School of Public Health

Development, Validation, and Application of a Questionnaire to Study Asthma Triggers among Saudi Arabian Children and Assessment of Parental Awareness

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DECLARATION

I certify that this dissertation or thesis does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma at any university. It does not contain any material previously published or written by another person except where due reference is made in the text. This dissertation does not exceed 100,000 words.

Ethics approval was obtained from the Human Research Ethics Committee of Curtin University, Perth, Western Australia. Written approval was also obtained from the King Fahad Medical City Ethics Committee before the data collection process commenced. The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007), which was updated in March 2014. The proposed research study was granted human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number #HR194/2015.

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ABSTRACT

Introduction

Asthma is the most common chronic paediatric respiratory condition, affecting millions of children globally. Asthma is strongly linked to the external environment in terms of its pathogenesis, pathophysiology, and overall symptom progression and disease control. Intensive research has examined asthma triggers in recent years, as trigger reduction and prevention have become increasingly pivotal in the pharmacological management of asthma. However, minimal research has investigated novel triggers of asthma in the paediatric population of the Kingdom of Saudi Arabia (KSA), and no single measurement instrument has been developed to accurately characterise perceptions of asthma triggers within the KSA. This research outlines the development, validation, and application of a KSA-specific version of the Asthma Trigger Inventory (Saudi-ATI).

Methods

Seven KSA-specific items were added to the original ATI before the ATI questionnaire was validated using data concerning the asthma triggers of 200 Saudi children. These triggers were identified based on a literature search of asthma triggers in the Middle East, as well as through consultation with respiratory physicians at King Fahad Medical City (KFMC). Reliability was assessed using inter-item, item total correlations, and internal consistencies (Cronbach's α) of the subscale scores; validity was assessed using Pearson's correlation coefficients between Saudi-ATI subscales and paediatric quality of life outcomes (PAQLQ) and bivariate correlations (Spearman's test) between skin-testing and allergens. Chi-squared testing was applied to determine the correlations between the categorical variables.

Results

The results of this study demonstrate that psychological triggers such as *depressed mood*, *excitement*, *stress*, and *arguments with others* (all of which received 42% 'most of the time' responses, $p \leq 0.05$) were highly prevalent triggers of asthma exacerbations among Saudi children, particularly male children relative to female children (52.4% as opposed to 41.4%, $p=0.002$). In terms of physical triggers, Bakhour (Arabic incense) was a significant and prevalent asthma trigger (46%) among Saudi children and exerted a particularly strong impact on asthma-related quality of life among children ($p=0.01$). Seasonal variance was observed between triggers as well: Atopic triggers (e.g., grass and tree pollens) and exercise were more frequently reported in spring and autumn; psychological (*stress, excitement,*

depression) and KSA-specific triggers (e.g., Bakhour) were more frequently reported in winter; lastly, infections were more commonly reported as triggers in winter and spring. Additionally, this study illustrates that up to three in ten parents (30%) are only minimally aware of what triggers their children's asthma. Furthermore, it demonstrates that parental awareness does not positively correlate with improved trigger management. The triggers which parents were least aware of included the following: toxic pollution from oil refineries (26%), tree pollens (24%), unhappiness (22%), and aerosols (22%). Finally, the Saudi ATI was determined to be both valid and reliable for assessing paediatric asthma within the KSA.

Significance

This research contributes to the asthma literature by providing the first insights into KSA-specific triggers of paediatric asthma; it also highlights the necessity of public health actions directed at improving public and professional knowledge of asthma triggers and paediatric asthma outcomes.

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ABBREVIATIONS AND ACRONYMS

KFMC = King Fahad Medical City

ATI = Asthma Trigger Inventory

KSA = Kingdom of Saudi Arabia

ACT = Asthma Control Test

PAQLQ = Paediatric Asthma Quality of Life Questionnaire

QOL = Quality of Life

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1.0. CHAPTER ONE: INTRODUCTION

1.1 Introduction

Asthma is the most common chronic disease among children globally (The Global Initiative for Asthma [GINA], 2010; Ferrante & La Grutta, 2018). The disease is characterised by variable, reversible, and recurring symptoms related to airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation (Balkissoon, 2008). Approximately 360 million people suffer from asthma globally, and this is projected to increase to 400 million by 2025 (Boulet et al., 2012). Children account for a substantial majority of this figure, since over 60% of asthma cases are diagnosed in childhood (Dida, 2013; Reddel et al., 2015).

A global increase in asthma incidence has occurred in recent decades (Chavasse and Kerr, 2016; Herrera & Fitzgerald, 2018) up until approximately 2005 to 2008, especially in countries such as Australia, the United States of America (USA), the United Kingdom (UK), Asia, Europe, and the Middle East (Engelkes, Janssens, de Ridder, de Jongste, Sturkenboom, and Verhamme, 2015). The steady rise in asthma prevalence from the 1980s to 2005 has been attributed to increased atopic sensitisation and has been accompanied by comparable increases in similar and related atopic conditions (e.g., eczema and allergic rhinitis) (Masoli, Fabian, Holt, Beasley, & GINA program, 2004). Its expanding prevalence during this period may also be a result of improvements in the recognition and diagnosis of asthma.

Despite the overall growth in asthma incidence and prevalence during the preceding decades, the incidence of asthma has slowly decreased throughout the previous several years (approximately 2005 to the present) in correlation with improved research and the development of increasingly effective therapeutic approaches to asthma management (Herrera & Fitzgerald, 2018). Nonetheless, symptomatic management of asthma remains relatively poor in some countries, and the worldwide mortality rate of asthma (which is generally considered to be preventable) is approximately 383,000 per year (World Health

Organisation [WHO], 2016; Chavasse & Kerr, 2016; Herrera & Fitzgerald, 2018). Epidemiological trends of asthma are discussed in greater detail below.

The costs of treating asthma have increased during the past 30 years as a result of more frequent emergency department visits and hospitalisations, reduced activity levels and increased disability, and increased absences from school among children and work among adults (Masoli, Fabian, Holt, Beasley, & GINA, 2004; Nunes et al., 2017; Bahadori et al., 2009). The current annual worldwide number of disability-adjusted life years (DALYs) lost due to asthma has been estimated to be approximately 15 million years; in fact, the disease accounts for approximately 1% of DALYs lost worldwide (Boulet et al., 2012).

In the Kingdom of Saudi Arabia (KSA), respiratory diseases, including asthma, are the fourth leading cause of death, accounting for 4% of all deaths in 2010 (Ministry of Health, 2010). There has been no consistent nationwide estimate of the prevalence of asthma amongst children in Saudi Arabia. However, several studies conducted in various regions of the country have reported prevalence values which vary between 8% and 25% based on the region assessed (Al Ghobain, Al-Hajjaj, Al Moamary, 2012; Al-Dawood, 2001). The highest prevalence (25%) was reported in the Riyadh region in 2004 (Sobki & Zakzouk, 2004). In 2012, the Saudi Initiative for Asthma (SINA) reported that over two million Saudi children suffered from asthma (Al-Moamary et al., 2012).

Children are commonly affected by asthma or transient asthma-like symptoms, and the disease is not only a chronic condition, but also one that may threaten a child's life. A plethora of studies have investigated the pathophysiology and pathogenesis of asthma as well as the efficacy of a new generation of asthma medications and environmental triggers of asthma. However, these studies have yielded minimal evidence concerning the triggers of asthma exacerbations in the KSA that affect the paediatric population. Nonetheless, various

environmental triggers of asthma and a unique climate render the KSA and the Middle East particularly distinct in relation to the environmental component of asthma.

This thesis describes the development and validation of a specific Saudi Asthma Trigger Index (Saudi-ATI) instrument, which was modified to examine novel environmental triggers present within the KSA. Furthermore, the Saudi-ATI is applied to a sample of 200 Saudi children to explore the associations between asthma exacerbations and specific Middle Eastern triggers as well as psychological triggers of asthma, climatic symptomatic variation, and symptom control.

1.2 Aims and Objectives

1.2.1 Aims

This study aims to develop, validate, and apply an Arabic version of the Asthma Trigger Inventory (ATI) to identify the most prevalent asthma triggers in a Saudi study population, examine the factors associated with these triggers, and assess their impact on the daily lives of Saudi children with asthma.

1.2.2 Objectives

The objectives of this study are as follows:

1. To develop an Arabic version of the Asthma Trigger Inventory (ATI);
2. To identify the major determinants of asthma triggers and the interrelationships among them;
3. To assess the general level of awareness of the Saudi population regarding asthma triggers;
4. To assess how parents or guardians of children with asthma avoid and mitigate the asthma triggers;
5. To generate a valid Arabic version of the ATI questionnaire.

1.3 Significance of this research

Asthma triggers are influential in asthma pathogenesis and symptomatic control. There is currently no single valid and reliable instrument to determine asthma triggers in the KSA. Moreover, there is minimal knowledge about specific asthma triggers in the KSA, particularly among children.

This research outlines the development and application of an Asthma Trigger Index (ATI) instrument for use in the KSA, which has been subsequently applied to a population of 200 Saudi children. The results demonstrate highly prevalent asthma triggers in this population, some of which are highly specific to the KSA culture and environment. If parents and clinicians are equipped with knowledge about the environmental triggers present within the unique environment of the Saudi paediatric population, then they can effectively implement evidence-based education and mitigation strategies to circumvent severe asthma exacerbations that contribute to significant morbidity and mortality in this population.

1.4 Overview

This dissertation contains the following six major chapters: 1) the introduction (above), 2) literature review, 3) methods, 4) results, 5) discussion, and 6) conclusions and recommendations. The significant theoretical aspects of asthma related to this thesis, including asthma pathogenesis, pathophysiology, and how these relate to the external environment and environmental triggers are examined in the literature review. The methods chapter outlines the methodology applied to construct and confirm the validity and reliability of the new Saudi-ATI. It also addresses sampling, the study population, and the method of applying the new Saudi-ATI to the sample of 200 Saudi children. The results chapter highlights the findings from this based on various demographic variables, seasonal variations, and symptom impacts on quality of life outcomes. The discussion chapter identifies key results and attempts to compare these results with other research to provide

meaningful and contextual public health insights. Lastly, the conclusion chapter reiterates the method, results, and key discussion points from this thesis and offers implementable recommendations to alleviate the burden of asthma triggers in the KSA among the paediatric population.

2.0. CHAPTER TWO: LITERATURE REVIEW

2.1 Overview

Asthma is a chronic reversible obstruction of the upper airway characterised by bronchial hyperreactivity to both atopic and non-atopic triggers. It is a particularly common disease throughout childhood and can precipitate death in some circumstances. This literature review endeavours to explore the increasing prevalence and incidence of asthma, and particularly paediatric asthma, globally and within the Kingdom of Saudi Arabia (KSA). It also aims to examine the growing socioeconomic burden of asthma, asthma pathogenesis including environmental and genetic factors, both physical and psychological triggers of asthma, and disease severity classifications and evaluative methods used among children. Lastly, this chapter discusses levels of awareness and knowledge of asthma triggers among the global and Middle Eastern population, particularly in the Kingdom of Saudi Arabia (KSA).

As previously mentioned in the introduction, the incidence and prevalence of asthma has increased markedly in Australia, the United States of America (USA), the United Kingdom (UK), Asia, Europe, and the Middle East since 1970. Therefore, the condition is continuing to exert increasing pressure on already-strained global healthcare systems (Lewis et al., 2013; Barnes, 2013; Nunes et al., 2017; Masoli, Fabian, Holt, Beasley, & GINA, 2004).

According to Martinez and Vercelli (2013), asthma can develop at any point in one's life; however, onset occurs most frequently in childhood (0 to 18 years). Asthma is characterised by recurrent attacks of dyspnoea (breathlessness or shortness of breath) and wheezing (a distinct sound of upper airway obstruction), which vary in severity and frequency between people and based on levels of airway reactivity (Lewis et al., 2013).

Substantial research has addressed asthma during the past 30 years. There have been advances in research investigating epidemiological trends, experimental and clinical asthma management, and overlapping atopic respiratory conditions in children (Dida, 2013; Henriksen et al., 2015; Shin et al., 2018, Reddel et al., 2015; Braman, 2006; Sly, 1999; Brabin

& Kelly, 1998; Robertson et al., 1991). Moreover, a considerable amount of research has explored the environmental associations of asthma (Balkissoon, 2008; Alloy & Tabachnik, 1986; Romanet-Manent, Charpin, Magnan, Lanteaume, & Vervloet, 2002; Wood et al., 2007; Luskin, Chipps, Rasouliyan, Miller, Haselkorn, Dorenbaum, 2014; Peterson, Gaeta, Birkhahn, Fernández , Mancuso, 2012) and how these can be avoided or mitigated to augment disease management (Brandt et al., 2008; Halterman et al., 2006; Gibson et al., 2002; Wakefield et al., 2002; itzpatrick, Coughlin, Chamberlin, 1992; McIntosh et al., 1994). Accordingly, new concepts of asthma immunology have been postulated, which has precipitated new therapeutic options for asthma management (Simpson & Sheikh, 2010). Increasing knowledge of asthma pathophysiology and therapeutic targets has enabled clinicians to more effectively manage asthma despite the condition's increasing prevalence throughout the past 30 years (Holgate, 2010). Nevertheless, asthma remains the most common chronic respiratory condition in the paediatric population and represents a significant overall cause of morbidity and mortality. Therefore, further research is necessary to investigate the nexus between individuals' external environments (physical and psychological stimuli) and asthma to enhance the non-pharmacological aspects of asthma symptom reduction.

2.1.2. Method

The method of identifying Middle Eastern triggers relevant to Saudi Arabia and how these were integrated into the newly formulated Saudi-ATI is outlined in the methods section of this thesis in greater detail. Middle Eastern triggers were identified by a literature search which included the following terms: 'child' OR 'paediatric' OR 'pediatric' AND 'asthma' AND 'trigger' OR 'parents' AND 'guardians' AND 'Saudi Arabia' OR 'Middle East'. The following databases were used to identify articles published between 1990 and 2015: PubMed, PsycINFO, Springerlink, and Science-Direct. The inclusion criteria included peer-reviewed primary research articles that focused on determining asthma triggers in the locations mentioned above. Exclusion criteria included review articles or those examining triggers

beyond the KSA or Middle East. The reference lists of each peer-reviewed article were assessed for additional articles examining Saudi-specific or Middle Eastern asthma triggers.

2.2 Asthma definitions and pathophysiological mechanism of the condition

2.2.1 Definition of asthma

Asthma is a chronic obstructive and inflammatory disorder of the upper respiratory tract involving many cellular pathways that induce inflammation, airway remodeling, and increased sensitivity to certain stimuli (Barnes and Drazen, 2002). The chronic inflammation is associated with airways that provoke recurrent paroxysms of air outflow obstruction, resulting in wheezing, dyspnoea, cough, and tightness in the chest, particularly at night or during early hours of the morning (Barnes & Drazen, 2002; Martinez & Vercelli, 2013). These paroxysms typically cause extensive airflow obstruction within the lungs, which is partially or entirely reversible with or without therapy (Global Initiative for Asthma [GIFA], 2017; Martinez & Vercelli, 2013; Barnes & Drazen, 2002).

2.2.2 Variants of asthma and their pathophysiological mechanisms

There are pathophysiological distinctions between known variants of asthma. Acute exacerbations are characterised by paroxysms of worsening symptoms that occur upon exposure to triggers such as exercise, viral upper respiratory tract infections (e.g., rhinovirus or respiratory syncytial virus [RSV]), or allergens. These triggers augment inflammation in the distal airways, resulting in acute inflammation combined with chronic inflammation that often provokes asthma symptoms for days or weeks (Tan, 2005).

The nocturnal variant of asthma is characterised by an airway response to altered circadian rhythms and associated alterations in plasma hormone levels (e.g., epinephrine, melatonin, and cortisol) as well as changes to neural tone (e.g., increasing cholinergic stimulation). Those

who experience nocturnal asthma are more likely to experience severe asthma and poorer control, precipitating a greater adverse impact on quality of life [QOL] (Calhoun, 2003).

A subset of severe asthmatics often progress to irreversible airflow obstruction. This is accompanied by an amplified and prolonged inflammatory process that progresses to pathological airway remodeling (Bumbacea et al., 2004). Moreover, severe asthmatics may be classified as having refractory asthma, wherein the signs, symptoms, and disease sequelae of asthma are relatively insensitive to commonly efficacious therapeutic interventions. While the pathophysiological underpinnings of this variant resemble other asthma variants, refractory asthma is differentiated by a higher number of neutrophils, involvement of the smaller, more distal, bronchioles, and substantially more progressive structural remodeling (Adams & Saglani, 2013).

Epidemiological studies have identified numerous differences in the interactions between patients' genetic makeup and their external environment (Bel, 2004; Stein & Martinez, 2004). These variants are referred to as phenotypes, which are categorised based on cluster analysis of clinical and non-clinical supplementary characteristics of asthma. One such phenotype, referred to as transient wheezing, is associated with signs and symptoms of asthma within only the first three to five years of life. This can be developed due to compromised pulmonary function throughout the peripartum period, smoking throughout pregnancy, or a family predisposition (Stein & Martinez, 2004). However, transient wheezing may occur in the absence of a positive family history of asthma or atopy.

Non-atopic asthma is an additional phenotype. Children who develop this type of asthma typically have a history of significant lower respiratory tract infections during their neonatal and younger developmental periods and frequently experience wheezing due to variable upper airway obstruction until the age of 13. In comparison, the atopic asthma phenotype mediated by IgE secretion by B-lymphocytes in response to sensitised allergens is associated

with high levels of atopy (e.g., allergic rhinitis [hay fever] and eczema), airway hyperresponsiveness, and substantially diminished pulmonary function (Stein & Martinez, 2004). Accordingly, allergic sensitisation in children is the primary risk factor for atopic asthma, which often persists into adulthood.

Lastly, late-onset childhood asthma generally surfaces either at the time of, or after, puberty (Bel, 2004; Stein & Martinez, 2004). This phenotype predominantly affects women and is associated with a limited degree of remission (Bel, 2004; Stein & Martinez, 2004). This asthma variant is characterised by significantly more bronchial hyperresponsiveness and atopy (Stein & Martinez, 2004)

2.2.3 Pathophysiology of asthma

Asthma is a multifaceted inflammatory airway disease that involves multiple body systems and complex cellular events. Asthma development involves the interaction between a genetically susceptible individual and a risk-prone environment. Although the clinical spectrum of asthma is broad, the presence of airway inflammation is a hallmark feature (Barnes & Drazen, 2002); persistently affects all airways from the trachea to the terminal bronchioles; however, it is most severe at the level of the medium-sized bronchi (Barnes & Drazen, 2002). This pattern appears to be consistent across all clinical variants of asthma (whether allergic or non-allergic and at all ages) and is characterised by the presence of many activated resident lung immune cells.

Asthma pathology is strongly linked to the environment, which presents various triggers that may cause asthma exacerbations; however, many triggers (particularly those of an atopic nature) are also pivotal in asthma pathogenesis. At the cellular level, certain environmental triggers activate resident lung cells, which results in an immunopathological cascade that causes asthma. These cells include mast cells, eosinophils, macrophages, natural killer (NK) cells, various T-lymphocytes subsets, and B-lymphocytes (Martinez & Vercelli, 2013; Barnes,

2013). These cells release inflammatory mediators that culminate in pathological events and the observed clinical syndrome of asthma.

Asthma can be theorised to occur in two distinct pathophysiological pathways based on whether the trigger is allergic or non-allergic. Allergic triggers, such as pollens or animal hair, do not elicit identical immunologic responses relative to non-allergic triggers, such as smoke. The latter group of triggers acts through airway irritation and is less central in the development of asthma relative to their role once asthma is established. Nonetheless, numerous non-allergic triggers (especially smoke inhalation) are interesting because they are connected to chronic obstructive pulmonary disease (COPD); although this develops via a different immunopathological pathway, it results in a similar clinical syndrome (Barnes, 2013). In addition, severe asthmatics who smoke exhibit an inflammatory pattern similar to that observed in COPD, with increased recruitment of peripheral airways and neutrophilic infiltration and an abundance of CD8+ T-lymphocytes (Barnes, 2013). This further obfuscates the distinction between pathological checkpoints in asthma.

Asthma is therefore difficult to define because of its clinical variability. This not only creates challenges in accurately diagnosing asthma, but also in developing asthma therapies targeted towards the specific pathological mechanisms experienced by given individuals (i.e., allergic or non-allergic). While substantial past research has focused on symptomatic management of asthma, recent research has increasingly focused on the development of drugs to attenuate the atopic cascades experienced by many asthmatics (Avila, 2007).

Previously sensitised mast cells degranulate preformed granules in response to contact with allergic stimuli; this causes the secretion of histamine and lipid mediator's leukotrienes (C_4, D_4, E_4) and prostaglandin D_2 (Barnes, 2013). These facilitate smooth muscle contraction and therefore bronchoconstriction in the airway, which is preconditioned to be hyperresponsive. Variable levels of secretion of these mediators may be responsible for the clinical variance

observed among asthmatics. This is illustrated by the variation in environmental triggers which have been demonstrated to provoke bronchoconstriction (i.e., allergens or non-allergic triggers); this is also provoked by activities such as exercise, which causes bronchoconstricting factors to be released in response to increased plasma osmolality and as a consequence of hyperventilation (Barnes, 2013). Moreover, mast cells liberate cytokines associated with allergies (IL-4, IL-5 and IL-13), which have been linked to airway hyperresponsiveness; this element of asthma differentiates it from similar conditions including COPD and eosinophilic bronchitis (Galli, Kalesnikoff, Grimbaldeston, Piliponsky, Williams, and Tsai, 2005; Brightling, Bradding, Symon, Holgate, Wardlaw, & Pavord, 2002). This group of cytokines is also linked to IgE synthesis by B-cells, which facilitates eosinophil (IL-5) and mast cell (IL-9) differentiation (Kay, 2006).

Asthmatics experience predominantly eosinophilic inflammation, which reflects the liberation of eosinophilic chemotactic factors (CC-chemokine ligand 11 [CCL-11] among other CC-chemokines) secreted by airway epithelial cells (Barnes, 2013). Nonetheless, the role of eosinophilia in airway hyperresponsivity remains unclear, primarily because the blockade of IL-5 that markedly reduces plasma and sputum eosinophilia does not correlate with reduced airway hyperresponsiveness (Leckie et al., 2000; Flood-Page et al., 2007). Because both eosinophilic bronchitis (which does not involve hyperresponsiveness) and asthma both entail subepithelial fibrosis, it is likely that eosinophils are pivotal in airway fibrosis (Barnes, 2013).

Inflammation is regulated by a series of chemokines and cytokines that have been demonstrated to be regulated by nuclear factor κB (NF-κB); this important transcription factor is activated in both epithelial cells and macrophages among individuals with asthma (Barnes, 2013). NF-κB may be pivotal in augmenting cytokine and chemokine responses to precipitate airway inflammation.

Macrophages are present in greater abundance in those with asthma relative to healthy individuals (Barnes, 2013). They are derived from naïve monocytes and are attracted to the pulmonary system in response to chemotactic signals [e.g., CCL-1 and CCL-2 acting on CCR-1 and CCR-2] (Travers, Smith, Barnes, & Donnelly, 2004). It is likely that macrophages trigger the activation of downstream inflammatory cells, including neutrophils, additional monocytes, and T-cells, although much of this evidence is based on studies involving COPD patients (Barnes, 2004).

T-cells are more abundant in the airways of asthmatic individuals. However, T-cell subsets are indicative of the pathogenesis of obstructive airway diseases. In asthma, CD4+ T-cells predominate (particularly Th-2 cells), whereas Th-1 cells predominate in healthy airways (Meyer, DeKruyff, & Umetsu, 2008) Th-2 cells are central in inflammatory processes and therefore represent an area of concentrated research. T-regulatory cells (Tregs) may potentially be crucial in modulating the actions of Th-2 cells in individuals with asthma (Meyer, DeKruyff, & Umetsu, 2008; Larche, 2007). Indeed, Ling et al. (2004) demonstrated that Tregs expressing forkhead box P3 transcription factor (FOXP3) are low in allergic rhinitis relative to controls, which may enable the unchecked proliferation of Th-2 cells in atopic diseases. Nonetheless, FOXP3-expressing Tregs in more severe asthmatics appear to be less abundant relative to mild asthma (Lee, Yu, Wang, Yang, Lin, and Chiang, 2007). Meanwhile, the presence of NK cells, particularly CD4+ invariant NK T-cells (iNKT-cells), which secrete IL-4 and IL-13, in individuals with asthma is debated (Akbari et al., 2006; Vijayanand et al., 2007). CD8+ T-cells are more central in the pathogenesis of COPD; however, they infiltrate the airways of those with increasingly severe asthma and irreversible obstruction (van Rensen et al., 2005).

B-cells are pivotal in the pathogenesis of asthma through the secretion of highly specific IgE antibodies that bind high-affinity Fc receptors present on the mast cell and basophil cell surface and low-affinity Fc receptors present on additional B-cells, macrophages, and

perhaps eosinophils (Gould, Beavil, and Vercelli, 2000). Allergic inflammation in response to B-cell IgE secretion is further illustrated by the attenuation of asthma exacerbations, airway inflammation, and responsivity to allergens by omalizumab (Avila, 2007). However, B-cells may generate local IgE in non-atopic individuals (Takhar et al., 2007).

As a result of the ongoing inflammatory reactions within the asthmatic airways, characteristic remodeling occurs in the airways of asthma patients. Histologically, the hallmark feature of asthma remodeling is subepithelial collagen deposition (basement membrane thickening), although the airways of moderate to severe asthmatics also exhibit hyperplastic and hypertrophic smooth muscle thickening (Benayoun, Druilhe, Dombret, Aubier, and Pretolani, 2003). Other changes include substantially increased goblet cells and mucosal hyperplasia, as well as significantly increased vascularity, which most likely results from increased vascular endothelial growth factor (VEGF) secretion (OrdoÑez et al., 2001; Siddiqui et al., 2007). These changes result in relatively permanent airway narrowing as well as the clinical signs and symptoms of asthma (James, 2005).

2.3 Classifications of asthma severity

Asthma severity can be classified in numerous ways. The gold standard categorical measurement of reversible airway obstruction in asthma is pulmonary function testing (PFT). Other methods of classifying symptom severity include assessing medication use or the self-reported frequency and severity of asthma symptoms.

A seminal study conducted by Bacharier, Strunk, Mauger, White, Lemanske Jr, and Sorkness (2004) in the USA compared the three aforementioned mechanisms of assessing asthma severity. Daytime, nocturnal, and exertional symptoms were examined to categorise the severity of paediatric asthma using the National Asthma Education and Prevention Program/Expert Panel Report Two (NAEPP/EPR2) guidelines and assess these in relation to

PFT results. The NAEPP/EPR2 guidelines quantify the symptoms of asthma in the following manner: Daytime symptoms which occur three to six days per week constitute mild persistent asthma; frequent nocturnal symptoms indicate moderate persistent asthma; lastly, restricted physical activity characterises severe persistent asthma (Bacharier et al., 2004). The guide also incorporates medication usage as a measure of asthma severity. The study assessed 219 children between the ages of 5 and 18 and classified them based on three severity classification scales to assess whether the guidelines were accurate in illustrating asthma disease severity. These included the following: classification based on symptom frequency alone, classification based on medication use alone, and classification based on frequency of severe symptoms or degree of medication use. Classifications based on the NAEPP/EPR2 guidelines were compared with PFT results, and the authors determined that the NAEPP/EPR2 classifications based on symptom frequency and medication utilisation did not correlate with the NAEPG severity classification system using forced expiratory volume in one second (FEV_1). This study demonstrates the limitations of isolated measurement of FEV_1 and highlights the benefits of assessing FEV1 to FVC ratios to determine asthma severity in the paediatric population.

According to Colice (2004), higher doses of inhaled corticosteroids (ICS) can solely be justified in cases of confirmed severe paediatric asthma. Despite the availability and dissemination of National Asthma Management Guidelines (NAMG) that propose methods of assessing asthma severity, global evidence suggests a failure to adhere to such guidelines (Colice, 2004). Addressing the difficulties and inherent limitations of current asthma severity assessment instruments is challenging. The most prominent failure of these tools appears to be their inability to rapidly and accurately measure the degree of airway inflammation (Colice, 2004). Therefore, in the absence of airway inflammation outcomes to assess and a method for assessing it, asthma severity classification methods could enable the systemic undertreatment of asthmatics and subsequently perpetuate the asthma exacerbations.

Other tests such as the methacholine challenge and sputum eosinophil counts could be integrated into routine assessments of asthma patients. These tests can enhance the assessment of disease severity in asthma by utilising the conditions of hallmark pathological features and airway inflammation as an outcome. Ultimately, this could facilitate improved effectiveness of care provision by utilising both mainstay and more sophisticated immunologic therapeutics.

2.4 Pathogenesis

In many ways, the pathogenesis of asthma is characterised by a multiple-hit pattern, wherein multiple events eventually precipitate clinical asthma. Multiple biological and environmental factors contribute to the pathogenesis of asthma. The pathogenesis of asthma is discussed below in terms of the condition's pathological progression.

2.5 Global epidemiological patterns of asthma

Asthma is a chronic disease of the upper and middle airways that is recurrent and often occurs in waves of symptomatic progression with intermittent periods of limited symptomatic perception (i.e., high symptom control), depending upon the severity of the disease. Therefore, given the nature of asthma pathobiology, it is difficult to accurately examine asthma prevalence and incidence separately. For this reason, this section combines asthma incidence and prevalence.

Asthma is prevalent among all ages and is regarded as one of the most common chronic diseases in childhood; between 1 and 20% of children suffer from asthma in the global population. According to the Global Asthma Report (2018), over 330 million individuals globally are estimated to currently have asthma (2018), and this is expected to increase in the future (The Global Asthma Network, 2018). Moreover, approximately 60% of all asthmatic patients are initially diagnosed with asthma in childhood (Dida, 2013; Reddel et al., 2015).

Many published studies describe a rise in the incidence and prevalence of asthma across many nations beginning around 1980 and continuing for 15 to 20 years until approximately 2005 to 2010, after which the rates have stabilised or even slightly decreased (Henriksen et al., 2015; Shin et al., 2018, Reddel et al., 2015; Braman, 2006; Sly, 1999; Brabin & Kelly, 1998; Robertson et al., 1991; Hussain, 2018; Henricksen et al., 2005; Martinez, 2008). In Italy and Finland, asthma prevalence increased from 4.1% and 5.5% in 1990 to 6.6% and 8.1% in 2010, respectively (de Marco et al., 2012, Laatikainen et al., 2011). In Canada, asthma prevalence increased 55% from 8.5% in 1996 to 13.3% in 2005, primarily among children, who accounted for 30% of the cases (Gershon, Guan, Wang, and To, 2010). Other countries, such as Greece (Wennergren, 2011) and Turkey (Demir, Celikel, Karakaya, & Kalyoncu, 2010), have exhibited similar trends.

Other studies assessing the trends in asthma incidence demonstrate a comparable increase. For instance, a study conducted in the Netherlands by Engelkes, Janssens, de Ridder, de Jongste, Sturkenboom, and Verhamme (2015) assessed a cohort of 176,516 children from 2000 to 2012; it determined that incidence significantly increased from 2000 to 2008 and then gradually plateaued before displaying a small decrease. The authors reported an incidence of asthma of approximately 7 per 1,000 children.

While numerous epidemiological studies have identified a cumulative increase in the prevalence (and therefore an increasing incidence) of wheezing and asthma in the paediatric population, it is difficult to ascertain whether this was due to a genuine increase in the incidence of asthma, an increase in the frequency and severity of asthma symptoms, or growing awareness among the medical profession or the public about the diagnoses and recognition of asthma. Nystad et al. (1997) indicate that the increase in asthma prevalence among school children is a genuine increase; however, they suggest that modifications in diagnostic criteria might be partly responsible.

The lack of consensus over the definition of asthma has imposed an obstacle to the accurate assessment of asthma prevalence and incidence (Jarama et al., 2007). Atopic diseases such as bronchial asthma, allergic rhinitis, eczema, and allergic rhinoconjunctivitis are the most common disorders in young children, with an overall prevalence of up to 41% in Western countries (Al-Frayh, Shakoor, El Rab, and Hasnain, 2001). Nonetheless, studies demonstrate that children often outgrow these conditions and that the frequency of asthma decreases inversely with age (Al-Ghamdy et al., 2000). Nonetheless, it is likely that many children diagnosed with asthma are not in fact asthmatic and that they instead suffer from transient wheezing as a result of infectious conditions such as bronchiolitis. Several studies support this perspective by indicating that asthma is perhaps over-diagnosed in childhood (Bush and Fleming, 2016; Looijmans-van den Akker, van Luijn, and Verheij, 2016).

While prevalence and incidence are important epidemiological measures, in the case of chronic life-long diseases such as asthma, disease control is potentially a more important measure. Despite recent advances in understanding of the pathogenesis of asthma and the development of more effective therapeutic approaches that enable improved clinical management of asthma, up to 70% of all asthmatics cannot achieve symptomatic control over their disease (To et al., 2012).

2.5.1 Epidemiology of asthma in the Middle East and Saudi Arabia

In the Kingdom of Saudi Arabia (KSA), chronic respiratory disease accounts for 3% of all deaths, and asthma is the most common primary diagnosis assigned to emergency department visits (Hasnain, Al-Qassim, Hasnain, Al-Frayh, 2016). Moreover, a review of asthma prevalence among Gulf nations and neighboring countries suggests that overall asthma prevalence was 10 to 23%; the KSA corresponded with the highest prevalence, at 23% (Hasnain, Al-Qassim, Hasnain, Al-Frayh, 2016). Asthma affects over two million Saudi

Arabians; the majority of individuals report uncontrolled asthma symptoms and impaired quality of life (QOL) (Al-Moamary et al., 2012).

There is conflicting evidence about not only the overall prevalence of asthma in the KSA and throughout the Middle Eastern region, but also about overall asthma prevalence in the KSA relative to the remainder of the world. A comparison between the European Community Respiratory Health Survey (ECRHS) questionnaire results for Saudi Arabian people with those for other countries indicates that asthma prevalence is significantly higher in the KSA, at 11.3%, relative to European countries (Al Ghobain, Algazlan, and Oreibi, 2018). Country-specific prevalences were reported as follows: 6.8% in Sweden, 4.4% in Germany, 5.5% in France, 8.4% in England, and 2.9% in Greece (Al Ghobain, Algazlan, and Oreibi, 2018). However, the European studies were conducted in the 1990s, while the KSA study was conducted in 2016. In contrast, a study conducted by El-Sharif et al. (2002) suggested that the prevalence of asthma was generally lower in the Middle East relative to more developed countries (7.0% compared to 10.3% in children born in developed countries as opposed to those born in developing countries). This aligns with data from the World Health Survey conducted by Sembajwe, Cifuentes, Tak, Kriebel, Gore, and Punnett (2010), which suggests that asthma incidence increases in parallel with industrialisation; it is also consistent with results from the 2013 KSA national household survey, which indicates that the prevalence of a self-reported clinical diagnosis of asthma is 4.05%. This would indeed place the KSA below other nations in terms of overall asthma prevalence (Moradi-Lakeh et al., 2015).

Hussain et al. (2018) report that the prevalence of asthma in the KSA varies based on the region of the country; however, they did not identify any disparity in prevalence among rural and urban areas. The highest incidence of asthma was reported in Hofuf, and the lowest was reported in Qassim. Similarly, to other studies, Hussain et al. (2013) report an increase in asthma prevalence from 1990 to 2000 (8% to 23%), with a slight decrease in asthma prevalence between 2010 and 2016 throughout the KSA. Nonetheless, the various studies

reviewed by Hussain et al. (2013) during this period examined different regional populations and yielded contrasting results. Additionally, alongside other studies, which report a similar phenomenon, a substantial increase in the asthma prevalence was observed between 1985 and 1995 in the KSA (Al-Frayh, Shakoor, El Rab, & Hasnain, 2001), from 8% in 1986 to 23% in 1995. This is potentially explained by increased exposure to tobacco smoke and other triggers such as domestic animals in the KSA during this period (Al-Frayh, Shakoor, El Rab, and Hasnain, 2001).

Several studies have been conducted in the Middle East concerning the prevalence of allergic diseases in individuals of different age groups and at different periods of time. Local reports in the KSA suggest that the prevalence of asthma is increasing despite an increasing abundance of high-quality health services and the availability of worldwide guidelines.

Al-Frayh, Shakoor, El Rab, and Hasnain (2001) conducted a nine-year longitudinal study which compared the prevalence of asthma among school children living in different regions of the KSA (Riyadh, Hail, Jeddah and Gizan – see Figure 1). This study demonstrated that the prevalence of bronchial asthma in age and sex-matched school children increased by 15% (8% in 1986 to 23% in 1995 [$p< 0.0001$]) across a nine-year period. Furthermore, the study indicated a high degree of exposure to the environmental causes or triggers of asthma, including smoking and indoor pets, which was most likely induced by the rapidly changing lifestyle and culture in the KSA.

A similar study was conducted in Al-Khobar by Al-Dawood (2001), who discovered that the prevalence of asthma among school children was 9.5% in 2001. A cross-sectional survey conducted using self-reported questionnaires with 1,020 urban and 424 rural 12-year-old children; it demonstrated an increased prevalence of allergic symptoms among children who live in urban areas relative to children who live in rural areas, and among Saudi children

relative to non-Saudi children (Al-Dawood, 2001). No effect was observed when assessing the impact of socioeconomic status on the prevalence of asthma.

Children between the ages of 7 and 12 were surveyed by Bener, Al-Jawadi, Ozkaragoz, and Anderson (1992) for asthma patterns using a cross-sectional questionnaire in two regions (Dammam and Riyadh, as shown in Figure 1) of Saudi Arabia (1986–1989). Symptoms of wheezing, rhinitis, and eczema among children in Riyadh were more prevalent than in Dammam. The prevalence of asthma was determined to be significantly ($p < 0.05$) higher amongst children in Riyadh (9.28%) relative to children in Dammam (3.59%). The study demonstrated a statistically significant association between asthma and breathlessness, second-hand smoke (father), pet ownership, coughing, and a family history of allergies (Bener, Al-Jawadi, Ozkaragoz, and Anderson, 1993).

An older cross-sectional study conducted by Bener, al-Jawadi, and Ozkaragoz, and Anderson (1993) from 1986 to 1989 compared the prevalence of physician-diagnosed asthma among Saudi school children in the industrial city of Yanbu (situated west of Medina on the coast – see Figure 1) with that in two non-industrial communities, namely Al-Furash and Al-Gafure. The prevalence of asthma in Yanbu (13.9%) was substantially higher than in the villages of Al-Furash and Al-Gafure (8%).

The prevalence of asthma and related symptoms in 16- to 18-year-old youths (1,504 boys and 1,569 girls) attending high schools in Riyadh was investigated using the International Study of Asthma and Allergies in Children questionnaire (Al Ghobain, Al-Hajjaj, and Al Moamary, 2012). This questionnaire-based diagnosis of asthma revealed a prevalence of lifetime wheezing of 25.3%, a prevalence of wheezing during the past 12 months of 18.5%, and a prevalence of physician-diagnosed asthma of 19.6% (Al Ghobain, Al-Hajjaj, and Al Moamary, 2012). The rates of exercise-induced wheezing and coughing during the night in the past 12 months were 20.2% and 25.7%, respectively.

Table 1. Reported asthma prevelance data among children in Saudi Arabia.

Authors	Year	Location	Variables	Prevalence
Al Ghobain, Algazlan, & Oreibi	2018	Kingdom of Saudi Arabia	Physician diagnosed asthma	11.3%
El-Sharif et al.	2002	Kingdom of Saudi Arabia	Physician diagnosed asthma	7.0%
Moradi-Lakeh et al.	2015	Kingdom of Saudi Arabia	Self-reported asthma diagnosis	4.05%
Hussain et al.	2013	Kingdom of Saudi Arabia	Physician diagnosed asthma	8-23%
Al-Frayh, Shakoor, El Rab, & Hasnain	2001	Kingdom of Saudi Arabia	Physician diagnosed asthma	23%
Al-Dawood	2001	Kingdom of Saudi Arabia	Self-reporated asthma diagnosis	9.5%
Bener, al-Jawadi, & Ozkaragoz	1993	Kingdom of Saudi Arabia	Physician diagnosed asthma	8-13.9%
Al Ghobain, Al-Hajjaj, and Al Moamary	2012	Kingdom of Saudi Arabia	Physician diagnosed asthma	19.6%
Hasnain, Al-Qassim, Hasnain, Al-Frayh	2016	Kingdome of Saudi Arabia	Physician diagnosed asthma	23.%
Bener, Al-Jawadi, Ozkaragoz, & Anderson	1992	Kingdom of Saudi Arabia	Physician diagnosed asthma	3.6-9.3%

Figure 1. A map of the KSA which depicts the major geographical cities discussed.

Image adopted from Maps of the World. (2014). Retrieved from http://www.maps-of-the-world.net/maps-of-asia/maps-of-saudi-arabia/

2.6 The burden of asthma

2.6.1 Asthma-related mortality

The World Health Organisation (WHO) (2017) estimates that approximately 235 million people suffer from asthma, and in 2015, an estimated 383,000 asthma-related deaths occurred. The Global Burden of Disease (GBD) study estimates that age-standardised mortality rates from asthma declined by about one-third between 1990 and 2010; they declined from 250 per million to 170 per million amongst males and from 130 per million to 90 per million amongst females (all ages).

Asthma mortality rates differ between and within countries. Mortality due to asthma ranged between as low as 0.1 per 100,000 in Finland, Sweden and Greece, to greater than 1.5 per 100,000 in South Africa, Kazakstan, and Turkmenistan (Masoli, Fabian, Holt, Beasley, and GINA program, 2004). Despite what appears to be a pattern of increasing mortality among less-developed nations, Chavasse and Kerr (2016) report that the United Kingdom's (UK) 10-year mortality rate for asthma is far higher than that of other nations (0.27 per 100,000 people as opposed to less than 0.10 per 100,000 people for other European nations) and that other developed nations also exhibit a relatively high asthma-related mortality rate (Figure 1). Notwithstanding this, the asthma mortality rate in Europe decreased by 26.7% from 1990 to 2015 and is comparatively low relative to other nations (Akinbami et al., 2012; Ferrante and La Grutta, 2018).

Most asthma-related deaths occur in less-developed nations and among socioeconomically disadvantaged groups (e.g., low and middle income) in all nations; there are also disparities in asthma mortality in terms of age, gender, and ethnicity (Herrera and Fitzgerald, 2018; Ferrante and La Grutta, 2018). Mortality among children with asthma is primarily attributable to poor treatment adherence; 80% of asthma-related deaths among children in the UK are attributed to poor asthma control and treatment adherence (Ferrante and La Grutta, 2018).

Additionally, asthma-related mortality is three times higher among black people relative to Caucasian people, death from asthma is more common in adults than children, and in children, deaths are significantly more common among male children than female children (Ferrante and La Grutta, 2018).

Ebmeier, Thayabaran, Braithwaite, Bénamara, Weatherall, and Beasley (2017) investigated the asthma mortality trends from 1993 to 2012 using the WHO mortality database from 46 nations and determined that the global mortality due to asthma declined from 0.44 per 100,000 people to 0.19 per 100,000 people. Nonetheless, no change was observed between 2006 and 2012 (Ebmeier et al., 2017). This may indicate that contemporary methods are becoming more effective in preventing asthma deaths; however, further adoption of evidence-based strategies is necessary, particularly in less-developed nations (Ebmeier et al., 2017).

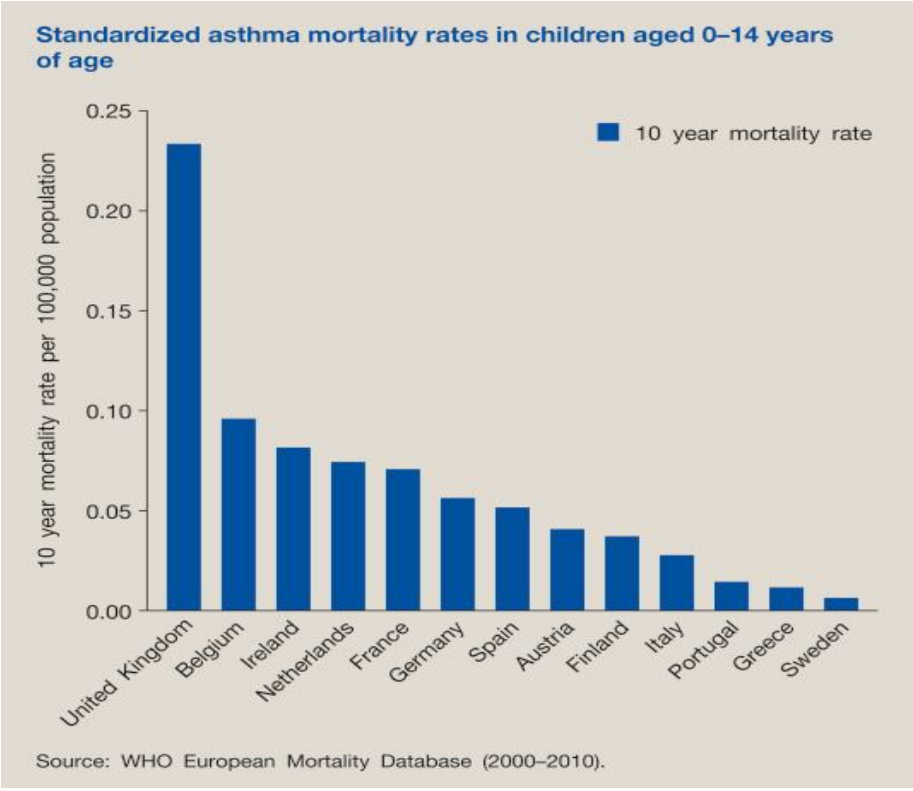

Figure 1. 10-year mortality rates for asthma among children between the ages of 0 and 14 in European nations.

as adopted from Chavasse, R. J., and Kerr, M. (2016). Asthma in children. Medicine, 44(5), 281-286.

Since evidence-based medical guidelines have been improved and increasingly disseminated, morbidity and mortality due to asthma remain unjustifiably high (Chavasse and Kerr, 2016; Herrera and Fitzgerald, 2018). It is imperative to understand the underlying factors contributing to asthma-related mortality among the global paediatric population to effectively ameliorate fatal asthma among children. Although the risk of any individual asthmatic patient dying of the disease is minimal, continued surveillance of asthma mortality rates is essential to monitor progress in asthma care and to provide an early warning of epidemics of fatal asthma, which have occurred in recent years. As stated by Ebmeier, Thayabaran, Braithwaite, Bénamara, Weatherall, and Beasley (2017), a substantial decrease in worldwide asthma mortality has occurred; however, to achieve further decreases, the implementation of proven management strategies and adjunct novel strategies are necessary.

2.6.2 Asthma-related quality of life

Asthma can substantially and adversely impact the quality of life (QOL) of individuals. Asthma-related QOL (ARQOL) relates to how an asthmatic individual feels in their daily life in response to their symptoms, irrespective of physical measures of disease or disease control (i.e., airway caliber, symptoms, pulmonary function testing, medication usage or responsivity, or reactivity to certain environmental precipitants) (Juniper, Guyatt, Feeny, Ferrie, Griffith, and Townsend, 1996). Since young children are unable to effectively communicate the impact of asthma on their QOL, the Paediatric Asthma Caregiver's QOL Questionnaire (PACQOLQ) was developed to provide parents and caregivers an objective measure of asthma's impact on children's QOL (Juniper et al., 1996).

Asthma is responsible for 1.1% of the global estimate of disability-adjusted life years (DALY's) per 100,000 people among all causes, which demonstrates its significant impact on quality of

life (Ferrante and La Grutta, 2018). Additionally, asthma is responsible for 3 to 8% of reports of adverse quality of life or health status outcomes (Mahboub et al., 2013). The KSA has the 19th worst asthma-related burden of disease in terms of DALYs and the 26th worst in terms of asthma-related deaths globally (Memish et al., 2014). Among KSA elementary students, the prevalence of life-long wheezing, wheezing in response to exercise, or wheezing in the past 12 months were indicated as being 17.8%, 14.7% and 11.4%, respectively (Khawaji et al., 2017). Another study conducted in the KSA by Hamam et al. (2015) uncovered an overall prevalence of asthma mortality of 1% among children between the ages of 0 and 18. The authors also highlighted that the highest prevalence of physician-diagnosed asthma was among children younger than three years old (29.7%). Minimal or no literature has been published concerning paediatric asthma-related mortality in the KSA, although it is known that chronic respiratory diseases comprise 3% of the total mortality and that asthma is a major contributor (Hussain, Farhana, and Alnasser, 2018).

2.6.3 The economic burden of asthma

As a highly prevalent and chronic non-communicable disease, asthma represents a substantial financial burden on the healthcare system and a significant social and health burden to those who live with the disease. Disease-related costs are conventionally divided into direct and indirect (intangible) costs. The economic effects of asthma have primarily been examined through two means: by using population-based sampling frames or administrative databases to provide cost estimates for entire regions or nations and by using clinical-based sampling frames. Population-based studies offer greater generalisability, whereas clinical-based studies provide greater diagnostic certainty and frequently offer data related to disease severity that is particularly relevant to asthma costs. The former is more suitable for assessing both direct and indirect costs, while the latter can more accurately assess direct costs for specific populations.

Direct costs due to asthma include all of the costs associated with disease management. This encompasses costs of medication provision or subsidies, human resource costs utilised in delivering asthma-related care, and public health costs for attempts to improve asthma recognition and management. Indirectly, asthma manifests a loss of productivity and absenteeism in schools, morbidity and disability, and potentially premature mortality. Finally, intangible costs include those that are difficult to quantify, such as decreased QOL, pain or suffering, limitation of physical activities, and limitations to opportunities.

Several studies report data on asthma costs, either at the individual patient level or societal level (regional or country level); this is expressed as an average annualised cost of approximately $5,000 USD per patient (Nunes, Pereira, and Morais-Almeida, 2017). Conversely, in Europe, the cost is substantially lower (USD $1,900) (Khadadah et al., 2009). According to the WHO (2004), the total global cost of asthma exceeds that of tuberculosis and HIV and AIDS combined.

Bahadori et al. (2009) conducted a systematic review of 68 studies that examined the economic impact of asthma and determined that hospitalisation and medications were the most important sources of direct costs, while work and school days lost accounted for the greatest percentage of indirect costs. Globally, asthma cost increases closely correlated with comorbidities, age, and asthma severity (Bahadori et al., 2009). Moreover, a study by Alzaabi, Alseiari, and Mahboub (2014) revealed that the annual direct cost of asthma in Abu Dhabi was substantial (US $29 million) and constituted a significant economic burden. These costs were primarily due to outpatient asthma care, which represented 81% of the total cost (Alzaabi, Alseiari, and Mahboub, 2014). Treatment of asthma during outpatient visits was the most substantial cause of direct medical expenditure. However, emergency visits and hospitalisations also produced significant economic costs; this suggests that the control of asthma is suboptimal. This issue could be alleviated by earlier diagnoses of the disease, use of effective control medications, and increasing awareness and information amongst the

general population. Asthma education concerning the prevention of asthma exacerbations (i.e., avoidance of individual asthma precipitants) would also enable savings. Such measures could generate significant healthcare resource savings in the long-term.

Annual data in the United Arab Emirates (UAE) was compiled by Alzaabi, Alseiari, and Mahboub (2014) from health insurance claims which encompassed all medical interventions or treatments coded for asthma. The total direct cost of treating 139,092 asthma patients was estimated to be 105 million UAE Dirhams (AED) ($29 million USD), which corresponds to approximately $750 per patient per annum AED (Alzaabi, Alseiari, and Mahboub, 2014). The cost was primarily driven by outpatient visits (>AED 85 million; 81% of the total cost), and 10.4% was due to episodes of care delivered within the emergency department. According to Mahboub et al. (2013), the total direct cost of asthma in Dubai was about 88 million Dirhams (AED $87,917,202). The setting appears to alter the cost of care delivery; for instance, the cost per visit was higher during hospital admissions (AED $7,123) relative to outpatient visits and emergency room visits (Alzaabi, Alseiari, and Mahboub, 2014). The direct cost of asthma medications was approximately AED $33 million (31% of the total cost).

The relationship between direct and indirect asthma costs varies by country and based on the type of study. For instance, in contrast to the costs of asthma in the KSA, the estimates of total annual asthma costs in the USA exhibit steady growth from $USD 12 billion in 1994 to $USD 56 billion in 2011 and 81.9 billion in 2013 (Nurmagambetov, Kuwahara, and Garbe, 2018; Loddenkemper et al., 2003; Kamble and Bharmal, 2009). Additionally, the direct annual cost of asthma in Europe was estimated to be €7.9 billion (Khadadah et al., 2009). Khadadah et al. (2009) reports that the cost of outpatient care comprises 48%, drug costs comprise 46% and in-patient care costs constitute 6% of asthma-related expenditure in European countries. Several asthma studies performed during the past two decades have demonstrated that direct costs were higher than indirect costs (Alzaabi, Alseiari, and Mahboub, 2014; Bahadori

et al., 2009; Nunes, Pereira, and Morais-Almeida, 2017; Nurmagambetov, Kuwahara, and Garbe, 2018). Directs costs typically contribute between 50% and 80% of the total costs.

Hospitalisation is one of the major direct asthma costs (Bahadori et al., 2009; Ferrante and La Grutta, 2018). According to Rosengart et al. (2007), 6% of asthmatics in Europe required overnight hospitalisation for asthma. Conversely, in Dubai, the percentage was significantly higher at 28% among adults and 38% among children (Mahboub et al., 2012). Likewise, children and adolescents demonstrate two times greater prevalence of asthma-related hospitalisations relative to adults; additionally, children between the ages of 0 and 4 years experience particularly frequent asthma-related hospitalisations (Nunes, Pereira, and Morais-Almeida, 2017). Various factors are likely responsible for the age disparity between hospital admissions; however, asthma is particularly difficult to manage in younger children, and their clinical trajectory can shift rapidly, often necessitating close observation in the hospital environment (Nunes, Pereira, and Morais-Almeida, 2017).

Costs related to hospital inpatient care are variable. Some studies have indicated up to 20 to 30% higher costs in private as opposed to public or non-profit hospitals (Antonicelli et al., 2004; Kiivet et al., 2001; Beyhun et al., 2007; Neville et al., 2003). However, according to Alzaabi, Alseiari, and Mahboub (2014) the largest contribution is from expenditure on outpatient visits (37%, AED $32,217,143), followed by in-patient care (23%, AED $23,587,008). The costs of medication and emergency department visits represented 20% and 16% of the direct costs, respectively (Alzaabi, Alseiari, and Mahboub, 2014).

Increasing asthma related costs highlight the need for implementing non-pharmacological, environemental and public health strategies to reduce asthma exacerbations. As asthma triggers are ubiquitous and increase the risk of asthma attacks, attenuating their impact will likely assist in reducing the economic impact of asthma.

2.6.4 Social, psychological, and educational impacts of asthma among children

Among children, asthma can detract from social activities, including sports or social gatherings, and can precipitate poor school attendance (Nunes, Pereira, and Morais-Almeida, 2017). This can impair children's academic performance, limit their future opportunities, and cause negative psychological consequences (Nunes, Pereira, and Morais-Almeida, 2017).

Bener et al. (2011) conducted a survey of children attending 30 primary schools in Al-Ain City in the United Arab Emirates (UAE) to assess the impact of asthma on school absenteeism. The study confirmed that asthma was a common chronic disease amongst primary school children and a common cause of absenteeism from school; it indicated a 34.7% rate of absenteeism among asthmatic children, as opposed to 22.8% among healthy peers (Bener et al., 2011). Moreover, according to Mahboub et al. (2013), absenteeism from school was reported by up to 50% of asthmatic children. The data from Dubai for absenteeism due to asthma aligns with that reported in Europe (14% among adults and 50% among children in Dubai as opposed to 17.1% among adults and 42.7% among children in Europe) (Mahboub et al., 2013).

When a child experiences an exacerbation of asthma symptoms, they are reported to lose an average of between three and five days from school (annually); this results in one or more parents or caregivers also losing the corresponding amount of work days (Nunes, Pereira, and Morais-Almeida, 2017). In this manner, the indirect costs of children with asthma are greater than those within the adult asthmatic population.

Asthma affects both the physical and psychological aspects of children's lives (Lehrer, Feldman, Giardino, Song, and Schmaling, 2002). For children, the physiological aspects of suffering from asthma precipitate fear of exacerbations, anxiety and fatigue following asthma attacks (Lehrer, Feldman, Giardino, Song, and Schmaling, 2002; Wilson et al., 2012). Adolescent and parental perceptions of asthma and asthma management reflect a broad

variety of beliefs that affect disease-related behaviour and emotional reactions. Living with a child suffering from asthma impacts the daily lives of entire families (Wilson et al., 2012). Parents (particularly mothers) report that they find it difficult to help their asthmatic children adapt to their illness and to the social problems they experience, such as those at school and throughout life (Wilson et al., 2012). Many parents are concerned about the side effects of the medicines that their children use (Wilson et al., 2012).

2.7 Asthma triggers in the external environment

A 'trigger' is a stimulus that causes asthma symptoms to increase, resulting in limitations in airflow (Balkissoon, 2008). Numerous factors trigger airway obstruction episodes in patients with asthma. The accurate identification of asthma triggers is contingent upon the accurate perception of the relationship between the trigger and the asthma symptoms (Alloy and Tabachnik, 1986). These symptoms include coughing, wheezing, shortness of breath or rapid breathing, and chest tightness (Romanet-Manent, Charpin, Magnan, Lanteaume, and Vervloet, 2002).

There are two types of physical asthma triggers. The first are atopic (allergic) triggers to environmental allergens such as dust mites, animal dander, grasses, and pollens that cause bronchoconstriction and inflammation of the airways (Romanet-Manent, Charpin, Magnan, Lanteaume, and Vervloet, 2002). The second type of trigger is non-allergic, and largely irritant, including triggers such as smoke, exercise, and cold air, which generally do not cause inflammation but may provoke airway hyperresponsiveness, particularly if airways are already inflamed (Romanet-Manent, Charpin, Magnan, Lanteaume, and Vervloet, 2002). Lastly, a significant amount of evidence has demonstrated that psychological triggers can exacerbate asthma. Emotional triggers involve emotional stimuli that are either positive (i.e.,

elation, happiness) or negative (i.e., sadness, stress) and which exacerbate asthma symptoms (Ritz et al., 2008).

Exposure to asthma triggers can cause daily functional limitations and reduced quality of life in children (Wood et al., 2007). They can also result in increased healthcare utilisation by necessitating additional medication usage, more frequent visits for medical consultation, emergency room care, and ultimately, higher rates of hospitalisation (Wood et al., 2007; Luskin, Chipps, Rasouliyan, Miller, Haselkorn, Dorenbaum, 2014; Peterson, Gaeta, Birkhahn, Fernández, Mancuso, 2012).

Although few studies have examined the association between asthma triggers and QOL among children, it is evident that the adverse physical and psychological effects are more substantial than initially believed (Wood et al., 2007; Luskin et al., 2014; Peterson, Gaeta, Birkhahn, Fernández, Mancuso, 2012). For example, Wood et al. (2007) demonstrate that when emotion, physical activity, and air pollution trigger asthma among children, this is predictive of poor asthma-related QOL ($r = 0.40$, $r = 0.44$ and $r = 0.30$, all $p < 0.001$, respectively).

An association between asthma triggers and asthma severity and exacerbation has also been indicated (Ritz, Steptoe, Bobb, Harris, & Edwards, 2007). Numerous studies have reported that a greater number of triggers correlate with the increased severity of patients' asthma symptoms (Luskin et al., 2014, Ritz, Steptoe, Bobb, Harris, and Edwards, 2007; Ritz, Kullowatz, Kanniess, Dahme, and Magnussen, 2008). In children with asthma, those who reported more asthma triggers (≥ 4) had a higher level of disease severity and asthma exacerbations (≥ 5 each year) relative to those who reported fewer asthma triggers ($p < 0.01$) (Luskin et al., 2014).

The identification of asthma triggers is a highly complex process which necessitates accurate perceptions of potential asthma triggers, asthma symptoms, and causal or contingent

relationships between these potential asthma symptoms and triggers (Janssens and Ritz, 2013). Notwithstanding the immense challenge of identifying these components, the components are regarded as interrelated and interdependent, thereby exerting an influence on each other (Janssens and Ritz, 2013). Moreover, in the case of children with asthma, identification of asthma triggers may be further complicated by conflicting parent and child reports of specific triggers (Janssens and Ritz, 2013; Lara et al., 1998; Yoos, Kitzman, McMullen, Sidora, 2003). For instance, Lara et al., (1998) uncovered disparate reports of symptoms from parents as opposed to children while exercising; 18% and 20% of children reported never coughing and never wheezing while exercising, respectively. However, parents reported fewer symptoms than their children: 34% percent of parents reported that their children did not cough during or after exercise, and 47% percent of parents reported that their child did not wheeze during or after exercise (Lara et al., 1998). The correlation between parent and child reports of asthma symptoms following exercise was weak (parent and child cough r = 0.23, p = 0.05; parent and child wheezing, r = 0.21, P = 0.08) (Lara et al., 1998).

2.7.1 Individual perceptions and reports of asthma triggers

Adequate asthma management is difficult without the accurate identification of asthma triggers. Moreover, it is highly difficult to assess asthma triggers in children because of children's limited comprehension of questionnaires and their inability to effectively communicate. Until recently, asthma trigger identification has received minimal attention. A lack of knowledge about important triggers may impede an individual's ability to identify personally relevant triggers and maintain optimal overall symptom control. Incorrect beliefs about triggers can precipitate the misidentification or incorrect perception of asthma triggers (Janssens and Ritz, 2013).

Individuals vary in their perceptions of asthma triggers, and perceptions have been demonstrated to trigger asthma (Janssens and Ritz, 2013). For this reason, research instruments must incorporate perceptions of asthma and not merely ask whether a physical trigger causes asthma symptoms. Moreover, there is only a modest correlation between self-reported asthma triggers and allergy tests (Janssens and Ritz, 2013; Ritz, Steptoe, Bobb, Harris, and Edwards, 2007; Ritz, Kullowatz, Kanniess, Dahme, and Magnussen, 2008). This is because many triggers have been proven to be non-atopic in nature, including those of intrinsic psychogenic origin (Ritz, Steptoe, Bobb, Harris, and Edwards, 2007). Various psychological mechanisms are involved in the process through which triggers are identified (Janssens, 2013).

Janssens (2013) argues that one of the reasons for the mixed success of trigger avoidance may be that individuals struggle to identify their personal triggers. In other words, if patients remain unaware of their personal asthma triggers, they are likely to remain exposed to critical triggers. Furthermore, they may attribute their symptoms to specific triggers despite an absence of any correlation between the trigger and any actual airway obstruction (Janssens and Ritz, 2013). Such misidentifications can exert a significant impact on symptom control; conversely, the over-perception of triggers may unnecessarily restrict daily activities and thereby impair QOL.

Typically, published research has recorded trigger identification by asking individual questions and has often lacked a scale to assess frequency. However, this technique may not accurately address physical and psychological asthma triggers since it does not account for trigger severity and frequency and may exclude psychological triggers of asthma (Harding, 2004; Takaro, Krieger, Song, 2004). Moreover, there is no clearly identifiable number of triggers reported by patients in various studies. Earlier instruments, such as the Asthma Trigger Index (ATX) constructed by Janson-Bjerklie et al. (1986), were used to evaluate the

emotional triggers of asthma. Despite the reported high reliability of the ATX, primary research results using this instrument were never published.

For this reason, the Asthma Trigger Inventory (ATI) was constructed; the ATI is a multi-dimensional questionnaire that assesses asthma triggers using a standardised technique (Ritz, Steptoe, Bobb, Harris, & Edwards, 2007). It assesses a broad spectrum of triggers in a standardised manner, and numerous studies have used the ATI instrument in different populations (Ritz, Steptoe, Bobb, Harris, Edwards, 2007; Wood et al., 2007; Ritz, Kullowatz, Kanniess, Dahme, and Magnussen, 2008). The ATI comprises 32 items divided into seven scales to assess trigger domains including animal allergens, pollen allergens, general allergens, air pollution and irritants, physical activity, infection, and psychological factors (Ritz, Steptoe, Bobb, Harris, Edwards, 2007). All seven domain scales have been demonstrated to be reliable and valid in adults with asthma (Ritz, Steptoe, Bobb, Harris, Edwards, 2007). Furthermore, the ATI has been proven in the US and Germany to be reliable and valid for use among parents or guardians of children with asthma (Wood et al., 2007; Ritz, Kullowatz, Kanniess, Dahme, and Magnussen, 2008).

Numerous variables alter asthma trigger reporting among asthmatics and parents of asthmatic children. Female patients report more asthma triggers than male patients (Goksel et al., 2009), while those with higher education tend to report fewer triggers (Ritz et al., 2008). However, no clear evidence of a relationship between race or ethnicity and reported asthma triggers exists. Findings also suggest cross-cultural consistencies and variations in perceptions of asthma triggers (Zeni et al., 2009). Self-reporting of animal-related asthma triggers is associated with a lower age of onset of asthma (Ritz et al., 2006), while obesity correlates with self-reports of exercise as a trigger (Peterson, Gaeta, Birkhahn, Fernández, and Mancuso, 2012). More severe asthma is correlated with emotional triggers, as are the existence of night time asthma symptoms and the use of oral corticosteroids (Ritz et al., 2006; Peterson, Gaeta, Birkhahn, Fernández, and Mancuso, 2012). Emotional triggers are also

correlated with QOL and heightened anxiety and depression (Ritz et al., 2006) Notably, allergic and non-allergic triggers are ostensibly unrelated in terms of symptom recognition, while it is known that the pathological mechanisms driving these two aspects of asthma exacerbation are also distinct (Ritz et al., 2006). Although these variations could result from different asthma phenotypes, a proportion of the variation observed may be further understood by examining the psychological processes involved in trigger identification.

2.7.2 Psychological and physical perceptions of asthma triggers

Asthma trigger identification is not simple, since it requires the simultaneous perception of asthma symptoms in relation to triggers and the recognition of a causal relationship between these triggers and symptoms. According to Lara et al. (1998), this endeavor is complicated by the fact that the components are mutually influential (Lara et al., 1998). Many asthma triggers (e.g., pollens, grasses, and house dust mites) are imperceptible; therefore, their presence is often inferred by association with symptoms in a particular environment. As delineated by Bobb et al. (2010), the correlation between perceived allergens and skin prick test wheal sizes are often highly strong for more perceptible triggers, such as felines, relative to triggers such as house dust mites or moulds. Nonetheless, it is known that not all triggers correspond with skin testing, since they are not atopic in nature.

Prior knowledge or beliefs about potential triggers may help in identifying nearly invisible triggers. This is supported by the fact that asthma sufferers with more knowledge about asthma routinely report more triggers and enhanced control (Peterson, Gaeta, Birkhahn, Fernández, and Mancuso, 2012). For instance, a lack of knowledge about the role of mould as a trigger for asthma would inevitably hinder one's accurate perception of mould as a personal trigger (Li et al., 2000). Stated differently, both knowledge and beliefs about triggers can help or hinder the identification of personal asthma triggers, depending upon whether knowledge or beliefs align with personal asthma trigger susceptibilities.

According to Janssens and Ritz (2013, pp. 1002), *'the perception of asthma symptoms occurs when changes in somatosensory information are matched to mental models of asthma symptoms'*. An asthma patient recognises an asthma exacerbation on the basis that the physical and sensory experience of symptoms mirrors preconceived beliefs or knowledge of the asthma symptoms (Figure 3). When the physical symptoms experienced do not align with the patient's understanding of what asthma involves, the risk of fatal asthma increases exponentially (Davenport et al., 2000). This is an important concept because symptom perception can also prevent seeking care and thereby result in increased morbidity and mortality (2000).

Any concurrent symptoms or environmental stimuli may also alter experiences of individual asthma symptoms. For instance, if a child were short of breath due to running but was known to be asthmatic, this could be identified as a result of asthma rather than physical activity. In a phenomenological sense, the interaction between the asthma sufferer and the environment partly creates the perceived reality of the environment and the inner experience of the asthma sufferer (De Peuter et al., 2007). Consequently, perceived asthma symptoms can appear in the absence of real triggers of asthma, and perceptions of factors unrelated to asthma can hinder the patient's own experience and impede their perception of asthma symptoms (Rietveld et al., 2006). These altered perceptions are possible in various contexts for different individuals, precisely because many other personal factors, such as gender, memory, personality, and different cultural norms and beliefs influence human perception and therefore perceptions of asthma symptoms (Fritz et al., 2010). Ultimately, it is evident that human perceptions are often flawed; therefore, individual perceptions of respiratory symptoms are complex and prone to inaccuracies. According to Janssens et al. (2009), up to 15% to 60% of asthma symptoms perceptions are inaccurate.

Awareness of the existence of asthma triggers can only arise if the causal relationship between the trigger and the asthma symptoms is clearly perceptible. Contingency

perception, as delineated by Janssens and Ritz (2013), is necessary to predict and therefore prevent the onset of asthma symptoms (see Figure 3). Several studies have indicated that the perceived unpleasantness of an event often becomes associated with an overestimation of the contingency between the event and its preceding cues (Grupe et al., 2011). This is most likely the cause of the delay between self-reported symptoms and their subsequent treatment (Nolte et al., 2006). In a survey of adolescent and adult asthma and rhinitis patients, they reported that although they experienced symptoms for a long time, treatment was only requested when the symptoms became intolerable (Figure 3). When symptoms are present but of no consequence to the asthma-sufferer, the individual will be more unaware of what the triggers are and less inclined to avoid them.

A priori beliefs, or prejudice, can influence perceptions of the contingent relationship between a potential trigger and asthma symptoms. In experimental contexts, expectations have been proven to influence symptom reports in the absence of any objective evidence (Devriese et al., 2004). As described by Janssens & Ritz (2013), both expectations and perceptions of asthma symptoms link ones perception of an asthma trigger to their perceptions of an asthma symptom (Figure 3). Perceptions of triggers and symptoms have a number of key determinents. As outlined in Figure 3, these include the degree of symptom instensity, the learnt expectations of a particular trigger-symptom, concurrent triggers which may alter symptom trigger perceptions and the symptom-trigger characteristics over time.

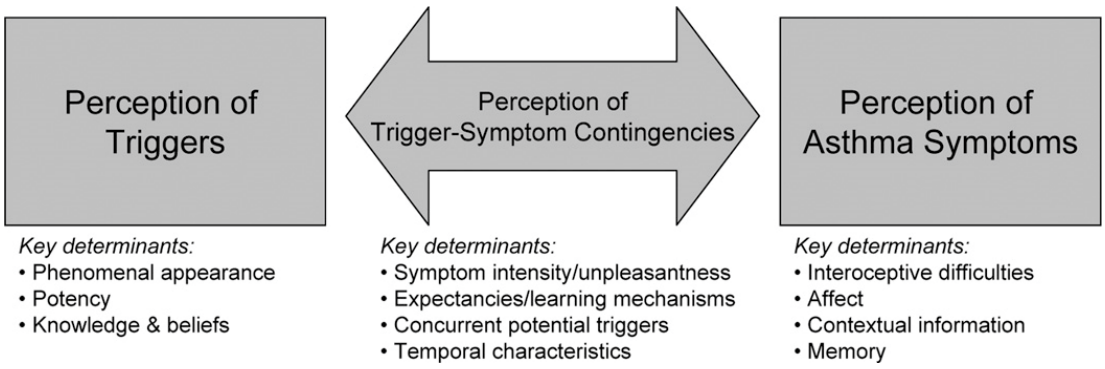

Figure 2. Key determinants of asthma trigger identifications.

Adopted from Janssens, T., & Ritz, T. (2013). Perceived triggers of asthma: key to symptom perception and management. Clinical and Experimental Allergy, 43(9), 1000-1008.

Levels of fear predispose individuals to expect negative outcomes, irrespective of whether fear levels are consistent with adverse outcomes on a repeated basis (Davey, Cavanagh, and Lamb, 2003). Therefore, fear and anxiety promote inaccurate perceptions of triggers that may be relevant to trigger identification. This is particularly the case among those who adopt a 'better safe than sorry' biased behaviour pattern after facing an adverse outcome (Weiser, 2007). These individuals imperil their own ability to perceive the contingencies between actual triggers and their asthma symptoms.

Moreover, asthma patients with comorbid depression are prone to a different bias. They often underestimate the real contingency in situations in which control is quite important (Fritzsche et al., 2010). This can reduce their ability to detect trigger contingencies and result in potentially deleterious outcomes (Fritzsche et al., 2010).

Apart from cognitive biases and bronchoconstriction due to emotional states, the temporal characteristics of allergic reactions may further enhance misperceptions of trigger-symptom contingencies (Scichilone et al., 2011). The late phase response of allergic reactions (four to 24 hours after exposure) may impede their ability to determine what initially triggered the response (acute phase) (Scichilone et al., 2011; Davey, Cavanagh, and Lamb, 2003). Additionally, triggers have been known to impact allergic reactions differently over time. The previous experience of an individual in terms of the contingency between specific triggers and specific asthmatic reactions can become redundant over time (Scichilone et al., 2011).

Some studies have indicated that stronger reactions to allergens occur during periods of increased stress. This may mean that it could be easier to perceive triggers during these periods, although the risk of inflammation-directed biased contingency perceptions could direct attention toward asthma-specific cues that are not involved in the airway response.

2.7.3 Suggestion-induced bronchoconstriction in asthmatics

The perception that an environmental agent is an asthma trigger can itself induce bronchoconstriction (Isenberg et al., 1992). In this manner, perceptions of trigger symptoms induced by suggestion can be maintained and may impact quality of life and interfere with the personal management of asthma.

The substantial associations between psychological states in asthmatic individuals and their perceptions of asthma triggers and symptoms render the determination of triggers particularly difficult (Davey, Cavanagh, and Lamb, 2003; Devriese et al., 2004; Grupe et al., 2011). Nonetheless, the identification of asthma triggers and developing a thorough understanding of how individuals form perceptions of triggers and develop a symptomatic response (or vice versa) may underpin the effective non-pharmacological management of asthma. The literature demonstrates that the perception of a trigger is perhaps equally important relative to an actual 'physical' trigger for a particular individual; therefore, psychological assessment of asthma triggers is imperative.

2.8 Risk factors and triggers of asthma

2.8.1 Overview of asthma risk factors and triggers

Asthma is highly associated with both the internal physiological and external environmental context of particular individuals. Therefore, there are numerous risk factors and triggers. Nevertheless, it is often difficult to distinguish between risk factors and triggers. This is because many triggers are also risk factors and are therefore differentiated based on whether they have affected an individual. For instance, if the risk factor affected the individual in the past, it would be described as a trigger; if it did not affect the individual but had the potential to do so, it would be described as a risk factor. The primary internal risk factors are discussed above; genetic predisposition to atopy is the primary intrinsic risk factor. The triggers, which

often interact with the internal risk factors, are described below and include a variety of environmental and non-environmental triggers.

Changes in environmental and lifestyle exposure are probable explanations for the increased prevalence of atopic diseases including asthma (Ekström et al., 2015). Both indoor and outdoor environmental factors have been demonstrated to influence the risk of asthma, in addition to psychological stimuli, dietary habits, and obesity (Seaton et al., 1994; Devereux and Seaton, 2005; Ekström et al., 2015).

Children are regarded as particularly susceptible to environmental exposures because of their immunological immaturity and biological focus on growth and development and because they eat, drink, and breathe more in relation to their body weight than adults (Castro-Rodriguez et al., 2016; Thacher et al., 2014). Genetic predisposition, parental allergic disease, second-hand exposure (e.g., tobacco smoke, air pollution), and prematurity are some of the established risk factors for childhood asthma and allergic disease (Castro-Rodriguez et al., 2016).

The timing of exposure during critical periods of organ and tissue development appear to be important determinants of future health outcomes. For example, *in utero* and early-life smoke exposure increases the risk of paediatric asthma (Neuman et al., 2012; Thacher et al., 2014). Similarly, *in utero* or early-life exposure to air pollution, such as that produced by heavy traffic and the burning of fossil fuels, may exert enduring impacts on respiratory outcomes later in life (Wright and Brunst, 2013; Hsu et al., 2015). However, since asthma development is a dynamic process throughout childhood, it is also of interest to examine exposure later in childhood in relation to disease (Wickman et al., 2014; Keil et al., 2010; Ballardini et al., 2012; Westman et al., 2015).

Triggers can elicit the rapid onset of asthma symptoms, although these symptoms may be short-lived and are often alleviated by β2 agonist rescue medication (e.g., Salbutamol).

Triggers vary across individuals, which indicates the importance of genetic factors and environmental sensitisation in the process of asthma development.

Frequently-reported asthma triggers include cigarette smoke, air pollution and fumes from various types of machinery, changes in weather conditions (e.g., rapid shifts to hot or cold temperatures or storms), strong psychological stimuli, physical activity, allergens, and viral and bacterial infectious microorganisms (Bobb et al., 2009). Some of these asthma triggers are difficult to perceive because they are not visible and due to their pervasive nature. This particularly applies to triggers such as allergens (e.g., pollens and grasses), dust mites within the home environment, various moulds, minute particulate matter in the atmosphere, and respiratory viruses (Ritz et al., 2006; Bobb et al., 2009). As a result, the presence of these triggers is regularly inferred based on the manifestation and type of asthma symptom.

This inferential difficulty reflects the connection between triggers that are perceived as asthma triggers due to allergens and empirical testing such as immunologic skin-testing outcomes. The relationship between subjective perceptions of allergic triggers and objective assessments of urticarial wheal proportions are often stronger for asthma triggers with more evident presentations. For instance, pet furs (e.g., dogs and felines) are typically more perceptual to asthmatics relative to less discrete triggers such as allergens (pollens, moulds, or grasses) (Ritz et al., 2006; Bobb et al., 2009). Likewise, a reduction in the presence of perceivable asthma triggers may manifest the observed weaker correlation between certain triggers in different contexts. For example, it partially explains the more limited reports of atopic asthma triggers among current smokers relative to atopic asthma triggers among non-smokers (Ritz et al., 2006; Peterson, Gaeta, Birkhahn, Fernández, Mancuso, 2012).

A study conducted by Rodica (2013) demonstrated that exposure to atmospheric and indoor pollution during early years of life are frequent triggers of asthma. According to Rodica (2013), this causes weaker pulmonary performance as a result of sensitisation and

inadequate pulmonary development and a far more labile response to anti-inflammatory treatment with ICS.

The clinical differentials between atopic and non-atopic asthma symptomologies, most notably surrounding nasosinusal involvement, demonstrate an increased predisposition toward non-atopic asthma among older individuals, females, and those with comorbid sinusal polyposis or FEV1 above 80% of the predicted value (Romanet-Manent et al., 2002). Conversely, a past medical history of atopy, including allergic rhinitis, seasonal asthma exacerbations, and longer duration of asthma symptoms exhibited a risk-reducing effect (Romanet-Manent et al., 2002). Notably, there was no difference in the presence or absence of rhinitic symptoms identified between atopic and non-atopic groups, which possibly indicate distinct aetiologies (Romanet-Manent et al., 2002).

Knowledge and awareness of potential asthma triggers would assist in the identification of generally unperceivable asthma triggers. Additionally, lower levels of awareness are likely to hinder trigger perceptibility. Individuals with greater knowledge regarding asthma and either their personal or their children's specifically observed or perceived triggers tend to report more triggers (Peterson et al., 2012) In contrast, the provision of information about the role of certain (typically unperceivable) triggers such as moulds or cockroach dander could potentially hinder individual perceptions of these asthma triggers, rendering them more psychologically perceivable than they truly are (Bobb et al., 2009; Li et al., 2000; Saengpanich et al., 2004). Since there is a substantial amount of individual variability in terms of asthma triggers, enhanced knowledge and awareness of common asthma triggers can either improve or interfere with the accurate identification of individual triggers; this is contingent upon whether psychological asthma trigger perceptions align with personal susceptibilities (Ritz et al., 2006; Heinzerling et al., 2009).

2.8.2 Atopic (allergic) triggers

Patients with the atopic form of asthma are predisposed to immunologically characteristic airway inflammation caused by allergic stimuli (Barnes and Drazen, 2002). In the presence of atopic inflammation, a plethora of non-atopic triggers are more likely to trigger overzealous airway hyperresponsivity, bronchoconstriction, and mucus hypersecretion (Barnes and Drazen, 2002). This particularly applies to exposure to respiratory viruses, cold air, physical activity, and tobacco smoke. Pollens, animal dander and saliva, cockroach faeces, dust mites and their faeces, mould spores and fragments, and occupational exposures are all atopic exposures to which an individuals can be sensitised and triggered as a result (DellaValle, Triche, Leaderer, and Bell, 2012).

During the past several decades, there has been significant conjecture within the literature concerning allergen exposure as the primary aetiology in asthma. Allergy skin prick testing (SPT) is an extremely safe procedure used to identify individuals' allergic susceptibility to allergens. If the individual responds to any of the common allergens, a local urticarial wheal erupts on the skin of the forearm where the test is conducted (Ritz et al., 2006). As indicated above, SPT is an important tool for validating asthma triggers at an individual level and validating instruments utilised to examine trigger perceptions, such as the asthma trigger inventories [ATI] (Ritz et al., 2006). The most up-to-date guidelines for asthma diagnosis produced by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) continue to incorporate allergic testing in the diagnostic algorithm (Thorley, 2015). However, Thorley (2015) assserts that the inclusion of such a line of testing is insignificant in the diagnosis of asthma. Likewise, the Global Initiative for Asthma guideline published by GIFA (2014) does not integrate allergic assessments into the diagnostic algorithm. As Thorley (2015) notes, the NICE guidelines recommend gold standard testing of PFT and fractional exhaled nitric oxide (FeNO) testing. Nonetheless, the guideline explicitly

delineates the inappropriateness of SPT to aeroallergens and measurement of total or specific serum IgE as diagnostic tests for asthma (NICE, 2015).

2.8.3 Pollens and other aeroallergens

Pollens and other aeroallergens are most likely the most well-studied risk factors and triggers for atopic asthma. Studies published up to over 90 years ago recognised the importance of pollens in the pathogenesis and ongoing pathophysiological pathways of asthma and atopic rhinitis (Johnstone, 1957; Citron, Frankland, and Sinclair, 1958; Peshkin, 1931). Allergen sensitisation is an important and established initial component in the pathogenesis of atopic asthma (DellaValle, Triche, Leaderer, and Bell, 2012). Pollens such as those from flowers, trees, ragweed, and grasses are allergens which are likely to interact with the body in various ways, which may explain the broad variance in asthma as a clinical condition and the reported triggers observed in the population. Various studies demonstrate the colossal biological impact of ambient aeroallergen concentrations and the ongoing progression of asthma; however, examining individual response differences is difficult due to limitations in the assessment of pollen exposures. A study conducted by DellaValle, Triche, Leaderer, and Bell (2012) attempted to model individual-level exposures to the above aeroallergens. The authors discovered that essentially all sensitised individuals had a significantly increased risk of experiencing asthma symptoms and required rescue medications in response to minimal levels of ragweed pollen (6 to 9 grains/m^3) as well as all-symptom risk increases in response to grass pollen among non-users of preventative medication. The authors also identified a pattern of declining asthma symptoms in the group with the highest-quartile exposures, which indicates likely behavioural modification in response to such aeroallergens (DellaValle, Triche, Leaderer, and Bell, 2012). Furthermore, additional studies have demonstrated increases in asthma symptom exacerbation in response to tree and ragweed pollens (Tobias, Galan, Banegas, and Aranguez, 2003; Newhouse and Levetin, 2004; Heguy, Garneau,

Goldberg, Raphoz, Guay and Valois, 2008; Dales, Cakmak, Judek, and Coates, 2008; Dales et al., 2004).

2.8.4 Indoor mould and dampness

Indoor mould and dampness are two of the major global problems that pose environmental risks for public health (Mudarri and Fisk, 2007). The estimated prevalence of dampness in households ranges between 10 and 50% worldwide; additionally at least 20% of households in Europe, the United States, and Canada have reported signs of dampness (WHO, 2009), which depends upon climate, air humidity, construction, and ventilation of the building as well as occupants' behaviour. Moist indoor conditions allow microorganisms to flourish, resulting in numerous microbiological aeroallergens and irritant exposures involving spores, toxic cell fragments, inflammatory substances, and other allergens (Cho et al., 2016). Consequently, these agents are immunostimulatory and act as irritants that induce an inflammatory response (WHO, 2009).

There are no recommended values under which microbiological contamination is safe because of a deficiency of valid exposure quantification methodologies. Therefore, the WHO (2009) currently recommends simply preventing or remediating indoor mould and dampness.

Self-reported visible mould or dampness in the home environment has been correlated with the onset of respiratory symptoms, increased risk of respiratory infections, increased likelihood of asthma exacerbations, and the development of asthma and rhinitis in both children and adults (WHO, 2009; Mendell et al., 2011; Fisk et al., 2007; Quansah et al., 2012; Jaakkola et al., 2013; Tischer et al., 2011). For instance, a study conducted by O'Driscol, Hopkinson, and Denning (2005) demonstrated that mould sensitisation among severe asthmatics was associated with more frequent hospital admissions. Mould sensitisation to Aspergillus fumigatus, *Alternaria alternata, Cladosporium herbarum, Penicillium notatum,*

and *Candida albicans* in the cohort of 181 patients in the study conducted by O'Driscol, Hopkinson, and Denning (2005) was relatively limited among mild asthmatics and highly common among severe asthmatics. This indicates that mould sensitisation and mould are crucial risk factors in the progression of severe asthma. Moreover, the reactivity to fungal allergens such as *Alternaria* has been proven to be common among patients with life-threatening asthma phenotypes (O'hollaren et al., 1991). In the study conducted by O'hollaren et al. (1991), exposure to the *Alternaria* fungus was associated with respiratory arrest in those with severe asthma.

Limited data has highlighted the possible relationship between mould exposure, oxidative-stress, and genetic susceptibility in the provocation of atopic asthma and other respiratory outcomes (Su et al., 2012).

2.8.5 Non-atopic triggers of asthma

Allergens do not represent the entirety of asthma triggers, since non-allergic triggers have also been hypothesised to cause asthma (Romanet-Manent, Charpin, Magnan, Lanteaume, and Vervloet, 2002, Barnes, 2013). Non-allergic triggers are irritants to the airway that pathologically alter airway physiology in the same manner as allergic asthma triggers (i.e., bronchoconstriction). These include triggers such as smoke, exercise, cold air, infections, etc., which produce a form of non-allergic inflammation (i.e., not involving cellular pathways involved in atopic reactions) but nonetheless provoke airway hyperresponsiveness (Romanet-Manent, Charpin, Magnan, Lanteaume, and Vervloet, 2002).

Non-atopic triggers cause irritation to the hyperinflammatory and hyperresponsive airway (Barnes and Drazen, 2002). Non-atopic triggers most frequently reported in the literature include physical activity, exercise, actively inhaled or secondary tobacco smoke inhalation, viral infections, cold air, air pollution such as smog or noxious fumes, and environmental odours (Barnes and Drazen, 2002). Notwithstanding the frequently investigated

environmental triggers, substantial evidence also supports the presence of stimulating psychological triggers such as stress, fear, or anxiety among others (Davey, Cavanagh, and Lamb, 2003).

The development of non-atopic asthma is less clear than that of atopic asthma. The disease variant demonstrates comparable levels of the characteristic inflammatory response within the airways, although the disease is not attributable to allergen sensitisation secondary to an exposure. Non-atopic asthma is not associated with serological evidence of elevated IgE to environmental allergens (Humbert et al., 1999). Non-atopic asthmatics typically have a past history of upper or lower respiratory tract infections or chemical exposures; in many cases, the condition is idiopathic.

The symptom profile of non-atopic asthma is similar, and synonymous triggers of atopic asthma can precipitate exacerbations. Melgaard et al. (2007) discovered that two-thirds of non-atopic individuals suffer from persistent symptoms, with an equal frequency of severe symptoms relative to atopic asthmatics during their most allergic season. This contradicts the findings of Bachert et al. (2006), who conducted a questionnaire-based study in Belgium that reported increasingly persistent and severe symptoms among atopic asthmatics as opposed to non-atopic asthmatics. According to Knudsen, Thomsen, Nolte, and Backer (2009), the prominent symptom among non-atopic asthmatics is coughing; however, atopic asthmatics experience more prominent wheezing.

Comorbid rhinitis, allergies to food, and hyperresponsivity are less common in non-atopic disease relative to atopic disease. Finally, while the entire population of asthmatics tends to be undertreated, non-atopic individuals are far more likely to be undertreated or not treated relative to individuals with atopic asthma (Knudsen, Thomsen, Nolte, and Backer, 2009).

Specific therapeutics facilitate the management of non-atopic asthma, which indicates that there is a shared pathological pathway despite varying aetiologies. As suggested by Humbert

et al. (1999), there are shared immunologic pathways, including the expression of CC chemokines and Th-2 cytokines relative to controls. This may indicate that non-atopic asthma occurs via a similar pathological process, with local IgE-mediated immunological action directed toward antigens that are non-atopic (e.g., viral antigens or potentially even autoantigens). Eosinophilic inflammation is also a pivotal feature of both variants, rendering the aforementioned mechanism highly plausible in the context of confirmed associations between certain triggers and non-atopic asthma (Gaga et al., 2002). Local IgE effects are further supported by the positive effect of omalizumab, a monoclonal antibody therapy directed at reducing IgE-mediated inflammation, on the Global Evaluation of Treatment Effectiveness (GETE) scale, the Asthma Control Test (ACT), FEV_1 measurements, and the frequency of asthma exacerbations (de Llano et al., 2013).

2.8.6 Cigarette smoke

Asthma, like most respiratory conditions, is associated with cigarette smoke, including smoking itself or exposure to second-hand smoke (SHS). Smoking triggers asthma regardless of how an individual is exposed (Stapleton, Howard-Thompson, George, Hoover, and Self, 2011). The symptoms of asthmatics who smoke or who are exposed to SHS are also worse relative to non-smokers and those not exposed to SHS, respectively, and these individuals experience an accelerated decline in pulmonary function and a poor therapeutic response to inhaled corticosteroids (ICS) (Thompson, Chaudhuri, and Livingston, 2004)

The underlying reasons for ICS-resistant asthma in asthmatic smokers are largely unknown, and there is a paucity of data regarding the subject. Thompson, Chaudhuri, and Livingston (2004) suggest that phenotypical alterations in inflammation may be pivotal due to a shift in the α-to-β ratio of glucocorticoid receptors in addition to augmented pro-inflammatory transcription factor activation and decreased histone deacetylase activity. Stapleton, Howard-Thompson, George, Hoover, and Self (2011) also report that decreased histone

deacetylase activity is likely to enable ICS resistance by reducing the ability of the steroids to effectively suppress cytokine production. An additional reason proposed by Stapleton, Howard-Thompson, George, Hoover, and Self (2011) for ICS resistance in smokers is the increased airway mucosal permeability observed among smokers, which could facilitate enhanced clearance of corticosteroid drugs.

Evidence suggests that the prevalence of smoking is more common among asthmatics as opposed to non-asthmatics (McLeish and Zvolensky, 2010). Additionally, asthmatic smokers have poorer overall control of their asthma and elevated risk of asthma exacerbations and asthma-related mortality (Stapleton, Howard-Thompson, George, Hoover, and Self, 2011). While smoking contributes to ICS resistance, smoking cessation itself has been illustrated to improve PFT results and substantially mitigate asthma symptoms (Thompson, Chaudhuri, and Livingston, 2004; Stapleton, Howard-Thompson, George, Hoover, and Self, 2011; McLeish and Zvolensky, 2010).

2.8.7 Air pollution

Air pollution is a complex mixture of compounds with different chemical and biological properties. The relative concentrations of these compounds depend upon their source, meteorological conditions, and geographical location. The components of ambient outdoor air pollution are referred to as particulate matter (PM), which includes a mixture of minute liquid droplets and particles such as gases (e.g., ozone, nitrogen oxide [NOx = nitric oxide {NO} combined with nitrogen dioxide {NO_2}] and carbon monoxide [CO]), as well as vapours [e.g., volatile organic carbons] (Perez et al., 2010). When NO is emitted into the air, it interacts with ozone and oxygen and forms NO_2.

Particle size is particularly important, since smaller particles can travel to smaller terminal bronchioles with a smaller diameter, and the properties can influence the pathological actions of the inhaled substance. Particles with an aerodynamic diameter of less than 10 µm

(PM-10) can reach the smaller distal airways upon inhalation and can include particles ranging between 2.5 µm and 10 µm and finer particles of less than 2.5 µm in diameter (PM-2.5) (Perez et al., 2010). Ultrafine particles with a diameter of less than 0.1 µm have been proposed to transgress the alveolar wall and reach the circulatory system (Perez et al., 2010).

Combustion of fossil fuels is the major underlying cause of global air pollution (Perez et al., 2010). Motor vehicles, aircrafts, industry, and households all contribute to fossil fuel utilisation (Perez et al., 2010). Traffic-induced air pollution is known to cause negative health effects for exposed children. In particular, air pollution exposure has been demonstrated to impair the development of the respiratory system in children and impair pulmonary function (Schultz et al., 2012; Gauderman et al., 2004; Gehring et al., 2013). Traffic air pollution is also known to cause asthma exacerbations and has been demonstrated to increase the risk of acute respiratory tract infections (Esposito et al., 2014).

Several studies have highlighted the relationship between air pollution due to traffic and the causation of paediatric asthma (Anderson et al., 2012; Bowatte et al., 2015; Health Effects Instititue, 2010; Gehring et al., 2015). Two meta-analyses indicated that early-life exposure was crucial in the development of paediatric asthma and that the exposure effect increased in association with age and duration of exposure (Bowatte et al., 2015; Gehring et al., 2015). Moreover, a recent systematic review described positive asthma associations related to exposure to black carbon and NO_2, PM2.5, and PM10 molecule exposures (Khreis et al., 2017). However, the mechanisms linking air pollution to asthma have not been fully explained, since studies attempting to assess sensitisation as a result of air pollution have yielded inconclusive results (HEI, 2010; Gruzieva et al., 2014). This is primarily because of the variety of complex endogenous (e.g., genetic predisposition) and exogenous (e.g., chemicals present in the air such as PM, NO, CO, and organic compounds) factors that interact to manifest asthma sensitisation or exacerbate symptoms in asthmatics (Ryan & Holguin, 2010).

2.8.8 Dietary antioxidants

In the Nordic Nutrition Recommendations (NNR), a diet rich in vegetables, fruits, berries, nuts, seeds, and whole grains is recommended to promote general health through the provision of essential amino acids, minerals, vitamins, and antioxidants (Nordic Council of Ministers, 2014). Decreased intake of antioxidants (fruits and vegetables) and n-3 polyunsaturated fatty acids obtained in fish oil and increased consumption of n-6 polyunsaturated fatty acids contained within margarines and vegetable oils have been hypothesised to increase asthma and atopy due to their anti-oxidative and anti-inflammatory properties (Devereux and Seaton, 2005; Allan et al., 2010). Dietary antioxidants can decrease oxidative stress by scavenging for free radicals and are required by the antioxidant defense system in the lung to inhibit damage by ROS in the context of asthma (Comhair and Erzurum, 2002).

Diet during pregnancy has been proposed to influence the development of asthma and atopic disease in the paediatric population (Maslova et al., 2014; Miller et al., 2015; Netting et al., 2014; West et al., 2012). Moreover, breast-feeding duration has also been hypothesised to be an influential factor, although observational studies concerning breast-feeding have been inconclusive (Matheson et al., 2012). In addition, increasing evidence suggests that the timing of the introduction of solid foods, particularly allergenic foods such as eggs, peanuts, and fish to the diet, may impact the development of atopic conditions (Lerodiakonou et al., 2016). The paediatric diet appears to be vital in asthma susceptibility; low antioxidant intake is associated with asthma and atopy development among children. However, results have been inconclusive, and few longitudinal studies have been conducted (Moreno-Macias and Romieu, 2014; Castro-Rodriguez et al., 2016; Nurmatov et al., 2011; Garcia-Larsen et al., 2016).

Antioxidant supplementation has been demonstrated to exert beneficial effects on functional pulmonary decline in response to ozone exposure among asthmatic children with genetic susceptibility to oxidative stress (Romieu et al., 2004). Nonetheless, clinical trials have not supported the use of antioxidant supplements to prevent or treat asthma or atopic disease (Moreno-Macias and Romieu, 2014). Alternatively, consumption of a balanced diet rich in antioxidants has been proven to effectively assist in the prevention of atopy and asthma (Garcia-Larsen et al., 2016; Han et al., 2015).

2.8.9 Triggers in the Middle East and the Kingdom of Saudi Arabia (KSA)

There is a scarcity of literature surrounding the environmental, physiological and psychological triggers of asthma from the Middle East. The Middle East has a unique environment, which makes the region an interesting context in which to examine asthma triggers. Hassain, Farhana, and Alnasser (2018) examined published studies that reported paediatric allergy and asthma prevalence across the Gulf region and several neighbouring countries. Asthma prevalence in the Middle Eastern region ranges from 10% to 23%, the highest of which is in KSA, at 23% (Mirzaei, Karimi, Beheshti, and Mohammadi, 2017).

Many of the asthma triggers reported to be present in Middle Eastern countries are not unlike those in other countries. These include aeroallergens such as pollen, dust, animal hair and dander (particularly cats, dogs and insects such as cockroaches) (Hasnain, Hasnain, & Al-Frayh, 2010; Alqahtani, Asaad, Awadalla, & Mahfouz, 2016; Al-Rawas, Al-Maniri, & Al-Riyami, 2009); fungal spores and moulds (Hasnain, Hasnain, & Al-Frayh, 2010; Alqahtani, Asaad, Awadalla, & Mahfouz, 2016); pollution from vehicles and oil refineries (El-Margoushy, El-Nashar, Khairy, El-Nashar, & Mohamad, 2013; Alqahtani, Asaad, Awadalla, & Mahfouz, 2016); smoke from traditional Arabic incense Bakhour or from cooking (Al-Rawas, Al-Maniri, & Al-Riyami, 2009; Alqahtani, Asaad, Awadalla, & Mahfouz, 2016); and climatic variations such as dust storms, extreme temperatures (hot, cold or humid) or black cloud (smog) as a result of

a significant culmination of airborne pollutants (Thalib & Al-Taiar, 2012; Leitzell, 2011; Marey, Gille, El-Askary, Shalaby, & El-Raey, 2010; Hashimoto. Fukuda, Shimizu, Watanabe, Watanuki, Eto, & Urashima, 2004; Al-Binali, Mahfouz, Al-Fifi, Naser, & Al-Gelban, 2008). These triggers are outlined in Table 1.

The most common Middle Eastern environmental allergens are weed pollen grains (e.g., *Amaranthus, Chenopodium,* and *Salsola*), house dust mites, and fungal spores (e.g., *Alternaria, Aspergillus, Cladosporium, Penicillium*), which is similar to other countries (Hasnain, Hasnain, and Al-Frayh, 2010; Alqahtani, Asaad, Awadalla, and Mahfouz, 2016). The distribution of reported aeroallergens is diverse, with significant differences between countries due to climatic and other environmental factors. A study conducted by Alqahtani, Asaad, Awadalla, and Mahfouz (2016) identified several modifiable environmental asthma triggers associated with physician-diagnosed severe asthma in Najran in Southwestern KSA. The authors examined environmental exposures to wood and coal smoke used for cooking, traffic pollution, allergens in the home, and secondhand smoke. Noticeable increases in asthma symptoms (e.g. worsened wheezing, dyspnoea, chest tightness, nocturnal coughing) occurred in response to dogs in the home, as well as *Cladosporium* moulds, Bermuda grass pollen, and pig weed (Alqahtani, Asaad, Awadalla, & Mahfouz, 2016). This study also observed a protective effect of eating seafood, fruit, and dairy products.

The unique environment in the KSA also renders it subject to significant pollution as a result of oil refining, as well as substantial vehicular traffic. Alqahtani, Asaad, Awadalla, & Mahfouz (2016) found traffic pollution increased asthma in the KSA. Severe pollution resulting in smog is termed 'black cloud' (Leitzell, 2011; Marey, Gille, El-Askary, Shalaby, & El-Raey, 2010). Black cloud has been attributed to increasing bronchial asthma, alongside other substantial shifts in weather such as desert dust storms, extremely humid weather, or both temperature extremes (hot and cold). This is further supported by physiological studies that have demonstrated that bronchoconstriction occurs in response to cold and heat or in which

correlate asthma-related admissions with these extreme climatic variations (Kanemitsu et al., 2016; Hyrkäs-Palmu, Ikäheimo, Laatikainen, Jousilahti, Jaakkola, & Jaakkola, 2018; Hyrkäs-Palmu, Ikäheimo, Laatikainen, Jousilahti, Jaakkola, & Jaakkola, 2018; Soneja, Jiang, Fisher, Upperman, Mitchell, & Sapkota, 2016).

Desert storms are particularly frequent in the KSA, and often result in significant mobilisation of sand, dust, heavy minerals and pollution (Kanatani et al., 2010; Thalib & Al-Taiar, 2012). Kanatani et al. (2010) demonstrate associated increases in asthma-related hospital admission during such desert dust storms. A similar phenomenon has been shown to occur in other countries, particularly throughout Asia (Park et al., 2005), Australia (Rutherford, Clark, McTainsh, Simpson, & Mitchell, 1999), and the Carribean (Gyan et al., 2005).

Smoke is often highlighted as an asthma trigger, whether it is primary smoking of tobacco or other products or secondhand smoke exposure. In the KSA, people often burn wood to

cook cultural feasts and burn wood products (incense) to produce a pleasant aroma. Al-Rawas, Al-Maniri, & Al-Riyami (2009) conducted a study on 2441 children in Oman, identifying an increase in adverse respiratory symptoms in response to Bakhour (Arabic incense) that was three times more likely among asthmatic children compared to non-asthmatic children. Moreover, Alqahtani, Asaad, Awadalla, & Mahfouz (2016) reported the use of wood for cooking as a risk factor for asthma. Similarly, airborne pollution has been reported to be associated with asthma, and increase the asthma-related hospitalisation rate in the KSA (El-Margoushy, El-Nashar, Khairy, El-Nashar, & Mohamad, 2013; Alqahtani, Asaad, Awadalla, & Mahfouz, 2016).

Table 2. Middle Eastern Asthma Triggers identified through the literature search.

Author(s)	Date	Location	Study design	Sample	Analysis	Triggers identified
Hasnain, Hasnain, & Al-Frayh	2016	KSA, UAE & Sudan	Observational	492	Meta-analysis	Weed pollen (Amaranthus viridis, Chenopodium murale, Salsola imbricata), house dust mites, cat hair and dander, cockroaches, fungal spores (Alternaria alternata, Ulocladium atrium, Cladosporium sphaerospermum).
Alqahtani, Asaad, Awadalla, & Mahfouz	2016	KSA (Najran)	Cross-sectional	1700	Multivariate Analysis	Dog hair, moulds (Cladosporium Spp.), grass pollens, pig weed (Amaranthus Spp.), traffic pollution, burning of wood for cooking, exercise.
Al-Rawas, Al-Maniri, & Al-Riyami	2009	Oman	Cohort	2535	Multivariate regression	Bakhour (Arabian incense), dust, changes in the weather, respiratory tract infections.
Thalib & Al-Taiar	2012	Kuwait	Retrospective cohort	88,267	Generalized additive model	Dust storms
Al-Ghamdi, Akbar, Qari, Fathaldin, & Al-Rhashed	2003	KSA	Prospective	160	Descriptive analysis	Cold weather
Al-Binali, Mahfouz, Al-Fifi, Naser, & Al-Gelban	2010	KSA	Cohort	171	Logistic regression analysis	Changes in the weather (undefined)
Tarraf, Aydin, Mungan, Albader, Mahboub, Doble & El Hasnaoui	2018	Egypt, Turkey, Kuwait, KSA & UAE	Cross-sectional	33,486	Multivariate analysis	Tobacco smoke
Al Ghobain, Algazlan, & Oreibi	2018	KSA	Cross-sectional	2,405	Pearson's Chi-squared tests	Dust storms
Al-Mousawi, Lovel, Behbehani, Arifhodzic, Woodcock & Custovic	2004	Kuwait	Controlled trial	463	Univariate analysis	Indoor and outdoor aeroallergens
Bener, al-Jawadi, Ozkaragoz, & Anderson	1993	KSA (Dammam, Riyadh)	Cross-sectional	2300	Meta-analysis	Animals and pets exposure, aeroallergens
El-Sharif, Abdeen, Qasrawi, Moens & Nemery	2002	Palestine	Cross-sectional	4000	Two-tailed Pearson T-test	Aeroallergens
Khawaji, Basudan, Moafa, Faqihi, Alhazmi, Mahnashi, Haddadi, & Yassin	2017	KSA (Jazan)	Cross-sectional	1400	Chi-square analysis	Exercise
Hamam et al.	2015	KSA (Taif)	Cross-sectional	4000	Chi-square analysis, ANOVA	Aeroallergens, Tobacco smoke
Hasnain, Alqassim, Hasnain, & Al-Frayh	2016	Middle East	Observational	354,076	Meta-analysis	Pollen grains (Salsola, Chenopodium, Amaranthms) indoor aeroallergens, house dust mites, fungal spores (Cladosporium, Aspergillus)
Abdalla et al.	2016	KSA (Tabuk)	Cross sectional	217	ANOVA	Upper respiratory tract infections, dust, coldness, incense, smoke of woods, household chemicals, passive smoking
Alqahatani, Asaad, Awadalla, & Mahfouz	2017	KSA (Najran)	Cross sectional	1700	Odds ratio, multivariate analysis	Dogs, traffic, use of wood as a cooking fuel, passive smoking, exercise.
Hamam et al.	2015	KSA (Taif)	Cross sectional	1700	Chi-squared, ANOVA	Passive smoking and exercise

2.9 Identification and measurement of asthma triggers

As discussed above, there are a multiplicity of well-researched asthma triggers that have an inferential, if not a proven causative effect, on bronchial obstruction. Effectively obtaining this information is pivotal for the appropriate investigation, diagnosis, and systematic management of asthma within the community, regardless of geographical location, as well as the formulation of remedial public health strategies.

Patient information concerning asthma symptomology and trigger perceptions are collected throughout an interview in which self-reported data is collected prior to proceeding to the objective quantification of individual pulmonary function and atopic responses (Ritz, Steptoe, Bobb, Harris, and Edwards, 2006). Nonetheless, notwithstanding the imperative of tests of asthma trigger self-perception, there has been minimal consideration of the reliability and validity of self-reported asthma triggers. In much of the literature, authors use singular questions and responses to determine the presence or absence of asthma triggers, although this approach is likely to be insensitive in the sense that genuine trigger susceptibility is underestimated. Additional asthma trigger analysis often incorporates quality of life (QOL) surveys, illness severity rating systems, or asthma management inventories. Ritz, Steptoe, Bobb, Harris, and Edwards (2006) created the Asthma Trigger Inventory (ATI) to assess individual perceptions of asthma triggers in a psychometrically valid and reliable manner.

2.10 Awareness of and knowledge about asthma among parents

As addressed above, awareness and knowledge of triggers is crucial for the psychological perception of triggers, as well as the management strategies that individuals can then apply to improve asthma management. Al-Harbi et al. (2016) conducted a study across Jeddah, Riyadh, and Dammam which utilised structured questionnaires regarding awareness of bronchial asthma (n = 1,039). The results indicated that only 67% of the populations were

aware that asthma is a potentially fatal disease; 13% were aware that asthma and allergies were distinct entities. Consequently, the authors determined that the knowledge regarding bronchial asthma in the Saudi Arabian population was insufficient. Minimal attention has been directed towards asthma knowledge among Saudi Arabian health professionals. Alghadeer et al. (2015) evaluated the knowledge and attitudes of pharmacists in relation to asthma therapy in both the hospital and community context.

Al-Anazi et al. (2014) constructed and utilised an Arabic version of the original asthma knowledge questionnaire (Arabic Asthma Knowledge Questionnaire; AAKQ), which was demonstrated to reliably assess parental awareness levels regarding asthma and associated factors related to poor asthma control. The findings of Al-Anazi and colleagues (2014) provide evidence that inadequate knowledge is an influential factor in precipitating poor asthma control in the presence of publicly available asthma guidelines in Saudi Arabia.

Al-Binali et al. (2010) interviewed mothers of children admitted to Aseer Central Hospital, Saudi Arabia, with asthma (n = 171) using a modified Chicago Community Asthma Survey. The authors aimed to determine maternal knowledge of, and behaviours directed towards, paediatric asthma. The authors illustrated a clear deficiency among parents related to the potential complications of paediatric asthma (Al-Binali et al., 2010). The study also demonstrates a significant connection between parental knowledge and asthma management provided to the child; asthma management techniques were identified as a major factor (Al-Binali et al., 2010).

2.11 Actions to avoid environmental and non-environmental triggers

2.11.1 Potential interventions to reduce the impacts of asthma triggers

The assessment of potential asthma triggers, as well as perceptions and knowledge regarding asthma triggers, drives individual actions toward trigger avoidance and improved asthma

management. However, while understanding asthma triggers and symptoms is important, adequate knowledge of effective avoidance or reduction strategies that can mitigate asthma exacerbations in response to known individual triggers is imperative. This section reviews the proposed methods for reducing and avoiding environmental and non-environmental asthma triggers within the literature.

2.11.2 Trigger education and psychological interventions

Halterman et al. (2006) suggest that less than half of asthmatic parents are advised about environmental triggers and control measures. Nonetheless, education about triggers is an indispensable component of asthma management (GINA, 2010). Education programs have been demonstrated to improve clinical (functional) and QOL outcomes in asthmatic individuals (Gibson et al., 2002). The environmental control measures are often expensive, difficult to implement, and dependent upon expertise which the patient generally lacks; over half of these control measures, if performed by patients, will provide no benefit to the patient (Brandt et al., 2008). For this reason, clinical asthma education from a medical or nursing professional is imperative to help disseminate effective asthma trigger avoidance strategies.

Programs which focus on the education of asthmatic children and their parents regarding healthier environments have yielded mixed results. A week-long asthma camp intervention to educate parents and their children about pharmacological and non-pharmacological strategies to alleviate asthma symptoms resulted in significantly reduced hospitalisations, emergency department visits, and school absences (Fitzpatrick, Coughlin, Chamberlin, 1992). However, Wakefield et al. (2002) and McIntosh et al. (1994) discovered no significant changes in parental home-smoking behaviour or in the health of asthmatic children following educational interventions. Some individuals may benefit more from educational interventions aimed at increasing the accuracy of trigger identification. For instance, individuals who often contract respiratory infections may have an amplified need to

distinguish between the synergy of allergen exposure and infections on asthma exacerbation (Bush et al., 2006). This particularly applies within the paediatric population in which asthma is frequently misdiagnosed, as in the case of virus-induced wheezing. Similarly, individuals who suffer from comorbid asthma and panic disorder, anxiety, or depression should be educated regarding distinguishing between symptomatic origins of their conditions (Bush et al., 2006). It is expected that treatment that exposes the patient to misidentified asthma triggers (exposure therapy) may result in a reduction of asthma symptoms that are associated with these triggers (Janssens 2013).

Cabana et al. (2004) demonstrated that 80% of parents of asthmatic children can identify at least one environmental asthma trigger. When the parents attempted to control this trigger, less than half of their control actions were deemed fruitful (Cabana et al., 2004). This indicates that further education is necessary. Since paediatric asthma disproportionally affects low-income urban households, the cost of effective interventions is also a highly important consideration.

Triggers are specific to certain individuals. Therefore, adopting a widespread trigger education approach that may enable over-exposure to psychologically-stimulating triggers with the potential to manifest the suggestion-induced phenomenon outlined by Janssens et al. (2009) may present dangers. Research suggests that knowledge of triggers correlates with self-reports of asthma triggers (Peterson, Gaeta, Birkhahn, Fernández, Mancuso, 2012). Therefore, when participants are informed about the dangers of environmental triggers, a learned symptom response may occur (Winters et al., 2003). Since suggestion can induce bronchoconstriction and the impact of contextual information and trigger beliefs on symptom perception, trigger beliefs can perhaps be modified through interventions to rectify inaccurate perceptions of asthma symptoms (Janssens et al., 2009).

2.11.3 Allergy skin-testing

From a physical perspective, asthmatics can be assessed for atopic triggers using objective allergen testing to identify physical triggers of which the patient may not have been aware; this could assist in de-programing psychologically-erroneous trigger beliefs. However, for non-allergic triggers, monitoring triggers and asthma symptoms may help identify triggers (Dahl, 1998). One means to satisfy patient needs would be to combine allergy skin prick testing with trigger evaluation and education.

2.11.4 Physical and mechanical prevention strategies

Central heating has been proposed as a preventative strategy to decrease indoor dampness and paediatric asthma symptoms (Somerville et al., 2000). According to a study conducted by Somerville et al. (2000), installing central heating diminished the dampness in homes; this corresponded with mitigated symptoms in children and significantly reduced asthma-related school absenteeism.

Mite-impermeable mattresses and pillow covers have been proposed as a prophylactic measure to combat high dust mite levels (Brunekreef et al. (2002)). However, mixed results were achieved in terms of changes in children's respiratory health. Halken (2004) discovered a significant decrease in the need for inhaled corticosteroids among asthmatic children, while Brunekreef et al. (2002) demonstrated no clinical benefits. However, Brunekreef et al. (2002) assessed the respiratory health of children up to two years old, which is before the typical onset of asthma and for which inhaled corticosteroids are generally not prescribed.

Popplewell et al. (2000) compared high-efficiency particulate air (HEPA) vacuum cleaners with standard vacuums in terms of efficiency in removing allergens and thereby improving the respiratory health of asthmatic children. HEPA vacuum cleaners significantly reduced allergens in homes over a 12-month period. Moreover, Warner et al. (2000) assessed entire-

house mechanical ventilation systems with heat recovery (MVHR) units and demonstrated that implementing these units improved the histamine levels in asthma patients.

Wu and Takaro (2007) conducted a comprehensive assessment of 32 paediatric asthma trigger reduction studies from 1995 to 2004, including 24 randomised control trials. The reduction strategies involved the following: mechanical intervention, central heating, bedding covers, various forms of vacuuming and cleaning, programs focusing on the education of children and their parents, and various combinations of these (Wu and Takaro, 2007). The authors concluded that a multimodal approach which involves improved cleaning, particulate vacuum cleaning, mechanical ventilation in homes, and parent education precipitated the greatest reduction in asthma symptoms and triggers among asthmatic children. This aligns with the results published by others in terms of the significant allergen reductions, improved children's health, and reduced hospital visits among children with acute asthma (Krieger et al., 2005; Kattan et al., 2005; Morgan et al., 2004; Sullivan et al., 2002; Carter et al., 2001; Hayden et al., 1997). In the study by Krieger et al (2005), the authors emphasised that higher-intensity interventions achieved greater improvements in the PACQOLQ (4.0 to 5.6 [high-intensity] as opposed to 4.4 to 5.5 [low intensity] p=0.05) and the asthma-related urgent health services utilisation (23.4 to 8.4 [high-intensity] as opposed to 20.2 to 16.4 [low intensity] p=0.026).

2.12 Individual assessments of psychological and physical impact of asthma

2.12.1 Paediatric Asthma Quality of Life Questionnaire (PAQLQ)

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) was constructed to assess the most challenging functional aspects of asthma, including physical (e.g., coughing), psychological (e.g., frustration), and social factors (e.g., being bothered due to being unable to be around people). The PAQLQ contains 23 questions which address three domains: 1)

symptoms, 2) limitations of activity, and 3) emotional functioning. The questionnaire asks patients to respond to all 32 questions based on how they have been feeling during the preceding week by providing answers on a seven-point scale. The PAQLQ test yields an overall mean value and means for each domain.

The validity of the PAQLQ has been confirmed in numerous studies conducted in various countries, such as Spain, Turkey, Egypt, Saudi Arabia, etc. (Yüksel, Yilmaz, Kirmaz, & Eser, 2009; Abdel, Taher, & Fattah, 2010, Tauler et al., 2001). Moreover, children as young as seven years of age can understand and respond to questions and provide accurate responses (Juniper, Gruffydd-Jones, Ward, and Svensson, 2010). According to Stelmach et al. (2012), the PAQLQ is a useful paediatric asthma-monitoring instrument and is helpful for integrating parents into the asthma care plan for their child.

2.12.2 Asthma Control Test (ACT)

Various studies have reported discordance between the assessment of asthma control between patients and health care professionals (Liu et al., 2007; Jan et al., 2007). This may be because of the difference in the interpretation of asthma 'control' among these two groups. For this reason, more formal assessment tools are constructed to ensure that both health professionals and patients communicate with the same understanding. The Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) are surveys used to assess levels of asthma control experienced by individuals (Liu et al., 2007; Jan et al., 2007).

The Childhood Asthma Control Test (C-ACT) was developed to formally examine asthma control in asthmatic children between the ages of 4 and 11 (Liu et al., 2007). The C-ACT is a seven-item self-administered questionnaire that elicits responses from both parents and children. The first four questions are completed by the child using a four-response scale (very bad [0 points] bad [1 points], good [2 points], very good [3 points]), and there is no requirement to recall asthma experiences. These items examine asthma-induced activity

limitations (e.g., running or playing sports), symptoms such as coughing, waking during the night, and the child's feelings regarding their asthma. There are variations in the C-ACT questionnaire for children between 4 and 11 years relative to the C-ACT for children between 12 and 17 (Liu et al., 2007). The subsequent three questions are completed by the parent by recalling asthma-related experiences which occurred during the preceding four weeks, including daytime symptoms and waking during the night due to asthma (six-response scale).

The C-ACT is scored out of 27, with scores below 19 indicating inadequately controlled asthma. Liu et al (2010) also incorporated an additional category to account for changes in the asthma management guidelines in the US; this modified the C-ACT to include the 'very poorly controlled' category (scores <15). Numerous studies have assessed the validity and reliability of the scale in assessing temporal changes in asthma control (Jan et al., 2007; Liu et al., 2007).

2.12.3 Pulmonary function testing in asthma

Pulmonary function testing (PFT) aims to establish the status of the respiratory system and the presence or absence of asthma. It is used in both clinical and research settings. Within the former context, PFTs are used as an office-based investigation as an adjunct to clinical history. They satisfactorily assist in differentiating between obstructive and restrictive respiratory disorders and monitoring disease course and therapeutic success.

As discussed above, the generic measurement of FEV_1 utilising spirometry is a poor indicator of asthma severity, and FEV1/FVC ratio should be used instead (Bacharier et al., 2004). This is further supported by Birnbaum et al. (2009), who assessed the ability of PFT to measure alterations in asthma severity classifications. In terms of comparing the National Asthma Education and Prevention Program categories and the PFT outcomes observed by Birnbaum et al. (2009), the PFT results would have resulted in a more severe asthma categorisation in merely a small fraction (10.9%) of patients.

2.13 Research gap

Asthma prevalence is increasing globally, which has intensified the burden on health systems and contributed to direct and indirect economic costs and poorer health. Asthma is highly prevalent in the KSA, a country with a highly unique environment in which alternate asthma triggers may be present. However, a paucity of data concerns the environmental triggers of asthma in the country. An increased focus has been directed towards harnessing environmental triggers of asthma to achieve a more in-depth understanding of the complexities of asthma, as well as utilising sophisticated research to develop new therapies and public health strategies to improve asthma outcomes. Despite significant global research into asthma triggers, scholars lack an understanding of specific Saudi Arabian triggers, the perception of these triggers among parents of asthmatic children, and the overall impact of awareness on control of asthma in response to trigger exposures. Nonetheless, a valid and reliable instrument has not been developed to assess novel asthma triggers in the KSA. There are therefore notable gaps in the literature in relation to the following: 1) the identification of Saudi-specific asthma triggers among the paediatric population, 2) understanding levels of parental awareness of paediatric asthma triggers, 3) understanding the actions Saudi parents pursued to avoid or mitigate the asthma triggers they identify for their children, and 4) a validated and reliable Saudi-specific asthma trigger instrument that incorporates triggers found in the literature to potentially trigger asthma in the KSA.

3.0. CHAPTER THREE: METHODS

3.1 General research design and setting

This study was conducted in three stages. Stage one involved developing the initial Arabic version of the ATI items list. Stage two entailed identifying the prevalence of perceived asthma triggers by applying the Arabic version of ATI questionnaire to a sample population (*n* = 200). Finally, in stage three, the reliability and validity of the Saudi-ATI questionnaire was tested.

3.2 Study Setting

The study was conducted at the King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. Hospital amenities such as copy machines and the Internet were available. The number of asthma-related admissions to the KFMC paediatric ward and intensive care unit at the KFMC was requested. The hospital statistics indicated that the KFMC admitted an average of eight children with asthma daily for acute exacerbation of the disease. This confirmed the feasibility of recruiting a sufficient number of parents and guardians of children with asthma during a five-month period.

The KFMC is regarded as the largest and most advanced medical complex in the Middle East (KFMC, 2018). The pulmonary clinic at KFMC provides integrated healthcare, including diagnosis and treatment of asthma, a unit for pulmonary function testing (PFT), and various outpatient services (KFMC, 2018). The KFMC represents the major hospital for a large geographical area extending beyond Riyadh. This health facility was selected to ensure that the sample population was representative of the broader population within the KSA.

3.3 Stage one: development of the initial Arabic version of the ATI

Stage one consisted of three phases. Phase one involved a literature review and consultation with local respiratory physicians from the KFMC to identify KSA-specific asthma triggers to be included in the original ATI. Phase two entailed the creation of the Saudi-ATI, incorporating the KSA specific triggers, and appropriately translating the document. Lastly,

phase three of stage one consisted of a small pilot study conducted on 10 parents of asthmatic children to ensure that the Saudi-ATI could be easily read, understood, and completed.

Phase one included the development of the Saudi-translated version of the original 32 trigger items included in the original English ATI published by Ritz et al. (2006). At this stage, seven additional KSA-specific triggers were integrated into the original ATI. These triggers were identified by a literature search which included the following terms: 'child' OR 'paediatric' OR 'pediatric' AND 'asthma' AND 'trigger' OR 'parents' AND 'guardians' AND 'Saudi Arabia' OR 'Middle East'. The following search engines were used to identify articles published between 1990 and 2015: PubMed, PsycINFO, Springerlink, and Science-Direct. The inclusion criteria included peer-reviewed primary research articles that focused on determining asthma triggers in the locations mentioned above. Exclusion criteria included review articles or those examining triggers beyond the KSA or Middle East. The reference lists of each peer-reviewed article were assessed for additional articles examining Saudi-specific or Middle Eastern asthma triggers.

Furthermore, two respiratory physicians with substantial expertise in the research and clinical management of asthma at KFMC were consulted to learn about clinically identifiable triggers of asthma that might be included in the Saudi ATI. Subsequently, food allergy as a trigger for asthma symptoms was integrated into the Saudi ATI from this consultative approach.

The original ATI contained 32 items ranked on a five-point scale (never, rarely, sometimes, often, and always). The five-point ATI scale indicates the associated impact of particular asthmatic triggers. To ascertain levels of awareness among individuals with asthma, the original ATI was modified to include an additional uncertain response ('I don't know'), which

enabled the study to gauge the levels of awareness among the Saudi Arabian participants regarding the asthma triggers.

Phase two of Stage One involved the development of the initial version of the Saudi-ATI following the addition of the new Saudi triggers. Two independent certified professional translators translated the original ATI from English into Arabic. The Arabic translation was then reviewed by an expert panel (two respiratory physicians, two respiratory nurses, and one psychologist) to identify any misunderstandings or mistranslations of the original ATI questionnaire. In order to randomly select these professionals from the Pulmonary Medicine Department, the clerk from the pulmonary clinic clerk randomly selected the names from a hat. The head of the Pulmonary Clinic at KFMC was requested to assist in recruiting these individuals for the study (children with asthma and their parents attending the KFMC outpatient respiratory clinic).

The candidate discussed the questionnaire with the expert panel as a collective, at which time one trigger was determined to be superfluous (hypovitaminosis D, which was initially suggested) and therefore removed. The health professionals then endorsed the Saudi version of the ATI. There were no specific interview questions utilised, however, a discussion was formed around what triggers the panel thought were relevant and if the panel considered the Arabic translation to effectively convey the appropriate message from a medical and psychological perspective.

Following the final revisions of the questionnaire, it was back translated into English by two additional independent and certified professional translators who were not familiar with the original items. This allowed a comparison between the original ATI and the Saudi-ATI to determine the consistency in the meaning conveyed by the newly developed Saudi-ATI.

During phase three of stage one, 10 parents or guardians of asthmatic children were randomly recruited from the KFMC Pulmonary Clinic patient list to pilot the initial Saudi-ATI

questionnaire. This was achieved by utilising a random number generator the day before each clinic (one to eight, which was the total clinic patient load per day), and requesting that the correlated case be enrolled in the pilot study. All participants randomly selected throughout the recruitment process were agreeable to enrollment the pilot study.

This pilot focused on assessing the comprehension and ease of completion of the new Saudi-ATI questionnaire. The candidate interviewed each of the pilot study participants following going through the questionnaire. On interviewing the 10 participating pilot families, there were three simple questions asked of each parent: 1) *Did you find the questionnaires easy to read?* 2) *Did you find the questionnaire easy to complete?* 3) *Did you comprehend all of the questions such that you could answer definitively?* No changes were made to the Saudi-ATI following this pilot study, since the participants reported ease of use and satisfactory comprehension of the questionnaire.

3.4 Stage two: applying the Saudi ATI questionnaire

This stage involved identifying the prevalence of perceived asthma triggers and their associated determinants. The Saudi-ATI questionnaire was applied through a cross-sectional design to a sample population of 200 parents of asthmatic children enrolled from the Pulmonary Clinic at KFMC in Riyadh.

Utilising a random number generator from the Pulmonary Outpatient Clinic, at KFMC in Riyadh, booking list, two hundred (n=200) parents and children were randomly recruited to this study. This was achieved over a period of five months where the doctoral candidate via a phone call the day before the clinic contacted the correlated case be participated in this study. Eligible participants included children with physician-diagnosed asthma between the ages of 10 and 17 years who were receiving maintenance therapy and their accompanying parent. Parents were recruited into the study via a phone call the day before attending the Pulmonary Clinic at KFMC in Riyadh. Of those selected, only eight parents refused participation and a further

nine parents were not contactable. In the case whereby a patient and parent selected were not contactable, an additional randomised child and parent were selected from the same clinic date and contacted.

The Saudi Initiative for Asthma - 2016 Update: Guidelines for the diagnosis and management of asthma in adults and children were used to ensure that all children were diagnosed with asthma using the same criteria (Al-Moamary et al., 2016). This protocol includes a detailed history and physical examination supplemented by spirometry, with reversibility testing to support the diagnosis. The study applied this guideline because the protocol is accepted as a national standard for the diagnosis of asthma in the KSA.

Participants (children and their parents) underwent face-to-face interviews with the doctoral candidate, wherein the parents were asked to complete a set of three questionnaires: the Saudi ATI developed in stage one of this study, the Arabic version of the PACQOLQ (Revel and Baynouna, 2011), and the Arabic version of the Asthma Control Test (ACT) (Lababidi, Hijaoui, Zarzour, 2008), all of which are available within the appendices. Socio-demographic and clinical information was also collected during the interview process. Additionally, laboratory results, including spirometry and skin prick tests, were obtained from the medical records of each child, as this data was necessary for the validation of subscales and tests of association of the Saudi-ATI.

Demographic data, gender, age, weight, seasonal, and 24-hour patterns of symptoms, asthma-related healthcare use, medication, and parents' smoking history was collected from the participant children's medical files. Additionally, socioeconomic status, family history of asthma, education level, occupation, and family income were collected from parents or guardians during the interview process.

For the purpose of sample size calculations, smoking habits were used as the primary exposure, because smoking was identified as the most common asthma trigger in the KSA (Al-Dawood,

2001). Previous studies have demonstrated that about 24% of parents or guardians of asthmatic children smoke (Bener, Al-Frayh, & Al-Jawadi, 1991); additionally, asthma attacks appear in about 10% of children whose parents or guardians do not smoke (Bener, Al-Frayh, and Al-Jawadi, 1991). To detect an additional 20% increase in the proportion of triggering asthma attacks in smokers (from 10% to 30%), at 5% significance and 80% power, the study must recruit 168 participants (Dupont & Plummer, 2018). Accounting for 20% non-response or missing response, the study has established a sample size of 200 participants

Responses to asthma trigger questions were treated as both continuous variables (Likert scale) and dichotomous variables (yes or no). Normality of responses was assessed graphically and analytically. Categorical variables were described using frequency tables. Univariate comparisons were performed by t-tests and chi squared tests for continuous and categorical variables, respectively. Statistical significance was set at a p-value of at least 5%. Confidence intervals of 95% were provided for each point estimate. All analyses were performed in Stata version 14.

3.5 Stage three: Generation of a reliable and valid Arabic version of the ATI

Data collected in stage two was used to test the reliability and validity of the Saudi-ATI. This stage applied construct validity and criterion validity approaches. For construct validity, the PAQLQ and ACT questionnaires were used. For criterion validity, the allergy skin test was used. The sample size from the cross-sectional study in stage two (200 people) allowed the detection of a correlation coefficient of at least 0.175, with 5% significance and 80% power (Dupont and Plummer, 2018).

3.5.1 Reliability analysis

Reliability analysis of the Arabic version of the ATI questionnaire was conducted using inter-item, item total correlations, and the Cronbach's alpha was measured using the internal consistency of the subscale scores. The reported estimates of internal consistencies were the

item intercorrelation and the item-total correlation. A score of over 0.7 is commonly accepted for Cronbach's alpha (Bland and Altman, 1997).

3.5.2 Validity analysis

In this stage, construct validity and criterion validity approaches were applied. Construct validity was assessed utilising the PAQLQ and ACT questionnaires; to assess criterion validity, the allergy skin test was used. Specifically, criterion validity evaluated the association between the allergy subscale score and the results of skin prick allergy tests. Construct validity examined the associations between the scores of the subscales with disease severity, asthma control, and quality of life data collected during the tests and measurements. Pearson's coefficient and Spearman correlations analyses tests were used to assess the associations.

3.6 Ethical considerations

Informed consent was obtained from all parents or guardians before any study-related procedures were undertaken. Participants were made aware that participation was voluntary and that they could refuse or terminate participation at any time without providing a reason. Ethical approval was obtained from the Human Research Ethics Committee of Curtin University. Similarly, written approval was obtained from the KFMC ethic committee before data collection.

For methodological purposes, the participants were parents or guardians of children with asthma. Based on children's mental development, the age of 18 is regarded as the threshold of adulthood in many parts of the world. This threshold applies legislatively in the KSA and is recognised by the organisation of health services to children. Accordingly, the parents or guardians of the children whose asthma symptoms were being assessed provided consent.

4.0. CHAPTER FOUR: RESULTS

4.1 Stage one: Development of the Saudi ATI questionnaire

The original ATI had 32 items; seven KSA-specific items were added, resulting in 39 items in the entire survey. Six triggers were identified from the integrated literature review, which addressed the topic of paediatric and Middle Eastern asthma triggers, and a further trigger (food allergy) was included as a result of consultation with respiratory physicians at the KFMC.

Six well-documented asthma triggers specific to the KSA were adopted based on a thorough literature review and consultation with respiratory physicians at KFMC. These included the following: Arabic incense (Bakhour), black clouds, dust storms, hot and humid weather, cold and dry weather, and toxic pollution.

Bakhour is a type of incense that is burnt in Arabic households. It consists of numerous substances that vary based on region; however, common components include frankincense (resin produced by the *Boswellia* Genus of trees), sandalwood, and other aromatic woods, herbs, flowers, oils, and perfumes (Wahab & Mostafa, 2007). It has been shown to provoke asthma symptoms among children in Oman (Al-Rawas, Al-Maniri, & Al-Riyami, 2009).

Among the environmental triggers integrated into the Saudi-ATI are black cloud, hot and humid weather, cold and dry weather, and pollution. Black clouds are defined by Leitzell (2011) as intense pollution that darkens the sky in the form of threatening smog that elevates pollution levels to up to 10 times the recommended levels established by the WHO. Hot and humid temperatures and cold and dry temperatures represent either end of the desert climate spectrum in Saudi Arabia. Meanwhile, pollution refers to the sensorium of toxic pollution from oil refinery or vehicular traffic. As outlined in the literature review, all of these triggers have been identified within the literature to potentially exacerbate pre-existing asthma among the paediatric and adult populations.

An additional item, food allergy, was integrated into the Saudi ATI based on the recommendation of respiratory physicians consulted at the KFMC on the basis of patients' anecdotal reports of food sources as a possible trigger. Notably, while food allergies did not present as an asthma trigger in the literture search, Alqahtani, Asaad, Awadalla, & Mahfouz (2016) reported the consumption of eggs and vegetables to be associated with asthma.

To determine what trigger provoked each child's asthma symptoms, the Saudi-ATI prompted participants to outline how frequently each trigger exacerbated their asthma. The back-translated versions of the questionnaire were remarkably similar to the original English versions. After the back-translated versions were compared with the original English versions, two individual translators agreed that the words conveyed the same meaning as the original words and that the overall assessment was equal.

A group of 10 randomly selected parents of asthmatic children attending the Pulmonary Clinic at KFMC were asked to pilot the initial Saudi-ATI questionnaire to confirm parent comprehension and the ease of completion. All participants in the pilot study who responded to the Saudi ATI reported that all items of the Arabic version of the ATI were easy to understand; although feedback was requested from each participating parent or guardian, no feedback was provided regarding potential improvements. The final Arabic ATI consisted of 39 items and seven trigger type subscales, as presented in Appendix 1. No changes were implemented following the pilot study.

During the enrollment period, eight parents and children were disagreeable to participating in the study. As there was no significant follow up (point of car questionnaires), no parents or children where lost to follow up. Nine parents were selected from the outpatient clinic booking list and subsequently failed to respond to a request for enrolment.

Table 3. Major literature identifying the six asthma triggers incorporated into the Saudi-ATI.

Trigger identified	Region(s) of KSA and/or broader Middle East identified	Supportive evidence for inclusion
Dust storms	Kuwait, Qatar, Jordan, Egypt, KSA (Jizan)	Al-Rawas, Al-Maniri, & Al-Riyami (2009) Thalib & Al-Taiar (2012) Al Ghobain, Algazlan, & Oreibi (2018) Hasnain, Alqassim, Hasnain, & Al-Frayh (2016) Hussain, Farhana, & Alnasser (2018)
Weather (cold weather, hot weather, humidity)	Oman, KSA (Makkah, Jeddah, Al-Mashaer, Arafat, Mina, Aseer, Najran)	Hussain, Farhana, & Alnasser (2018) Al-Binali, Mahfouz, Al-Fifi, Naser, & Al-Gelban (2010) Al-Ghamdi, Akbar, Qari, Fathaldin, & Al-Rhashed (2003) Al-Rawas, Al-Maniri, & Al-Riyami (2009)
Allergens, including weed pollen, fungal spores, molds grass pollens, indoor and outdoor (aero)allergens [undefined], pollen grains, black cloud, and household chemicals.	KSA (Abha, Najran, Dammam, Riyadh and Taif), Kuwait, Palestine, Lebanon, Israel	Hasnain, Hasnain, & Al-Frayh (2018) Alqahtani, Asaad, Awadalla, & Mahfouz (2016) Alghadeer et al. (2015) Al-Mousawi et al. (2004) Bener, al-Jawadi, Ozkaragoz, & Anderson (1993) El-Sharif, Abdeen, Qasrawi, Moens & Nemery (2002) El Margoushy, El Nashar, Khairy, El Nashar, & Mohamad (2013) Hamam et al. (2015) Hasnain, Alqassim, Hasnain, & Al-Frayh (2016) Hussain, Farhana, & Alnasser (2018) Al-Rawas, Al-Maniri, & Al-Riyami (2009)
Animal and pet exposure	KSA (Abha, Najran, Dammam, Riyadh), Egypt, Kuwait, Jordan	Hussain, Farhana, & Alnasser (2018) Bener, al-Jawadi, Ozkaragoz, & Anderson (1993) Alqahtani, Asaad, Awadalla, & Mahfouz (2016) Hasnain, Hasnain, & Al-Frayh (2018)
Tobacco smoke	Kuwait, Egypt, Turkey, Saudi Arabia, Lebanon, Israel, UAE	Tarraf, Aydin, Mungan, Albader, Mahboub, Doble & El Hasnaoui (2018) El Margoushy, El Nashar, Khairy, El Nashar, & Mohamad (2013) Hamam, et al. (2015) Hussain, Farhana, & Alnasser (2018)
Exercise	KSA (Jazan, Najran)	Hussain, Farhana, & Alnasser (2018) Khawaji et al. (2017) Alqahtani, Asaad, Awadalla, & Mahfouz (2016)

Respiratory tract infections	Oman	Al-Rawas, Al-Maniri, & Al-Riyami (2009) Hussain, Farhana, & Alnasser (2018) Abdalla et al. (2016)
Medications	KSA, Kuwait, Lebanon, Israel	El Margoushy, El Nashar, Khairy, El Nashar, & Mohamad (2013) Al-Rawas, Al-Maniri, & Al-Riyami (2009)
Traffic pollution	KSA (Najran)	Alqahtani, Asaad, Awadalla, & Mahfouz (2016) El Margoushy, El Nashar, Khairy, El Nashar, & Mohamad (2013)
Burning wood	KSA (Najran)	Alqahtani, Asaad, Awadalla, & Mahfouz (2016) Abdalla et al. (2016)
Barkour	KSA	Al-Rawas, Al-Maniri, & Al-Riyami (2009) Abdalla et al. (2016)

4.2 Stage two: Applying the Saudi ATI questionnaire

4.2.1 Demographic characteristics of the study population

A randomly selected sample of parents and guardians of 200 children attending the KFMC Pulmonary Clinic completed the ATI. The majority of respondents were mothers (124, 62.0%), were under the age of 40 years (152, 76.0%), had received a graduate- or post-graduate-level education (159, 79.5%), and belonged to the middle-income group (96, 48%) (Table 4). Although most of the parents reported not smoking (136, 68%), most respondents (164, 82%) indicated that someone with whom they reside smokes at home, thereby predisposing their children to passive smoke inhalation. Over half of responding parents (108, 54%) reported a family history of asthma or atopy (e.g., hay fever or eczema). Of the children assessed, 147 (73.5%) were between 10 and 13 years of age, 116 (58%) were female, 86 (43%) were overweight (BMI=25-29.99 kg/m^2) or obese (BMI≥30 kg/m^2), and 114 (57%) had a normal BMI (BMI=18-24.99 kg/m^2). Note that specific triggers are italicised.

Table 4. Demographic characteristics of the sample of 200 parents and children attending the KFMC Outpatient Pulmonary Clinic.

DEMOGRAPHIC DATA		Frequency	Percent
Age	10 - 13 years	147	73.5%
	14 - 17 years	53	26.5%
Sex	Male	84	42.0%
	Female	116	58.0%
BMI	Healthy BMI (18.5-24.99 kg/m^2)	114	57.0%
	Overweight (25-29.99 kg/m^2)	47	23.5%
	Obese (≥30 kg/m^2)	39	19.5%
Parental age	20 -29 years	60	30.0%
	30 - 39 years	92	46.0%
	40 - 49 years	48	24.0%
Parental gender	Male	76	38.0%
	Female	124	62.0%

Parental education	Secondary level	41	20.5%
	Graduate level	134	67.0%
	Post-graduate level	25	12.5%
Income	Low-income group	60	30.0%
	Middle-income group	96	48.0%
	Higher-income group	44	22.0%
Have you ever smoked any form of tobacco or any other substance?	Yes	64	32.0%
	No	136	68.0%
Does anybody in the household smoke?	Yes	164	82.0%
	No	36	18.0%
Does anyone else have asthma or allergies in the family?	Yes	108	54.0%
	No	92	46.0%

4.2.2 Prevalence of asthma triggers based on the Saudi ATI

Of the seven newly integrated Saudi ATI triggers, Arabic incense (Bakhour) was reported as the most prevalent trigger, since 92 participants (46%) indicated that Bakhour typically triggers asthma exacerbations (Table 5). The next most frequent triggers of asthma exacerbations were psychogenic, including *being excited* (88, 44%), *stress at home* (84, 42%), *depressed mood* (84, 42%), and *arguments with people* (84, 42%); a significant portion of the sample responded that these typically act as triggers. Other highly frequent triggers included *animal allergens from bird feathers* (84, 42%) and *air pollution* due to *exhaust fumes* (80, 40%). All of the psychological triggers were observably linked with asthma exacerbations; approximately 40% of children reported suffering from asthma symptoms in response to psychological triggers most of the time, and roughly 45 to 50% reported 'sometimes' experiencing asthma exacerbations in response to these psychogenic triggers (Table 5).

Table 5. Prevalence of various asthma triggers according to the Saudi ATI among 200 Saudi children diagnosed with asthma at King Fahad Medical City, 2016.

		Asthma triggers		
ATI Subscales	**Trigger description**	**Sometimes**	**Most of the time**	**I don't know**
Psychological	**Being angry**	96 (48%)	**80 (40%)**	24 (12%)
	Feeling alone	104 (52%)	**80 (40%)**	16 (8%)
	Stress at home	92 (46%)	**84 (42%)**	24 (12%)
	Feeling tense	96 (48%)	76 (38%)	28 (14%)
	Depressed mood	88 (44%)	**84 (42%)**	28 (14%)
	Arguments with people	88 (44%)	**84 (42%)**	28 (14%)
	Being excited	100 (50%)	**88 (44%)**	12 (6%)
	Intense worries	96 (48%)	76 (38%)	28 (14%)
	Feeling unhappy	108 (54%)	48 (24%)	44 (22%)
	Feeling weak	96 (48%)	76 (38%)	28 (14%)
Animal allergens	**Animal hair**	92 (46%)	72 (36%)	36 (18%)
	Feathers from birds	92 (46%)	**84 (42%)**	24 (12%)
	Cat dander or fur	92 (46%)	72 (36%)	36 (18%)
Allergens (pollen)	**Pollen from grass**	100 (50%)	72 (36%)	28 (14%)
	Pollen from trees	88 (44%)	64 (32%)	48 (24%)
	Pollen from weeds	88 (44%)	72 (36%)	40 (20%)
	House dust	96 (48%)	64 (32%)	40 (20%)
Exercise	**Running**	88 (44%)	76 (38%)	36 (18%)
	Bicycle-riding	100 (50%)	76 (38%)	24 (12%)
	Climbing flights of stairs	100 (50%)	64 (32%)	36 (18%)
	Sports activities	112 (56%)	64 (32%)	24 (12%)
	Overexertion	100 (50%)	72 (36%)	28 (14%)
Air pollution	**Cigarette smoke**	92 (46%)	72 (36%)	36 (18%)
	Exhaust fumes	104 (52%)	**80 (40%)**	16 (8%)
	Certain intensive odours	104 (52%)	72 (36%)	24 (12%)
	Smell of paint	92 (46%)	68 (34%)	40 (20%)
	Sprays	96 (48%)	60 (30%)	44 (22%)
	Perfumes	112 (56%)	72 (36%)	16 (8%)
Infection	**Having a cold**	124 (62%)	56 (28%)	20 (10%)
	Flu	128 (64%)	68 (34%)	20 (10%)
	Sinus problems	120 (60%)	68 (34%)	12 (6%)
	Viruses	124 (62%)	48 (24%)	28 (14%)
Middle East Origin	**Arabian incense (Bakhour)**	92 (46%)	**92 (46%)**	16 (8%)
	Black cloud	100 (50%)	68 (34%)	32 (16%)
	Dust storms	100 (50%)	64 (32%)	36 (18%)
	Hot and humid weather	92 (46%)	68 (34%)	40 (20%)
	Cold, dry weather	100 (50%)	64 (32%)	36 (18%)
	Toxic pollution from oil refinery	80 (40%)	68 (34%)	52 (26%)
	Food allergy	104 (52%)	56 (28%)	40 (20%)

Bold Ξ Most prevalent triggers.

Depressed mood represented the most common trigger of asthma exacerbation (74, 37.0%), occurring across multiple sociodemographic characteristics (Table 6). Parental characteristics that were statistically associated with reports of depressed mood as an asthma trigger included the following: ages between 30 and 39 years (p=0.003), middle-income level (p=0.004), non-smoking status (p=0.03), and positive family history of asthma (p=0.02). Child characteristics that were associated with depressed mood as a reported trigger included aged between 10 and 13 years (p=0.002) and male sex (p=0.03).

Arguing with people was a commonly cited asthma trigger among children of male parents (40, 52.6%, p=0.003), high-income earners (24, 54.5%, p=0.003) and non-smokers (64, 47.1%, p=0.002). Among children, there was a statistically significant association between arguments with people as an asthma trigger and children between the ages of 10 and 13 years (p=0.04) and male (p=0.03). Meanwhile, stress at home was a statistically significant trigger among male children (p=0.003), male parents (p=0.002), parents earning a high income (p=0.002), and parents who did not smoke (p=0.002). Excitation as an asthma trigger was cited more commonly among younger parents between the ages of 20 and 29 years (28, 46.7%, p=0.04), and a statistically significant relationship was discovered between parents with a high income (p=0.03), non-smokers (p=0.003), and parents with a positive family history of asthma (p=0.004) (Table 6).

Bakhour (Arabian incense) was the only culturally specific environmental trigger added to the Saudi ATI and examined in this study. Bakhour was reported as an asthma trigger more commonly among low-income and non-smoking parents with no family history of asthma ($p \leq 0.01$).

Household income was significantly associated with the top five asthma triggers; higher income was associated with an increased probability of psychological triggers, and low income was significantly associated with Bakhour (Arabic incense). Parents were also more

likely to report asthma triggers such as stress, depressed mood, and arguments if their child was male. Meanwhile, active and passive smoking were not associated with most of the top asthma triggers. A significant relationship was observed between non-smoking parents in the children's homes and reports of Bakhour as a trigger (24, 66.7%), as well as stress at home (24, 66.7%) and depressed mood (28, 77.8%) (Table 6).

Parental education and BMI did not significantly affect asthma triggers. A significant association was noted between positive family history of asthma or allergies and excitement and depressed mood as asthma triggers, but not other triggers. Conversely, a negative family history of asthma or allergies was associated with increased reports of Bakhour as an asthma trigger.

Psychological triggers were commonly reported across all sociodemographic groupings (Table 6). Most parents reported psychological triggers of asthma in their children. While male parents were more likely to report psychological asthma triggers (44, 52.4%, p=0.003), most female parents did not believe psychological factors were a significant trigger of their children's asthma (52, 41.9%, p=0.17). Parents reported that animal allergens and plant pollen allergens were significant triggers of their children's asthma. This was particularly the case among children between the ages of 10 and 13 years: 59 (40.1%, p=0.002) parents reported animal allergens, and 59 (39.5%, p=0.003) reported plant pollen allergens as triggers. Both animal (36, 39.1%, p=0.003) and pollen (40, 43.5%, p=0.002) allergens were significantly more likely to be reported among parents between the ages of 30 and 39 years relative to parents between the ages of 20 and 29 years or 40 and 49 years. Similarly, male parents more commonly reported animal (32, 42.1%, p=0.003) and pollen (44, 57.9%, p=0.001) allergens as asthma triggers among children relative to female parents.

Table 6. Distribution of the five most prevalent triggers and sociodemographic characteristics.

SOCIODEMOGRAPHIC CHARACTERISTICS		Arabian incense (Bakhour)	Being excited	Stress at home	Depressed mood	Arguments with people
Age	10 - 13 years	69 (46.9%)	67 (45.6%)	65 (44.2%)	68 (46.3%)**	63 (42.9%)*
	14 - 17 years	23 (43.4%)	21 (39.6%)	19 (35.8%)	16 (30.2%)	21 (39.6%)
Sex	Male	44 (52.6%)	40 (47.6%)	36 (42.9%)**	40 (47.6%)*	40 (47.6%)*
	Female	48 (41.4%)	48 (41.4%)	48 (41.4%)	44 (37.9%)	44 (37.9%)
BMI	Normal	57 (50.0%)	47 (41.2%)	45 (39.5%)	48 (42.1%)	45 (39.5%)
	Overweight	19 (40.4%)	21 (44.7%)	17 (36.2%)	19 (40.4%)	19 (40.4%)
	Obese	16 (41.0%)	20 (51.3%)	22 (56.4%)	17 (43.6%)	20 (51.3%)
Parental age	20 -29 years	28 (46.7%)	28 (46.7%)*	28 (46.7%)	28 (46.7%)	28 (46.7%)
	30 - 39 years	44 (47.8%)	40 (43.5%)	40 (43.5%)	44 (47.8%)**	40 (43.5%)
	40 - 49 years	20 (41.7%)	20 (41.7%)	16 (33.3%)	12 (25.0%)	16 (33.3%)
Parental gender	Male	32 (42.1%)	36 (47.4%)	44 (57.9%)**	32 (42.1%)	40 52.6%)**
	Female	60 (48.4%)	52 (41.9%)	40 (32.3%)	52 (41.9%)	44 (35.5%)
Parental education	Secondary level	24 (58.5%)	15 (36.6%)	12 (29.3%)	19 (46.3%)	19 (46.3%)
	Graduate level	57 (42.5%)	59 (44.0%)	58 (43.3%)	55 (41.0%)	55 (41.0%)
	Post-graduate level	11 (44.0%)	14 (56.0%)	14 (56.0%)	10 (40.0%)	10 (40.0%)
Income	Low-income	36 (60.0%)**	16 (26.7%)	8 (13.3%)	20 (33.3%)	24 (40.0%)
	Middle-income	40 (41.7%)	48 (50.0%)	52 (54.2%)	44 (45.8%)**	40 (41.7%)
	Higher-income	16 (36.4%)	24 (54.5%) *	24 (54.5%) **	20 (45.5%)	24 54.5%)**
Have you ever smoked any form of tobacco or any other substance?	Yes	32 (50.0%)	16 (25.0%)	16 (25.0%)	24 (37.5%)	20 (31.2%)
	No	60 (44.1%)	72 (52.9%)**	68 (50.0%)**	60 (44.1%)*	64 47.1%)**
Does anybody in the household smoke?	Yes	68 (41.5%)	72 (43.9%)	60 (36.6%)	56 (34.1%)	68 (41.5%)
	No	24 (66.7%)**	16 (44.4%)	24 (66.7%)**	28 (77.8%)**	16 (44.4%)
Does anyone else have asthma or allergies in the family?	Yes	44 (40.7%)	64 (59.3%)**	52 (48.1%)	48 (44.4%)*	44 (40.7%)
	No	48 (52.2%)**	24 (26.1%)	32 (34.8%)	36 (39.1%)	40 (43.5%)

** Association significant at < 0.01, *Association significant at <0.05.

Parents reported that male children are more likely to experience asthma triggers in response to psychological events (44, 52.4%, p=0.002), air pollution (52, 61.9%, p=0.001), and infection (28, 33.3%, p=0.003). Overall, male children were reported to experience all triggers more commonly relative to females, with the exception of animal allergens, which were significantly more common among female children (48, 41.4%, p=0.03) relative to male children (24, 28.6%, p=0.18) (Table 7).

The grouped Saudi asthma triggers were observed to be more commonly associated with male children (33.3%, p=0.003) as opposed to female children (24.1%, p=0.009) (Table 7). Saudi triggers were more likely to be reported among parents of children at a middle-income level (32, 33.3%, p=0.03) and those with smokers in the household (48, 29.3%, p=0.002). Saudi triggers were not associated with children's age, parental BMI, parental sex, parental education level, parental smoking status, or positive family history of asthma or allergies.

Table 7: Associations between asthma triggers and characteristics of 200 Saudi parents and their children diagnosed with asthma at King Fahad Medical City in 2016.

DEMOGRAPHIC DATA		Psychological	Allergens (animal)	Allergens (Pollen)	Exercise	Air pollution	Infection	Saudi Triggers
Age	10-13 year	70 (47.6%)	59 (40.1%)**	58 (39.5%)**	68 (46.3%)	75 (51.0%)	43 (29.3%)	37 (25.2%)
	14-17 year	22 (41.5%)	13 (24.5%)	6 (11.3%)	28 (52.8%)	21 (39.6%)	17 (32.1%)	19 (35.8%)
Sex	Male	44 (52.4%)**	24 (28.6%)	28 (33.3%)	48 (57.1%)	52 (61.9%)**	28 (33.3%)**	28 (33.3%)*
	Female	48 (41.4%)	48 (41.4%)*	36 (31.0%)	48 (41.4%)	44 (37.9%)	32 (27.6%)	28 (24.1%)
BMI	Normal	52 (45.6%)	46 (40.4%)	32 (28.1%)	47 (41.2%)	62 (54.3%)*	40 (35.1%)	28 (24.6%)
	Overweight	18 (38.3%)	16 (34.0%)	17 (36.2%)	26 (55.3%)	17 (36.2%)	12 (25.5%)	18 (38.3%)
	Obese	22 (56.4%)	14 (35.9%)	15 (38.5%)	23 (59.0%)	17 (43.6%)	8 (20.5%)	10 (25.6%)
Parental age	20-29 year	32 (53.3%)**	20 (33.3%)	16 (26.7%)	32 (53.3%)	32 (53.3%)	12 (20.0%)	12 (20.0%)
	30-39 year	48 (52.2%)	36 (39.1%)**	40 (43.5%)**	44 (47.8%)	44 (47.8%)	28 (30.4%)	16 (17.4%)
	40-49 year	12 (25.0%)	16 (33.3%)	8 (16.7%)	44 (47.8%)	44 (47.8%)	44 (47.8%)	28 (58.3%)**
Parental gender	Male	40 (52.6%)*	32 (42.1%)**	44 (57.9%)**	28 (36.8%)	36 (47.4%)	16 (21.2%)	16 (21.1%)
	Female	52 (41.9%)	40 (32.3%)	20 (16.1%)	68 (54.8%)**	60 (48.4%)	44 (35.5%)*	40 (32.3%)
Parental education	Secondary	21 (51.2%)	15 (36.6%)	11 (26.8%)	14 (34.1%)	20 (48.8%)	15 (36.6%)	15 (36.6%)
	Graduate	59 (44.0%)	50 (37.3%)	44 (32.8%)	72 (53.7%)**	65 (48.5%)	39 (29.1%)	33 (24.6%)
	Post-	12 (48.0%)	7 (28.0%)	9 (36.0%)	10 (40.0%)	11 (44.0%)	6 (24.0%)	8 (32.0%)
Income	Low	20 (33.3%)	28 (46.7%)**	28 (46.7%)	32 (53.3%)	28 (46.7%)	24 (40.0%)*	16 (26.7%)
	Middle	40 (41.7%)	36 (37.5%)	20 (20.8%)	32 (33.3%)	48 (50.0%)**	20 (20.8%)	32 (33.3%)*
	Higher	32 (72.7%)**	8 (18.2%)	16 (36.4%)	32 (72.7%)**	20 (45.5%)	16 (36.4%)	8 (18.2%)
Have you ever smoked any form of tobacco or any other substance?	Yes	20 (31.3%)	36 (56.3%)*	16 (25.0%)	32 (50.0%)	32 (50.0%)	28 (43.8%)**	24 (37.5%)
	No	72 (52.9%)**	36 (26.5%)	48 (35.3%)	64 (47.1%)	64 (47.1%)	32 (23.5%)	32 (23.5%)
Does anybody in the household smoke?	Yes	64 (39.0%)	64 (39.0%)**	52 (31.7%)	76 (46.3%)	72 (43.9%)	44 (26.8%)	48(29.3%)**
	No	28 (77.8%)**	8 (22.2%)	12 (33.3%)	20 (55.6%)*	24 (66.7%)*	16 (44.4%)*	8 (22.2%)
Does anyone else have asthma or allergies in the family?	Yes	52 (48.1%)	24 (22.2%)	28 (25.9%)	56 (51.9%)	48 (44.4%)	32 (29.6%)	32 (29.6%)
	No	40 (43.5%)	48 (52.2%)**	36 (39.1%)	40 (43.5%)	48 (52.2%)**	28 (30.4%)	24 (26.1%)

4.3 Association between asthma symptomology and seasonal variance

Autumn and winter were associated with the highest frequency of asthma symptoms, with 82% and 80%, respectively, of participants reporting active symptoms during these seasons (Table 8). Summer was least likely to trigger asthma symptoms; only half (52%) of the participants experienced active symptoms.

Table 8. Association between the top five triggers in the KSA and seasonal asthma symptoms among children diagnosed with asthma at King Fahad Medical City in 2016.

SEASONAL DATA		Frequency	Percent
Autumn	Active	164	82%
	Inactive	36	18%
Winter	Active	160	80%
	Inactive	40	20%
Spring	Active	124	62%
	Inactive	76	38%
Summer	Active	104	52%
	Inactive	96	48%

Most respondents reported that their children experience active asthma symptoms as a result of *depressed mood* during all seasons (autumn: 72, 43.9%, p=0.02; winter: 68, 43.9%, p=0.02; spring 56, 45.2%, p=0.001) (Table 9). Arabic incense was a significant trigger during autumn (84, 51.2%, p=0.002) and spring (64, 51.6%, p=0.03) but not in other seasons. Conversely, excitement was a common trigger in spring (64, 51.5%, p=0.02) and summer (60, 57.7%, p=0.003); asthma symptoms during these seasons were frequently reported as active. Stress was the only trigger that increased during seasons when children were reported to exhibit inactive symptoms. Triggers among children reported to have inactive seasonal symptoms included the following: stress (24, 66.7, p=0.003) and arguments (28, 77.8%, p=0.001) during autumn, stress during winter (20. 50.0%, p=0.002) and spring (44, 57.9%, p=0.001), and depressed mood during summer (52, 54.2%, p=0.003).

Despite barely reaching statistical significance during autumn and spring, Arabian incense was the most frequently reported trigger in winter. Excitement was equally frequent as a trigger in winter and spring, as were arguments during spring. Similarly, excitement was the most frequently reported asthma trigger in summer.

Table 9. Associations between the top five triggers in Saudi Arabia with seasonal data among children diagnosed with asthma at King Fahad Medical City in 2016.

SEASONAL AND TOP FIVE TRIGGERS		Arabian incense (Bakhour)	Excitement	Stress at home	Depressed mood	Arguments with people
Autumn	Active	84 (51.2%)**	68 (41.5%)	60 (36.6%)	72 (43.9%)**	56 (34.1%)
	Inactive	8 (22.2%)	12 (33.3%)	24 (66.7%)**	12 (33.3%)	28 (77.8%)**
Winter	Active	72 (45.0%)	72 (45.0%)	64 (40.0%)	68 (42.5%)**	68 (42.5%)
	Inactive	20 (50.0%)	16 (40.0%)	20 (50.0%)**	16 (40.0%)	16 (40.0%)
Spring	Active	64 (51.6%)*	64 (51.6%)*	48 (38.7%)	56 (45.2%)**	64 (51.6%)**
	Inactive	28 (36.8%)	24 (31.6%)	44 (57.9%)**	28 (36.8%)	20 (26.3%)
Summer	Active	48 (46.2%)	60 (57.7%)**	40 (38.5%)	32 (30.8%)	44 (42.3%)
	Inactive	44 (45.8%)	40 (41.7%)	44 (45.8%)	52 (54.2%)**	40 (41.7%)

** Association significant at < 0.01, *Association significant at <0.05.

Autumn and spring were associated with the most triggers among children with active symptoms, as indicated above. Winter, however, did not correspond with a substantial number of triggers, despite being associated with the second highest rate of active symptoms. Pollen allergens were observed most frequently during autumn (60, 36.6%, p=0.003), spring (48, 38.7%, p=0.003), and summer (48, 46.2%, p=0.002), when active asthma symptoms were present (Table 10). Among participants who experienced active symptoms during autumn, animal allergens (64, 39.0%, p=0.03), exercise (84, 51.2%, p=0.003), air pollution (90, 54.9%, p=0.002), and infections (56, 34.1%, p=0.004) were significant asthma triggers. Likewise, animal allergens (52, 41.9%, p=0.003), pollen allergens (48, 38.7%,

p=0.003), exercise (64, 51.6%, p=0.002), air pollution (68, 54.8%, p=0.001), and infection (40, 32.3%, p=0.003) were all reported when asthma symptoms were present during spring. Animal (48, 46.2%, p=0.002) and pollen (32, 30.8%, p=0.003) allergens were the only asthma triggers reported during summer, in which asthma symptoms were active. Conversely, psychological (80, 50.0%, p=0.002) and Saudi-specific triggers (48, 30.0%, p=0.03) were reported during winter among children with active symptoms. Winter was the only season during which children were reported to have active asthma symptoms triggered by either psychological or Saudi-specific triggers. Two triggers were demonstrated to be statistically significant during seasons when participants reported inactive symptoms among their children: psychological triggers during autumn (24, 66.7%, p=0.001) and specific Saudi Arabian triggers during summer (32, 33.3%, p=0.003) (Table 10).

Triggers varied based on season are outlined in Tables 9 (top five) and 10 (subscales). Participants reported animal allergens most frequently during autumn (40.7%), winter (40.7%), and summer (55.6%) and the least frequently during spring (37.5%). In addition, pollen reactions were most common during summer (44.4%) and least common during spring (25.0%). Infections were associated with seasons and occurred most commonly during winter. Air pollution was a common trigger during all seasons aside from spring, which was associated with reduced reports of air pollution as a trigger among children with both active and inactive symptoms. In contrast, this occurred most frequently during autumn and summer.

Table 10. Association between asthma triggers and ATI subscales with seasonal data among children diagnosed with asthma at King Fahad Medical City in 2016.

Seasonal and ATI Subscales		Psychological	Allergens (animal)	Allergens (Pollen)	Exercise	Air pollution	Infection	Saudi Triggers
Autumn	Active	68 (41.5%)	64 (39.0%)*	60 (36.6%)**	84(51.2%)**	90 (54.9%)**	56 (34.1%)**	44 (26.8%)
	Inactive	24 (66.7%)**	8 (22.2%)	4 (11.1%)	12 (33.3%)	12 (33.3%)	4 (11.1%)	12 (33.3%)
Winter	Active	80 (50.0%)**	52 (32.5%)	48 (30.0%)	80 (50.0%)	76 (47.5%)	70 (43.8%)	48 (30.0%)**
	Inactive	12 (30.0%)	20 (50.0%)	16 (40.0%)	16 (40.0%)	20 (50.0%)	16 (40.0%)	8 (20.0%)
Spring	Active	64 (51.6%)	52 (41.9%)**	48 (38.7%)**	64(51.6%)**	68 (54.8%)**	40 (32.3%)**	36 (29.0%)

	Inactive	28 (36.8%)	20 (26.3%)	16 (21.1%)	32 (42.1%)	28 (36.8%)	20 (26.3%)	20 (26.3%)
Summer	Active	44 (42.3%)	48 (46.2%)**	32 (30.8%)**	48 (46.2%)	52 (50.0%)	24 (23.1%)	24 (23.1%)
	Inactive	48 (50.0%)	24 (25.0%)	4 (4.2%)	48 (50.0%)	44 (45.8%)	36 (37.5%)	32 (33.3%)**

** Association significant at < 0.01, *Association significant at <0.05.

4.4 Parental awareness of significant asthma triggers

The top four Saudi-specific triggers according to parents have been assessed in relation to lack of parental awareness and their distribution based on parental demographic characteristics. A lack of awareness about asthma triggers among parents was analysed utilising the 'I don't know' answer on the administered questionnaire. As Table 4 indicates, the four triggers associated with the highest frequency of lack of awareness in this sample were the following: toxic pollution from oil refineries (52, 26%), pollen from trees (48, 24%), unhappiness (44, 22%), and aerosol sprays (44, 22%).

As Table 8 illustrates, toxic pollution from oil refineries was not well understood as an asthma trigger among parents between the ages of 30 and 39 years (28, 30.4%, p=0.003), particularly among low-income parents (24, 40%, p=0.003) and those with no smoking history (40, 29.4%, p=0.004) or no family history of asthma or allergies (24, 26.1%, p=0.004). Male parents (28, 36.8%, p=0.003) between the ages of 30 and 39 years (28, 30.4%, p=0.003) were least aware of tree pollen as a trigger. Feeling unhappy was a frequently neglected trigger among parents; those with the least awareness of this trigger in autumn were younger parents between the ages of 20 and 29 years (20, 33.3%, p=0.003), those with secondary schooling as their highest level of educational attainment (11, 26.8%, p=0.004), higher-income parents (16, 36.4%, p=0.003), non-smokers (32, 23.5%, p=0.003), and parents with positive family histories of asthma or allergies (24, 22.2%, p=0.003). Low-income parents (16, 26.7%, p=0.03) and those with a negative family history of asthma or allergies (36, 39.1%, p=0.003) were most likely to be unaware of aerosol sprays as a potential asthma trigger (Table 11).

Table 11. Associations between the top Saudi asthma triggers and parental unawareness based on parental and child demographics

** Association significant at < 0.01, *Association significant at <0.05.

		Triggers			
		Toxic pollution from oil refinery	**Pollen from trees**	**Feeling unhappy**	**Sprays**
Parental gender	Male	20 (26.3%)	28 (36.8%)**	16 (21.1%)	12 (15.8%
	Female	32 (25.8%)	20 (16.1%)	28 (22.6%)	32 (25.8%)
Parental age	20 -29 years	4 (6.7%)	12 (20.0%)	20 (33.3%)**	16 (26.7%)
	30 - 39 years	36 (39.1%)**	28 (30.4%)**	24 (26.1%)	20 (21.7%)
	40 - 49 years	12 (25.0%)	8 (16.7%)	0 (0.0%)	8 (16.7%
Parental education	Secondary level	5 (12.2%)	10 (24.4%0	11 (26.8%)**	7 (17.0%)
	Graduate level	41 (30.6%)	33 (24.6%)	29 (21.6%)	33 (24.6%)
	Post-graduate level	6 (24.0%)	5 (20.0%)	4 (16.0%)	4 (16.0%)
Income	Low-income	24 (40.0%)**	16 (26.7%)	8 (13.3%)	16 (26.7%)*
	Middle-income	20 (20.8%)	24 (25.0%)	20 (20.8%)	20 (20.8%)
	Higher-income	8 (18.2%)	8 (18.2%)	16 (36.4%)**	8 (18.2%)
Have you ever smoked any form of tobacco or any other substance?	Yes	12 (18.8%)	20 (31.3%)	12 (18.8%)	16 (25.0%)
	No	40 (29.4%)**	28 (20.6%)	32 (23.5%)**	28 (20.6%)
Does anybody in the household smoke?	Yes	40 (24.4%)	40 (24.4%)	40 (24.4%)	40 (24.4%)
	No	12 (33.3%)	8 (22.2%)	4 (11.1%)	4 (11.1%)
Does anyone else have asthma or allergies in the family?	Yes	28 (25.9%)	28 (25.9%)	24 (22.2%)**	8 (7.4%)
	No	24 (26.1%)**	20 (21.7%)	20 (21.7%)	36 (39.1%)**

4.5 Parental mitigation and non-pharmacological control of asthma triggers

Table 12 shows the frequencies and percentages corresponding with sample respondents who reported symptomatic control of their children's asthma using non-pharmacological measures. 'Symptomatic control' refers to the ability of parents to circumvent the exacerbation of asthma symptoms by avoiding their children's key triggers. More than one-third (140, 70%) of parents reported a high degree of asthma control among their children, while 60 (30%) parents reported a poor degree of asthma control.

Table 12. Frequencies of respondents corresponding with whether asthma symptoms were controlled or uncontrolled.

Control	Frequency	Percent
Controlled	140	70.0%
Not controlled	60	30.0%
Total	200	100.0%

Of the top five triggers among Saudi-specific ATI items, Bakhour was associated with a high degree of controllability in relation to children who experience asthma symptoms (68, 48.6%, p=0.0002). Likewise, more parents believed that symptomatic control could be achieved among children who experienced depressed mood (64, 45.7%) and arguments (60, 42.9%) as asthma triggers. Conversely, more parents reported poor control in response to excitement (32, 53.3%) and stress at home (28, 46.7%) as triggers (Table 13).

Table 13. Degree of control among children reported to experience the five most common triggers in Saudi Arabia based on the newly integrated ATI items.

Control	Top five triggers				
	Arabian incense (Bakhour)	Excitement	Stress at home	Depressed mood	Arguments with people
Controlled	68 (48.6%)**	56 (40.0%)	56 (40.0%)	64 (45.7%)	60 (42.9%)
Not controlled	24 (40.0%)	32 (53.3%)	28 (46.7%)	20 (33.3%)	24 (40.0%)

4.6 Impact of asthma on quality of life (QOL) among children

Part two of the ATI assessed the impact of asthma on the daily lives of children as reported by parents. Approximately one-third of parents indicated that asthma symptoms exerted a severe impact on their children's life (68, 34.0%). The impact of the top five Arabic triggers was then assessed (Table 14). Among children whose quality of life was severely impacted by asthma, Arabian incense (Bakhour) was reported by 36 (52.9%, p=0.002) parents. Triggers associated with a mild impact on children's lives included excitement (60, 45.5%, p=0.003)

and arguments with people (60, 45.5%, p=0.003). Both stress at home and depressed mood were not statistically associated with either high or low impact on QOL (Table 14).

Table 14. Impact of asthma symptoms on children's quality of life according to parents.

Impact	Frequency	Percent
High impact	68	34.0%
Low impact	132	66.0%
Total	200	100.0%

Overall, the application of the Saudi ATI demonstrates Saudi Arabian asthmatic children's predisposition to symptom exacerbation in response to certain environmental triggers, such as Arabic incense (Bakhour) and exhaust fumes; it also indicates their predisposition to asthma exacerbations in response to psychological stimuli (excitement, arguments, depressed mood, stress, feeling alone, and anger). This was particularly the case among male children and male parents. Increased adverse triggers were observed among non-smokers and those who were not exposed to smoking in the home. Autumn and spring were associated with most of the top five triggers, regardless of whether symptoms were active or inactive at the time. Parental lack of awareness was associated with low-income earners, lower education levels, non-smokers, and those with a negative family history of asthma. Over two-thirds of the sample (70%) believed that their children's symptoms were controlled when the questionnaire was administered. Nonetheless, despite being the most commonly reported asthma trigger in this study, Bakhour was reported by parents as being the most controllable. The other four top triggers that were reported to be less controllable were psychological. Over one-third of parents reported that their children's asthma exerted a high impact on their overall quality of life. Despite being considered highly controllable by parents, Bakhour was reported as the having the highest impact on quality of life (Table 15).

Table 15. Life impact among children reported by parents in relation to the five most common Saudi-specific triggers of asthma symptoms.

Impact	Top five triggers				
	Arabian incense (Bakhour)	Excitement	Stress at home	Depressed mood	Arguments with people
High impact	36 (52.9%)**	28 (41.2%)	24 (35.3%)	32 (47.1%)	24 (35.3%)
Low impact	56 (42.4%)	60 (45.5%)**	60 (45.5%)	52 (39.4%)	60 (45.5%)**

** Association significant at < 0.01 *Association significant at <0.05

4.7 Stage three: Assessment of reliability and validity of the Saudi ATI

4.7.1 Analysis of reliability

The reliability of the Saudi ATI was assessed by inter-item, item total correlations, and internal consistencies (Cronbach's α) of the subscale scores. Table 16 presents the means, standard deviations, correlations, and internal consistencies of the trigger subscales for the children assessed in this sample. The internal consistencies (α) were generally high (> 0.70).

Table 16. Psychometric properties of the ATI subscales, including item means, inter-item correlations, item–total correlations, and internal consistencies.

Trigger subscale	No. of items	$Mean_i \pm SD_i$	r_{ii} (Mean)	r_{it} (Range)	α
Psychological	10	3.62 ± 0.11	0.72	0.63 - 0.82	0.95
Allergens (animal)	3	3.64 ± 0.08	0.78	0.67 - 0.89	0.95
Allergens (pollen)	3	3.60 ± 0.05	0.75	0.62 - 0.89	0.96
Exercise	5	3.57 ± 0.15	0.75	0.61 - 0.83	0.94
Air pollution	4	3.53 ± 0.06	0.74	0.65 - 0.80	0.92
Symptoms	4	3.28 ± 0.13	0.77	0.71 - 0.84	0.93
Middle East	8	3.50 ± 0.26	-0.01	-0.13 – 0.18	-0.11

Mi = item mean; SDi = item standard deviation; rii = item intercorrelation; rit = item-total correlation; α = Cronbach alpha

4.7.2 Analysis of validity

Construct validity was assessed by examining the correlation between ATI subscales and quality of life outcomes, as outlined in Table 17. The psychological (r = -0.307, p<0.001) and

exercise (r = -0.662, p<0.001) subscales were predictive of poor quality of life in relation to asthma. Significant positive correlations were observed between air pollution and Saudi triggers and quality of life (r = 0.222, p < 0.001 and r = 0.245, p <0.001 respectively). No correlations were observed between animal or pollen allergen-induced asthma symptoms and quality of life (r>0.001).

Table 17. Pearson's correlation coefficients between ATI subscales and paediatric quality of life outcomes based on the PAQLQ.

	Psych-ological	Animal allergens	Pollen	General allergens	Exercise	Air pollution	Infection	Middle East
p	-.307**	.100	-.013	-.018	-.662**	.222**	.047	.245**

** Correlation is significant at p <0.01.

An additional inverse association was identified between asthma control and both air pollution and infection. This indicates that higher reported asthma control is associated with a more limited effect of both air pollution and infection on asthma symptoms (Table 18).

Table 18. Associations between air pollution and infection on the level of asthma control among Saudi children.

Asthma control	Air pollution (Mean ± SD)	Infection (Mean ± SD)	P-value
Low	3.80 ± 1.30	3.50 ± 1.50	0.045*
High	2.98 ± 1.27	2.87 ± 0.82	

* Correlation is significant at p <0.05.

Skin test results were negatively correlated with all types of allergens (e.g., pollen from trees or grass and animal hair) (Table 19).

Table 19. Bivariate correlations (Spearman's test) between skin testing and allergens.

Correlations		Tree pollen	Grass pollen	Animal hair	Weed pollen	Bird feathers	Cats	House dust
Skin test	Correlation Coefficient	-0.67**	-0.53**	-0.56**	-0.635**	-0.65**	-0.66**	-0.60**

** Correlation is significant at p <0.01.

5.0. CHAPTER FIVE: DISCUSSION

5.1 Discussion

This study has identified numerous associations between both KSA-specific and universal asthma triggers and asthma symptom exacerbations within the population of children assessed using the first validated Saudi-specific Asthma Trigger Inventory (Saudi-ATI) instrument. Firstly, strong and significant associations were discovered between psychological triggers and asthma exacerbations. Notably, psychological triggers of asthma exacerbations were not exclusively associated with either positive psychological phenomena (e.g., happiness or excitement) or negative psychological phenomena (e.g., depression or stress), demonstrating that the presence of a psychological stimuli (positive or negative) can provoke asthma. Bakhour was the most apparent environmental asthma trigger reported in the population of children, and this trigger heavily impacted children's quality of life outcomes (impact on activities in their daily lives). The results also indicate that up to 30% of parents were unaware of these common asthma triggers; however, a positive correlation was observed between the frequency of the trigger and parental awareness.

5.2 Psychological stimuli as the most prevalent asthma triggers among Saudi children

The results indicate that, with the exception of the Arabian incense (Bakhour), asthma symptom exacerbation was most commonly related to the psychological state of the child. Psychological triggers such as *excitement* (44% most of the time), *stress* (42% most of the time), *depressed mood* (42% most of the time), and *arguments with others* (42% most of the time) were pivotal in triggering asthma symptoms among children. Increased bronchoconstriction as a result of psychogenic triggers has been observed in other studies (Isenberg, Lehrer, & Hochron, 1992). For instance, Isenberg, Lehrer, and Hochron (1992) determined that psychological triggers, such as *passive stress* and *embarrassment,* were clinically significant triggers among up to 40% of asthmatics. This study has identified a similar

prevalence of *stress-induced* asthma symptoms; however, not all asthmatics responded to psychological triggers in a homogenous manner. Indeed, these responses may be correlated with individuals' unique psychological makeup, which may modulate individual psychophysiological responses to psychological stimuli.

Several mechanisms strengthen the observed association between reportedly intensifying facets of upper-airway obstruction and associated symptoms and psychological stimuli. Other studies (Lehrer, Hochron, Mayne, Isenberg, & Lasoski, 1997; Nadal & Barnes, 1984; Van Lieshout & MacQueen, 2008; Ritz, & Steptoe, 2000; Kullowatz, Rosenfield, Dahme, Magnussen, Kanniess, & Ritz, 2008) have described pathological airway obstruction in response to psychogenic stimuli. Asthma symptomology is likely to be caused by multiple interrelated physiological responses to psychological stimuli. This may include the combined activation of respiratory, neural, and immunological pathways which collectively compromise the upper airway. The temporal pattern of neural activation following stressful stimuli has been demonstrated to begin with increased sympathetic tone, followed by a rebound increase in parasympathetic tone (Lehrer, Hochron, Mayne, Isenberg, & Lasoski, 1997). Psychological stimuli may increase sympathetic autonomic tone; alpha-adrenergic receptors respond by increasing bronchoconstriction, and beta-adrenergic receptors respond by facilitating bronchodilation (Nadal & Barnes, 1984). This interplay between psychological stimuli and neurophysiological responsivity partly explains the frequency of psychogenic triggers among the children in this study.

Various studies have demonstrated that bronchoconstriction among asthmatics is readily triggered by intense emotions (i.e., anxiety, stress depression, elation) and that both positive and negative emotions are correlated with reduced FEV_1 relative to neutral states (Ritz, & Steptoe, 2000; Kullowatz et al., 2008). Both positive and negative psychological states have been demonstrated to be positively correlated with worsening asthma symptoms among children. For instance, positive emotional stimuli such as *excitation* as an asthma trigger were

reported as frequently as negative stimuli such as *depressed mood* or *stress at home*. While the differences in responses between positive or negative psychogenic stimuli were not quantified (i.e., whether bronchoconstriction was worse between positively associated or negatively associated psychological stimuli), they occurred in similar frequencies throughout the sample population. Likewise, the degree of adverse effects caused by positive as opposed to negative psychogenic stimuli could not be distinguished, although negative psychological states have been observed to elicit more substantial decreases in pulmonary function relative to positive psychological states (Ritz & Steptoe, 2000).

Notably, chronic psychological influences may also determine the degree of asthma symptoms; therefore, chronic psychological factors must be distinguished from acute psychological triggers. For instance, there is a known psychophysiological relationship between psychiatric conditions such as major depressive disorder and asthma, including shared risk factors and pathogenic elements such as neuroendocrine, cytokine, and neuropeptide responses (Van Lieshout & MacQueen, 2008). A study conducted by Kullowatz et al. (2008) demonstrated that fraction of expired nitric oxide (FeNO), a measure of airway inflammation, and FEV_1 were associated with chronic and acute psychological stressors. The authors discovered a correlation between increased negative chronic psychological distress and intensifying FEV_1, but an inverse relationship between chronic daily psychological stress and FeNO. This study illustrated that FeNO results modulated the association between acute and chronic psychological triggers and changes in lung function. This indicates the potential role of psychological stressors in the degree of airway inflammation and not merely bronchial constriction, which suggests that psychological triggers are capable of producing the constellation of asthma symptoms observed in classical atopic or exercise-induced asthma.

Hyperventilation is another potential link between psychological triggers and asthma exacerbation. Psychological triggers were highly frequent and perceivable among this cohort of children relative to other triggers. A study published by Ritz et al. (2008) highlights that the

ATI explained only 13 to 37% of the variance in hyperventilation and hypocapnia symptoms; psychological triggers were responsible for 11 to 27% of the variance. Collectively, this study and the results outlined by Ritz et al. (2008) demonstrate that the sequelae of worsening asthma symptoms is partially explained by psychological factors.

The clinical impact of these findings is twofold: Firstly, as asthma is frequently triggered by psychogenic stimuli, psychotherapy may potentially contribute to management of asthma; secondly, asthmatic individuals are more susceptible to treatment failure or poor therapeutic adherence as a result of psychological factors. This study contributes to the evidence supporting the requirement for strategies to manage psychologically-induced asthma symptoms or worsening perceptions of asthma control among vulnerable asthmatic patients.

5.3 Bakhour as a frequent and controllable asthma trigger with a high impact on QOL

Of the seven newly integrated KSA-specific ATI triggers, Bakhour was the most prominent asthma trigger. Nearly half of the parents of asthmatic children surveyed (46%) reported that Bakhour caused asthma symptoms either sometimes or most of the time. Only 4% of the population did not believe that Bakhour ever triggered their child's asthma.

Bakhour is a traditional incense used in the Middle East which consists of charcoal, starch, karaya gum, aromatic chemical, plant woods, perfumes, and essential oils (Wahab & Mostafa, 2007). Evidence suggests that Bakhour exacerbates asthma symptoms in populations beyond Saudi Arabia as well. For instance, Al-Rawis, Al-Maniri, and Al-Raiyami (2009) examined 2,441 children with and without asthma in Oman and identified a three-fold overall increase in dyspnoea among those who used Bakhour (OR 3.01, 95% CI 2.23-4.08) and 2.55 times more breathing difficulty among asthmatic children relative to non-asthmatic children (OR 2.55, 95% CI 1.97-3.31). Additionally, 38% of asthmatics experienced intensifying wheeze in response to Bakhour. Wahab and Mostafa (2007) conducted a study that assessed Bakhour use in Qatar; they observed a statistically significant increase in

asthma attacks among atopic families. Notwithstanding the clinically evident adverse impact among asthmatic children, it remains unknown whether the physiological response to Bakhour and other Arabian incense variants is caused by allergenicity, irritation of hyperresponsive airways, or a combination of both.

This study has demonstrated a significant relationship between children who were not exposed to passive smoking and perceptions that the Arabic incense is a significant trigger. This finding conflicts with evidence which suggests that smoke exposure augments trigger responsiveness (Polosa et al., 2008). However, this result may represent an unconscious bias wherein non-smokers negatively associate smoke (tobacco, Bakhour, or otherwise) with their child's asthma.

Of all the highly prevalent triggers, Bakhour was the only trigger which was significantly associated with perceptions of increased symptoms among parents of children with no family history of asthma. A study conducted by Roorda, Gerritsen, Van Aalderen, and Knol (1992) analysed the correlation between positive family history of asthma and atopy and symptom progression among 406 asthmatic children. The authors discovered no correlation between positive family history or comorbid allergic conditions and the progression of asthma symptoms; they therefore concluded that environmental exposure and individual disease severity were more important prognostic factors.

5.4 Indoor triggers as prevalent causes of asthma exacerbations among Saudi children

In this study, house dust and tobacco smoke were reported as being triggers 'most of the time' by 32% and 36% of the sample, respectively. Meanwhile, asthma symptom exacerbation in response to animal allergen triggers was reported by 36% of the sample for animal hair and cat dander and 40% for bird feathers. Approximately one-third of the parents

also perceived a correlation between odours and intensifying asthma symptoms among their children.

Indoor asthma triggers are an important consideration in the Middle East, since people spend substantial time indoors to avoid extreme climatic variations and also because indoor environmental triggers tend to be more easily controllable (Wu & Tackaro, 2007; Krieger et al., 2014; Myatt, Minegishi, Allen, & MacIntosh, 2008). While this study is the first to demonstrate these triggers among asthmatic children in the KSA, causal relationships between these indoor triggers have been demonstrated by other studies (Morgan et al., 2011; Dales, Liu, Wheeler, & Gilbert, 2008; Gilmour, Jaakkola, London, Nel, & Rogers, 2006).

5.5 Sex-specific trends observed in asthma triggers of Saudi children

This study has indicated that allergens such as animal hair, cats, and bird feathers were frequent triggers among one-third of the children assessed; these triggers were statistically associated with asthma exacerbations among female children and children between the ages of 10 and 13 years ($p<0.01$). Similarly, other studies have reported that overall asthma symptoms occur more commonly among female children and children younger than 16 years of age (Zein and Erzurum, 2015; Mirabelli, Beavers, Chatterjee, & Moorman, 2013). Overall, females exhibit a higher prevalence and incidence of asthma and experience greater symptom severity (Zein and Erzurum, 2015). Following puberty onset, asthma increases in prevalence and severity among women but not among men; this illustrates a potential endocrinological influence in the pathological progression of asthma (Zein and Erzurum, 2015).

The link between age of onset and increased frequency of reporting responsivity to animal allergens among younger children could perhaps be explained by the fact that earlier onset asthma is typically associated with a stronger family history of atopy and previous sensitisation (Miranda, Busacker, Balzar, Trudeau, and Wenzel, 2004). While this study has

not demonstrated a significant association between children with a family history of asthma and animal allergens as a trigger, a significant association has been observed between negative family history and animal allergens as a trigger. Moreover, as postulated by Miranda, Busacker, Balzar, Trudeau, and Wenzel (2004), a significant association was discovered between asthma exacerbations in response to allergic triggers in the younger subset of children (10 to 13 years of age). A statistically significant relationship has also been observed between current or previous parental smoking and current household smoking (passive smoking) and animal allergens as a trigger. This may indicate that smoke inhalation and resultant airway irritation could augment responses to animal allergens as asthmatic triggers. These responses may be further augmented among females.

Strikingly, the results of this study have demonstrated a different trend among male children. As explained above, male children were significantly more likely to experience asthma exacerbations due to psychological triggers (males = 52.4%, $p<0.01$; females = 41.4%); all psychological subscale triggers were more commonly associated with male children, including triggers such as *stress* (42.9%, $p<0.01$), *depressed mood* (47.6%, $p<0.05$), and *arguments with others* (47.6%, $p<0.05$).

Unlike female children who demonstrated a predisposition to airway hyperresponsivness to atopic triggers, males children appeared to respond more to irritant triggers, such as Bakhour and air pollution. Bakhour was more frequently described as a trigger among male children relative to female children (52.6% as opposed to 41.4%); however, the reason for this disparity is unclear. KSA-specific triggers of asthma exacerbations were significantly more commonly associated with male children (33.3%, $p<0.05$) relative to female children (24.1%), according to parents. Meanwhile, male children reportedly experienced drastically more exacerbations in response to air pollution (61.9%, $p<0.01$) relative to female children (37.9%). Since smoking has been demonstrated to be associated with increased trigger reduction behaviours among parents compared to other triggers, the effect of Bakhour smoke can likely

be effectively mitigated or avoided, particularly in light of the triggers' high impact on the male children and (to a lesser degree) female children in this study (Cabana et al., 2004).

One could speculate that gender inequities in Saudi Arabia are a possible underlying explaination for the differences observed between genders, especially in relation to psychological triggers. As children are differentially socialised according to gender in the KSA this could modulate trigger perceptions or trigger-symptom responses.

5.6 Seasonal variance in asthma triggers and asthma symptom activity

Seasonal variations in asthma frequency and severity have been thoroughly recognised for centuries and have been reported prolifically across Australia, the US, and Europe during the past several decades (Derrick, 1972; Booth, Groot, Markush, & Horton, 1965; Salvaggio, Hasselblad, Seabury, and Heiderscheit, 1970; Ribon, Glasser, & Sudhivoraseth, 1972; Tromp, 1968; Khot, Evans, and Lenney, 1983). Nevertheless, no studies have reported seasonal variations in asthma symptom frequency in the KSA.

This study has demonstrated that asthma symptoms are the most active in autumn (82%) and winter (80%). *Depressed mood* and *excitation* were the most significant triggers among children during these seasons. In contrast, *excitation* was a trigger in spring and summer. *Stress* and *arguments* were the only triggers observed to exert a significant impact among children when their symptoms were inactive. Additionally, Bakhour was a significant trigger during autumn, but not winter. Sources of seasonal variation in asthma symptoms include the amount of allergens in the environment, the climate, seasonal paediatric illnesses, and behavioural and cultural elements.

Perhaps levels of allergen exposure are the clearest association between seasonal changes and asthma (Brito et al., 2007; Walker, Giovanni, Lima, Wilson, and Durham, 2001). The results this study align with the reported seasonal variations in allergen abundance. A statistically significant correlation has been observed between pollen and animal allergens

and asthma symptoms during autumn and spring. Several studies link increasing asthma symptoms with seasonal variations in allergic triggers, particularly pollens from grasses and trees (Brito et al., 2007; Walker, Giovanni, Lima, Wilson, and Durham, 2001; Subiza, 1994). For instance, Erbas et al. (2012) has demonstrated that seasonal pollen levels positively correlate with emergency department visits for asthma, independent of weather variation. Furthermore, immunotherapy is effective against seasonal allergic asthma (Kopp et al., 2009).

This study has also explored the impact of hot and cold temperatures on asthma symptoms; approximately one-third of patients describe increases in asthma symptoms among their children 'most of the time', and half describe hot and cold weather as an occasional trigger. Climatic variation can rapidly manifest symptoms in asthmatic children. This is particularly the case in thunderstorms, which are frequently discussed in the asthma literature (D'Amato, Liccardi, & Frenguelli, 2007; Davis, Thien, and Hew, 2018; Silver et al., 2018; D'Amato et al., 2016). Storms can mobilise dormant allergens, causing them to burst, and subsequently affect those with asthma by inducing '*thunderstorm asthma*' (Silver et al., 2018). Additionally, periods of high humidity have been proven to exacerbate obstructive symptoms and are predictive of asthma-related presentations to the emergency department (Silver et al., 2018).

The KSA has a desert climate; while humidity is high around coastal areas (85-100%), the relative humidity in Riyadh is comparatively lower (up to 47% in December-January and down to 10% in July). Nevertheless, temperatures tend to reach both extremes of the temperature spectrum throughout the seasons in Riyadh, from 0° degrees Celsius in Winter to over 50° Celsius in Summer (Tarawneh and Chowdhury, 2018). Additionally, environmental ambient temperature is an individual predictor of asthma exacerbations and is a pivotal pathological component in exercise-induced asthma (Soneja, Jiang, Upperman, Mitchell, and Sapkota, 2016; Del Giacco, Firinu, Bjermer, and Carlsen, 2015). Accordingly, temperatures may range between very cold (0° Celsius), which has been demonstrated to decrease pulmonary

function in the context of obstructive airway disease, and very warm (up to 50° Celsius), which can precipitate asthma symptoms (Donaldson, Seemungal, Jeffries, and Wedzicha, 1999; Wang and Lin, 2014). Prolonged exposure to elevated temperatures, as observed frequently in Saudi Arabia, is also associated with increased healthcare utilisation among those with obstructive respiratory disease (Wang and Lin, 2014).

The infection-related asthma exacerbations observed in this study were most pronounced during winter (43.8%). A relationship was also identified between infection and asthma exacerbations during autumn and spring among those who typically suffer active symptoms during these periods. The elevation of active asthma symptoms in winter is likely to be caused by more frequent viral illnesses, which often exacerbate comorbid asthma in the paediatric population (Silver et al., 2018; Beigelman and Bacharier, 2013). Over 60% of the participants in this study were aware that influenza, respiratory viruses, and other infections increase the likelihood of an asthma attack, which indicates its prevalence as a trigger. Infections during autumn and spring are likely to contribute to more intense active symptoms during these periods. Notably, while winter is most highly associated with viral and bacterial respiratory infections, infections remain a constant threat to all asthmatic individuals during all seasons.

Additional elements of seasonal variation in asthma triggers include behavioural, cultural, and psychological factors. A significant relationship has been observed between psychological triggers and asthma symptoms among those with active asthma symptoms during winter and inactive symptoms during autumn. Seasons are known to affect individual psychology (e.g., seasonal affective disorders), and pulmonary physiology is adversely affected by psychological stimuli (Tonello, 2008). Therefore, affective changes are likely to explain a proportion of exacerbations among the asthmatic children investigated; studies which have assessed the connection between seasonal variations in affective disorders and suicide among those with atopic disorders and asthma have illustrated an increased risk among this population during spring (Timonen et al., 2004). Similarly, the highest prevalence

of reported asthma exacerbations among symptomatic children in response to psychological triggers in this study occurred during spring. Subscale analysis of this study cohort also indicated a statistically significant correlation between *depressed mood* and asthma exacerbations throughout spring and autumn among symptomatic children.

Bakhour was associated with asthma exacerbations most frequently during autumn and spring. It is used throughout Riyadh as an adjunct to prayer and feasts and in the home for its fragrant properties. A study conducted by Al-Rawas, Al-Maniri, and Al-Riyami (2009) in Oman (*n*=2441) determined that Bakhour was used over two times per week among 58% of the sample and one or two times per week by 22.5% of the sample. While Bakhour was reported as a trigger slightly more frequently in some seasons relative to others, it was reported as a trigger by at least half of the sample population throughout all of the seasons. Clusters of cultural events during these seasons may explain the slight increases in asthma attacks in response to Bakhour.

5.7 Frequently reported triggers associated with higher parental awareness

Parents were most aware of the triggers that were frequently reported and less aware of triggers that were less frequently reported. Nonetheless, approximately 1 to 3 out of every 10 parents surveyed lacked awareness of common asthma triggers, including prevalent environmental triggers as well as triggers specific to the Middle East and the KSA. For example, Middle Eastern triggers, such as the hot and humid weather and toxic pollution from oil refineries, were associated with minimal parental awareness; one in five parents were unaware of these universal asthma triggers.

A paucity of data has been published concerning the degree of parental awareness of the triggers of asthma in children. The existing literature supports the results from this study which indicate that parents of children with asthma and individuals with asthma harbor a poor understanding of environmental asthma triggers and how they can be avoided to

improve asthma control (Cabana et al., 2004; Zhao et al., 2013; Göksel, Çelik, Erkekol, Güllü, Mungan, and Misirligil, 2009).

To achieve adequate asthma management and improve asthmatic children's outcomes, parental knowledge of asthma triggers is necessary (Janssens and Ritz, 2013; Zhao et al., 2013). The control of known environmental asthma triggers is an important self-management strategy (Lowe, & Mikita, 2005; Cabana et al., 2004). Among sensitised children, control of environmental triggers can mitigate the frequency and severity of asthma symptoms. Similarly, poor parental awareness can result in inappropriate management practices (Zhao et al. 2013). While some guidelines propose education concerning asthma triggers and preventative environmental modification measures such as those published by the National Asthma Council Australia (2015), this study indicates that Saudi children nevertheless remain exposed to environmental triggers.

The common lack of parental awareness of asthma triggers in this study correlates with the overall prevalence of uncontrolled asthma in the subset of parents assessed. This emphasises the significant role of a lack of parental awareness of environmental triggers and the level of asthma control achieved among their children. It also highlights the difficulty of controlling certain pervasive environmental triggers, such as exposure to pollens and toxic pollution from oil refineries.

Despite being reported as the most frequent group of triggers of asthma in this sample, 1 to 2 out of every 10 parents surveyed were unaware of psychological triggers of asthma. The psychological trigger of which parents were least aware was *feelings of unhappiness* (22%). However, knowledge of psychological triggers was high among parents who frequently reported asthma exacerbations as a result of this subscale trigger. Awareness of psychological triggers of asthma may be intimately linked to an unconscious reporting bias, when parents report this trigger more frequently as a result of their preconceptions.

According to Ritz, Bobb, and Griffiths (2014), psychological triggers of asthma have been linked to adverse asthma control. In the study conducted by Ritz, Bobb, and Griffiths (2014), triggers were discovered to be highly positively correlated with self-reports of asthma control and symptoms, but not pulmonary function. This indicates that while 80 to 90% of the sample who reported psychological triggers in this sample may perceive their children's asthma to be suboptimally controlled and may therefore be more likely to report adverse symptoms in response to psychological triggers. Alternatively, as outlined above, true positive psychological symptoms in the sample of children can alter respiratory physiology to provoke an asthma exacerbation.

Parents in this sample were more likely to be aware of triggers with a high frequency and impact (e.g., psychological triggers and Bakhour). In comparison, environmental triggers such as pollens, house dust, odours from paint and aerosol sprays, toxic pollution, hot and humid weather, and food allergies were less commonly reported and less likely to be known. This could be because of the limited ability of parents to recognise the association between more pervasive but less perceivable environmental triggers and their children's asthma symptoms. Conversely, perhaps the minimisation of symptoms in response to overt psychological triggers (i.e., an argument or a stressful event provoking an asthma attack at home) or the complete avoidance of burning Bakhour (i.e., avoiding burning the incense at home improves symptoms in their child) is more evident.

The correlation between the frequency of symptom reporting and parental awareness of it as a trigger highlights the crucial interplay between parental awareness and the controllability of asthma symptoms. This is particularly evident in relation to Bakhour, which can be avoided more seamlessly relative to other ubiquitous environmental triggers. Despite Bakhour being the most frequent asthma trigger and exerting a high impact on patient QOL, 16 parents (8%) reported being unaware of Bakhour as a trigger; approximately half (48.6%) of the sample believed that Bakhour was a satisfactorily controlled trigger. In other words,

lack of awareness could not explain the frequency or impact of Bakhour as an asthma trigger, which contradicts the reported effectiveness of parental interventions. This is supported by Cabana et al. (2004), who reported that 51% of parent's actions were unlikely to prevent or attenuate the impact of a specific asthma trigger.

Triggers perceived as more complex or difficult to avoid tended to be associated with lower control in this population. For example, cigarette smoke, which is both a common airway irritant and particularly difficult to eliminate or diminish in an environment, was demonstrated by Cabana et al. (2004) to correspond with action among only 7% of families. Moreover, one out of every four or five parents was unaware of allergic triggers; although not indicated in the results, parents described poor control over these triggers. Ritz, Kullowatz, Kanniess, Dahme, and Magnussen (2008) support this finding, reporting that allergic triggers are associated with lower overall control relative to non-allergic triggers. This is most likely a result of increasing complexity involved in implementing control strategies for these triggers, as well as the pervasive nature of the triggers themselves. This emphasises the importance of parental education for recognition and prevention of asthma triggers.

5.8 Reliability and validity of the Saudi ATI

One of the primary aims of this study was to validate the use of the Saudi ATI as a psychometrically validated measure of perceived asthma triggers in the KSA. It has assessed the reliability of the Saudi ATI utilising inter-item, item total correlations, and internal consistencies (Cronbach's α) of the subscale scores. Internal consistencies were generally high, at $\alpha > 0.90$, and there were high intercorrelations across all of the original major subscales. These outcomes align with those of other studies which have reported the reliability and validity of the original ATI (Ritz, Kullowatz, Kanniess, Dahme, and Magnussen, 2008; Ritz, Steptoe, Harris, and Edwards, 2006). The Middle Eastern triggers displayed more limited overall item intercorrelation (-0.01) and internal consistency (-0.11). However, the

inter-item correlation range was broad (-0.13 - 0.18), which indicates that some triggers may have been more related than others. Lower inter-item correlations were expected, since the Middle Eastern variables differ from pre-existing ATI subscales.

In this study, evidence supporting construct validity was illustrated by associations between subscale triggers and paediatric asthma-related quality of life (PAQLQ) scores. Both physical subscales, such as exercise ($r=-0.662$, $p<0.001$) and the psychological subscales ($r=-0.307$, $p<0.001$), were predictive of poor scores on the PAQLQ. The assessment of disease severity and asthma control demonstrated a significant inverse relationship between asthma control triggering of asthma symptoms in response to air pollution and infections ($p<0.05$). Among those with higher asthma control, air pollution and infections represented less significant triggers; however, among those who reported lower overall asthma control, both air pollution and infections were more significant triggers, which confirms construct validity. This aligns with the validity results reported by Ritz, Kullowatz, Kanniess, Dahme, and Magnussen (2008) and Ritz, Steptoe, Harris, and Edwards (2006), who assessed the original ATI.

Bivariate correlation (Spearman's test) between skin testing outcomes and reports of asthma symptoms triggered by general allergens confirmed criterion validity, thereby revealing that tree pollen (-0.67, $p<0.01$), grass pollen (-0.53, $p<0.01$), animal hair (-0.56, $p<0.01$), weed pollen (-0.64, $p<0.01$), bird feathers (-0.65, $p<0.01$), cats (-0.66, $p<0.01$), and house dust (-0.60, $p<0.01$) allergen scores of the ATI were significantly correlated with skin test results for relevant allergens.

5.9 Generalisability of these results to the broader KSA population

The ATI was completed by a random sample of parents of 200 asthmatic children (n=200) at KFMC. Of the parental respondents, there were more mothers than fathers; however, the division was sufficiently limited to accurately assess parental perceptions.

Most parents were below 40 years of age and highly educated. The former parallels the broader KSA population, in which most of the population is below 45 years old (General Authority for Statistics, 2016). Nonetheless, the level of educational attainment was higher in the sample relative to the KSA population despite an increasing proportion of Saudi nationals pursuing higher education (United Nations Educational, Scientific and Cultural Organisation, 2018). The increased relative level of the sample population is likely to favour appropriate reports of parental perceptions, increased parental awareness of asthma triggers, and enhanced ability to mitigate effects of triggers.

As expected, half of the sample belonged to the middle-income group. The survey was conducted in Riyadh, a metropolitan city where the average income is higher than in rural and remote regions of the KSA (General Authority for Statistics, 2013). Most of the parents reported being non-smokers, although most indicated that somebody smoked at home, which predisposed the children to secondhand smoke. This indicates probable passive smoke within the home environment and is consistent with the literature that suggests that smokers are highly prevalent in the KSA (Bassiony, 2009). Moreover, many pregnant women are exposed to passive smoking (over 50%) in the KSA, and 33% and 49% of adolescents are exposed to secondhand smoke inside and outside of the home, respectively (Al-Zalabani, Amer, Kasim, Alqabshawi, and Abdallah, 2015; Rashid and Rashid, 2003). Furthermore, an additional 25% are exposed to both indoor and outdoor smoke (Al-Zalabani, Amer, Kasim, Alqabshawi, and Abdallah, 2015). This indicates a high probability of ongoing second-hand smoke exposure within the paediatric population, as well as increased risk of asthma attacks, as illustrated by Moradi-Lakeh et al. (2013).

Over half of parents reported a positive family history of asthma or atopy (e.g., hay fever or eczema), which is consistent with the high risk of asthma among those with a family history of asthma (Paaso, Jaakkola, Lajunen, Hugg, and Jaakkola, 2013). A 20-year prospective study conducted by Paaso, Jaakkola, Lajunen, Hugg, and Jaakkola (2013) on 1,623 families in

Finland found that asthma risk was two to nearly four times greater among children with a positive family history of asthma. Moreover, it has been demonstrated that of all asthma risk factors, the most powerful determinant of lifetime asthma prevalence is a positive family history (Liu et al., 2009). Notwithstanding family history of asthma itself, atopic conditions such as allergic rhinitis or eczema are also significantly correlated with asthma (Al Ghobain, Algazlan, and Oreibi, 2018).

Four in every ten Saudi children (43%) whose parents responded to the questionnaire were overweight or obese (BMI≥25 kg/m^2). Notably, evidence suggests a potential link between asthma and obesity; although the mechanisms are poorly understood, overweight and obesity are associated with increased rates of asthma in Saudi Arabia as well as other countries (Moradi-Lakeh et al., 2013). Furthermore, evidence suggests that physical inactivity could contribute to the pathogenesis of asthma, independent of increased BMI (Lucas and Platts-Mills, 2006). As a result, a significant amount of research has demonstrated the benefits of exercise programs in improving pulmonary function among asthmatic children (Lucas and Platts-Mills, 2006). While the discussion of proposed mechanisms connecting increasing BMI to elevated risk of asthma is beyond the scope of this paper, it is imperative that over 40% of the paediatric population indirectly assessed in this study were either overweight or obese, and this could represent a potential upstream confounding variable.

5.10 Strengths

This study has several strengths. Firstly, this is the first study to successfully modify and confirm the validity and reliability of the Saudi-ATI, which incorporates novel asthma triggers specific to the KSA. Secondly, the demography of the sample population is representative of the broader population within the KSA, which demonstrates the significant generalisability of this study. Several strong statistically significant associations have been observed between

asthma triggers and demographic characteristics, which illustrates that these associations are most likely not merely due to chance. This is further supported by the successful confirmation of content and construct validity, particularly between objective skin-testing and reporting of allergic triggers.

The original ATI assesses various perceptions of physical, psychological, and environmental triggers. Seven triggers perceived to be specific to the KSA population were added to this. These included environmental triggers such as Arabic incense (Bakhour), black cloud, dust storms, hot and humid weather, cold and dry weather, and pollution from oil refineries, and food allergy. These asthma triggers are documented in the literature within the context of the Middle East (Al-Rawis, Al-Maniri, and Al-Raiyami, 2009).

5.11 Limitations

This study has several limitations. Firstly, the study was limited to descriptive and Chi-squared analysis due to the sample size. However, because Chi-square analysis is highly sensitive to sample size, the sample size obtained was intended to enable the detection of a correlation coefficient above 0.175 with confidence greater than or equal to 95% and power greater than or equal to 80% (168 participants and 20% allowance for incorrectly completed surveys responses). Further analysis using multivariate logistic regression would have been useful to predict causality and estimate relative risk due to trigger exposure. Nonetheless, chi-squared analysis suited the assessment of grouped observations among trigger subscales. Moreover, further analysis of interactive and synergistic effects would also be helpful to assess how specific aspects of asthma are altered due to trigger exposure and trigger interactions.

While the ATI has been demonstrated to be a valid and reliable test of perceptions related to asthma triggers, it relies strongly upon parental knowledge of asthma as a condition and its symptomatology. It also relies strongly upon the recall of signs and symptoms of asthma during the course of a year and in response to myriad triggers. The ATI does not allow for

scale construction for less common triggers of asthma to be assessed within the survey instrument. Of the newly assessed Saudi ATI items, some items did not display internal consistency and intercorrelations. Furthermore, a significantly positive association was observed between air pollution and Saudi triggers and the PAQLQ outcomes. Some associations could be partly formed due to the interaction between the Saudi trigger subscale and air pollution. The questionnaire cannot incorporate triggers which may be substantially impactful while being simultaneously under-perceived by the asthmatic individual. Moulds are an example of such a trigger; these have been demonstrated to be allergic yet barely recognisable as a trigger (Bobb et al., 2010). Similarly, the ATI cannot assess patient perceptions of triggers to which patients are not exposed but may be sensitive. Ultimately, however, the primary objective of this study was not to examine the comparative importance or impact of asthma triggers. Instead, the major aim was to investigate self-reported perceptions of triggers among parents and children in Saudi Arabia, including newly integrated country-specific triggers, to observe the results and psychometrically validate the Saudi-ATI instrument.

Parents in this study had higher levels of education than the general Saudi population. While this is likely to have strengthened the understanding of the requirements among participants within the study, it may also have inflated the level of awareness of asthma triggers observed in this study relative to the potential actual level of parental awareness in the general population.

This study did not incorporate the use of rescue bronchodilators as a confounding or indicative factor in the children's asthma outcomes. This is highly pertinent as 61% of children use one or more metered dose inhaler (Hammad et al., 2016). Further research in this area should explore rescue medication utilisation in association with should explore the reduction in asthma exacerbations in correlation with preventive medication use. The study was

designed to avoid interference by preventive medications by making the use of preventive medication an inclusion criterion.

Lastly because the study collected recalled information based on previous asthma exacerbatons potentially occurring a number of months earlier, there is likely to be a degree of recall bias present in the data examined. Further longitudinal studies with an increased frequency of follow up would facilitate more accurate recall, and mitigate the risk of recall bias in the sample.

6.0. CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions and recommendations

Asthma is a common, chronic, and often debilitating illness. In light of the increasing asthma prevalence in the KSA and globally, it has become imperative to identify extrinsic and intrinsic triggers and thereby prevent the exacerbation of asthma symptoms. This research has sought to develop an Arabic version of the Asthma Trigger Inventory (ATI), a valid scale used to assess asthma triggers, and apply the newly developed and validated Saudi ATI triggers to accomplish the following: a) examine the asthma triggers among 200 Saudi children, b) identify parents' levels of awareness about certain asthma triggers, c) identify the major determinants of perceived asthma triggers and their associated interrelationships, and d) assess the ability of the parents of the children to avoid asthma triggers and control asthma symptoms in the absence of pharmacological interventions. Lastly, as a result of the aforementioned outcomes, this research has also sought to confirm the reliability and validity of the Arabic version of the ATI questionnaire. Further validation of the Saudi-modified ATI questionnaire at other hospitals and regions within Saudi Arabia for generalizability.

A modified asthma trigger inventory (ATI) was constructed using country-specific triggers from the KSA to more accurately investigate asthma triggers among Saudi children. Several key patterns were identified among asthma triggers in the KSA using the newly developed and validated Saudi ATI. This research is the first to demonstrate that psychological stimuli are among the most frequent asthma triggers in Saudi Arabian children. In addition, this research highlights the high frequency of the Arabic incense Bakhour as an asthma trigger and as a threat to children's asthma-related quality of life. More importantly, this research identifies that Bakhour is a recognisable and controllable trigger among the parents of Saudi children and illustrates a high level of awareness and mitigative action to circumvent asthma exacerbations in response to Bakhour.

Additionally, this research demonstrates that the increased frequency of asthma triggers is typically associated with increased parental awareness of the trigger. However, awareness was not significantly associated with altered parental behaviours (i.e., trigger avoidance) as illustrated by asthma control outcomes. Numerous common environmental asthma triggers have also been identified, such as pollens and pollution, of which Saudi parents were less commonly aware, despite pollution being a salient industrial element in the country.

The results of this study illustrate that more robust and progressive public health strategies are necessary to facilitate community awareness of asthma triggers in Saudi Arabia, of their importance for asthma management and control among the paediatric population, and of actions that can mitigate asthma triggers in the unique context of Saudi Arabia. Education of parents regarding asthma triggers and how children's triggers can most effectively be avoided or minimised has been demonstrated to be crucial in the management of childhood asthma.

This research recommends that the Ministry of Health in Saudi Arabia should adopt and publicly disseminate clear and understandable national guidelines for asthma control that incorporate empirically validated strategies for identifying and mitigating asthma triggers. Such guidelines should address the country-specific and culturally specific triggers in Saudi Arabia, including the aforementioned psychological triggers and Bakhour. In relation to Bakhour and other sources of air contamination in Saudi Arabia, public health policy development to mitigate these highly impactful respiratory irritants is recommended. This is because Bakhour inhalation, while under-researched relative to tobacco smoke exposure, could represent a similarly significant risk factor for other respiratory diseases aside from asthma, as demonstrated in this study. Ultimately, this research contributes to the literature concerning asthma by offering the first insights into country-specific triggers in Saudi Arabia; it also highlights the need for public health actions directed at improving public and professional knowledge of asthma triggers to enhance paediatric asthma outcomes.

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7.0. Appendices

8.1. Appendix A - The validated Saudi Asthma Trigger Inventory (ATI) questionnaire (Arabic)

تبيان حول المؤثرات التي تزيد من حالة الربو

هناك أسباب مختلفة كثيرة لأعراض الربو وتختلف الحالات المسببة لأعراض الربو من شخص لآخر، نرجو التكرم بتوضيح أي الأسباب الموضحة في الجدول أدناه تسبب أعراض الربو لطفلك، نرجو أن تكون إجابتك بناء على تجربتك الشخصية وليس ما تعتقده مسبباً للربو لدى المريض. (المؤثرات أدناه أدت لإصابتي بالربو الرجاء عمل دائرة حول الرقم الذي في الغالب ينطبق عليك)

لأعلم	دائما	معظم الوقت	أحيانا	نادرا	لا يؤثر		
6	5	4	3	2	1	التعرض للبرد	1.
6	5	4	3	2	1	تدخين السجائر	2.
6	5	4	3	2	1	الجري	3.
6	5	4	3	2	1	عند الغضب	4.
6	5	4	3	2	1	لقاح الأشجار	5.
6	5	4	3	2	1	الشعور بالوحدة	6.
6	5	4	3	2	1	أدخنة العوادم	7.
6	5	4	3	2	1	ركوب الدراجة	8.
6	5	4	3	2	1	الإجهاد بالمنزل	9.
6	5	4	3	2	1	روائح مركزة معينة	10.
6	5	4	3	2	1	لقاح الحشائش	11.
6	5	4	3	2	1	الشعور بالتوتر	12.

6	5	4	3	2	1	تسلق السلالم	13.
6	5	4	3	2	1	الاكتئاب	14.
6	5	4	3	2	1	رائحة الطلاء	15.
6	5	4	3	2	1	النشاطات الرياضية	16.
6	5	4	3	2	1	العطور	17.
6	5	4	3	2	1	الجدل مع الناس	18.
6	5	4	3	2	1	الأنفلونزا	19.
6	5	4	3	2	1	مشاكل الجيوب الأنفية	20.
6	5	4	3	2	1	عند الانفعال	21.
6	5	4	3	2	1	المخاوف الشديدة	22.
6	5	4	3	2	1	الشعور بعدم السعادة	23.
6	5	4	3	2	1	شعر الحيوان	24.
6	5	4	3	2	1	الإجهاد الزائد	25.
6	5	4	3	2	1	الفيروسات	26.
6	5	4	3	2	1	الشعور بالضعف	27.
6	5	4	3	2	1	لقاح الأعشاب	28.
6	5	4	3	2	1	ريش الطيور	29.
6	5	4	3	2	1	الرزاز	30.
6	5	4	3	2	1	القطط	31.
6	5	4	3	2	1	غبار المنزل	32.

6	5	4	3	2	1	البخور العربي	33.
6	5	4	3	2	1	السحب السوداء	34.
6	5	4	3	2	1	العواصف الترابية	35.
6	5	4	3	2	1	الطقس الحار والرطب	36.
6	5	4	3	2	1	الطقس الجاف البارد	37.
6	5	4	3	2	1	التلوث السام	38.
6	5	4	3	2	1	حساسية الأطعمة	39.

رجاء التأكد من أنك رسمت دائرة حول إجابة واحدة لكل منبه

الرجاء كتابة أقوى المثيرات للربو لدى طفلك

أقوى المثيرات للربو لدى طفلي هي:

1.....

2.....

3 .....

4.....

5.....

6.....

الرجاء توضيح إلى أي مدى تؤثر تلك المثيرات على حياة طفلك اليومية:

هذه المثيرات توثر على حياة طفلي اليومية

أقوى المؤثرات

1.....	لا تؤثر	قليلاً	معتدل	كثير	تأثير قوي
2.....	0	1	2	3	4
3.....	0	1	2	3	4
4.....	0	1	2	3	4
5.....	0	1	2	3	4
6.....	0	1	2	3	4

الرجاء توضيح إلى أي مدى تستطيع السيطرة على هذه المؤثرات أو تجنبها في حياة طفلك اليومية بدون تناول علاج

(علاجات موسعات الشعب الهوائية أو مخففات الألم أو علاجات منقذة)

أستطيع السيطرة على هذا المؤثر

أقوى المؤثرات

1.....	لا تؤثر	قليلاً	معتدل	كثير جداً	تأثير قوي
2.....	0	1	2	3	4
3.....	0	1	2	3	4
4.....	0	1	2	3	4
5.....	0	1	2	3	4
6.....	0	1	2	3	4

8.2. Appendix B - The validated Saudi Asthma Trigger Inventory (ATI) questionnaire (English)

Saudi Arabia Asthma Trigger Inventory (Saudi ATI)

There are many different causes for asthmatic symptoms. Situations causing symptoms can vary considerably from one person to the other. Please indicate for each of the listed causes below how often they are involved when your child experience symptoms of asthma. Please base your answers on your *own personal experience, not* on what you think should lead to asthma for the typical patient.

The following things can trigger my asthma alone or in part: (for *each* trigger please circle the number that applies most to you)

	Never	Rarely	Sometimes	Most of the time	Always	I don't know
1. Having a cold	0	1	2	3	4	5
2. Cigarette smoke	0	1	2	3	4	5
3. Running	0	1	2	3	4	5
4. Being angry	0	1	2	3	4	5
5. Pollen from trees	0	1	2	3	4	5
6. Feeling alone	0	1	2	3	4	5
7. Exhaust fumes	0	1	2	3	4	5
8. Bicycle riding	0	1	2	3	4	5
9. Stress at home	0	1	2	3	4	5
10. Certain intensive odors	0	1	2	3	4	5
11. Pollen from grass	0	1	2	3	4	5
12. Feeling tense	0	1	2	3	4	5
13. Climbing flights of stairs	0	1	2	3	4	5
14. Depressed mood	0	1	2	3	4	5
15. Smell of paint	0	1	2	3	4	5
16. Sport activities	0	1	2	3	4	5
17. Perfumes	0	1	2	3	4	5
18. Arguments with people	0	1	2	3	4	5
19. Flu	0	1	2	3	4	5
20. Sinus problems	0	1	2	3	4	5
21. Being excited	0	1	2	3	4	5
22. Intense worries	0	1	2	3	4	5
23. Feeling unhappy	0	1	2	3	4	5
24. Animal hair	0	1	2	3	4	5
25. Overexertion	0	1	2	3	4	5
26. Viruses	0	1	2	3	4	5
27. Feeling weak	0	1	2	3	4	5
28. Pollen from weeds	0	1	2	3	4	5
29. Feathers from birds	0	1	2	3	4	5
30. Sprays	0	1	2	3	4	5
31. Cats	0	1	2	3	4	5
32. House dust	0	1	2	3	4	5
33. Arabian incense (bakhour)	0	1	2	3	4	5
34. Black Cloud	0	1	2	3	4	5
35. Dust storms	0	1	2	3	4	5
36. Hot and humid weather	0	1	2	3	4	5
37. Cold, dry weather	0	1	2	3	4	5
38. Toxic pollution from oil refinery	0	1	2	3	4	5
39. Food allergy	0	1	2	3	4	5

Please make sure you have circled *one* answer for *each* trigger.

Please list below up to six of the strongest triggers of your child asthma.
My strongest child asthma triggers are:

1.……
2.……
3.……
4.……
5.……
6.……

Please indicate below how much each of these triggers affects your child daily life:

This trigger affects my child daily life…

My Strongest Trigger	Not at All	Slightly	Moderately	Very Much	Completely
1. ….	0	1	2	3	4
2. ….	0	1	2	3	4
3. ….	0	1	2	3	4
4. ….	0	1	2	3	4
5. ….	0	1	2	3	4
6. ….	0	1	2	3	4

Please indicate below to what extent you are able to control or avoid each of these triggers in your child daily life without medication (bronchodilators, reliever or rescue medication):

I can control this trigger…

My Strongest Trigger	Not at All	Slightly	Moderately	Very Much	Completely
1. ….	0	1	2	3	4
2. ….	0	1	2	3	4
3. ….	0	1	2	3	4
4. ….	0	1	2	3	4
5. ….	0	1	2	3	4
6. ….	0	1	2	3	4

8.3. Appendix C – Sociodemographic data collection instrument

SOCIO-DEMOGRAPHIC QUESTIONNAIRE

*How old is your child (in years)?

*What is your child sex?

☐ Male ☐ Female

*What is your child Length?

*What is your child Weight?

*For each season of the year, to what extent does your child usually have asthma symptoms? (Mark an X for each season below)

	A lot	A little	None
Fall	☐	☐	☐
Winter	☐	☐	☐
Spring	☐	☐	☐
Summer	☐	☐	☐

Please check one box for each question where there are check boxes. If you do not wish to answer a question, please draw a line through it.

*EDUCATION

1. What is the highest level of education you have completed?

(Check one box)

a. Elementary, Intermediate & Secondary Level or less……☐

b. High school graduate ……☐

c. Some college/AA degree/Technical school training …… ☐

d. College graduate (BA or BS) ……☐

e. Graduate school degree: Master's or Doctorate degree (MD, PhD, JD) ……☐

* INCOME

5. What is your total combined family income for the past 12 months, from all sources, wages, public assistance/benefits, help from relatives, alimony, and so on?

If you don't know your exact income, please estimate.

(Check one box)

a. Less than SR 5,000 ……☐

b. SR 5,000 - SR19,999 ……☐

c. SR 20,000 – SR 49,999 ……☐

d. SR 50,000 - SR 99,999 ……☐

e. SR 100,000 - SR 149,999 ……☐

f. More than SR 150,000 ……☐

g. Don't know ……☐

h. Chose not to answer ……☐

* SMOKING STATUS

a. Have you ever smoked any form of tobacco or any other substance?

☐ Yes ☐ No

b. Does anybody in the household smoke?

☐ Yes ☐ No

*FAMILY ASTHMA HISTORY

a. Does anyone else have asthma or allergies in the family?

☐ Yes ☐ No

Thank you very much for completing this questionnaire.

8.4. Appendix D - Ethics Approval from Curtin University

MEMORANDUM

Curtin University

To:	Dr Helman Alfonso School of Public Health
CC:	
From	Prof Peter O'Leary, Chair HREC
Subject	Extension of approval Approval number: HR194/2015
Date	02-May-16

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for submitting a request to the Human Research Ethics Office to extend the approval for project:

HR194/2015 Identification and avoidance of asthma triggers in parents and/or guardians of children with asthma in the Saudi population' to 'Knowledge and Determinants of Asthma Triggers in Saudi Arabian Children'

The Human Research Ethics Office approves the extension of the project.

Your ethics approval for this project will now expire on 12-Oct-19

Please ensure that all data are stored in accordance with WAUSDA and Curtin University Policy.

Yours sincerely,

Professor Peter O'Leary
Chair, Human Research Ethics Committee

8.4. Appendix E - Ethics Approval from King Fahad Medical City

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

مدينة الملك فهد الطبية
King Fahad Medical City

IRB Registration Number with KACST, KSA: H-01-R-012
IRB Registration Number with OHRP/NIH, USA: IRB00008644
Approval Number Federal Wide Assurance NIH, USA: FWA00018774

October 5, 2015
IRB Log Number: 15-348E
Department: External
Category of Approval: EXEMPT

Dear Fahad Balharith,

I am pleased to inform you that your submission dated September 16, 2015 for the study titled '**Identification and avoidance of asthma triggers in parents and/or guardians of children with asthma in the Saudi population**' was reviewed and was approved. Please note that this approval is from the research ethics perspective only. You will still need to get permission from the head of department or unit in KFMC or an external institution to commence data collection.

We wish you well as you proceed with the study and request you to keep the IRB informed of the progress on a regular basis, using the IRB log number shown above.

Please be advised that regulations require that you submit a progress report on your research every 6 months. You are also required to submit any manuscript resulting from this research for approval by IRB before submission to journals for publication.

If you have any further questions feel free to contact me.

Sincerely yours,

Prof. Omar H. Kasule
Chairman Institutional Review Board--IRB.
King Fahad Medical City, Riyadh, KSA.
Tel: + 966 1 288 9999 Ext. 26913
E-mail: okasule@kfmc.med.sa

F M
Approved
05 OCT 2015
I R B

8.5. Appendix F - Consent forms utilised for this study (English)

Consent Form

Research Title: Development, Validation, and Application of a Questionnaire to Study Asthma Triggers among Saudi Arabian Children and Assessment of Parental Awareness

I have been informed of and understand the purpose of the study, by consenting I agree to take part in this research as outlined to me.

I understand that my participation in this study is voluntary and that I can withdraw from the study at any time without prejudice or negative consequences.

I have had adequate time to think about the study and have had the opportunity to ask questions.

Any information which might potentially identify me will not be used in published material.

Participant Details

Name (Printed): _____

Signature: _____

Date: _____

Principal Investigator Fahad Hamad Balharith
Research Supervisors
Dr Helman Alfonso
+61 892663707
Helman.Alfonso@curtin.edu.au

Dr Alison Reid
+61 8 9266 1361
Alison.Reid@curtin.edu.au

Curtin University Human Research Ethics Committee
c/- Office of Research and Development,
Curtin University, GPO Box U1987, Perth
+61 89266 9223
hrec@curtin.edu.au

8.6. Appendix F – Participant information statement and consent in Arabic

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH

King Fahad Medical City
مدينة الملك فهد الطبية
Riyadh, Kingdom of Saudi Arabia
المملكة العربية السعودية-الرياض

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH
أقرار بالموافقة على المشاركة في دراسة بحثية

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH	موافقة للمشاركة في البحث
Protocol Number: N/A	رقم الدراسة:
Name of Subject: ……	اسم المشار.....:
Medical Record Number: ……	رقم السجل الطبي.....:
Study Title: Identification and avoidance of asthma triggers in parents and/or guardians of children with asthma in Saudi population.	الربو مسببات تحديد وتجنب : الدراسة عنوان في الآباء و / أو الأوصياء على الأطفال الذين يعانون من الربو في الشعب السعودي
Principal Investigator: Fahad Hamad Balharith	فهد حمد بالحارث الباحث الرئيس :
Address: Curtin University. GPO Box U 1987 Perth Western Australia 6845	U البريد صندوق, بيرث جامعة كيرتن :العنوان بيرث أستراليا الغربية 19876845
Telephone: +61 (08) 9266 7863	رقم الهاتف+61 (08) 9266 7863 :
A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, and how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form and will be given a copy for your records. Throughout this consent form, "you" will refer to you or your child, as appropriate.	هذه محتويات فريق البحث من عضو لك سيشرح الإقرار هذا. عليك سيؤثر وكيف الدراسة ، والمخاطر والفوائد من المشاركة دراسة ال إجراءات . الرجاء المعلومات تسجيل الحفاظ على ية، وكيف تتخذ لك الأسئلة في طرح الكافي وقت تأخذ ال موافقة لا. وهذه الأمنت سنشارك كإذا ما ك قرار المشاركة ت قرر إذا. المستنيرة الموافقة تسمى التوقيع على هذا منك ، سيطلب الدراسة في هذه هذا. وطوال سوف تعطى نسخة الإقرار أو إلى إليك يشير سوف "أنت"، الإقرار الحفظ ، حسب الاقتضاء. كطفل
	الدراسة هذه جري تلماذا؟

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH

WHY IS THIS STUDY BEING DONE? This study will provide parents with a deeper understanding of asthma triggers, which will in turn stimulate strategies on how they can help their children avoid those specific triggers.	عن قدم أعمق ل هذه الدراسة تقديم الآباء والأمهات الربو، مما يؤدي بدوره إلى تحفيز مسببات استراتيجيات بشأن الكيفية التي يمكن أن مسببات المحفزة تساعد أطفالهم تجنب تلك ال.
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY? 200 people	• الدراسة ؟ هذه في عدد المشاركين سوف 200 شخص
WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY? You will be interviewed. You will also have the opportunity to implement steps that may improve your ability to manage and avoid asthma for your child.	في هذه الدراسة ؟ تشاركإذا ماذا سيحدث . الأسئلة من أقوم بإجابة على بعض سيتم سيكون لديك أيضا فرصة لتنفيذ الخطوات التي قد تحسن من قدرتك على إدارة وتجنب الربو لطفلك.
• **Study location:** King Fahad Medical City, Saudi Arabia	دراسة الموقع . مدينة الملك فهد الطبية
WHAT IS EXPECTED OF ME DURING THE STUDY? Only to participate freely and honestly in the interview process.	ما هو متوقع من خلال دراسة لي؟ فقط في المشاركة بحرية وبصدق في والإجابة عن الأسئلة المقابلة
HOW LONG WILL I BE IN THE STUDY? Approximately 1 hour.	ما هي مدة المشاركة في هذه الدراسة؟ حوالي ساعة واحدة
CAN I STOP BEING IN THE STUDY?	؟ المشاركةإنهاءهل أستطيع
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or you've decided to stop. He or she will tell you how to stop your participation safely. No one will try to get you to change your mind.	تقرر التوقف في أي وقت. أن نعم. يمكنك لي وضح قررت التوقف. إذا الطبيب فقط إخبر ملك مشاركتك بأمان. لا أحد سيحاول إنهاء لك كيفية رأيك على تغيير.

ARE THERE RISKS IF I STOP BEING IN THE STUDY? No. There are absolutely no risks.	**المشاركة في أنه يت إذا متوقع قد ل هناك مخاطر الدراسة ؟** هناك على الإطلاق أي مخاطر لي س.
WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? None. There are absolutely no risks or side effects.	**التي يمكن جانبية ال الآثار أوالمخاطر هي ما في الدراسة؟! من جراء المشاركة حدوثه** هناك على الإطلاق أي مخاطر أو آثار جانبية. لي س
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?	**في الدراسة ؟ قد شارك من المحتمل هناك فوائد**
Taking part in this study may or may not make your health better. While doctors hope intervention will be more effective than the standard (usual) treatment, there is no proof of this yet.	إلى يتؤدي في هذه الدراسة قد لا تكشاركم أن يكون الأطباء يأملون لكن. تكا حتمل ن التدخل أكثر فعالية من العلاج القياسي ولا يوجد دليل على ذلك حتى الآن. المعتاد.
WHAT OTHER OPTIONS ARE THERE? Instead of being in this study, you have these options: N/A	**الأخرى ما هي الخيارات؟** **لديك خيارات أخرى بدلا عن المشاركة في الدراسة:** يمكنك قبول او رفض الإشتراك في هذا البحث
WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?	**تعرضت للإصابة بسبب أنني ماذا يحدث لو في هذه الدراسة ؟ قد شاركالم**
It is important that you tell the person who conduct the interview with you if you feel that you have been injured because of taking part in this study. You can tell the primary investigator in person or call him at 0509010393. If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by KFMC, depending on a number of factors. KFMC and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board (IRB) at +966-1-288-9999 ext 7415.	الشخص الذي يجري المقابلة تكبلغ انمن المهم للإصابتعرضت كنت تظن انك قد إذامعك أن. يمكنك الدراسة في هذه تكشاركمبسببب على به الاتصال أو يا شخص أخص اي التبلغ في حال تعرضك للإصابة . 0509010393 سيقدم لك مدينة العلك والعلاج مجانا. سيكون ويتوقف ذلك على العلاج، تكاليف فعد الطبية مدينة العلك فعد عادة لا تقدمعدد من العوامل. أشكال أي شكل آخر من الدراسة ممول وأ الطبية التعويض عن الضرر. وللحصول على مزيد من الاتصال يمكنك الموضوع، المعلومات عن هذا المكتب المؤسسي استعراض المجلس (IRB) ب على الرقم +966-1-288-9999 ext 7415.

WHAT ARE THE COSTS OF TAKING PART IN THE STUDY?	وما هي تكاليف المشاركة في الدراسة ؟
You will not be charged for any study activities.	لن تتحمل أي من تكاليف الدراسة.
WILL I BE PAID FOR MY TAKING PART IN THIS STUDY?	هل سأتقاضى أجر نظير المشاركة في هذه الدراسة ؟
No. There is no payment made for taking part in this study.	لا. لن يكون هناك أجر.
WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?	هل سيتم الحفاظ على المعلومات الطبية الخاصة بي سرية ؟
We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.	سنبذل قصارى جهدنا للحفاظ على سرية المعلومات الشخصية الخاصة بك في سجلك الطبي. ومع ذلك، لا يمكننا ضمان السرية التامة. قد يتم الإفصاح عن معلوماتك الشخصية إذا كان ذلك مطلوبًا بموجب القانون. و الأمر اقتضى إذا تم نشر أو عرض نتائج هذه الدراسة في اجتماعات علمية، فلن يتم استخدام اسمك أو أي معلومات شخصية أخرى تعرف عنك.
WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?	ما هي حقوقي إذا وافقت على المشاركة في هذه الدراسة ؟
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you. Leaving the study will not affect your medical care. You can still get your medical care from KFMC.	المشاركة في هذه الدراسة هي اختيارك. لك الحرية في اختيار المشاركة أو لا. أو لا تشارك في هذه الدراسة. إذا قررت المشاركة في هذه الدراسة، فيمكنك الانسحاب في أي وقت. مهما كان قرارك، لن يكون هناك أي عقوبة أو تأثير سلبي عليك. ترك الدراسة لن يؤثر على الرعاية الطبية العادية التي تتلقاها من مدينة الملك فهد الطبية.
We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.	سوف نبلغك بأي معلومات جديدة أو تغييرات في الدراسة التي يمكن أن تؤثر على صحتك أو رغبتك في مواصلة الدراسة.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.	النتائج عن هذه الإصابة في حالة تحقيق , لن الإقرار بهذا في هذا الدراسة ، في طلب القانونية أيا من الحقوق التعويض.
WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?	**أو كانت لدي أي أسئلة بمن يمكنني الاتصال إذا مشاكل؟**
Before you agree to be in this study, you will talk to a study team member qualified to tell you about this study. You can ask questions about any aspect of the research. If you have further questions about the study, you may ask them at any time. You may call the primary investigator on 0509010393	هذه الدراسة المشاركة توافق على أن قبل دراسة فريق أعضاء إلى احد حديث سوف تتحدث، عن هذه الدراسة . لي يخبرك بين المزيد جانب أي حول الأسئلة تطرح أن يمكنك كان لديك المزيد من إذا من جوانب البحث. في يمكنك السؤال عن الدراسة ،الأسئلة الاتصال الباحث وقت. يمكنك أي 0509010393 الرئيس على الرقم

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH

CONSENT	موافقةإقرار بال
Subject:	المشارك
The research and procedures have been explained to me. I have been allowed to ask any questions I have at this time. I can ask any additional questions I may think of later. I may quit being in the study at any time without affecting my health care.	بان يلسمح و لي. والإجراءاتالبحث قد تم شرح ل اس أل أن في هذا الوقت. ويمكنني لذي سؤالأي س أل ا ويمكنني إنهاء في وقت لاحق. إضافية أسئلةأي يوثر ذلك وقت دون أي في الدراسة المشاركة في الحقدمة لي الصحيةالرعاية على .
I will receive a signed copy of this consent form.	الإقرار ذا موقعة من نسخةاحصل على س موافقة.بال
I agree to participate in this study. My agreement is voluntary. I do not have to sign this form if I do not want to be part of this research study.	على المشاركة في هذه الدراسة.أقر بالموافقة إنا التوقيع على إلى ولست بحاجة, قوعيطموافقتي الدراسة هذه في أريد المشاركة كنت لا إذا الإقرارهذا البحثية.
Subject Signature.....	المشارك:توقيع
Date.....	التاريخ
Time (AM ☐ PM ☐)	م☐الوقت ص ☐
Witness Signature.....	الشاهد:توقيع
Date.....	التاريخ
Time (AM ☐ PM ☐)	م☐الوقت ص ☐
Person Obtaining Consent:	م و ا ف ق ة : ال ع ل ى ال ح ا ص ل الشخص
I have explained the nature and purpose of the study and the risks involved. I have answered and will continue to answer questions to the best of my ability. I will give a signed copy of the consent form to the subject.	وما هاوالغرض من الدراسة طبيعةقد شرحت لي عوس أجيبأجبت قد وستطوي على يه من مخاطر. س أعطي قدر من استطاعتي على أفضل ال أس ئلة إلى المشارك الموافقة ب الإقرار من موقعةنسخة المذكور أعلاه.
Signature of Person Obtaining Consent.....	على الموافقةاصلتوقيع الشخص الح
Date.....	التاريخ
Time (AM☐ PM ☐)	م☐الوقت ص ☐
Principal Investigator: Fahad Hamad Balharith	فهد حمد بالحارثالباحث الرئيس :
Signature of Principal Investigator.....	توقيع الباحث الرئيسي

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH

Time (AM ☐ PM ☐)	الوقت ص☐ م☐

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH

[STOP! Do not use the following signature lines unless third party consent is being requested and has been.]	الثالثة إلى خطوط توقيع [قف! لا تستخدم إذا تم طلب موافقة طرف ثالث]
AND/OR:	و / أو :
Legally Authorized Representative.....	ممثل المخول قانونا ال
Date	تاريخ ال
Person Obtaining Consent.....	موافقة ال على ال حاصل الشخص
Date	تاريخ ال
OR	أو
The person being considered for this study is unable to consent for himself/herself because he/she is a minor. By signing below, you are giving your permission for your child to be included in this study.	موافقة ال قادر على بالدراسة غير العين الشخص أدناه، قاصر. من خلال التوقيع إن ابن نفسه لأنه / دراسة في هذه الذهاب ين من ك لطفل إذن ك تعطي أن ت
Parent or Legal Guardian----------	الأبوين أو الوصي قانونا----------
Date: / /	التاريخ: / /