2$ μg/m³ and $O_3$ μg/m³ readings for one year**

**Table A 3. Air Quality Data Capture Form**

| Days | Jan | Feb | Mar | Apr | May | June | July | Aug | Sept | Oct | Nov | Dec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | | |
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# Appendix D: Meteorological Data Capture Form

Temperature data sheet for capturing minimum, maximum and average temperature readings for one year.

**Table A 4. Meteorological Data Capture Form**

| Days | Jan | Feb | Mar | Apr | May | June | July | Aug | Sept | Oct | Nov | Dec |
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| 1 | | | | | | | | | | | | |
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# Appendix E: Letter of Approval by Research Ethics Committee, UCT

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room G50- Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** hrec-enquiries@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

03 November 2020

**HREC REF: 677/2020**

**Prof A Rother**
Environmental Health Division
Public Health & Family Medicine
FHS
Email: andrea.rother@uct.ac.za
Student: PHKTSH006@myuct.ac.za

Dear Prof Rother

**PROJECT TITLE: ASSESSING THE ROLE OF TEMPERATURE AND AIR POLLUTION IN EXACERBATING CHILDHOOD ASTHMA IN CAPE TOWN, SOUTH AFRICA. (MASTERS CANDIDATE: MR T PHAKISI)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.**

**Approval is granted for one year until the 30 November 2021.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***The HREC acknowledge that the student: - Mr Tshepo Phakisi will also be involved in this study.***

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 677/2020sa

# Appendix F: Permission Letter by RXH Research Committee

Western Cape Government
Health

**DR AN PARBHOO**
**Manager: Medical Services**
**Red Cross War Memorial Children's Hospital**
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

**27 November 2020**

Mr T Phakisi
UCT

Dear Mr Phakisi,

**RESEARCH: RXH: RCC 251 / WC_202011_025**

**PROJECT TITLE: Assessing the role of temperature and air pollution in exacerbating childhood asthma in Cape Town, South Africa**

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

**DR AN PARBHOO**
**MANAGER: MEDICAL SERVICES**

# Appendix G: Permission Letter by the City of Cape Town

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Natacha Berkowitz
Epidemiologist: City Health

T: 021 400 6864 F: 021 421 4894
E: Natacha.Berkowitz@capetown.gov.za

Ref: 28110 2021-02-18

**RE: ASSESSING THE ROLE OF TEMPERATURE AND AIR POLLUTION IN EXACERBATING CHILDHOOD ASTHMA IN CAPE TOWN**

Dear HannaAndrea Rother

Your research request has been approved as per your protocol. Please refer to the subsequent pages for the approval of any facilities or focus areas requested. Approval comments on any proposed impact on City Health resources are also provided.

Contact Person: Mr Ian Gildenhuys (Head: Environmental Health Specialised)

Tel/Cell: 021 590 5200/ 084 220 0139

Email: ian.gildenhuys@capetown.gov.za

**Please note the following:**

1. All individual patient information obtained must be kept confidential.
2. Access to the clinic and its patients must be arranged with the relevant Manager such that normal activities are not disrupted.
3. A copy of the final report must be uploaded to https://web1.capetown.gov.za/web1/mars/ProjectClosure/UploadReport/0/9370, within 6 months of its completion and feedback must also be given to the clinics involved.
4. Your project has been given an ID Number (9370). Please use this in any future correspondence with us.
5. No monetary incentives to be paid to clients on the City Health premises
6. If this research gives rise to a publication , please submit a draft before publication for City Health comment and include a disclaimer in the publication that "the research findings and recommendations do not represent an official view of the City of Cape Town "

Thank you for your co-operation and please contact me if you require any further information or assistance.

Kind Regards
Dr Natacha Berkowitz Epidemiologist: City Health

# Appendix H: ICD Code 10 Asthma Disease

**Table A 5. ICD Code 10 Asthma Disease**

| *ICD10 Codes* | *Description of the disease* |
|---|---|
| **J45** | Asthma |
| **J45.0** | Predominantly allergic asthma |
| **J45.1** | Nonallergic asthma |
| **J45.8** | Mixed asthma |
| **J45.9** | Asthma, unspecified |
| **J46** | Status asthmaticus |
| | |

# Appendix I: Correlation Coefficient between Air Pollution and Temperature

**Table A 6. Spearman's correlation coefficients between daily PM10 and temperature variables in Khayelitsha, Cape Town for the year 2009**

| | **$PM_{10}$** | **Maximum Temperature** | **Minimum Temperature** | **Average Temperature** | **Diurnal Temperature** |
|---|---|---|---|---|---|
| $PM_{10}$ | 1 | | | | |
| Maximum Temperature | 0.486** | 1 | | | |
| Minimum Temperature | -0.087 | 0.592** | 1 | | |
| Average Temperature | 0.236** | 0.902** | 0.870** | 1 | |
| Diurnal Temperature | 0.700** | 0.629** | -0.206** | 0.261** | 1 |

** P < 0.01

**Table A 7. Spearman's correlation coefficients between daily PM10 and temperature variables in Goodwood, Cape Town for the year 2014**

| | **$PM_{10}$** | **Maximum Temperature** | **Minimum Temperature** | **Average Temperature** | **Diurnal Temperature** |
|---|---|---|---|---|---|
| $PM_{10}$ | 1 | | | | |
| Maximum Temperature | 0.337** | 1 | | | |
| Minimum Temperature | -0.185** | 0.660** | 1 | | |
| Average Temperature | 0.091 | 0.911** | 0.901** | 1 | |
| Diurnal Temperature | 0.678** | 0.516** | -0.237** | 0.159** | 1 |

** P < 0.01

**Table A 8. Spearman's correlation coefficients between daily NO2 and temperature variables in the City Centre (City Hall), Cape Town for the year 2014**

| | **$NO_2$** | **Maximum Temperature** | **Minimum Temperature** | **Average Temperature** | **Diurnal Temperature** |
|---|---|---|---|---|---|
| $NO_2$ | 1 | | | | |
| Maximum Temperature | 0.149** | 1 | | | |
| Minimum Temperature | 0.124* | 0.660** | 1 | | |
| Average Temperature | 0.147** | 0.911** | 0.901 | 1 | |
| Diurnal Temperature | 0.036 | 0.516** | -0.237** | 0.159** | 1 |

*P < 0.05 ** P < 0.01

**Table A 9. Spearman's correlation coefficients between daily O3 and temperature variables in the Atlantis. Cape Town for the year 2019**

| | **$O_3$** | **Maximum Temperature** | **Minimum Temperature** | **Average Temperature** | **Diurnal Temperature** |
|---|---|---|---|---|---|
| $O_3$ | 1 | | | | |
| Maximum Temperature | 0.045 | 1 | | | |
| Minimum Temperature | 0.111* | 0.629** | 1 | | |
| Average Temperature | 0.077 | 0.913** | 0.878** | 1 | |
| Diurnal Temperature | -0.061 | 0.518** | -0.269** | 0.166** | 1 |

*P < 0.05 ** P < 0.01

# Appendix J: Multivariate Poisson's regression coefficients (Temperature and Seasonality)

In Table A10 below, in 2009 (A – D), the rate of asthma exacerbation treated at RXH was significantly higher in the seasons autumn, winter and spring compared to summer while holding independent model temperature constant (i.e., minimum, maximum, average, and diurnal temperatures).

For sub-table C, there was a 2.4% increase in the number of asthma cases for each extra degree in average temperature, holding seasonality at constant (i.e., autumn, winter, spring, and summer). Whereas in sub-table D for diurnal temperature during the same year, there was a 1.4% increase in the number of asthma cases for each extra degree in diurnal temperature, holding seasonality constant (i.e., autumn, winter, spring, and summer).

In sub-table G, during 2014, the rate of asthma exacerbations was significantly higher only during autumn and spring seasons compared to summer, while holding average temperature constant. However, in sub-table H, the rate of asthma exacerbation cases treated at RXH was significantly higher in the season autumn, winter and spring compared to summer, while holding constant diurnal temperature. It is important to note that only during 2009 as shown in sub-tables A, C, and D and 2019 in sub-table L were temperature (i.e., maximum, average, and diurnal) significantly associated with the number of asthma cases while controlling for seasonality (i.e., autumn, winter, spring, and summer).

In sub-tables I – L, during 2019, the incident rate of asthma cases was significantly higher in the season autumn, winter, and spring compared to summer in separate models while holding constant temperature (i.e., maximum, minimum, average, and diurnal temperatures). Based on the analysis, seasonality seems to be associated with the number of exacerbations of asthma cases treated at RXH for all the three independent study years.

**Table A 10. Poisson's regression coefficients for risk of asthma exacerbation with air pollutants and temperature variables**

| **A** | | | | | **B** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **2009 (n=1953)** | **RR** | **95% CI** | | **Sig.** | **2009 (n=1953)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.44 | 1.26 | 1.64 | 0.00 | **Autumn** | 1.40 | 1.22 | 1.61 | 0.00 |
| **Winter** | 1.52 | 1.31 | 1.78 | 0.00 | **Winter** | 1.41 | 1.18 | 1.69 | 0.00 |
| **Spring** | 1.44 | 1.25 | 1.65 | 0.00 | **Spring** | 1.37 | 1.18 | 1.59 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Maximum Temperature** | 1.01 | 1.00 | 1.02 | 0.00 | **Minimum Temperature** | 1.00 | 0.99 | 1.02 | 0.37 |
| **C** | | | | | **D** | | | | |
| **2009 (n=1953)** | **RR** | **95% CI** | | **Sig.** | **2009 (n=1953)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.46 | 1.27 | 1.68 | 0.00 | **Autumn** | 1.37 | 1.20 | 1.56 | 0.00 |
| **Winter** | 1.59 | 1.33 | 1.90 | 0.00 | **Winter** | 1.33 | 1.16 | 1.52 | 0.00 |
| **Spring** | 1.46 | 1.26 | 1.70 | 0.00 | **Spring** | 1.33 | 1.17 | 1.52 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |
| **Average Temperature** | 1.02 | 1.00 | 1.04 | 0.00 | **Diurnal Temperature** | 1.01 | 1.00 | 1.02 | 0.00 |
| **E** | | | | | **F** | | | | |
| **2014 (n=2701)** | **RR** | **95% CI** | | **Sig.** | **2014 (n=2701)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.13 | 1.01 | 1.27 | 0.02 | **Autumn** | 1.17 | 1.03 | 1.33 | 0.01 |
| **Winter** | 1.05 | 0.91 | 1.21 | 0.48 | **Winter** | 1.13 | 0.96 | 1.33 | 0.14 |
| **Spring** | 1.18 | 1.05 | 1.33 | 0.00 | **Spring** | 1.21 | 1.07 | 1.38 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |
| **Maximum Temperature** | 0.99 | 0.98 | 1.00 | 0.20 | **Minimum Temperature** | 1.00 | 0.98 | 1.01 | 0.87 |
| **G** | | | | | **H** | | | | |
| **2014 (n=2701)** | **RR** | **95% CI** | | **Sig.** | **2014 (n=2701)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.14 | 1.00 | 1.29 | 0.03 | **Autumn** | 1.17 | 1.052 | 1.30 | 0.00 |
| **Winter** | 1.06 | 0.89 | 1.26 | 0.46 | **Winter** | 1.12 | 1.004 | 1.25 | 0.04 |
| **Spring** | 1.18 | 1.04 | 1.34 | 0.00 | **Spring** | 1.22 | 1.095 | 1.36 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |
| **Average Temperature** | 0.99 | 0.98 | 1.00 | 0.46 | **Diurnal Temperature** | 0.99 | .984 | 1.00 | 0.21 |
| **I** | | | | | **J** | | | | |
| **2019 (n=3099)** | **RR** | **95% CI** | | **Sig.** | **2019 (n=3099)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.30 | 1.16 | 1.45 | 0.00 | **Autumn** | 1.36 | 1.22 | 1.52 | 0.00 |
| **Winter** | 1.15 | 1.00 | 1.32 | 0.03 | **Winter** | 1.32 | 1.14 | 1.52 | 0.00 |
| **Spring** | 1.31 | 1.17 | 1.47 | 0.00 | **Spring** | 1.39 | 1.24 | 1.56 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Maximum Temperature** | 0.99 | 0.98 | 1.00 | 0.25 | **Minimum Temperature** | 1.01 | 0.99 | 1.02 | 0.14 |
| **K** | | | | | **L** | | | | |
| **2019 (n=3099)** | **RR** | **95% CI** | | **Sig.** | **2019 (n=3099)** | **RR** | **95% CI** | | **Sig.** |
| **Autumn** | 1.32 | 1.18 | 1.48 | 0.00 | **Autumn** | 1.32 | 1.19 | 1.46 | 0.00 |
| **Winter** | 1.20 | 1.02 | 1.40 | 0.02 | **Winter** | 1.22 | 1.09 | 1.35 | 0.00 |
| **Spring** | 1.33 | 1.19 | 1.50 | 0.00 | **Spring** | 1.34 | 1.21 | 1.49 | 0.00 |
| **Summer** | 1 | . | . | . | **Summer** | 1 | . | . | . |
| **Average Temperature** | 0.99 | 0.98 | 1.01 | 0.82 | **Diurnal Temperature** | 0.99 | 0.98 | 0.99 | 0.03 |

*P < 0.05 ** P < 0.01

# Appendix K: Guidelines for Publication in the International Journal of Environmental Research and Public Health

Journal of Environmental Research and Public Health

Instructions for Authors

Shortcuts



Submission Checklist

Please:

1. read the Aims & Scope to gain an overview and assess if your manuscript is suitable for this journal;
2. use the Microsoft Word template or LaTeX template or Free Format Submission to prepare your manuscript;

3. make sure that issues about publication ethics, research ethics, copyright, authorship, figure formats, data and references format have been appropriately considered;
4. Ensure that all authors have approved the content of the submitted manuscript.
5. Authors are encouraged to add a biography (optional) to the submission and publish it.

Manuscript Submission Overview

Types of Publications

*IJERPH* has no restrictions on the length of manuscripts, provided that the text is concise and comprehensive. Full experimental details must be provided so that the results can be reproduced. *IJERPH* requires that authors publish all experimental controls and make full datasets available where possible (see the guidelines on Supplementary Materials and references to unpublished data).

Manuscripts submitted to *IJERPH* should neither be published previously nor be under consideration for publication in another journal. The main article types are as follows:

- *Articles:* Original research manuscripts. The journal considers all original research manuscripts provided that the work reports scientifically sound experiments and provides a substantial amount of new information. Authors should not unnecessarily divide their work into several related manuscripts, although Short *Communications* of preliminary, but significant, results will be considered. The quality and impact of the study will be considered during peer review. Articles should have a main text of around 3000 words at minimum.
- *Reviews:* These provide concise and precise updates on the latest progress made in a given area of research. Systematic reviews should follow the PRISMA guidelines. The main text of review papers should be around 4000 words at minimum.
- *Case reports:* Case reports present detailed information on the symptoms, signs, diagnosis, treatment (including all types of interventions), and outcomes of an individual patient. Case reports usually describe new or uncommon conditions that serve to enhance medical care or highlight diagnostic approaches.

Submission Process

Manuscripts for *IJERPH* should be submitted online at susy.mdpi.com. The submitting author, who is generally the corresponding author, is responsible for the manuscript during the submission and peer-review process. The submitting author must ensure that all eligible co-authors have been included in the author list (read the criteria to qualify for authorship) and that they have all read and approved the submitted version of the manuscript. To submit

your manuscript, register and log in to the submission website. Once you have registered, click here to go to the submission form for *IJERPH*. All co-authors can see the manuscript details in the submission system, if they register and log in using the e-mail address provided during manuscript submission.

Accepted File Formats

Authors must use the Microsoft Word template or LaTeX template to prepare their manuscript. Using the template file will substantially shorten the time to complete copy-editing and publication of accepted manuscripts. The total amount of data for all files must not exceed 120 MB. If this is a problem, please contact the Editorial Office ijerph@mdpi.com. Accepted file formats are:

- *Microsoft Word:* Manuscripts prepared in Microsoft Word must be converted into a single file before submission. When preparing manuscripts in Microsoft Word, the *IJERPH* Microsoft Word template file must be used. Please insert your graphics (schemes, figures, *etc.*) in the main text after the paragraph of its first citation.

- *LaTeX:* Manuscripts prepared in LaTeX must be collated into one ZIP folder (including all source files and images, so that the Editorial Office can recompile the submitted PDF). When preparing manuscripts in LaTeX, please use the *IJERPH* LaTeX template files. You can now also use the online application writeLaTeX to submit articles directly to *IJERPH*. The MDPI LaTeX template file should be selected from the writeLaTeX template gallery.

- *Supplementary files:* May be any format, but it is recommended that you use common, non-proprietary formats where possible (see below for further details).

Disclaimer: Usage of these templates is exclusively intended for submission to the journal for peer-review, and strictly limited to this purpose and it cannot be used for posting online on preprint servers or other websites.

Free Format Submission

*IJERPH* now accepts free format submission:

- We do not have strict formatting requirements, but all manuscripts must contain the required sections: Author Information, Abstract, Keywords, Introduction, Materials & Methods, Results, Conclusions, Figures and Tables with Captions, Funding Information, Author Contributions, Conflict of Interest and other Ethics Statements. Check the Journal *Instructions for Authors* for more details.

- Your references may be in any style, provided that you use the consistent formatting throughout. It is essential to include author(s) name(s), journal or book title, article or chapter title (where required), year of publication, volume and issue (where appropriate) and pagination. DOI numbers (Digital Object Identifier) are not

mandatory but highly encouraged. The bibliography software package *EndNote*, *Zotero*, *Mendeley*, *Reference Manager* are recommended.

- When your manuscript reaches the revision stage, you will be requested to format the manuscript according to the journal guidelines.

Cover Letter

A cover letter must be included with each manuscript submission. It should be concise and explain why the content of the paper is significant, placing the findings in the context of existing work and why it fits the scope of the journal. Confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal. Any prior submissions of the manuscript to MDPI journals must be acknowledged. The names of proposed and excluded reviewers should be provided in the submission system, not in the cover letter.

Author Biography

Authors are encouraged to add a biography (maximum 150 words) to the submission and publish it. This should be a single paragraph and should contain the following points:

1. Authors' full names followed by current positions;
2. Education background including institution information and year of graduation (type and level of degree received);
3. Work experience;
4. Current and previous research interests;
5. Memberships of professional societies and awards received.

Note for Authors Funded by the National Institutes of Health (NIH)

This journal automatically deposits papers to PubMed Central after publication of an issue. Authors do not need to separately submit their papers through the NIH Manuscript Submission System (NIHMS, http://nihms.nih.gov/).

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Manuscript Preparation

General Considerations

- Research manuscripts should comprise:
    - Front matter: Title, Author list, Affiliations, Abstract, Keywords

- Research manuscript sections: Introduction, Materials and Methods, Results, Discussion, Conclusions.
- Back matter: Supplementary Materials, Acknowledgments, Author Contributions, Conflicts of Interest, References.

- Review manuscripts should comprise the front matter, literature review sections and the back matter. The template file can also be used to prepare the front and back matter of your review manuscript. It is not necessary to follow the remaining structure. Structured reviews and meta-analyses should use the same structure as research articles and ensure they conform to the PRISMA guidelines.
- Case reports should include a succinct introduction about the general medical condition or relevant symptoms that will be discussed in the case report; the case presentation including all of the relevant de-identified demographic and descriptive information about the patient(s), and a description of the symptoms, diagnosis, treatment, and outcome; a discussion providing context and any necessary explanation of specific treatment decisions; a conclusion briefly outlining the take-home message and the lessons learned.
- Graphical Abstract:

A graphical abstract (GA) is an image that appears alongside the text abstract in the Table of Contents. In addition to summarizing content, it should represent the topic of the article in an attention-grabbing way.

The GA should be a high-quality illustration or diagram in any of the following formats: PNG, JPEG, EPS, SVG, PSD or AI. Written text in a GA should be clear and easy to read, using one of the following fonts: Times, Arial, Courier, Helvetica, Ubuntu or Calibri.

The minimum required size for the GA is 560 × 1100 pixels (height × width). When submitting larger images, please make sure to keep to the same ratio.

- Abbreviations should be defined in parentheses the first time they appear in the abstract, main text, and in figure or table captions and used consistently thereafter.
- SI Units (International System of Units) should be used. Imperial, US customary and other units should be converted to SI units whenever possible.
- Accession numbers of RNA, DNA and protein sequences used in the manuscript should be provided in the Materials and Methods section. Also see the section on Deposition of Sequences and of Expression Data.

- Equations: If you are using Word, please use either the Microsoft Equation Editor or the MathType add-on. Equations should be editable by the editorial office and not appear in a picture format.

- Research Data and supplementary materials: Note that publication of your manuscript implies that you must make all materials, data, and protocols associated with the publication available to readers. Disclose at the submission stage any restrictions on the availability of materials or information. Read the information about Supplementary Materials and Data Deposit for additional guidelines.

- Preregistration: Where authors have preregistered studies or analysis plans, links to the preregistration must be provided in the manuscript.

- Guidelines and standards: MDPI follows standards and guidelines for certain types of research. See https://www.mdpi.com/editorial_process for further information.

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Front Matter

These sections should appear in all manuscript types

- Title: The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis or replication study. When gene or protein names are included, the abbreviated name rather than full name should be used.

- Author List and Affiliations: Authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations: complete address information including city, zip code, state/province, and country. At least one author should be designated as corresponding author, and his or her email address and other details should be included at the end of the affiliation section. Please read the criteria to qualify for authorship.

- Abstract: The abstract should be a total of about 200 words maximum. The abstract should be a single paragraph and should follow the style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied. Include any relevant preregistration numbers, and species and strains of any animals used. 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract should be an objective representation of the article: it must not contain results which are not

presented and substantiated in the main text and should not exaggerate the main conclusions.

- Keywords: Three to ten pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.

Research Manuscript Sections

- Introduction: The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance, including specific hypotheses being tested. The current state of the research field should be reviewed carefully and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the workand highlight the main conclusions. Keep the introduction comprehensible to scientists working outside the topic of the paper.

- Materials and Methods: They should be described with sufficient detail to allow others to replicate and build on published results. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Give the name and version of any software used and make clear whether computer code used is available. Include any pre-registration codes.

- Results: Provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.

- Discussion: Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with Results.

- Conclusions: This section is mandatory, and should provide readers with a brief summary of the main conclusions.

- Patents: This section is not mandatory, but may be added if there are patents resulting from the work reported in this manuscript.

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Back Matter

- Supplementary Materials: Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.

- Funding: All sources of funding of the study should be disclosed. Clearly indicate grants that you have received in support of your research work and if you received funds to cover publication costs. Note that some funders will not refund article processing charges (APC) if the funder and grant number are not clearly and correctly identified in the paper. Funding information can be entered separately into the submission system by the authors during submission of their manuscript. Such funding information, if available, will be deposited to FundRef if the manuscript is finally published.
  Please add: "This research received no external funding" or "This research was funded by [name of funder] grant number [xxx]" and "The APC was funded by [XXX]" in this section. Check carefully that the details given are accurate and use the standard spelling of funding agency names at https://search.crossref.org/funding, any errors may affect your future funding.

- Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

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  For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; Methodology, X.X.; Software, X.X.; Validation, X.X., Y.Y. and Z.Z.; Formal Analysis, X.X.; Investigation, X.X.; Resources, X.X.; Data Curation, X.X.; Writing – Original Draft Preparation, X.X.; Writing – Review & Editing, X.X.; Visualization, X.X.; Supervision, X.X.; Project Administration, X.X.; Funding Acquisition, Y.Y.", please turn to the CRediT taxonomy for the term explanation. For more background on CRediT, see here. "Authorship must include and be limited to those who have contributed substantially to the work. Please read the section concerning the criteria to qualify for authorship carefully".

- Institutional Review Board Statement: In this section, please add the Institutional Review Board Statement and approval number for studies involving humans or

animals. Please note that the Editorial Office might ask you for further information. Please add "The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." OR "Ethical review and approval were waived for this study, due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans or animals. You might also choose to exclude this statement if the study did not involve humans or animals.

- Informed Consent Statement: Any research article describing a study involving humans should contain this statement. Please add "Informed consent was obtained from all subjects involved in the study." OR "Patient consent was waived due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans. You might also choose to exclude this statement if the study did not involve humans.
  Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patient(s) to publish this paper" if applicable.

- Data Availability Statement: In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section "MDPI Research Data Policies". You might choose to exclude this statement if the study did not report any data.

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◎ Journal Articles:
1. Author 1, A.B.; Author 2, C.D. Title of the article. *Abbreviated Journal Name* Year, *Volume*, page range.

◎ Books and Book Chapters:
2. Author 1, A.; Author 2, B. *Book Title*, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154–196.
3. Author 1, A.; Author 2, B. Title of the chapter. In *Book Title*, 2nd ed.; Editor 1, A., Editor 2, B., Eds.; Publisher: Publisher Location, Country, Year; Volume 3, pp. 154–196.

◎ Unpublished work, submitted work, personal communication:
4. Author 1, A.B.; Author 2, C. Title of Unpublished Work. status (unpublished; manuscript in preparation).
5. Author 1, A.B.; Author 2, C. Title of Unpublished Work. *Abbreviated Journal Name* stage of publication (under review; accepted; in press).
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◎ Conference Proceedings:
7. Author 1, A.B.; Author 2, C.D.; Author 3, E.F. Title of Presentation. In *Title of the Collected Work* (if available), Proceedings of the Name of the Conference, Location of Conference, Country, Date of Conference; Editor 1, Editor 2, Eds. (if available); Publisher: City, Country, Year (if available); Abstract Number (optional), Pagination (optional).

◎ Thesis:
8. Author 1, A.B. Title of Thesis. Level of Thesis, Degree-Granting University, Location of University, Date of Completion.

◎ Websites:
9. Title of Site. Available online: URL (accessed on Day Month Year). Unlike published works, websites may change over time or disappear, so we encourage you

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Preparing Figures, Schemes and Tables

- File for Figures and Schemes must be provided during submission in a single zip archive and at a sufficiently high resolution (minimum 1000 pixels width/height, or a resolution of 300 dpi or higher). Common formats are accepted, however, TIFF, JPEG, EPS and PDF are preferred.
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- All table columns should have an explanatory heading. To facilitate the copy-editing of larger tables, smaller fonts may be used, but no less than 8 pt. in size. Authors should use the Table option of Microsoft Word to create tables.
- Authors are encouraged to prepare figures and schemes in color (RGB at 8-bit per channel). There is no additional cost for publishing full color graphics.

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Supplementary Materials, Data Deposit and Software Source Code

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MDPI is committed to supporting open scientific exchange and enabling our authors to achieve best practices in sharing and archiving research data. We encourage all authors of articles published in MDPI journals to share their research data. Individual journal guidelines can be found at the journal 'Instructions for Authors' page. Data sharing policies concern the minimal dataset that supports the central findings of a published study. Generated data should be publicly available and cited in accordance with journal guidelines.

MDPI data policies are informed by TOP Guidelines.

Where ethical, legal or privacy issues are present, data should not be shared. The authors should make any limitations clear in the Data Availability Statement upon submission.

Authors should ensure that data shared are in accordance with consent provided by participants on the use of confidential data.

Data Availability Statements provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study.

Below are suggested Data Availability Statements:

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  The data presented in this study are openly available in [repository name e.g., FigShare] at [doi], reference number [reference number].

- Data available in a publicly accessible repository that does not issue DOIs
  Publicly available datasets were analyzed in this study. This data can be found here: [link/accession number]

- Data available on request due to restrictions eg privacy or ethical
  The data presented in this study are available on request from the corresponding author. The data are not publicly available due to [insert reason here]

- 3rd Party Data
  Restrictions apply to the availability of these data. Data was obtained from [third party] and are available [from the authors / at URL] with the permission of [third party].

- Data sharing not applicable
  No new data were created or analyzed in this study. Data sharing is not applicable to this article.

- Data is contained within the article or supplementary material
  The data presented in this study are available in [insert article or supplementary material here]

Data citation:

- [dataset] Authors. Year. Dataset title; Data repository or archive; Version (if any); Persistent identifier (e.g., DOI).

*Computer Code and Software*

For work where novel computer code was developed, authors should release the code either by depositing in a recognized, public repository such as GitHub or uploading as supplementary information to the publication. The name, version, corporation and location information for all software used should be clearly indicated. Please include all the parameters used to run software/programs analyses.

*Supplementary Material*

Additional data and files can be uploaded as "Supplementary Files" during the manuscript submission process. The supplementary files will also be available to the referees as part of the peer-review process. Any file format is acceptable; however, we recommend that common, non-proprietary formats are used where possible.

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*Unpublished Data*

Restrictions on data availability should be noted during submission and in the manuscript. "Data not shown" should be avoided: authors are encouraged to publish all observations related to the submitted manuscript as Supplementary Material. "Unpublished data" intended for publication in a manuscript that is either planned, "in preparation" or "submitted" but not yet accepted, should be cited in the text and a reference should be added in the References section. "Personal Communication" should also be cited in the text and reference added in the References section. (see also the MDPI reference list and citations style guide).

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Data may be deposited with specialized service providers or institutional/subject repositories, preferably those that use the DataCite mechanism. Large data sets and files greater than 60 MB must be deposited in this way. For a list of other repositories specialized in scientific and experimental data, please consult databib.org or re3data.org. The data repository name, link to the data set (URL) and accession number, doi or handle number of the data set must be provided in the paper. The journal Data also accepts submissions of data set papers.

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New sequence information must be deposited to the appropriate database prior to submission of the manuscript. Accession numbers provided by the database should be included in the submitted manuscript. Manuscripts will not be published until the accession number is provided.

- *New nucleic acid sequences* must be deposited in one of the following databases: GenBank, EMBL, or DDBJ. Sequences should be submitted to only one database.
- *New high throughput sequencing (HTS) datasets* (RNA-seq, ChIP-Seq, degradome analysis, …) must be deposited either in the GEO database or in the NCBI's Sequence Read Archive (SRA).
- *New microarray data* must be deposited either in the GEO or the ArrayExpress databases.The "Minimal Information About a Microarray

Experiment" (MIAME) guidelines published by the Microarray Gene Expression Data Society must be followed.

- *New protein sequences* obtained by protein sequencing must be submitted to UniProt (submission tool SPIN). Annotated protein structure and its reference sequence must be submitted to RCSB of Protein Data Bank.

All sequence names and the accession numbers provided by the databases must be provided in the Materials and Methods section of the article.

*Deposition of Proteomics Data*

Methods used to generate the proteomics data should be described in detail and we encourage authors to adhere to the "Minimum Information About a Proteomics Experiment". All generated mass spectrometry raw data must be deposited in the appropriate public database such as ProteomeXchange, PRIDE or jPOST. At the time of submission, please include all relevant information in the materials and methods section, such as repository where the data was submitted and link, data set identifier, username and password needed to access the data.

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Research and Publication Ethics

Research Ethics

Research Involving Human Subjects

When reporting on research that involves human subjects, human material, human tissues, or human data, authors must declare that the investigations were carried out following the rules of the Declaration of Helsinki of 1975 (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/), revised in 2013. According to point 23 of this declaration, an approval from an ethics committee should have been obtained before undertaking the research. At a minimum, a statement including the project identification code, date of approval, and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement' of the article. Data relating to individual participants must be described in detail, but private information identifying participants need not be included unless the identifiable materials are of relevance to the research (for example, photographs of participants' faces that show a particular symptom). Editors reserve the right to reject any submission that does not meet these requirements.

Example of an ethical statement: "All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of XXX (Project identification code)."

A written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Patients' initials or other personal

identifiers must not appear in any images. For manuscripts that include any case details, personal information, and/or images of patients, authors must obtain signed informed consent from patients (or their relatives/guardians) before submitting to an MDPI journal. Patient details must be anonymized as far as possible, e.g., do not mention specific age, ethnicity, or occupation where they are not relevant to the conclusions. A template permission form is available to download. A blank version of the form used to obtain permission (without the patient names or signature) must be uploaded with your submission.

You may refer to our sample form and provide an appropriate form after consulting with your affiliated institution. Alternatively, you may provide a detailed justification of why informed consent is not necessary. For the purposes of publishing in MDPI journals, a consent, permission, or release form should include unlimited permission for publication in all formats (including print, electronic, and online), in sublicensed and reprinted versions (including translations and derived works), and in other works and products under open access license. To respect patients' and any other individual's privacy, please do not send signed forms. The journal reserves the right to ask authors to provide signed forms if necessary.

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The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers. Authors should particularly ensure that their research complies with the commonly-accepted '3Rs':

- Replacement of animals by alternatives wherever possible,
- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

Any experimental work must also have been conducted in accordance with relevant national legislation on the use of animals for research. For further guidance authors should refer to the Code of Practice for the Housing and Care of Animals Used in Scientific Procedures [1].

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1. Home Office. Animals (Scientific Procedures) Act 1986. Code of Practice for the Housing and Care of Animals Used in Scientific Procedures. Available online: http://www.official-documents.gov.uk/document/hc8889/hc01/0107/0107.pdf.

Research Involving Cell Lines

Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.

An example of Ethical Statements:

The HCT116 cell line was obtained from XXXX. The $MLH1^{+}$ cell line was provided by XXXXX, Ltd. The DLD-1 cell line was obtained from Dr. XXXX. The DR-GFP and SA-GFP reporter plasmids were obtained from Dr. XXX and the Rad51K133A expression vector was obtained from Dr. XXXX.

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Experimental research on plants (either cultivated or wild) including collection of plant material, must comply with institutional, national, or international guidelines. We recommend that authors comply with the Convention on Biological Diversity and the Convention on the Trade in Endangered Species of Wild Fauna and Flora.

For each submitted manuscript supporting genetic information and origin must be provided. For research manuscripts involving rare and non-model plants (other than, e.g., *Arabidopsis thaliana, Nicotiana benthamiana, Oryza sativa*, or many other typical model plants), voucher specimens must be deposited in an accessible herbarium or museum. Vouchers may be requested for review by future investigators to verify the identity of the material used in the study (especially if taxonomic rearrangements occur in the future). They should include details of the populations sampled on the site of collection (GPS coordinates), date of collection, and document the part(s) used in the study where appropriate. For rare, threatened or endangered species this can be waived but it is necessary for the author to describe this in the cover letter.

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An example of Ethical Statements:

*Torenia fournieri* plants were used in this study. White-flowered Crown White (CrW) and violet-flowered Crown Violet (CrV) cultivars selected from 'Crown Mix' (XXX Company, City, Country) were kindly provided by Dr. XXX (XXX Institute, City, Country).

*Arabidopis* mutant lines (SALKxxxx, SAILxxxx,…) were kindly provided by Dr. XXX , institute, city, country).

Clinical Trials Registration

*Registration*

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- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.
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English Corrections

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- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Any change to the author list should be approved by all authors including any who have been removed from the list. The corresponding author should act as a point of contact between the editor and the other authors and should keep co-authors informed and involve them in major decisions about the publication. We reserve the right to request confirmation that all authors meet the authorship conditions.

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Editorial Procedures and Peer-Review

*Initial Checks*

All submitted manuscripts received by the Editorial Office will be checked by a professional in-house *Managing Editor* to determine whether they are properly prepared and whether they follow the ethical policies of the journal, including those for human and animal experimentation. Manuscripts that do not fit the journal's ethics policy or do not meet the standards of the journal will be rejected before peer-review. Manuscripts that are not properly prepared will be returned to the authors for revision and resubmission. After these checks, the *Managing Editor* will consult the journals' *Editor-in-Chief* or *Associate Editors* to determine whether the manuscript fits the scope of the journal and whether it is scientifically sound. No judgment on the potential impact of the work will be made at this stage. Reject decisions at this stage will be verified by the *Editor-in-Chief*.

*Peer-Review*

Once a manuscript passes the initial checks, it will be assigned to at least two independent experts for peer-review. A single-blind review is applied, where authors' identities are known to reviewers. Peer review comments are confidential and will only be disclosed with the express agreement of the reviewer.

In the case of regular submissions, in-house assistant editors will invite experts, including recommendations by an academic editor. These experts may also include *Editorial Board Members* and Guest Editors of the journal. Potential reviewers suggested by the authors may also be considered. Reviewers should not have published with any of the co-authors during the past five years and should not currently work or collaborate with any of the institutions of the co-authors of the submitted manuscript.

*Optional Open Peer-Review*

The journal operates optional open peer-review: *Authors are given the option for all review reports and editorial decisions to be published alongside their manuscript. In addition, reviewers can sign their review, i.e., identify themselves in the published review reports.* Authors can alter their choice for open review at any time before publication, but once the paper has been published changes will only be made at the discretion of the *Publisher* and *Editor-in-Chief*. We encourage authors to take advantage of this opportunity as proof of the rigorous process employed in publishing their research. To guarantee impartial refereeing, the names of referees will be revealed only if the referees agree to do so, and after a paper has been accepted for publication.

*Editorial Decision and Revision*

All the articles, reviews and communications published in MDPI journals go through the peer-review process and receive at least two reviews. The in-house editor will communicate the decision of the academic editor, which will be one of the following:

- *Accept after Minor Revisions*:
  The paper is in principle accepted after revision based on the reviewer's comments. Authors are given five days for minor revisions.

- *Reconsider after Major Revisions*:
  The acceptance of the manuscript would depend on the revisions. The author needs to provide a point by point response or provide a rebuttal if some of the reviewer's comments cannot be revised. Usually, only one round of major revisions is allowed. Authors will be asked to resubmit the revised paper within a suitable time frame, and the revised version will be returned to the reviewer for further comments.

- *Reject and Encourage Resubmission*:
  If additional experiments are needed to support the conclusions, the manuscript will be rejected and the authors will be encouraged to re-submit the paper once further experiments have been conducted.

- *Reject*:
  The article has serious flaws, and/or makes no original significant contribution. No offer of resubmission to the journal is provided.

All reviewer comments should be responded to in a point-by-point fashion. Where the authors disagree with a reviewer, they must provide a clear response.

*Author Appeals*

Authors may appeal a rejection by sending an e-mail to the Editorial Office of the journal. The appeal must provide a detailed justification, including point-by-point responses to the reviewers' and/or Editor's comments. The *Managing Editor* of the journal will forward the manuscript and related information (including the identities of the referees) to the Editor-in-

Chief, Associate Editor, or Editorial Board member. The academic Editor being consulted will be asked to give an advisory recommendation on the manuscript and may recommend acceptance, further peer-review, or uphold the original rejection decision. A reject decision at this stage is final and cannot be reversed.

In the case of a special issue, the *Managing Editor* of the journal will forward the manuscript and related information (including the identities of the referees) to the *Editor-in-Chief* who will be asked to give an advisory recommendation on the manuscript and may recommend acceptance, further peer-review, or uphold the original rejection decision. A reject decision at this stage will be final and cannot be reversed.

*Production and Publication*

Once accepted, the manuscript will undergo professional copy-editing, English editing, proofreading by the authors, final corrections, pagination, and, publication on the www.mdpi.com website.

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Resource Identification Initiative

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We encourage authors to include unique identifiers - RRIDs- provided by the Resource Identification Portal in the dedicated section of the manuscript.

To help authors quickly find the correct identifiers for their materials, there is a single website where all resource types can be found and a 'cite this' button next to each resource, that contains a proper citation text that should be included in the methods section of the manuscript.