Strathclyde institute of pharmacy and biomedical sciences

"Investigating asthma aetiology and remedies in Saudi Arabia and the UK: Assessing the impact of indoor air pollution and healthcare expertise on prescription expenses, within the realm of public health".

by

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Thesis submitted to the University of Strathclyde for

the degree of Doctor of Philosophy

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Declaration of Authenticity and Author's Rights

Dedication

"In the name of Allah, the most merciful, the most compassionate"

This thesis is dedicated to:

My kind parents,

My dearest wife, Hero

My beloved children,

My university

And

My country

Preface

This thesis presents a comprehensive exploration into the multifaceted aspects of asthma, particularly emphasizing the interplay between asthma and various environmental and societal factors, including the COVID-19 pandemic, indoor air pollution, and healthcare practices. The research is contextualized within the Kingdom of Saudi Arabia and the United Kingdom, providing a comparative perspective on global and regional healthcare challenges and responses.

Chapter 1: Introduction to the Thesis

The opening chapter sets the stage for the entire thesis by providing an in-depth overview of asthma. This section is meticulously structured to cover a broad spectrum of topics related to this chronic respiratory condition. It begins with a clear definition of asthma, laying the foundation for subsequent discussions. The chapter proceeds to delve into the epidemiology of asthma, providing a critical analysis of its prevalence and impact on different populations. This is followed by an exploration of the pathophysiology and causes of asthma, offering insights into the biological and environmental factors contributing to its development. The clinical picture and diagnosis of asthma are then comprehensively discussed, highlighting the symptoms and diagnostic procedures. Finally, the chapter concludes with a detailed examination of asthma treatment, encompassing various therapeutic approaches and management strategies.

Chapter 2: The Indoor Air Pollution and Childhood Asthma in the Kingdom of Saudi Arabia

The second chapter narrows the focus to the relationship between indoor air pollution and childhood asthma in the Kingdom of Saudi Arabia. This segment of the thesis commences with an introduction that sets the context for the research, followed by a justification of the study. The chapter adopts a systematic approach in its methodology, delineating the steps taken from identifying the research question to charting the data and reporting the results. The findings section presents a detailed analysis of the diagnosis of childhood asthma in relation to indoor pollution. The discussion synthesizes the findings, and the chapter concludes with remarks and recommendations for future studies, proposing a prospective cohort study.

Chapter 3: Knowledge, Attitude, and Practices of Primary Healthcare Providers in Makkah

Chapter three shifts the focus to the knowledge, attitude, and practices of primary healthcare providers in Makkah regarding the assessment and management of acute asthma. This segment begins with an introduction that outlines the objective of the study. The method section details the approach taken for the research, followed by a results and discussion section that interprets the findings.

Chapter 4: Prescription Pattern for Asthma Medications in the UK

In chapter four, the thesis transitions to an examination of the prescription patterns for asthma medications in the UK, covering a decade from 2011 to 2021. This analysis is particularly poignant in the context of the COVID-19 pandemic. The chapter begins with an introduction that sets the stage for a detailed discussion on the impact of the pandemic on asthma in the COVID era. The aims of the study are clearly outlined, followed by a comprehensive description of the methods used, including study design, data sources, and ethical considerations. The results section presents a thorough analysis of the prescription patterns.

Chapter 5: Impact of Lockdown During COVID-19 Pandemic on Asthma Medication Utilization in the UK

The fifth chapter addresses the impact of the COVID-19 lockdown on the utilization patterns of asthma medications in the UK. This chapter begins with an introduction that frames the study within the context of the pandemic's broader medical impacts, especially on asthma exacerbations and medication use. The methods section delineates the study design, data sources, and analysis approach. The results are then presented, followed by a comprehensive discussion that delves into the findings and their implications.

Conclusion

The thesis culminates with a set of references and appendices that supplement the research. The references section provides a comprehensive list of all the sources cited throughout the thesis, ensuring that the research is grounded in existing literature and scientific evidence. The appendices section includes supplementary materials that support the research findings, such as data tables, questionnaires, and additional analyses.

In summary, this thesis offers a holistic and nuanced examination of asthma, a condition that affects millions worldwide. By analyzing various factors such as indoor air pollution, healthcare practices, and the impact of the COVID-19 pandemic, the research provides valuable insights into the management and treatment of asthma. The comparative analysis between the Kingdom of Saudi Arabia and the United Kingdom offers a unique perspective on the global and regional dimensions of asthma, making this thesis a significant contribution to the field of public health.

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This journey has been a transformative experience, and the contributions of these individuals and institutions have been the cornerstone of my success.

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List of abbreviations

ACE2	Angiotensin-converting enzyme 2
AHR	Air way hyperresponsiveness
ALRI	Acute lower respiratory infections
APHEA	European Approach
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
ATS	American Thoracic Society
BC	Black carbon
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CFR	Case fatality rate
CO	Carbon
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CVD	Cardiovascular disease
DALYs	Disability Adjusted Life Years
DDD	Defined Daily Doses
ELISA	Enzyme-Linked Immunosorbent Assay
FeNO	Fractional-exhaled nitric oxide measurement
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GI	Gastrointestinal
GINA	Global initiative for asthma
H2S	Hydrogen sulfide
HAP	Household air pollution
HCHO	Formaldehyde
HD	Hemodialysis
HDMs	House dust mites
ICF	Informed Consent Form
ICS	inhaled corticosteroids
IgE	Immunoglobulin
KSA	Kingdom of Saudi Arabia
LABA	Long-Acting Beta 2 agonist
LABA-ICS	Long-acting beta agonists- inhaled corticosteroids combinations
LABAs	Long-acting beta2 agonists
LAMA	Long-acting muscarinic antagonists
LFI	Lateral flow immunoassay
LTRA	Leukotriene receptor antagonists
MABs	Monoclonal antibodies
MCs	Mast cell stabilizers
MYP	Med year population
NCD	Non-communicable disease

NCICAS	National Cooperative Inner-City Asthma Study
NHS	National Health Service
NMMAPS	National Mortality and Morbidity Air Pollution Studies
NO2	Nitrogen dioxide
NOx	Nitrogen oxides
OCS	Oral corticosteroids
PAHs	Polycyclic aromatic hydrocarbons
PCA	Prescription Cost Analysis
PCC	Population/ Concept/ Context
PHCCs	Primary healthcare centers
PHCs	Primary healthcare clinics
PICO	Population, Intervention, Comparator, and Outcome
PIS	Participant Information Sheet
PM	Particulate matter
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCEP	Royal Commission on Environmental Pollution
RDTs	Rapid diagnostic tests
RRR	Relative risk reduction
RT-PCR	Reverse-transcription polymerase chain reaction
Rα	Receptor alpha
SABA	Short acting beta agonists
SABAs	Short -Acting Beta2 –Agonists
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SINA	Saudi Initiative for Asthma
SO2	Sulfur dioxide
T	Temperature
TLC	Total lung capacity
URT	Upper respiratory tract
USEPA	USA Environment Protection Agency
WD	Wind direction
WHO	World Health Organization
WS	Wind speed

Chapter One: Introduction to the thesis

1. Asthma

1.1. Definition

Asthma is a persistent inflammatory condition affecting the air passages in the lungs, characterized by hypersensitivity and an excessive, reversible constriction of the airways triggered by factors like viruses, allergens, and physical activity. This leads to repeated instances of shortness of breath, wheezing, and a sensation of tightness in the chest. (Global Initiative for Asthma (GINA), 2022). These occurrences can either resolve on their own or be effectively managed with suitable treatments, including short-acting bronchodilators and inhaled corticosteroids. (Myers, 2008). Acute asthma exacerbation is the acute onset of asthma symptoms and deterioration in the expiratory flow of short duration. Asthma exacerbation can last for several minutes up to several hours; the symptoms may go away spontaneously or in response to urgent treatment (Global Initiative for Asthma (GINA), 2022).

1.2. Epidemiology

Asthma is a common non communicable global health problem affecting about 334 million people worldwide (Papi et al., 2018). The prevalence of asthma is estimated to be 15% to 20% in developed countries and around 2% to 4% in less developed countries, however, underdiagnosis may contribute to these low rates, (Enilari and Sinha, 2019, Dharmage et al., 2019). It is significantly more common in children representing the most common chronic disease of childhood (Dharmage et al., 2019, Trikamjee et al., 2022). Asthma usually coexists with other atopic disorders such as allergic rhinitis (Bourdin et al., 2009). In addition to the negative impact on quality of life and survival, treatment of asthma and COPD represent a huge burden on health care system. Factors (Table 1.1) that influence the risk of developing asthma can be divided into host factors and environmental factors (Global Initiative for Asthma (GINA), 2022).

Table 1.1. Factors influencing the development and expression of asthma.

Host factors	Environmental factors
Genetic (e.g., genes predisposing to atopy, airway hyperresponsiveness, airway inflammation)	Allergens: - Indoor: domestic mites, furred animals (e.g. dogs, cats, mice), cockroaches, fungi, molds, yeasts -Outdoor: pollen, molds
Obesity	Occupational sensitizers and allergens (e.g. flour, laboratory rodents, paints)
Gender	Infections (predominantly viral)
Microbiome	Stress and exercise
	Exposure to tobacco smoke: -Passive smoking -Active smoking
	Outdoor or indoor air pollution
	Diet
	Paracetamol (acetaminophen) use

1.3. Pathophysiology and causes

Asthma pathophysiology can be interpreted by interplay of genetic redisposition and environmental exposures (Subbarao et al., 2009). Lower airway inflammation result from an immune over response by T helper cells to external triggers such as pollens, dust, mold, viral infection, tobacco smoking and exercise which result in release of cytokines and interleukins such as IL-4, IL-5 promoting eosinophilic infiltration and production of Immunoglobulin E (IgE). IgE is responsible for the release of histamine and other inflammatory mediators causing bronchospasm and increased mucous secretion(Lemanske and Busse, 2010, Wenzel, 2012). The resultant airway obstruction causes symptoms of dyspnea, wheezes, and cough. Over time airway remodeling can occur due to epithelial hyperplasia, submucosal mucus glands and goblet cells hypertrophy, smooth muscle hypertrophy and hyperplasia and collagen deposition leading to more frequent and severe exacerbations (Mims, 2015).

1.4. Clinical picture and diagnosis

Patients having asthma reports episodic attacks of respiratory wheezing, shortness of breath, chest tightness, and cough. These symptoms vary over time in duration, frequency, and intensity (Mims, 2015). By clinical examination patients may have expiratory wheezing, swollen nasal mucosa and polyps, and atopic dermatitis.

However, patients may be completely free at time of clinical examination (Lemanske and Busse, 2010, Wenzel, 2012). Associated family history of atopic disease supports the diagnosis of asthma. Presence of a variable and significantly reversible expiratory airflow limitation, measured by spirometry or peak flow is essential to confirm the diagnosis of asthma (Global Initiative for Asthma (GINA), 2019). (Table 1.2)

Table 1.2 Signs of airflow limitation variability

Positive bronchodilator reversibility test
increase in forced expiratory volume in second 1 (FEV1) ≥12% and ≥200 mL from baseline 10-15 minutes after administrating 200-400 ug albuterol or equivalent. (More likely to be positive if bronchodilator is withheld before test: short acting beta agonist for at least 4 hours and long-acting beta agonist for at least 15 hours before test)
High variability in peak expiratory flow (highest of 3 readings) performed twice daily for 2 weeks
Average daily diurnal variability >10%
Significant increase in lung function after 4 weeks of anti-inflammatory treatment
Increase in FEV1 by ≥12% and ≥200 mL (or peak expiratory flow > 20%) from baseline
Positive exercise challenge test
Fall in FEV1 of > 10% and > 200 ml from baseline
Positive bronchial challenge test
Fall in FEV1 from baseline of > 20% with standard doses of methacholine of histamine or > 15% with standardized hyperventilation, hypertonic saline or mannitol
Excessive variation in lung function between visits
Variation in FEV1 of ≥12% and ≥200 mL

1.5. Treatment

Asthma treatment based on a stepwise approach, aims to achieve good symptom control, reduce future risk of asthma-associated mortality and exacerbations, and reduce ongoing airflow limitation (McCoy et al., 2006, Meltzer et al., 2011, Schatz et al., 2012). Table1.3 summarizes the risk factors of exacerbations, (Horak et al., 2016) while Table 1.4 lists the factor that increase the risk of asthma related-death according to Global Initiative for Asthma, 2021 (Global Initiative for Asthma (GINA), 2022).

Table 1.3 Risk factors of asthma exacerbations.

1	Having uncontrolled asthma symptoms
2	Inadequate medications
	Medical conditions such as: obesity, chronic rhinosinusitis, Gastroesophageal Reflux Disease (GERD), confirmed food allergy and pregnancy.
3	Exposures: smoking, allergen exposure if sensitized and air pollution.
4	Major psychological or socioeconomic problems.
5	Lung function
6	Ever intubated or in intensive care unit for asthma.
7	≥ 1 severe exacerbation in last 12 months.
8	Other tests in patients with Type 2 inflammation: blood eosinophils and elevated fractional concentration of exhaled nitric oxide (FeNO).

Table 1.4. Factors increasing the risk of asthma-related death.

1	A history of near-fatal asthma requiring intubation and mechanical ventilation.
2	Hospitalization or emergency care visit for asthma in the past year.
	Currently using or having recently stopped using oral corticosteroids.
3	Not currently using inhaled corticosteroids.
4	Over-use of Short -Acting Beta2 –Agonists (SABAs).
5	Poor adherence with ICS-containing medications and/or poor adherence with (or lack of) a written asthma action plan.
6	A history of psychiatric disease or psychosocial problems.
7	Food allergy in a patient with asthma.
8	Several comorbidities including pneumonia, diabetes and arrhythmias.

The Global Initiative for Asthma 2019 guidelines provide recommendations for asthma management organized into five steps correlating with symptoms severity(Global Initiative for Asthma (GINA), 2019). All patients should be assessed regarding modifiable risk factors and exacerbation triggers, such as smoking, medications (e.g., nonselective beta-blockers), allergens, gastroesophageal reflux, obesity related sleep-disordered, and anxiety (Global Initiative for Asthma (GINA), 2019). Management of Patients with asthma should be done in a stepwise approach, escalating or de-escalating medications according to symptom control, and number of exacerbations. Medication options include inhaled corticosteroids (ICS), long-acting beta2 agonists (LABAs), short-acting beta2 agonists (SABAs), leukotriene receptor antagonists (LTRA), and oral corticosteroids (OCS).

ICS represent the first-line treatment for majority of patients. ICS result in reduced decline in lung functions, exacerbations, hospitalizations and mortality (O'Byrne et al., 2017, O'Byrne et al., 2019). If the patient failed to control symptoms with ICS alone, adding LABAs with ICS is recommended (Myers, 2008). During acute exacerbations, combined ICS with formoterol (a LABA) is now preferred to SABA as rescue therapy. They are associated with 55% reduction in risk of exacerbations and 65% reduction in risk of hospitalization compared with using SABA alone as a reliever (Global Initiative for Asthma (GINA), 2022). SABA is no longer recommended alone for management of asthma in adults as regular use of SABA, even for 1–2 weeks, is associated with increased air way hyperresponsiveness (AHR), reduced bronchodilator effect, increased allergic response, increased eosinophils which can lead to a cycle encouraging overuse (Nwaru et al., 2020). In the meantime, Global initiative for asthma (GINA) has adopted two tracks for management of asthma in adults and adolescents (>12 years old) (track 1: controller and preferred reliver and track 2 : controller and alternative reliver). GINA recommend if Track 1 is not available due to lack of access or affordability, Track 2 treatment may be preferable, although less effective in reducing exacerbations (Global Initiative for Asthma (GINA), 2019). If track 2 options are also not available, taking ICS whenever SABA is taken may be preferable to LTRA or maintenance OCS because of concerns about efficacy and/or safety (Figure 1.1). As asthma progresses in severity, treatment should be continuous rather than when needed with an increase in doses. A long-acting muscarinic antagonist should be added. Blocking M2 receptors decrease bronchoconstriction, mucus secretion, inflammation, and airway remodeling (Muiser et al., 2022). With escalating treatment, physicians should ensure that the patient is correctly using the prescribed inhalers and avoiding asthma triggers. The choice of inhaler device and simplicity of use play an important role in maintaining adherence and ensure best care.

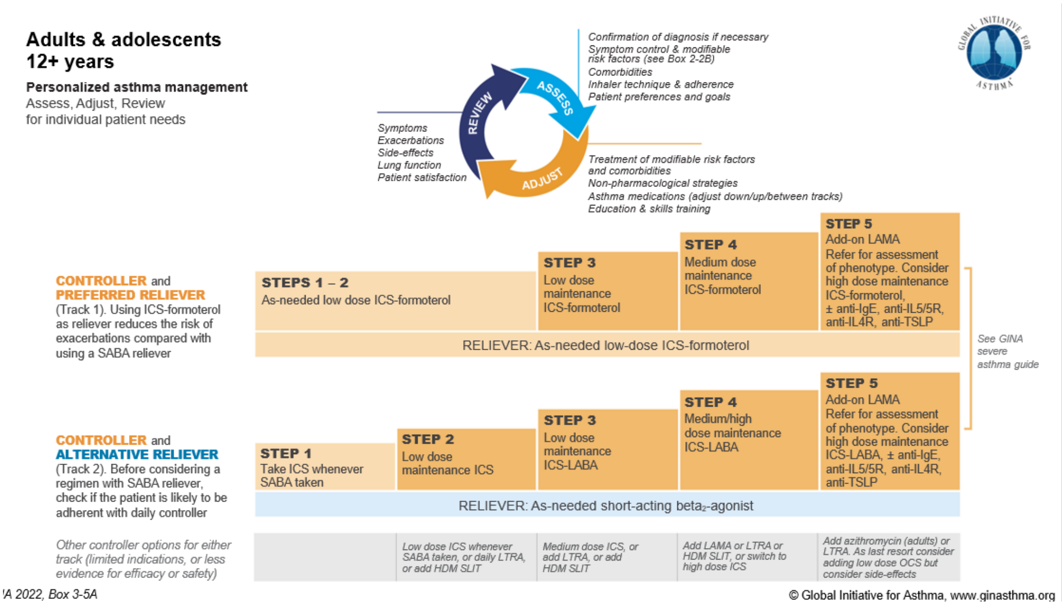


Figure (1.1): Stepwise approach for asthma management according to GINA guidelines 2019 (Reddel et al., 2019)

The 2017 NICE guideline for *Diagnosis, Monitoring and Chronic Asthma Management* (NG80)[1] is now being updated in a joint initiative with the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) NICE divides patients with asthma into three groups by age: 17 years and over, 5–16 years and under 5 years. It recommends reviewing patients 4-8 weeks after any adjustment, ICS use should be regular not intermittent . For newly diagnosed adults with minor symptoms, *SABA alone should be considered. If asthma was not controlled after 8 weeks, adding a maintenance low-dose ICS is recommended with* a SABA used for symptom relief. The next step is adding LTRA followed by regular use of LABA. The next options include increasing the dose of ICS then trialling a long-acting antimuscarinic (LAMA) or theophylline. For those aged 5 to 16-year, the same pathway is recommended except that LAMA is not an option,

The BTS/SIGN guideline classify patients using different age boundaries: over 12 years, 5 to 12 years and under five years. Briefly, adults are recommended to use as-required SABA first for those with infrequent, short-lived wheeze, then low-dose ICS, followed by add-on LABA as the next step then either an add-on LTRA or increasing the ICS dose. Specialist referral is the next step. It recommends use of an LTRA at an earlier stage in children.

GINA divides patients into 12 years and older, 6 to 11-year-olds and five years and younger. For the ≥12s, it no longer recommends SABA-only treatment, stating that there is no evidence that it is effective or safe. An as-required SABA increases the airways allergic response and inflammation and down-regulates beta receptors; high use increases the risk of emergency visits or hospitalizations and death.

GINA recommend for those aged 12 years and over begins with as-required low-dose ICS/LABA (Steps 1–2), moving to low-dose maintenance ICS/LABA (Step 3), then medium-dose maintenance ICS/LABA (Step 4), then adding a LAMA with referral for further assessment at Step 5. High-dose ICS/LABA, add-on azithromycin and biological therapy are further treatment options after specialist referral. Throughout, reliever therapy is a low-dose ICS/LABA.

Formoterol is the only LABA recommended by GINA as a part of ICS/LABA therapy due to the huge evidence from clinical trials using formoterol rather than other LABAs licensed for asthma (eg salmeterol, vilanterol).

An alternative pathway includes a SABA as reliever therapy at Step 1 (if symptoms occur less than twice a month) but a dose of ICS should be taken with every dose of SABA, with low-dose maintenance ICS recommended at Step 2 and low-dose maintenance ICS/LABA at Step 3.

For 6 to 11-year-olds, a SABA remains the initial reliever, but a dose of ICS should always be taken at the same time. In the under-5s, treatment starts with as-needed SABA, with daily low-dose ICS or daily LRTA at Step 2; the dose of ICS may be increased at Step 3, or a low-dose ICS taken together with a LTRA, but early referral to a specialist is recommended (at Step 3 or 4).

Biologic agents are humanized monoclonal antibodies (MABs) targeting inflammatory mediators implicated in the pathogenesis of asthma. They are now approved for treatment of severe asthma in children more than 6 years old. Omalizumab is anti-IgE, which is approved for severe allergic asthma (Gaspar-Marques et al., 2022). Anti-IL-5 (mepolizumab and reslizumab) and anti-IL-5 receptor alpha (Rα) (benralizumab) monoclonal antibodies are indicated for severe eosinophilic/type 2 asthma, they act by depletion of tissue and peripheral blood eosinophils (Gaspar-Marques et al., 2022). Dupilumab is anti-IL-4Rα which is also approved for treatment of severe eosinophilic/Type 2 asthma however, it is not used/indicated if blood eosinophils more than 1500/µl as Dupilumab is associated with an initial increase in blood eosinophils with a maximum increase occurring at approximately 16-20 weeks after starting therapy, and could result in eosinophilic pneumonia or vasculitis (Reddel et al., 2019). Tezepelumab, an anti-TSLP medication, has received approval for treating severe asthma in individuals aged 12 and older. Its clinical efficacy is notably enhanced in cases with elevated blood eosinophil counts and/or higher levels of fractional exhaled nitric oxide (FeNO).(Reddel et al., 2019)

2. Air pollution and asthma

2.1. Background

The UK Royal Commission on Environmental Pollution (RCEP) has defined pollution as "the introduction by man into the environment of substances or energy liable to cause a hazard to human health, harm to living resources and ecological systems, damage to structure or amenity or interference with legitimate use of the environment"(Ghorani-Azam et al., 2016). While the USA Environment Protection Agency (USEPA) has defined the term as "the presence of contaminants or pollutant substances in the air that interfere with human health or welfare or produce other harmful environmental effects". Both definitions agree on the harm air pollution causes to human health (Ghorani-Azam et al., 2016).

The World Health Organization (WHO) has produced some compelling scientific evidence to support the argument that exposure to air pollutants either individually or combined have severe health effects that can be acute or chronic (World Health Organization (WHO), 2002, World Health Organization (WHO), 2005). (World Health Organization (WHO), 2018). These health problems depend on the exposure duration, frequency and also the type and size of the pollutants. (World Health Organization (WHO), 2006).

Studies revealed that even slight daily variations in exposure to particulate matter pollution (measured as PM10 and PM2.5) have a detrimental impact on respiratory and cardiovascular (CV) mortality (Brunekreef, 2010) especially in infants and children (Autrup, 2010),(Ashmore and Dimitroulopoulou, 2009).

2.2. Indoor air pollution: The health impact

Both indoor and outdoor air pollution are the main factors contributing to asthma, specifically in children. Indoor air pollutants include sulfur dioxide (SO_2), nitrogen dioxide (NO_2), hydrogen sulfide (H_2S), formaldehyde (HCHO), carbon monoxide (CO), and particulate matter (Breysse et al., 2005, Oliveira et al., 2019, Pérez-Padilla et al., 2010, Sweileh et al., 2018). The study by Yeats et al. has shown that exposure to excessive levels of SO2, NO2, and H2S had a twice risk to suffer from Asthma (Yeatts et al., 2012). Exposure to higher-than-normal levels of HCHO was associated with neurologic abnormalities such as difficulty concentrating. People living in houses where incense was regularly burnt had suffered from higher incidents of headaches, difficulty concentration and remembering things (Yeatts et al., 2012, Al Frayh et al., 2001, Hijazi et al., 1998, Jie et al., 2013). House Mites (family Pyroglyphidae) were established many years ago as an essential source of house dust allergens. Exposure to indoor allergens such as House dust mites (HDMs) contributes to asthma symptoms, allergic rhinitis, and atopic dermatitis(Al Frayh et al., 2001). Burning mosquito coils can lead to health issues such as irritation of the bronchi, respiratory problems like coughing and asthma, and irritation of the eyes. (Liu et al., 2007, Pauluhn and Mohr, 2006). Moreover, the smoke emitted by kerosene lamps, often used for illumination, is significantly high in black carbon (BC) and is linked to tuberculosis. The link between the smoke emitted by kerosene lamps and tuberculosis is rooted in the presence of black carbon (BC) within the smoke. Black carbon, a component of fine particulate matter, is released during inefficient combustion of fuels like kerosene. Prolonged exposure to high levels of black carbon, particularly in poorly ventilated indoor environments where kerosene lamps are often used, can lead to respiratory issues. Black carbon particles are small enough to penetrate deep into the lungs, causing inflammation and impairing the immune system's ability to combat infections (Pokhrel et al., 2010) For instance, the smoke produced by burning a coil, which is utilized by around 2 billion people worldwide, may have particulate matter (PM2.5) levels equivalent to roughly 137 cigarettes. This smoke also contains cancer-causing substances, including polycyclic aromatic hydrocarbons (PAHs) and formaldehyde. (Liu et al., 2007, Pauluhn and Mohr, 2006).

Prolonged exposure to air particles resulting from cooking with solid fuels is linked to a rise in conditions such as chronic obstructive pulmonary disease (COPD), acute lower respiratory infections (ALRI), cardiovascular disease, tuberculosis, higher rates of infant mortality, and lung cancer. (Liu et al., 2007, Lee et al., 2015, Sinha et al., 2019).

Household air pollution (HAP), a major contributor to the worldwide prevalence of asthma, has been predominantly examined for the harmful effects of particulate matter, particularly fine particles less than 2.5 microns in size (PM2.5). These particles can infiltrate deep into the bronchial and lung tissue, causing oxidative damage that leads to inflammation and lung damage. However, specific components of PM2.5, like black carbon (BC), are also critical in impacting human health. Recent reviews of epidemiological studies on BC's health effects suggest that: 1) BC might pose greater health risks than other PM2.5 components, and 2) BC has been linked to various respiratory issues, including acute and chronic bronchitis, as well as asthma.

(Liu et al., 2007, Pauluhn and Mohr, 2006, Lee et al., 2015, Spira-Cohen et al., 2011, Zhang et al., 2010).

2.3. Indoor air pollution: The global burden.

Almost 3 billion people worldwide rely on solid fuels such as wood, charcoal, and animal dung for all their domestic needs (Legros et al., 2009, Lim et al., 2012). Estimates show that household Air Pollution is the cause of the second highest risk factor of diseases in sub-Saharan Africa and the fourth risk factor throughout the world, leading to 3.9 million deaths and 4.8% of disabilities across the world, based on the Disability

Adjusted Life Years (DALYs) (Smith et al., 2014). Harmful emissions and particulate matter, as well as carbon monoxide, oxygenated and chlorinated organics, hydrocarbon free radicals, black carbon and other substances, are released due to the inefficient burning of fuels using traditional stoves (Bruce et al., 2000, Von Schirnding et al., 2002).

Women and children typically bear the health burden of this pollution due to the nature of traditions amongst low and middle-income families in developing countries and, in particular, countries of sub-Saharan Africa where more than 90% of rural areas populations depend on solid fuels for their daily needs (Naeher et al., 2007). Household air pollution generated from the burning of solid fuels accounts for 6.4% of the global Disability Adjusted Life Years (DALYs) and rating as the third leading risk factor for children under the age of 5 years old and the second risk factor for diseases in women worldwide (Lim et al., 2012). Exposure to a mixture of HAP by inhaling smoke from cooking with biomass fuels is not the only contributor to the health risks mentioned above. Non-solid cooking fuels (e.g. kerosene) and other polluting combustion sources such as space heating and lighting (e.g. kerosene lamps) are also contributors to these health risks (Zhang et al., 2010, Smith et al., 2014, Lim et al., 2012).

Over deforestation and the emissions of BC and greenhouse gases such as carbon dioxide, methane, and nitrogen dioxide are essential factors that harm the environment (Rehfuess et al., 2006, Lam et al., 2012). Approximately 45% of the global emissions of BC, a climate-change agent with a short half-life, are estimated to come from biomass burning (Braun et al., 2008, Wallack and Ramanathan, 2009). Although the risks from biomass fuel burning are well researched with sufficient literature published on the harm, this causes both humans and the environment. More data are needed to inform the development of emission and exposure mitigation strategies to improve the technology used in household cooking stoves and general energy provisions that can be clean and environmentally generated (Martin et al., 2014, Martin et al., 2021).

Nitrogen dioxide (NO_2) is a product of high-temperature combustion that can be produced indoors using unvented gas appliances such as stoves and furnaces (Breysse et al., 2010). This is a particularly problematic issue in inner cities where gas stoves for cooking and heating are commonly used and where proper venting is often not considered due to the lack of understanding of the risks involved (Martin et al., 2014). This has been reported in a BIESAK study analyzing the high concentration of NO_2 households in the USA. In addition, NO_2 is an irritant gas that has a detrimental effect on the respiratory system. Many studies have found adverse respiratory health effects from indoor NO_2, yet other studies have failed to make this association (Breysse et al., 2005, Breysse et al., 2010).

The National Cooperative Inner-City Asthma Study (NCICAS) conducted in eight inner cities across the United States reported a connection between higher concentrations of indoor NO_2 and higher symptoms in children with Asthma (Kattan et al., 2007). Particulate matter is a significant component of household indoor air pollution, which comes from various ecological and human-made resources (Albalak et al., 2001). Ecological sources contain pollen, spores, fungi, plant and animal waste, and suspended crystal materials. Human-made sources are chemical waste and by-products of combustion from furnaces, automobiles and power plants (Albalak et al., 2001, Hersoug et al., 2010, Braun et al., 2008).

Heath care system in the UK and the KSA

The UK has one of the largest, well-developed healthcare systems in the world with universal healthcare coverage provided by the National Health Service (NHS) which developed by the end of the second world war (Grosios et al., 2010). The NHS is funded by taxes and national insurance contributions. and provides free healthcare to all UK residents including primary care, hospital care, mental health services, and social care with emphasis on Predictive, Preventive and Personalized Medicine. Major strengths of the NHS include its universality, equity, and accessibility, as well as its commitment to evidence-based medicine and patient-centered care. According to the Commonwealth Fund's 2020 report, the UK ranked first among 11 high-income countries in terms of healthcare outcomes, access to healthcare, and quality of care. NHS faces several challenges, including the growing demand for healthcare services, rising healthcare costs, and an aging population with complex health needs especially during the COVID-19 pandemic (Grosios et al., 2010).

On the other hand, the Kingdom of Saudi Arabia (KSA) healthcare system is still developing with the majority of healthcare services provided by the government. It includes both public and private healthcare providers, and responsible for providing primary care, hospital care, and specialized services. Private healthcare facilities are also available but are expensive (Alkhamis, 2012).

The KSA healthcare system faces several challenges including shortage of Saudi healthcare professionals especially in rural areas, unequal distribution of healthcare facilities, high prevalence of chronic diseases, limited funding, absence of a national crisis management policy, lack of a national health information system, and the underutilization of the potential of electronic health strategies. The KSA needs to invest in healthcare infrastructure, recruit and train healthcare professionals, and implement health insurance coverage to address these challenges (Alkhamis, 2012).

3. Healthcare providers knowledge about asthma

Healthcare providers have a crucial role in managing asthma and improving the quality of life for patients through accurate diagnoses and evidence-based treatment strategies. In Saudi Arabia, asthma prevelence increased from 2.16% in 1990 to 2.77% in 2019 (Our World in Data (OWD), 2019). However, a study in Riyadh, the capital of KSA found that about half of asthma patients are poorly controlled with a high percentage of uncontrolled BA and their frequent visit to ER departments in hospitals.(Alsahn et al., 2017)

This could be interpreted by patient factors and healthcare factors. Patient factors include lack of medical awareness, poor compliance to medications, reluctance to follow up, and heavy exposure to allergens and air pollution.(Al Dawood, 2002)

On the other hand, health care facilities related factors that contribute to poor asthma management result from limited access to health care facilities which can vary across different regions in Saudia Arabia, with challenges especially in rural areas, Lack of coordination and communication between primary care physicians, specialists, and other health care professionals, overcrowding of primary health care facilities, lack of continuous medical knowledge update programs. (Assiri et al., 2021, Blake, 2017)

Assiri et al conducted a cross-sectional study among physicians in Abha, Khamis Mushayt and Ahad Rufeida cities, Aseer region KSA in 2018 to assess the knowledge, attitude, and practices of PHC physicians regarding the diagnosis and management of patients with acute asthma. They found that the main knowledge gaps were drug doses in severe asthma attack (36%), and diagnosis of acute severe asthma attack (51.5%). Only two third of them use guidelines as their main source of knowledge (Assiri et al., 2021).

The Saudi Initiative for Asthma (SINA) has made excellent efforts to improve the quality of asthma care at all levels, including primary healthcare centers. They have published and updated the National Asthma Guidelines and made it available in various formats (Al-Moamary et al., 2016).

To date, few studies investigated the knowledge, attitude and clinical practices of health team providers working at different healthcare facilities (Alatawi and Alsayed, 2021, Assiri et al., 2021). There is a clear need for an improvement in asthma management knowledge, management among health care providers in Saudi Arabia to facilitate adherence to asthma management guidelines. Continuous medical education programs providing standardized local clinical guidelines and protocols for asthma management serve as valuable to ensure that asthma patients receive the highest standard of care.(Cheng et al., 2007) A proper training program can increase patient quality of life and satisfaction, improve patient outcomes, and reduce unnecessary healthcare expenditure.

4. Effect of COVID-19 pandemic on asthma

4.1. Background

In December 2019, an outbreak of pneumonia of unknown etiology was noticed in Wuhan, a city in Hubei Province of China (Chen et al., 2020). The patients presented mostly with symptoms of dry cough, dyspnea, fever, and in severe cases with respiratory failure (Xu et al., 2020). Later on, the causative agent was identified by the Chinese Centre for Disease Control and Prevention as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on the 7th of January 2020 (Lu et al., 2020). In February, the disease was named COVID-19, (which stands for coronavirus disease 2019), by the WHO (Huang et al., 2020). With the rapid rising of cases number, China implemented strict public measures to control the COVID-19 outbreak including city shut down, block all travel and transportation, restrict outdoor activities and gatherings (Fisher and Heymann, 2020). However, within a short period of time, thousands of humans all over the world were infected with SARS-CoV-2 as a result of high viral transmissibility and abundance of international travel. On 30th of Jan, 2020 the WHO declared the outbreak of the new coronavirus as public health emergency of international concern and by March 11, 2020, it was declared as a global pandemic (Zhu et al., 2020a).

SARS-CoV-2 belongs to the beta coronavirus family. SARS-CoV-2 has a high tropism for the respiratory tract as it enters the host cell through attachment of the spike protein to angiotensin-converting enzyme 2 (ACE2) receptor which is expressed highly on pneumocytes type 2 (Gupta et al., 2020). SARS-CoV-2-induced pneumonia is characterized by hyperactivation of T cells and dysregulated release of inflammatory cytokines mainly IL-1β, IL-6, IL-12, IL-18, IL-33 and TNFα which is known as a cytokine storm, This abnormal response of the immune system occurs in some patients with unknown etiology and can result in acute respiratory distress syndrome (ARDS) and multi-organ failure (Coperchini et al., 2020). ARDS is defined as acute diffuse alveolar injury results in characteristic pulmonary infiltrates and severe hypoxemia in absence of evidence of cardiogenic pulmonary edema (Bernard et al., 1994).

4.2. Clinical picture of COVID-19 infection

Clinical presentations vary from asymptomatic or mild non-specific symptoms to acute respiratory distress syndrome (ARDS) that requires invasive mechanical ventilation (Sahu et al., 2020). Its incubation period is estimated to be from 1 to 14 days. Viral shedding can occur from respiratory droplets 1-2 days before and till 2 weeks after onset of symptoms (Woelfel et al., 2020). Persistence on inanimate surfaces for days in addition to probability of human-human transmission by asymptomatic infected subjects pose a prolonged risk and make it very difficult to be contained (Hu et al., 2020).

The most common presenting symptoms include fever (88%), dry cough (68%), fatigue (38%), and sputum production (33%) (European Centre for Disease Prevention and Control (ECDC), 2020). Self- reported olfactory and taste disorders were also noticed by patients (Giacomelli et al., 2020). Non-respiratory affection has been reported such as thrombotic events, acute cardiac injury, gastrointestinal (GI) manifestations (diarrhea, abdominal pain) (Huang et al., 2020). Most cases have mild to moderate symptoms (80%), severe presentations occurred in 13.8% of laboratory confirmed cases (European Centre for Disease Prevention and Control (ECDC), 2020). Severe and critical presentations usually occur in old age and in patients with associated comorbidities e.g., hypertension, diabetes, cardiovascular disease (CVD), and chronic pulmonary diseases.

4.3. Diagnosis of COVID-19 infection

Diagnosis of COVID-19 infection is challenging for many reasons. There is a wide range of symptoms affecting many body systems with varying severity. Moreover, the high prevalence of asymptomatic carriers makes it more difficult to establish true contact with confirmed cases.

Detection of viral RNA by reverse-transcription polymerase chain reaction (RT-PCR) is considered the gold standard method for diagnosis of SARS-CoV2 infection. However reduced detection and false negative results can occur due to large amount of sequence variation in RNA viruses. This results in mismatches of probes and target sequences. Moreover, incorrect sampling location of the swab test, and insufficient viral material in the specimen or procedural error can result in false negative results (Elizabeth et al., 2020). Therefore RT-PCR detection of SARS-Cov2 is highly specific but its sensitivity for viral detection ranged from 59%-71% (Fang et al., 2020, Ai et al., 2020).

Computed tomography (CT) examination of the chest provides a quick and simple screening tool that can compensate for the limitations of RT-PCR test and play an important role in the diagnosis and monitor progression of COVID-19 patients. In patients with high suspicion of COVID-19 infection, chest CT evidence of viral pneumonia may precede initial positive RT-PCR test results (Xie et al., 2020). Two reports have shown that CT is more sensitive than initial RT-PCR (98% vs. 71%, and 88% vs. 59%) for COVID-19 diagnosis (Fang et al., 2020, Ai et al., 2020).

Rapid point-of-care molecular diagnostic tests have also been developed but they are less sensitive than laboratory-based tests. Serological tests can detect (IgA, IgM, and IgG) antibodies from blood or saliva against viral N or S protein with sensitivity ranging from 82% to 100%, and specificities ranging from 96% to 100% (Hopkins, 2020). The available tests include four types: rapid diagnostic tests (RDTs), chemiluminescent immunoassays, enzyme linked immunosorbent assays (ELISA), and neutralization assays (Hopkins, 2020). However, it is well known that antibody response to infection takes weeks to be detected and the extent and duration of immunity are still unclear.

Therefore, these tests cannot be used for rapid diagnosis of infection (Cheng et al., 2020). Rapid diagnostic tests to detect SARS-CoV2 viral antigens have been developed. The most used test is the lateral flow immunoassay (LFI) which could be completed within 30 minutes (Li et al., 2020). It is highly specific especially at the initial phase of infection with high viral load but it is less sensitive as there is no amplification of the target protein (World Health Organization (WHO), 2020).

4.4. Asthma In COVID Era

During the early months of the COVID-19 pandemic, it was expected that patients having chronic lung disease were more likely to attract severe infection, develop worse outcomes, and need hospitalization and ICU admission. This assumption was based more on common clinical sense rather than evidence. However, results from data published later revealed conflicting results. There is considerable uncertainty whether asthma increases risk of infection or severe outcomes from SARS-CoV2 infection.

A report from WHO addressed the impact of COVID-19 pandemic on patients with asthma from published systematic reviews revealed that patients with asthma were at higher risk for catching SARS-CoV2 infection in comparison to general population (Yang et al., 2020, Zhu et al., 2020b), however, the rate of ICU admission was similar to general population (Castro-Rodriguez and Forno, 2020, Choi et al., 2021). A meta-analysis by Wang et al. from four studies included 744 asthmatic patients infected with COVID-19 found no association between asthma and deaths in COVID-19 infected patients (Wang et al., 2021). Another meta-analysis by Morais-Almeida et al. including three studies with more than 200 patients showed conflicting results about association of asthma with higher mortality rate (Morais-Almeida et al., 2020). Different outcomes could be interpreted by different patient characteristics, study designs timing, SARS-Cov2 variants and environmental. Analysis of data from patients with asthma who had COVID-19 infection revealed that having comorbid

COPD, being older, or non-white ethnicity were the most factors associated with worse outcomes(Wang et al., 2020a).

Of five studies evaluated whether asthma medication was associated with worse SARS-CoV2 outcomes (Elizabeth et al., 2020, Choi et al., 2021, Wang et al., 2020a, Chhiba et al., 2020, Schultze et al., 2020), only one study found that high-dose inhaled corticosteroids were associated with higher risk of death from SARS-CoV2 infection(Schultze et al., 2020).

The impact of COVID-19 pandemic on healthcare system during subsequent waves exceeded the immediate effect of viral morbidity and mortality to affect quality of care for other chronic conditions and elective procedures and resulted in psychological and economic burden (Chudasama et al., 2020). The continued disruption of supply chain resulted in resources restriction and critical shortfalls due to travel restrictions, giving priorities to critical care units treating COVD-19 patients and providing personal protective equipment PPEs (Ashley et al., 2022).

During the early months of the COVID-19 pandemic, there was a major concern regarding the increased need for asthma inhalers. In the United States, the adherence of patients to asthma controller medications was assessed using digital platform that tracks inhaler use through electronic medication monitors and sends alerts to patients for missed doses, there was a 14.5% increase in adherence during March, 2020 (Kaye et al., 2020). In UK, a surge in prescription of asthma medications was reported were 212.96% and 170.78% increase in prescriptions of Clenil Modulite and Fostair -the most frequently prescribed inhalers for asthma- in March 2020 (Bloom et al., 2021). A shortage has been reported by manufacturers for certain inhalers during March 2020 (Bloom et al., 2021). This coincided with a decrease in number of reported asthma exacerbations presenting to primary health care facilities (Shah et al., 2021). This could also be attributed to the public health message during COVID-19 pandemic which focuses on prevention, social distancing, wearing face masks and staying at home which resulted in reduced exposure to viral infection and also adherence of patients to their medications. Dhruve H et al (2022) had reported improved overall adherence to ICS in 2020 in comparison to 2019 across England ($P < .001$), and increase in the proportion of patients meeting "good adherence" (≥75%) from 33.9% in 2019 to 42.0% in 2020 ($P < .001$) (Dhruve et al., 2022). Some authors suggest a false decrease in number of exacerbation due to the fear from presenting to health care facilities during the COVID-19 pandemic (Fan et al., 2021, Yang et al., 2022).

It has been reported that during the COVID-19 pandemic the number of admissions for common emergencies such as heart attack, stroke or asthma exacerbations decreased (Rosenbaum, 2020), this does not necessarily reflect lower incidence but may be due to less presentation to heath facilities for the fear of exposure to COVID-19 infected patients. Many studies have described the impact of delayed immunizations, elective surgeries and dental procedures, organ transplantation which can influence the type of procedure, recovery time and patient outcomes. The number of emergency visits decreased by 40% in many communities across US and the proportion of infectious disease–related visits was four times higher during the early pandemic period (Hartnett et al., 2020). There was a 23.7%-27.8% increase in visits for exacerbations of chronic medical conditions (DeLaroche et al., 2021). A report from Centers for Disease Control and Prevention (CDC) identified about 300,000 excess deaths in the U.S. from January 26 through October 3, 2020, up to 60% of deaths are directly COVID-19 related while the remaining deaths may be attributed to delayed medical care and exacerbation of underlying chronic conditions (Rossen et al., 2020).

4.5. Lockdown and its impact on Asthma

In order to control the spread of COVID-19 in absence of vaccines or specific antivirals, the governments of many countries have imposed a lockdown and self-quarantine to maintain social isolation. In UK, by 24th March 2020 the government has suspended all flights, closed schools, universities, and all public gatherings places and entertainment services, suspended all prayers in mosques and churches (Chang et al., 2020). The number of on-site staff was reduced in non-vital work by encouraging employees to work remotely and minimize contact and contamination of workplaces. A night curfew was imposed in many countries with suspension of all public transportation (Hassany et al., 2020). “Stay home, stay safe” campaign and adopting social distancing habits was encouraged on the social media to increase the public awareness of COVID-19 symptoms and preventive measures (Wilder-Smith and Freedman, 2020).

With closure of industries, energy sectors, ban of air travel and limit of public transportation during lockdown period, the concentration of contaminants in air had been reduced, the emission level of air pollutants including PM10, PM2.5, CO and nitrous oxide showed significant decrease resulting in improvement of air quality (Tobías et al., 2020).

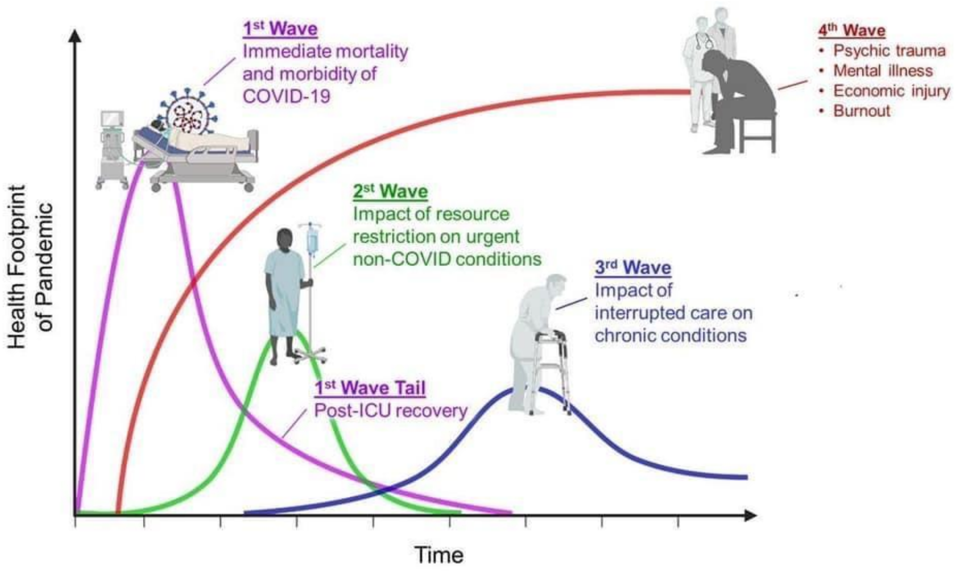


Figure (1.3): Health footprint of COVID-19 pandemic(Morris et al., 2022)

4.6. Impacts of lockdown on patients with asthma: asthma exacerbations and medication use

During the start of the COVID-19 pandemic, it was expected that patients having asthma and COPD contracting SARS-CoV2 infection would have more severe respiratory symptoms and more vulnerable to worse outcomes and need for hospitalization. There was a major concern about medication availability and adherence to drugs during lockdown periods due to difficult accessibility to heath care facilities. On the other hand, application of social distancing measures and self-quarantine have been resulted in less air pollution, and less exposure to allergens and viruses which decreased number of asthma exacerbations.

During the first year of COVID-19 pandemic, there was 62% decrease in asthma exacerbation in children and 70% decrease in positivity of common respiratory viral infection compared to pre-COVID years (Hazan et al., 2022). The seasonal variation in positive viral tests and ER visits was suppressed during Lockdown period (Hazan et al., 2022).

A survey addressing the burden of respiratory symptoms and asthma exacerbation frequency among asthma patients in Italy during the COVID-19 lockdown period showed that although the patients reported worsening of respiratory symptoms and need to step-up the doses of medication, only 17% reported asthma exacerbations and no one had a confirmed diagnosis of COVID-19. 82% had good adherence to their medications (Caruso et al., 2021). Another survey included 339 healthcare professionals treating asthma patients from 52 different countries reported that during lockdown period, about 80% of follow up consultations have been replaced by phone calls, and in about 70% of new patients, the diagnosis and prescription of inhalers was based only on clinical assessment without use of lung function tests (Eguiluz-Gracia et al., 2021).

In the UK, the prescription of asthma inhalers was doubled at start of the COVID-19 lockdown and as a result, problems with inhaler availability have been reported (Bloom et al., 2021). There was 52.5% , 44.2%, 17.3% and 12.9% increase in use of inhaled corticosteroids (ICS), short acting beta agonists (SABA), oral corticosteroids (OCS) and long-acting beta agonists- inhaled corticosteroids combinations (LABA-ICS) respectively early during the pandemic (Bloom et al., 2021). Despite a reduction in the number of primary care visits during first 4 months of the pandemic, the number of ICS prescribed per appointment increased by 26% (Crook et al., 2022).

Analysis of English Prescribing Dataset comparing dispensing of asthma medications 14 months before the pandemic (from January 2019 to February 2020 and 8 months after the pandemic March to October 2020 (8 months after its onset) revealed a significant increase in use of salbutamol (P = 0.033) and ipratropium (P = 0.001) from March to October 2020 then continued to decrease gradually, however they have not returned to their pre-pandemic levels (Barrett and Barrett, 2021).

Many factors led to increase the requests of asthma medications including stockpiling; early ordering, multiple medication items prescribed by doctors (Ow et al., 2022). Patients reported adopting this shortage by starting stockpiling; ordering prescriptions early; try alternative prescriptions; requesting ‘emergency prescriptions’; and try ordering online and contacting drug manufacturers (Ow et al., 2022). Higher prescriptions of ICS corticosteroids were more in younger patients of higher socioeconomic status, with milder asthma symptoms (Bloom et al., 2021). OCS orders were more in patients having one exacerbation during the past year, having COPD and using high dose of ICS (Bloom et al., 2021). Another factor that could be implicated in the increase in prescription is the prevalence of virtual consultations through telemedicine which represents a challenge for the physician. With absence of clinical examination and difficult confirmation of right inhaler technique is used, the physician is usually under pressure for over prescription (Crook et al., 2022).

In Finland, prescription of antibiotics and asthma medications for children aged 0-5 years was decreased by 55.3% and 19.8%respectively during 2020 in comparison to 2019. This could be attributed to application of COVID-19 restrictions which decreased risk of upper respiratory tract (URT) infections (Haapanen et al., 2022).

The impact of COVID-19 pandemic and lockdown on the prescription and availability of asthma medications is not fully investigated. A change in patient behavior regarding taking medications, self-management, adherence to drugs, and stockpiling of acute respiratory inhalers were also reported (Crook et al., 2022).

5. Thesis rational

The dispensing and availability of asthma medications during the first year of the COVID-19 pandemic were affected by many factors. While many studies reported that asthma patients had higher risk for severe respiratory symptoms, Others reported lesser exacerbations which could be related to application of social distancing and lockdown or the fear of presenting to the health care facilities. An urge in prescription of ICS was reported during the first wave of the pandemic in the UK. The impact of COVID-19 pandemic and its related lockdown on management of asthma patients in the UK is not fully investigated. In the first part of this study, we aim to assess the impact of COVID pandemic on asthma patients and lockdown related effects on drug dispensing. There are no available national prescription registries in the KSA to track the rate of dispensing asthma medications, so we collected the data from the UK.

The Kingdom of Saudi Arabia is considered a highly industrialized country due to its high dependency on its well-established oil industry and resulting air pollution. In addition, due to the very high temperatures, most people spend much time indoors where indoor air pollution may be very high caused by the ingress of polluted ambient air, parents' smoking habits, the habit of burning incense and other cooking fuel like wood, poor ventilation, and poorly maintained air conditions, as well as house mites. Furthermore, increasing numbers of pets indoors adds to the risk of allergens that can increase asthma in children. There are several reviews on the prevalence of asthma and its associated risk in Saudi Arabia. However, very few studies have investigated the specific impacts of each allergen and what measures are put in place to reduce their effects on human health, particularly on children's health and the risk of developing asthma. More studies are needed in this field to help understand the prevalence of asthma in more detail to compact the causes and mitigate the risks. Such a study will provide insights that will help inform policymakers and professionals and assist with future research strategies to help bring this disease under control and diminish its burden.

In the second part of the study, we try to explore the impact of air pollution on children's asthma. Finally, we will investigate the knowledge, attitude, and practice of health care providers in Makkah region regarding asthma management.

Overall, The COVID-19 pandemic has had a significant impact on the way people live and work, and this has also had an impact on the way to manage asthma. The lockdown measures that were implemented in many countries have led to a decrease in the number of people going to the doctor, and this has meant that they have not been able to get the treatment they need. This is a concern, as asthma is a serious condition that can be fatal if it is not managed properly.

Indoor air pollution is also a major problem, and it is estimated that it is responsible for up to 40% of all asthma cases. There are many different indoor pollutants that can trigger asthma attacks, including dust mites, mold, pet dander, and tobacco smoke.

The research questions that I have listed are important because they will help to better understand the impact of COVID-19 and indoor air pollution on asthma. Results will help to better understand and manage asthma in the covid era.

There is currently very little research on the impact of COVID-19 and indoor air pollution on asthma. This research will provide much-needed information about these important issues, and it will help us to better understand how to manage asthma in the future.

6. Research questions.

1. What indoor pollutant factors contribute to developing asthma in children in the Kingdom of Saudi Arabia?
2. What is the knowledge, attitude, and practice of Primary health care providers (PHC) in Makkah region regarding asthma management?
3. What are the patterns of Asthma drugs prescriptions in the UK?

4. What is the impact of the coronavirus pandemic related lockdown on the dispensing of medications used in the management and control of respiratory symptoms of asthma in different countries of the UK?

7. Aim and objectives.

Overall Aim

To assess childhood asthma in Saudi Arabia including its association with indoor air pollution and healthcare professionals' knowledge, attitude, and practice toward acute asthma.

And to investigate the impact of COVID-19 pandemic on asthma medication utilization (in the UK) as well as

Chapter 2

The Indoor Air Pollution and Childhood Asthma in the Kingdom of Saudi Arabia.

Abstract:

Background: Childhood asthma is a growing public health concern in Saudi Arabia, with increasing evidence linking it to indoor air pollution. This chapter explores the relationship between various indoor pollutants and the prevalence of asthma among children in Saudi Arabia, aiming to inform future research and public health initiatives in the region.

Methods: A thorough literature review was conducted, utilizing databases such as EMBASE, MEDLINE, CINAHL, Web of Science, SCOPUS, and COCHRANE. The review followed the six-step methodology of Arksey and O'Malley, incorporating adaptations by Levac et al. and the Joanna Briggs Institute (131). Primary and secondary research articles focusing on indoor air pollution and childhood asthma within Saudi Arabia were included. Data extraction and analysis were performed, focusing on pollutants such as NO2, SO2, PM10, PM2.5, CO2, tobacco smoke, and the presence of indoor pets.

Results: The review identified a significant positive association between indoor air pollution and the incidence of asthma in children. Key findings include the prevalence of asthma due to environmental factors such as tobacco smoke, pet allergens, and various indoor air pollutants. Despite this, there is a notable gap in empirical evidence regarding specific indoor gaseous pollutants in Saudi Arabia. The studies predominantly relied on self-reported data, indicating a need for more rigorous, science-based research methodologies.

Conclusion: The chapter highlights the urgent need for targeted public health strategies and policies to mitigate the impact of indoor air pollution on childhood asthma in Saudi Arabia. It emphasizes the importance of developing research that

can separate the individual effects of various indoor pollutants. This understanding is crucial for formulating effective interventions and improving the overall respiratory health of children in the region. Future research should focus on observational studies, utilizing objective measurement tools to accurately assess indoor air quality and its direct impact on childhood asthma.

2.1. Introduction

Asthma is increasingly becoming a public health issue that affects children in Saudi Arabia (Al-Moamary et al., 2019). Studies on this topic worldwide have shown a strong link between asthma and air pollution (Al-Zahrani et al., 2014). This study will investigate this link in Saudi Arabia and explore if asthma in children is a disease that continues into adulthood (Al-Moamary et al., 2019, BinSaeed, 2014). In addition, research has shown that air pollution has increased respiratory health(Pérez-Padilla et al., 2010). Therefore, there is an urgent need to improve public awareness to help reduce the levels of air pollution in some countries to help improve public health(Sweileh et al., 2018). The noticeable increase in cases of respiratory disease, including asthma, is adding to the health burden in the Kingdom of Saudi Arabia (KSA).

This work aims to review the literature on indoor air pollution and children with asthma to provide a basis for future research in the Kingdom. This review has followed the six steps methodology adopted by Arksey and O'Malley (Arksey and O'Malley, 2005). In addition, we have also applied the scoping methodology adopted by Levac et al. and the Joanna Briggs Institute methodology (Peters et al., 2015) as adaptations to the methodology used by Arksey and O'Malley. We conducted our search using the electronic databases EMBASE, MEDLINE, CINAHL, Web of Science, SCOPUS and COCHRANE and used search terms that are relevant to the research questions identified in our research proposal. The screening process used a review mechanism whereby two reviewers independently reviewed the search outcome of predefined inclusion criteria that corresponds to that defined in research questions. Studies that were deemed by both reviewers as being relevant to our study and met our search criteria were marked as "accepted" for inclusion. The results were reported using the PRISMA flowchart. We also used the expertise of Saudi Arabia asthma researchers to provide feedback on our literature list to inform our gap analysis exercise and to identify any omissions that have occurred in our literature search. Our scoping and systematic review has identified the evidence in relevant Asthma literature on asthma in children in the Kingdom of Saudi Arabia. The findings were focused on indoor air pollution, including indoor pets, traffic fumes, wood burning, and passive smoking and their prevalence levels in communities. The review uncovered the lack of empirical evidence on indoor gaseous pollutants in Saudi Arabia, such as NO2, SO2, PM10, PM2.5, and CO2, the most dominant indoor air pollutants in other contexts. Furthermore, there was a lack of rigorous science-based evidence to mitigate these pollutants that could reduce the emission and the exposure of these pollutants in Saudi Arabia. This review advances asthma research and informs the decision-makers, clinicians, and the public health sector on the prevalence of indoor-caused asthma and its impact on children in the Kingdom.

This work aimed to develop a clear understanding of the existing literature on the impact of indoor pollution factors on children developing asthma. As a result, a gap was identified that, if filled, would be better to inform the decision-makers and public health professionals to encourage future research in the methods needed to be adopted to mitigate the risk of asthma in children from indoor air pollution.

2.2. Research justification.

Asthma is caused by an inflammation or sensitivity in the airways and the lung that can restrict the airflow and disrupts regular breathing. In addition, it is thought to be caused by toxins in the air. As a significant global health issue, asthma seriously impacts the sufferer's quality of life and life expectancy. Despite it being preventable, the number of people with asthma in Saudi Arabia is expected to increase, with children being part of the population most at risk. Saudi Arabia is considered a highly industrialised country due to its high dependency on its well-established oil industry and resulting air pollution. In addition, due to the very high temperatures, most people spend much time indoors where indoor air pollution may be very high caused by the ingress of polluted ambient air, parents' smoking habits, the habit of burning incense and other cooking fuel like wood, poor ventilation, and poorly maintained air conditions, as well as house mites.

Furthermore, increasing numbers of pets indoors add to the risk of allergens that can increase asthma in children. Asthma and other respiratory diseases have been widely under-explored in the Middle East, including the Kingdom of Saudi Arabia. There are several reviews on the prevalence of asthma and its associated risk in Saudi Arabia. However, very few studies have investigated the specific impacts of each allergen and what measures are put in place to reduce their effects on human health, particularly on children's health and the risk of developing asthma. More studies are needed in this field to help understand the prevalence of asthma in more detail to compact the causes and mitigate the risks. Such a study will provide insights that will help inform policymakers and professionals and assist with future research strategies to help bring this disease under control and diminish its burden. This work aims to develop a clear understanding of the existing literature on the impact of Indoor Air Quality and indoor pollution factors on children developing asthma. In order to assess the size of indoor air pollution in the Kingdom of Saudi Arabia, it may be necessary to compare our results with those available in western developed countries. The systematic literature review provides insight into the research that has already been conducted on children's asthma in the Kingdom. We aim to identify the gaps that need to be filled better to inform the decision-makers and public health professionals to encourage future research in the methods needed to be adopted to mitigate the risk of asthma in children from indoor air pollution.

2.3. Factors affecting Asthma in Saudi Arabia

Several factors can influence the prevalence and management of asthma in Saudi Arabia. These factors can be broadly categorized into environmental, genetic, socioeconomic, and healthcare-related factors. Here's an overview with authentic references supporting each factor:

1. Environmental Factors:

   Air Pollution: High levels of air pollution, including particulate matter and ozone, have been linked to increased asthma prevalence and exacerbations. Saudi Arabia, particularly urban areas, faces challenges with air quality due to industrial activities, vehicle emissions, and dust storms (Alrubaish 2020)

   Allergen Exposure: Exposure to allergens such as dust mites, pollen, mold, and animal dander can trigger asthma symptoms. Saudi Arabia's climate and vegetation contribute to allergen exposure, with dust mites being a significant indoor allergen (Al-Moamary,2011)

2. Genetic Factors:

   Family History: Asthma often has a genetic component, and individuals with a family history of asthma or allergic conditions are at higher risk. Genetic studies in Saudi Arabia have identified polymorphisms associated with asthma susceptibility and severity (Al-Muhsen, 2017)

   Ethnicity: Genetic variations among different ethnic groups in Saudi Arabia can influence asthma prevalence and phenotype. Studies have explored genetic factors contributing to asthma in Saudi Arabian populations (Alrubaish 2020).

3. Socioeconomic Factors:

   Urbanization and Lifestyle Changes: Rapid urbanization and lifestyle changes in Saudi Arabia have led to increased exposure to indoor pollutants, sedentary lifestyles, and dietary shifts, all of which can impact asthma prevalence and control (Al-Hajjaj 2013)

   Access to Healthcare: Disparities in access to healthcare services, including asthma diagnosis, medications, and specialized care, can affect asthma management outcomes. Socioeconomic status influences access to healthcare resources in Saudi Arabia (Alangari,2011).

4. Healthcare-related Factors:

Asthma Education and Awareness: Adequate patient education, awareness programs, and healthcare provider training are crucial for effective asthma management. Initiatives to improve asthma education and awareness have been implemented in Saudi Arabia.

Guidelines Adherence: Adherence to evidence-based asthma management guidelines, such as those from the Global Initiative for Asthma (GINA), can improve outcomes. Challenges in guideline adherence and healthcare provider practices impact asthma care in Saudi Arabia.

These factors interact in complex ways to influence asthma prevalence, severity, and control in Saudi Arabia. Addressing these factors requires a multifaceted approach involving environmental regulations, genetic research, socioeconomic interventions, and improvements in healthcare infrastructure and education.

2.4. Methodology

To synthesise and review the evidence for our research, and based on the objectives of our study, we used Arksey and O'Malley's scoping review technique to map the evidence of asthma in the Kingdom of Saudi Arabia (Arksey and O'Malley, 2005). Arksey and O'Malley's methodological framework uses a 6-step process which is visualised in figure. 2.1. The current review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. In addition, their six-step review process incorporates elements from the more recent frameworks of Levac et al. in 2010 and The Joanna Briggs Institute (Peters et al., 2015, Levac et al., 2010). Bias often carries a risk of producing studies of poor quality. Therefore, the findings of such studies can be questioned and challenged by other researchers, practitioners, and policy-makers (Glasziou et al., 2004). Therefore, every study must undergo a rigorous appraisal process to assess the risk of bias and assure the reliability of the results. With that in mind and by adopting the Levac et al. recommendations (Levac et al., 2010), an extra step to the six-step process was added to include the quality assurance needed to eliminate bias.

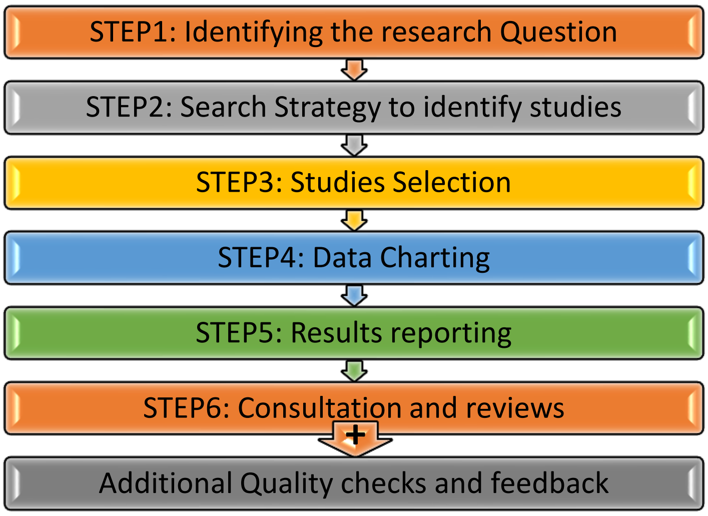


Figure 2.1. Arksey and O'Malley's six-step methodological framework

2.4.1. *Step 1: identifying the research question.*

The first step of the process was to consider the factors that impact asthma in children in the Kingdom of Saudi Arabia and to identify the most critical aspects that need to be addressed in the scoping review for our study. This helped us identify the areas that need to be researched to develop and define the initial research questions to form our research. Several meetings were held to discuss our systematic review's scoping and agree on the finalised research questions. The questions were then articulated clearly and precisely with little or no room for misinterpretation by the reader. The research questions helped define the concept, the population to be studied, and the health interests from which the research will benefit to clarify the focus of this scoping study. We identified three research questions that guided the scoping review.

3. What is the prevalence of Children's Asthma caused by indoor air pollution in the Kingdom of Saudi Arabia?
4. What indoor pollutant factors contribute to developing asthma in children in the Kingdom of Saudi Arabia?

2.3.2. Step 2: Search strategy to identify relevant studies.

In this step, we identified the eligible published academic studies and literature covering the criteria related to our research questions. The critical inclusion criteria are listed in table 2.1 and are categorised using the PCC model: Population/ Concept/ Context, which guides our research strategy as recommended by the Joanna Briggs Institute for scoping reviews.(figure 2.2) This model presents fewer restrictions than the alternative PICO (Population, Intervention, Comparator, and Outcome), generally utilised for systematic reviews (Arksey and O'Malley, 2005, Stern et al., 2014).

Search Strategy:

- Databases: EMBASE, MEDLINE, CINAHL, Web of Science, SCOPUS, COCHRANE.
- Keywords:
- Population: Children, pediatric, youth.
- Concept: Asthma, wheezing, respiratory symptoms.
- Context: Indoor air pollution, indoor pollutants, indoor allergens, household pollutants, air quality, environmental exposure, particulate matter, nitrogen dioxide, sulfur dioxide, carbon dioxide, tobacco smoke, pet allergens, indoor pets.
- Geographic location: Saudi Arabia.
- Search string.
- ("Child*" OR "Pediatric" OR "Youth") AND ("Asthma" OR "Wheezing" OR "Respiratory symptoms") AND ("Indoor air pollution" OR "Indoor pollutants" OR "Indoor allergens" OR "Household pollutants" OR "Air quality" OR "Environmental exposure" OR "Particulate matter" OR "Nitrogen dioxide" OR "Sulfur dioxide" OR "Carbon dioxide" OR "Tobacco smoke" OR "Pet allergens" OR "Indoor pets") AND ("Saudi Arabia").

Table 2.1 Inclusion criteria of the proposed scoping review (PCC)

Population	Concept	Context
Children of both genders.	Studies that report the prevalence, risk factors, and interventions regarding indoor air pollution and its impact on asthma	Research articles conducted on populations in the Kingdom of Saudi Arabia,

We maximised the inclusion of articles for our review by using the snowballing technique for the backward chaining of references and forward chaining of citations for each identified result from the database search output. This part of the process utilised Google Scholar to find the references and citations examined for inclusion and further snowballing checks if selected. First, initial exploratory searches in Google and Google Scholar were conducted using keywords relating to our research scope. Next, the search terms were combined using Boolean operators such as AND, NOT, and OR to eliminate unwanted results. Next, we extracted the data from the relevant databases we chose to work with (EMBASE, MEDLINE, CINAHL, Web of Science, SCOPUS, and COCHRANE Library) in this review into EndNote, where we identified and eliminated duplications. We then exported the resulting literature into the Rayyan QCRI software for closer examination and discarded any publications that did not fully meet our set inclusion criteria. Rayyan QCRI is an online software tool developed by the Qatar Computing Research Institute (http://rayyan.qcri.org).

Rayyan was developed through the Qatar Computing Research Institute, funded by the Qatar Foundation, a nonprofit that supports education, science, research, and community development initiatives in Qatar. It is completely web-based, with offline compatibility through its app. Users can initiate and/or participate in an unlimited number of reviews. As opposed to Covidence, Rayyan does not easily mirror the multiphase citation review process and is only designed to aid with the reference screening. It takes a minimalist approach, placing more of the logistical and workflow burden on the users themselves.

In comparing Covidence and Rayyan for systematic review workflows, (Liz Kellermeyer 2018) noted that Covidence is distinguished for its robust features that safeguard the integrity of the review process. It follows a structured workflow designed to minimize reviewer actions that could compromise data reporting or review integrity, ensuring a standardized approach to systematic reviews. Covidence's built-in capabilities, such as automated screening processes that track include/exclude decisions, streamline the review workload among team members by reducing duplicate efforts. Additionally, Covidence facilitates conflict resolution with designated tie-breaker roles and blinding functionalities during screening and conflict resolution, contributing to a more efficient and organized review process.

On the other hand, Rayyan offers flexibility in its approach, allowing reviewers more freedom in structuring their reviews and workflows. While it lacks the prescribed workflow of Covidence, Rayyan's reviewer blinding function provides some level of blinding during the review process. However, conflicts in Rayyan must be resolved manually through unblinded consensus, requiring reviewers to discuss and manually change votes, which can be more time-consuming compared to Covidence's integrated conflict resolution workflow. Rayyan's interface does not support advanced stages of the systematic review workflow beyond screening, limiting its suitability for more complex systematic reviews requiring robust data extraction and reporting tools.

In summary, Covidence is preferred for its structured approach, automated processes, and comprehensive tools for conflict resolution, data extraction, and reporting, making it well-suited for rigorous systematic reviews that adhere to standardized methodologies. Rayyan, while offering flexibility and a user-friendly initial screening process, may require additional manual efforts and workflows for tasks such as conflict resolution and data extraction in more complex systematic reviews.

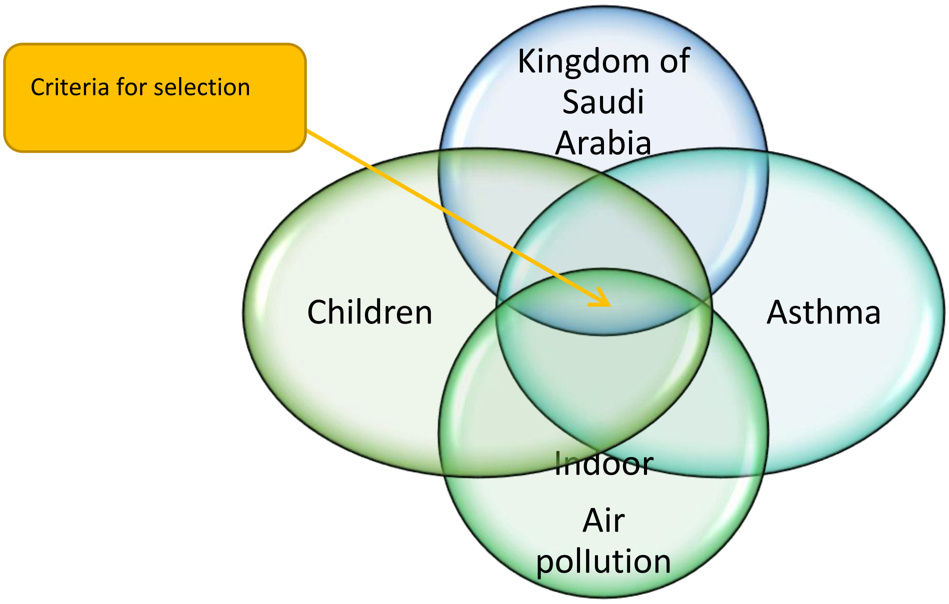


Figure 2.2 The process of forming a database search syntax.

2.3.3. Step 3: study selection

Our review and literature search criteria have only included articles written in Arabic and in English. We have not searched or included any literature written in any other language unless authentically translated into Arabic or English. No limit was put on the age of publications, although if the article meets our selection criteria, the article's age will be considered during the analysis stage to check for the continued validity of the information. We limited our review to quantitative studies. Publications of studies conducted on indoor air pollution in Saudi Arabia and the effects on asthma in children deemed relevant to our research questions were selected for analysis. We included both the primary studies and reviews of those studies that were applicable. The reviews have given us some pointers when examining the primary articles to avoid conducting the full review in areas of the primary publication that have already been reviewed. Two reviewers were involved throughout this process to ensure the selection process was thorough and remained within the scope of our study questions. We followed a process using two screening stages, and the first was to screen the articles` titles and abstracts which two researchers conducted independently to decide on the articles` suitability for inclusion. Where disagreement occurred, the two researchers discussed each article on which disagreement occurred and decided jointly on whether to include the article. A sample of selected articles was evaluated by reviewing their abstracts to ensure the success of the selection criteria. A complete abstract review of all selected publications followed this. Any article that was found not to inform our research questions was deselected. In the second stage, we conducted a full-text review for each article that remained in scope (figure 2.3). Thus, each article was fully read by both reviewers independently. Further, filtering of articles that did not inform our research questions following a discussion between the two researchers and following a review by a third researcher with the subject matter expertise.

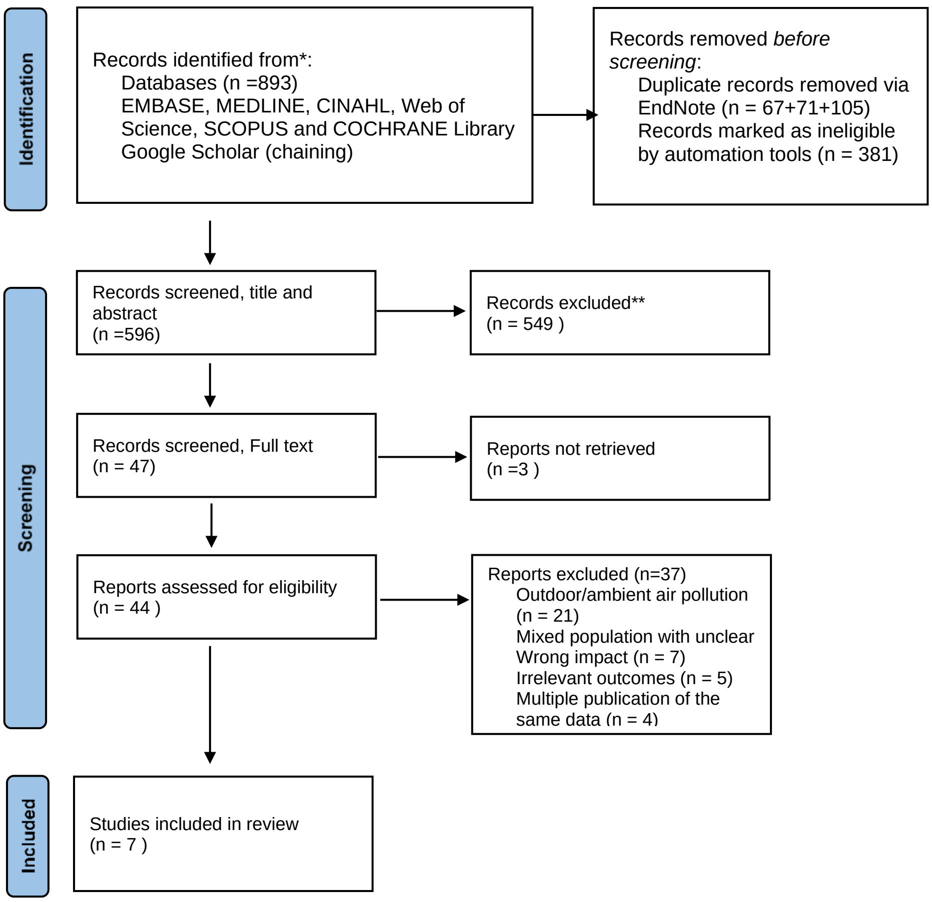


Figure 2.3 PRISMA Chart for the identification of studies via databases and registers

2.3.4. Step 4: charting the data.

This step focused on collating the relevant information from each article that maps to our concept and research questions. An excel 365 spreadsheet was created for this purpose. The outcome is a descriptive summary of critical points gathered from the articles we included in the review. This summary includes the author/researcher's name, type of publication, year of publication, and study objectives. In addition, data directly related to our study questions, such as the prevalence of asthma, sample size, results, and indoor risk factors affecting asthma, were captured. The articles found were then grouped into three domains; 1st group included articles reporting prevalence, the second reported indoor air pollution sources and the 3rd group for articles that reported a combination of observational and meteorological data. Two independent reviewers reviewed the form to confirm its suitability for the purpose and objectives of our research regarding data inclusion. The abstracted data of each reviewer will be compared to identify and rectify any discrepancies between them. Any discrepancy found was thoroughly discussed with two primary and third reviewers, ensuring a consensus between reviewers on what to include in our research outcome.

2.3.5. Step 5: collating, summarising, and reporting the results.

The data search results are presented using the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) (PRISMA, 2018) (figure 2.3). In addition, the checklist has been amended to enable us to incorporate elements derived from our research questions. The following three stages have been used to present our result accurately and verifiably, as proposed by Levac et al.(Levac et al., 2010). The first stage presented a descriptive summary, including the articles' characteristics (table 2.2). The second stage presented a table of the results to represent the data that are easy to read and comprehend and satisfy the purposes of the research questions of our scoping review (table 2.3). Finally, the last stage adds meaning to the results regarding gaseous pollutants and a visual representation of them to help the interpretation, discussion, and recommendations align with our research questions and approach. However, this section is omitted due to the lack of these findings in this review.

2.3.6. Step 6: Consultation

The study used Arksey and O'Malley's methodological framework as an optional step to identify the gaps in step 2 of our literature review, "**Search strategy to identify relevant studies**." The searches have identified researchers who have researched asthma in Saudi Arabia and have a good history in publishing literature or research in this field during the literature review. The investigator attempted to contact some of these researchers and seek suggestions for additional literature to consider and include such suggested literature if it meets our study's inclusion and exclusion criteria. Ethical approval is not required for this study, considering that the review explores readily available material in the public domain to answer the research questions of the scoping review. In addition, the study was not interested in collecting any personal information during this review that will require ethical approval.

2.3.7. Additional step: quality assessment

In this step, we conducted a quality assessment to evaluate the quality of the studies we selected to include in our scoping review. Such assessment enhanced our understanding of the meanings derived from the study result. This quality assessment did not form part of our inclusion criteria; therefore, none of the studies' inclusion status is altered due to this quality assessment. The Joanna Briggs Institute's critical appraisal tools were used to conduct this quality assessment. The Joanna Briggs Institute provides different tools with different questions to assess different study designs. Responses were yes, 'no', 'unclear or not applicable; a score of 1 was given for a yes response, while 0 was given for a nonresponse. Two independent reviewers conducted the quality appraisal process. The results will be presented in a table based on the Joanna Briggs Institute's questions about critical appraisal tools. The tools present the reviewers with three response options for each of the questions; these are (1) the study has met the criteria, (2) the study has not met the criteria, or (3) whether the answer to the question is apparent in the reviewed document. On the other hand, only two studies had high scores. Accordingly, the overall quality score of the studies was modest.

2.4. Findings: Children Asthma and indoor pollution diagnosis study in the Kingdom of Saudi Arabia

Given the noticeable increase in asthma rates among children and their related health burden in the Kingdom of Saudi Arabia, this review aimed to review the literature on indoor air pollution and children with asthma to provide a basis for future research on the subject in the Kingdom. The searched databases included EMBASE, MEDLINE, CINAHL, Web of Science, SCOPUS, and COCHRANE Library. The online Rayyan tool was used to search the databases and review the suitability of the selected studies based on our search criteria and further analysis of the studies for inclusion or exclusion. All the retrieved studies through the database search and their relevant studies were combined and imported into EndNote. The reviewer has identified and excluded duplicates that may have been identified due to searching several databases. Finally, title and abstract screening of all the remaining records was conducted and compared against predetermined eligibility criteria, which needed to cover the combined characteristics of Saudi Arabia, Asthma, Children, and indoor air pollution.

2.4.1. Characteristics of the study included.

A total of 893 studies were identified from the search of various databases. We identified 243 duplicates that were removed. We investigated 596 studies using titles and abstract screening. Of those, 44 studies underwent full-text screening and were included in the eligibility assessment. Unfortunately, three records could not be retrieved and were excluded. Of the 44 studies, 37 were excluded for several reasons; 21 were more focused on outdoor ambient pollution, seven focused on pollution but were unclear as to their impact, 5 showed irrelevant outcomes, and showed duplication of data already covered elsewhere. The search resulted in 7 studies that are relevant and focus on indoor air pollution in the Kingdom of Saudi Arabia and the impact on developing asthma in children.

Table 2.2 Data Extraction Table.

AUTHOR & DATE	OBJECTIVES	STUDY DESIGN	LOCATION	SAMPLE NO.	AGE	TOOL	PREVALENCE	POLLUTION SOURCE	POLLUTANTS
ALQAHTANI ET AL., 2017 (ALQAHTANI ET AL., 2017)	possible environmental determinants of asthma among school-aged children	cross-sectional	Najran	1700	7 to 19 years average 12.21 median 12 years.	Arabic version of the modified ISAAC	Total (468) 27.5% for asthma Including (353) 20.8% severe form of asthma	Indoor pet, traffic fumes, wood burning, Passive smoking	Not studied
AL FRAYH ET AL. 1989 (AL FRAYH ET AL., 1989)	possible environmental determinants of asthma and allergic rhinitis	cross-sectional	Jeddah and Dammam	1953	7 to 12 years Mean 9.84 years.	Questionnaire	Jeddah 20.19% Damman 12.53%	passive smoking	Not Studied
AL FRAYH ET AL. 2001 (AL FRAYH ET AL., 2001)	changing in the prevalence of asthma between 1986 and 1995	cross-sectional	Riyadh Hail	2123	8 to16 years old	Questionnaire	Increase from 8% in 1986 to 23% in 1995.	both parents smoked 17% in 1986 and 35% in 1995.	Not Studied
MUSHARRAFIEH ET AL, 2020 (MUSHARRAFIEH ET AL., 2020)	Asthma correlation between parents' lifestyle changes and asthma among adolescents	Cross-sectional SURVEYFREQ	all 13 regions of the Kingdom of Saudi Arabia	11,348	12 to 18 years	questionnaire	children with parents who smoke, less educated parents, male, overweight, unhealthy diets.	Passive smoking, Adolescent smoking.	Not studied
BENER ET AL. 1993 (BENER ET AL., 1993)	association between parental smoking habits and diagnosed wheezy bronchitis in schoolchildren	Cross-sectional	Cities of Dammam, Jeddah, Riyadh	3041	7 to 12 years	Questionnaire	NA	Atopic parents. Pets at home.	Not studied
ALSHEHRI EL AL, 2000 (ALSHEHRI ET AL., 2000)	Prevalence of asthma and asthma-related symptoms among male schoolchildren	Cross-cross-sectional	City of Abha	4300 schoolboys	7 to 15 years	Rush Medical College and International Study of Asthma and Allergies in Children Questionnaire	Asthma 9%. Ratio=437.11, P<0.001), Ratio=2.91, p<0.001),	Family history of the atopic condition. Pets	
AL-DAWOOD 2001 (AL-DAWOOD, 2001)	Prevalence variation of asthma due to social class and history of parents' health	Cross-sectional	Al-Khobar City	1482 schoolboys	6 to 15 years	questionnaire	Asthma prevalence is 9.5%. No difference in prevalence due to social class.	Passive smoking. Pets at home.	Not studied.

Table 2.3 A summary of findings from the included studies.

1. Environmental determinants of bronchial Asthma among Saudi school children in southwestern Saudi Arabia **Authors:** Alqahtani, J. M.; Asaad, A. M.; Awadalla, N. J.; Mahfouz, A. A.;
AL Qahtani and colleagues conducted a study in 2018 to determine the possible environmental and dietary effects of asthma in school-aged children in the city of Najran in southern Saudi Arabia. They used a cross-sectional method. Skin Prick tests were conducted on 1700 children, and parents completed a questionnaire. The study revealed an asthma prevalence of 27.5%, with 20.8% suffering from severe asthma. Causes for this prevalence were identified as being caused by dog hair, indoor wood burning, proximity to heavy traffic, and other causes. In addition, certain types of food seemed to add to the risk of asthma, while other types seemed to reduce the risk.
2. Epidemiology of asthma and allergic rhinitis in two coastal regions of Saudi Arabia **Authors:** al Frayh, A. R.; al Nahdi, M.; Bener, A. R.; Jawadi, T. Q.
The study used a questionnaire to collate data on 1953 school children in the coastal urban areas of the Kingdom of Saudi Arabia. The aim was to determine if parents' smoking habits affect the prevalence of Asthma in Children. The study used logistic regression and linear modelling analysis. A statistically significant relationship between asthma and fathers' smoking was found as well as an effect of having pets at home pets. The study also found that allergy in family history did impact the prevalence of asthma in the tested population sample. However, Jeddah had a higher asthma prevalence than Dammam, 20% and 12%, respectively.
3. Increased prevalence of asthma in Saudi Arabia **Authors:** Al Frayh, A. R.; Shakoor, Z.; Gad El Rab, M. O.; Hasnain, S. M.;
The study investigated the changes in the prevalence of asthma among school children in the Kingdom of Saudi Arabia. The study was conducted in 1986 and repeated in 1995 to determine the difference in prevalence over nine years. A sample of 2123 children (Jeddah and Riyadh) in 1986 and 1008 (Hail and Gizan) in 1995 participated in the study. A simple internationally used questionnaire was used in these studies. The results showed that the prevalence increased from 8% in 1986 to 23% in similar environments in 1995. The studies further revealed that allergic rhinitis increased from 20% to 25% over the same period. Increased exposure to tobacco smoke and other indoor environmental pollutants and an increase in house pets have directly contributed to the changes in Asthma prevalence.
4. A nationwide study of asthma correlates among adolescents in Saudi Arabia **Authors:** Musharrafieh, U.; Tamim, H.; Houry, R.; Albuhairan, F.;
The study examined the relationship between environmental factors and asthma prevalence in asthmatic children self-reporting in all 13 regions of the Kingdom of Saudi Arabia. A cross-sectional study selected a sample of 11,348 adolescent school children. The results showed a prevalence of 8.2% of asthmatic children across the Kingdom. In addition, family education, dietary, and being overweight among males were associated with higher asthma and related burden.
5. Passive smoking effects on wheezy bronchitis **Authors:** Bener, A.; Al-Frayh, A.; Ozkaragoz, F.; Al-Jawadi, T. Q.;
The objective of this study was to investigate the relationship between the indoor smoking habits of parents and asthma prevalence in schoolchildren in Saudi Arabia. A cross-sectional study randomly selected 3,041 schoolchildren aged between seven from the Saudi cities of Dammam, Jeddah, and Riyadh: essential this selection of geo-climatic considerations. A standard questionnaire was used in all areas of this study. The results confirmed that indoor smoking by parents has a direct and significant detrimental effect on the frequency of wheezy when parents smoke inside the house. Furthermore, the association between parental passive smoking and asthmatic wheezing attack frequency is highly significant ($P<0.0001$).
6. Screening for asthma and associated risk factors among urban schoolboys in Abha city **Authors:** Alshehri, M. A.; Abolfotouh, M. A.; Sadeg, A.; Al Najjar, Y. M.; Asindi, A. A.; Al Harthi, A. M.; Al Trabulsi, H.; Al Fifi, S.; Al Frayh, A.;
The objective of the present study was to measure the prevalence of asthma and asthma-related symptoms among male schoolchildren in Abha City and to determine some of the possible risk factors influencing its occurrence. A randomly selected sample of 4300 male school children aged 7 to 15 years in Abha were subjected to a previously validated questionnaire for asthma to be completed by parents. Asthma was identified based on the Rush Medical College and International Study of Asthma and Allergies in Children questionnaire. In addition, information on asthma family history, asthma-related symptoms, other atopic conditions, smokers in the family, pet ownership and monthly family income was collected. The overall prevalence of asthma was 9% (95% Confidence Interval: 7.73%-9.67%). Doctor-diagnosed asthma was reported by 4%, exercise-induced asthma by 4% and wheezing in the past year by 8%. Multiple logistic regression analysis showed that positive family history of an atopic condition (Odds Ratio=437.11, $P<0.001$), pets' ownership (Odds Ratio=2.91, $p<0.001$), and lower monthly family income (Odds Ratio=2.00, $P<0.02$) were significant factors correlated with the development of asthma.
7. Epidemiology of bronchial asthma among schoolboys in Al-Khobar city, Saudi Arabia **Authors:** Al-Dawood, K. M.;
This cross-sectional study aimed to determine the prevalence of bronchial asthma among Saudi schoolboys in Al-Khobar city. The methodology included distributing a self-administered questionnaire from the parents of 1482 schoolboys who satisfied the study's selection criteria. Results: The prevalence rate of Questionnaire Diagnosed Asthma and Physician Diagnosed Asthma were 9.5% and 8%. Questionnaire Diagnosed Asthma schoolboys and their parents suffered significantly higher rates of allergenic diseases and environmental factors (pets at home, passive smoking) than boys diagnosed with asthma. Conclusions: The prevalence of Questionnaire Diagnosed Asthma among schoolboys in Al-Khobar city was more than that described earlier. However, this rate was less than those reported from other parts of the Kingdom but higher than those reported from Arab, developing, and European countries. There is evidence that a combination of genetic and environmental factors plays a significant role in the aetiology of this disease. Based on the results of this study, appropriate and practical measures need to be taken to identify causes and initiate control programs.

2.5. Discussion

As far as we know, there has been no previous attempt to research and understand the impact of indoor air pollution on childhood asthma or to address gaseous pollutants triggering asthma in children in the Kingdom of Saudi Arabia. We can therefore justify using a scoping review method that followed rigorous, transparent, and replicable methods. The study focused on indoor air pollution in Saudi Arabia, including Indoor pets, traffic fumes, wood-burning, and passive smoking. Indoor pollution findings were presented based on scholarly peer-reviewed articles on several micro-environments in Saudi Arabia. The review uncovered the lack of empirical evidence on indoor gaseous pollutants in Saudi Arabia, such as NO2, SO2, PM10, PM2.5, and CO2, the most dominant indoor air pollutants in other contexts. Furthermore, there was a lack of science-based mitigation studies that could reduce the emission and exposure of these pollutants in Saudi Arabia.

However, this study also showed that most assessments in Saudi Arabia are based on self-reporting using questionnaires, leading to speculative assessments and their conclusions being based on interpretations rather than quantitative data, as seen in figure 2.4. A proposal for an observational study to address the current gap in this field is presented later in this chapter.

The environmental risk factors affecting asthma are complex, and their impact on asthma are not understood. Furthermore, the study has determined that quality research in this field is extremely limited in the Kingdom of Saudi Arabia. Furthermore, deploying biomedical research techniques, including monitoring air quality, meteorological data, and their impact on respiratory health in terms of differentiating between the individual risk factors for asthma and other respiratory symptoms in children, would assist in tackling the devastating burden of asthma. The impacts of respiratory diseases are due to multiple risk factors, leading to complex issues. Therefore, it is difficult and impractical to address the risk factors using the current collating data that are often biased and subjective.

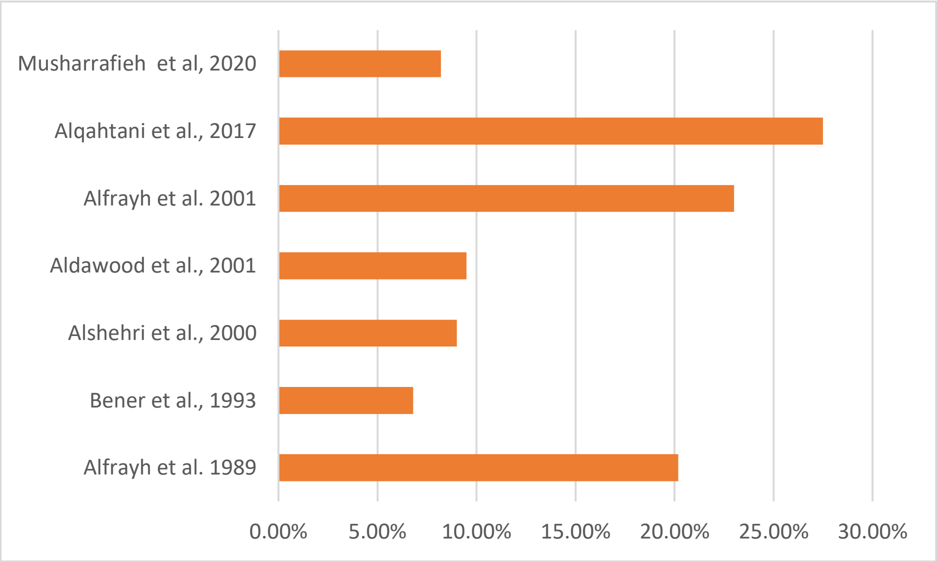


Figure 2.4. The prevalence of childhood asthma from the included studies, 1993-2020.

It is still challenging to identify the individual roles of indoor air pollutants in the reviewed studies and how the individual pollutant may affect the health symptoms as the studies have not conducted individual agent exposure characterisation. In addition, further studies should focus on using reliable tools other than questionnaires for establishing asthma, which is known to be less effective. Therefore, it is impossible to conclude with any confidence level if the health symptoms identified in these studies can be attributed to any of the confounders identified in the studies or from another unidentified contributor (s).

Nevertheless, this review has shown that indoor air quality in Saudi Arabia is less than the recommended standards. These sub-standard air quality conditions support the need for further research that can identify the individual impact of indoor air pollution risk factors and health symptoms. Due to the amount of time, children spend indoors in Saudi Arabia, the indoor environment is crucial to the health and wellbeing of these children. Future observational health-based indoor air quality studies in the Kingdom of Saudi Arabia could focus on designing and measuring multiple indoor pollutants such as bioaerosols, mites, airborne pollutants, and other related environmental factors such as temperature and air circulation in homes and schools. This can be coupled with the frequency of clinic visits and hospital visits due to asthma and other respiratory conditions.

The study highlights the limited research conducted on the impact of indoor air pollution on childhood asthma in the Kingdom of Saudi Arabia (KSA) compared to studies conducted in other countries. For example, research from the United States, such as the National Health and Nutrition Examination Survey (NHANES) and studies by Trasande et al., has extensively explored the association between indoor pollutants like NO2, PM2.5, and asthma prevalence in children, employing rigorous methodologies including objective measurements and longitudinal assessments (Trasande et al., 2016; U.S. Environmental Protection Agency, 2022). Similarly, studies from European countries like Sweden, as demonstrated by Gruzieva et al., have focused on specific indoor pollutants such as tobacco smoke and their impact on childhood asthma, using advanced epidemiological techniques and exposure assessments (Gruzieva et al., 2019).

In contrast, the research landscape in KSA, as outlined in this review, lacks empirical evidence on indoor gaseous pollutants and relies heavily on self-reporting methods, leading to speculative assessments rather than quantitative data (Khoja et al., 2020; Al-Anazi et al., 2018). The absence of robust studies with objective measurements and validated diagnostic criteria in KSA contrasts with the comprehensive investigations conducted in countries like the United States and Sweden, highlighting the need for improved research methodologies and data collection practices in KSA to align with international standards and enhance understanding of indoor air pollution's impact on childhood asthma.

Some limitations apply, primarily if the article covers a wider geographical area than our study scope without providing specifically for Saudi Arabia. Although such a study may be informative, it would not provide any specifics that inform our study. We contacted the respective authors of the studies and inquired about any specific data, even if the data was unpublished. However, from the multiple communication attempts we have not received any feedback or response. Some articles may not be country-specific in their title or abstract and can be missed even if they include studies from Saudi Arabia. However, we can overcome this issue to a certain extent by running a search on Google Scholar and doing a backward search of the relevant review articles described in step 2 of this methodology. Such additional steps also help minimise bias if we fail to include such articles in our scoping review.

Also, the involved studies had some limitations. Being cross sectional studies lacking the time factor impairs the causal relation or correlation. None of them investigated the impact of specific pollutants on asthma in children. Only one study investigated the effect of outdoor pollutants such as traffic fumes and wood burning, and the other six studies specified on passive smoking, pets and history of atopy among the family. The self-reported data through questionnaires filled by children or their parents may be subjected to self-recall bias. The diagnosis of asthma was not verified through pulmonary function tests or medical documents, so the results are subjected to under or over estimation and the prevalence of asthma was highly variable among the different studies.

2.6. Concluding remarks

In this scoping review, we completed a picture of indoor asthma in children in the Kingdom of Saudi Arabia. The study intends to inform and assist public health researchers, clinicians, and policymakers in enhancing the causes and preventative measures and supporting children with indoor asthma in Saudi Arabia. A further belief is that this study scoping can be a precursor to systematic reviews or meta-analyses and help reviewers set their research questions and prioritise and adopt broad inclusion criteria for future systematic reviews and meta-analyses. It is believed that this scoping document offers a transparent protocol approach that will help eliminate some problems and minimise the effect of others while conducting the study.

Furthermore, the reviewed studies have revealed evidence of indoor pollution factors being a significant cause of the disease. However, more robust steps are recommended, particularly the more practical ones needed to identify the causes and introduce control measures to overcome the disease.

2.7. Future Studies recommendations: One-year prospective cohort study

2.7.1. Study overview

The Kingdom of Saudi Arabia is undergoing massive infrastructure development as it diversifies its economy, adding manufacturing, construction and sports to its existing oil and petrochemical industries. These new economic activities necessitate new assessment and mitigation strategies to combat the risks of indoor air pollution as a health threat to exposed populations. Therefore, it is recommended that the following knowledge gaps be scientifically and adequately investigated to understand and mitigate the risks of indoor air pollution on the paediatric population having asthma in the Kingdom of Saudi Arabia.

This study will be a nationwide multi-purpose design to focus on gaseous pollutants CO, NO2, O3, SO2, and three sizes of particulate matter (PM). The study will be conducted at fifteen to twenty buildings in Mecca and Jeddah cities, Saudi Arabia, to explore the relationship between indoor air pollutants and asthma symptoms among schoolchildren. The selected homes for participation will follow a two-stage cluster sample design that includes stratification by geographic area and population density. The sample should comprise houses and schools located in areas with high, medium, and low population intensity. The prioritised areas will include an urban industrial or visitor area, a semi-urban area outside the city centre, and a rural area more than 80 km outside both cities.

Additionally, an area of low population density with negligible air pollutants exposure having similar social and economic characteristics will be identified to maximise contrasts in exposure levels to the various levels of household air pollutants. The study will be conducted over the period between the spring to early summer. It will comprise a baseline study and a 12-monthly follow-up study of the cohort in which all examinations, including a Health and exposure questionnaire, lung function testing in the form of spirometry, exhaled nitric-oxide test and allergy testing.

2.7.2. Subject recruitment

Children with asthma will be recruited for the study through outpatient health clinics. Participants will be selected from those attending their regular follow-up appointments in healthcare settings located in three prioritized areas. The recruitment process will adhere to specific eligibility criteria consistent with those used in the initial study. These criteria include an age range of 12 to 17 years, verified medical documentation confirming the diagnosis of asthma, information on the duration and degree of control of the disease, details of current medications, and confirmation of the absence of other lung diseases or significant illnesses. To determine the optimal number of participants for robust and statistically significant results, a comprehensive sample size calculation will be conducted. This calculation will consider the study's objectives, expected effect sizes, and the statistical power required to detect meaningful differences or associations.

2.7.3. Assessment of Environmental Exposure

Home inspections.

A public health researcher will inspect participant residencies. The basic information included the number of children, room volume (m3), heating and ventilation system types, and mould growth or dampness signs. In addition, Crowdedness (Ns/m2) will be calculated as the average person per m2 of the room floor area and a dust/ air sample collection.

Allergens in the saved samples from grasses, trees, weeds, mold, pet dander, pests, and dust mites.

Enzyme-Linked Immunosorbent Assay (ELISA) and amplified ELISA will be applied to determine the allergen levels in the samples, as suggested by Rosias et al (Rosias et al., 2004).

Gaseous indoor air pollutants.

Chemical air pollutants will be measured indoors for SO2, NO2, and O3All these samplers are small, silent, and lightweight without electricity. The sampling technique is based on the molecular diffusion of gases which are quantitatively collected on an impregnated filter or an adsorbent material, giving a concentration value integrated over time. The final concentrations will be calculated by accredited laboratories specialising in these sampler analyses, reported as the average value across the 7-day measurement period. In addition, the ratios (I/O) between indoor and outdoor air pollutant concentrations will be calculated to evaluate how outdoor air will affect indoor air.

2.7.4. Air monitoring data

Complete monitoring data for outdoor pollutants carbon monoxide (CO), nitrogen oxides (NOx), nitrogen monoxide (NO), nitrogen dioxides (NO2), sulfur dioxide (SO2), particulate matter with a 50% cut-off aerodynamic diameter of 2.5 (PM2.5), and 10 (PM10) will be obtained periodically for the period of study from the air pollution and meteorological data of the Royal Commission Environmental Control Department in Al Jubail, Saudi Arabia. The data will be collected from seven fixed-site monitoring stations across various locations within Mecca. The data selection will include the following pollutants: PM10, PM2.5, SO2, NO2 and CO. Temperature (T), wind speed (WS), direction (WD), and relative humidity (RH). The data from all stations will be automatically transmitted wirelessly continually at 10-minute intervals to a central computer and filed explicitly for this project at the central computer of the Royal Commission Environmental Control Department in Al Jubail. The data file will be transferred to the research team in a format and transfer method to be agreed with the RCECD.

2.7.5. Asthma severity assessment

Pulmonary function assessments for the school cohort study are conducted during the school visits, comprising spirometry conducted according to the American Thoracic Society (ATS) guidelines(Pellegrino et al., 2005) and fractional-exhaled nitric oxide measurement (FeNO) and Composite Asthma severity index. The asthma severity assessment tools will be conducted at baseline and in the follow-up period

1. **Spirometry:** This is a common pulmonary function test that measures how much air a patient can inhale and exhale, as well as how quickly they can exhale. Spirometry is crucial for the diagnosis and assessment of asthma, as it can provide objective data on lung function. The Forced Expiratory Volume in one second (FEV1) is a key measure in spirometry used to assess asthma severity.

2. **Fractional-exhaled nitric oxide (FeNO)** Fractional-exhaled nitric oxide (FeNO) testing is another important tool used in the assessment and management of asthma. This non-invasive test measures the level of nitric oxide in the exhaled breath, which is a marker of inflammation in the airways. Elevated levels of FeNO indicate eosinophilic inflammation, which is often associated with asthma.

2.7.6. Spirometry

Spirometry tests will be conducted by a specialist technician using a hand-held volume flow spirometer. The participants' characteristics will be obscured and security coded. As protocol, the spirometry testing will be performed in a semi-Fowler's or upright position with nose clips. Each participating child will perform a maximum of eight trials to produce three acceptable chart curves. Testing reproducibility criteria will be based on the best two FEV1 and FVC tracings. The primary interest lung function indices include Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC). The best FEV1 and FVC results are used regardless of whether they belong to the exact tracing. Participants are instructed not to take asthma inhalers twelve hours before testing or oral asthma medications two days before the test. Participants are administered an inhaled bronchodilator and have spirometry tests repeated after a minimum of 10 min waiting periods. All participating children are assessed during school hours.

2.7.7. Fractional-exhaled nitric oxide (FeNO)

Fractional-exhaled nitric oxide (FeNO) measurement is a recognised non-invasive method for assessing allergic airway inflammations (Quirce et al., 2010). The Fractional-exhaled nitric oxide (FeNO) testing is conducted by a trained practitioner using a hand-held nitric oxide sampling device. The child is advised to sit comfortably and breathe normally for about five minutes to acclimatise. After that, the child is instructed to inhale close to total lung capacity (TLC). An immediate exhalation follows this at a constant flow rate of 50 ml/s for at least four seconds. The American Thoracic Society and European Respiratory Society recommend two measurements to be performed with a time gap of not less than thirty seconds (Nici et al., 2006)

Children with upper and lower respiratory tract infections will defer their measurements until recovery or have their measurements taken with the infection state recorded. The participant's height and weight will be measured, and the information will be used to compute the body mass index (BMI). Ambient NO and temperature are also recorded.

2.7.8. Ethical considerations

After the study protocol and ethics approval by the Institutional Review Board at the University of Strathclyde and the Saudi ministry of health and education, meetings will be scheduled with the school principals to inform them about the study and obtain their permission and willingness to take part in the study. In addition, each child's parent or legal guardian will be provided with a research package containing a Participant Information Sheet (PIS), an Informed Consent Form (ICF), the study plan and a flyer designed to enhance the awareness of people living in Makkah and Jeddah for recruitment purposes. All documents and forms will be provided in Arabic, and the completed content form will be formally translated into English as proof of relevant documentation.

Chapter three: Knowledge, attitude, and practices of primary healthcare providers in Makkah regarding the assessment and management of acute asthma

Abstract

Background

Asthma is a major non-communicable disease (NCD), affecting both children and adults. In 2019, asthma affected approximately 262 million people and caused 461,000 deaths worldwide. In Saudi Arabia, asthma control remains a big problem, with only 5% of patients having the disease under control.

Objective

This study aims to explore knowledge, attitude, and practices of primary healthcare providers in Makkah region regarding the assessment and management of acute asthma.

Methods

A self-administered questionnaire was distributed online among primary healthcare providers working in thirty primary healthcare clinics (PHCs) in Makkah region.

Results

The mean knowledge score was 5.01 (±2.79), with a percentage of 38.55 (±21.46) %. While the mean attitude score was 3.51 (±2.06) with a percentage of 43.86 (±25.80) %. The mean practice score was 4.86 (±2.29), with a percentage of 48.65 (±22.92) %. The mean total score was 13.38 (±5.87), with a percentage of 43.18 (±18.95) %.

Conclusion

This study shed light on the reduced level of knowledge, attitude, and practice about asthma among primary healthcare providers in Makkah, KSA. The results highlight the need for more educational activities with role-plays and case scenarios.

1.1. Introduction

According to the World Health Organization(World Health Organization (WHO), 2023), asthma is a major non-communicable disease (NCD), affecting both children and adults. It affected approximately 262 million people in 2019 and caused 461,000 deaths. In addition, asthma is the most common chronic disease among children (Global Initiative for Asthma (GINA), 2022).

The prevalence of asthma varies from one country to another and ranges from 1.11% (in Nepal) to 11.25% (in USA) (Our World in Data (OWD), 2019). In Saudi Arabia, asthma prevelence increased from 2.16% in 1990 to 2.77% in 2019 as shown in Figure 2.4 (Our World in Data (OWD), 2019).

Asthma control remains a big problem in Saudia Arabia, with only 5% of sufferers having it under control, 31% having it somewhat controlled, and 64% having it uncontrolled.(Yousef et al., 2015) Alsahn et al. found that the estimated prevalence of uncontrolled asthma was 45.2% from a cross-sectional descriptive study among 292 patients in the outpatient pulmonary clinic at King Fahad Medical City in Riyadh (Alsahn et al., 2017). Many key reasons contribute to the spread of this burden, including a lack of information, apprehension when using new medicines, and a lack of awareness of the necessity of asthma control, different studies indicated the lack of understanding GINA guideline among physician, pulmonary therapist, and nursing during treating asthma patients in Saudi Arabia (Alsahn et al., 2017, Yousef et al., 2015, Assiri et al., 2021).

The Saudi Initiative for Asthma (SINA) has made excellent efforts to improve the quality of asthma care at all levels, including primary healthcare centers (PHCCs). They have published and updated the National Asthma Guidelines and made it available in various formats; online document, and pocket guide for healthcare professionals (Al-Moamary et al., 2016). To date, few studies explore knowledge, attitude and practices of health team providers working at primary healthcare facilities (PHC) (Alatawi and Alsayed, 2021, Assiri et al., 2021).

Enhancing the knowledge, attitude, and practice regarding asthma management among healthcare providers at Primary Health Centers (PHCs) in Saudi Arabia could contribute to better adherence to asthma management guidelines. Implementing a well-structured training program may potentially lead to improved patient outcomes and satisfaction, increased patient productivity, and potentially more efficient healthcare spending.

1.2. Objective of the study

The study aims to explore knowledge, attitude and practices of health team providers working at PHC in Makkah region regarding the assessment and management of acute asthma. Makkah is the third largest region in Saudia Arabia and is considered the most populous region with a population of 8,557,766 as of 2017, with different foreign nationalities.

1.3. Method

Based on the literature review, a survey was designed composed of a section for participants' demographics and three domains: knowledge, attitude, and practice. The questionnaire included 31 questions. The questions were adapted from the Gina guidelines questions to HCP and were categorized according to its specified domain. The self-administered survey was distributed among Primary healthcare professionals in primary healthcare centers in Makkah region. The centers were randomly selected to ensure an unbiased representation of healthcare settings within our target population. Each center in the list was assigned a unique numerical value. To ensure transparency and eliminate subjectivity, we employed a random number generator, a tool widely recognized for its unbiased and objective nature. The random number generator generated a sequence of random values within the range corresponding to the numerical assignments of the centers. Using the random number generator outputs, we selected a subset of centers based on the random values generated. This ensured that the chosen centers were entirely independent of any personal bias or preconceived notions.

By utilizing this random number generator-based approach, we aimed to minimize selection bias and increase the generalizability of our findings to a broader population of healthcare professionals. Thirty centers were selected out of 60 centers in Makkah region.

Convenience sampling was used for selecting the respondents. Convenience sampling was chosen for this study due to its practicality and feasibility in accessing a specific population of interest within the available time and resource constraints. As cross-sectional studies often aim to gather data from a wide range of participants efficiently, convenience sampling provided us with a means to conveniently recruit participants from easily accessible sources, such as healthcare settings and professional networks.

Statistical analysis methods

The continuous variables were described as mean and standard deviation. Categorical variables were described as frequency and percentage. An independent t-test was performed to test for the difference in the total score between categorical variables with two continuous levels. For categorical variables with more than two levels, One-way ANOVA (with Tukey post hoc test used if ANOVA result was statistically significant). Eta correlation was used for correlating the total score with categorical variables. Variables with a bivariate analysis p-value less than 0.2 were considered for the multiple linear regression analysis.

Data preparation for analysis was conducted in MS Excel 365, while analysis was conducted in IBM SPSS version 28. The alpha level for hypothesis testing was set at 0.05; therefore, any p-value less than this level was considered statistically significant.

1.4. Results and Discussion

The current study included 385 health care providers' responses, 257 (66.8%) of them were males, while 128 (33.2%) were females. The mean age of the responders was 35.51 (±7.39) years. The respondents were mostly Family Medicine and general practitioners (38% each). Most of the participants work in the private sector (63%). Most of the respondents were family medicine physicians (37%) and general practitioners (38%). The full baseline characteristics are detailed in table 3.1. The mean knowledge score was 5.01(±2.79), with a percentage of 38.55 (±21.46) %, while the mean attitude score was 3.51 (±2.06) with a percentage of 43.86 (±25.80) %.

The mean practice score was 4.86 (±2.29), with a percentage of 48.65 (±22.92) %. And the mean total score was 13.38 (±5.87), with a percentage of 43.18 (±18.95) %. The full results of the scores are detailed in table 3.2. The mean scores are represented in figure 3.1.

The knowledge questions revealed that the knowledge was highest about inhaled steroids (241, 62.6%), and lowest (27, 7.0%) for the long-term control of asthma.

The Attitude questions proved that the best attitude was about the recommendation for most patients presenting with an acute asthma exacerbation (227, 59.0%), while the least attitude was about the long-term management of asthma patients without symptoms between attacks (86, 22.3%). The practices questions showed that the best practice was about asthmatic patients' categorization (273, 70.9%), while the lowest practice was about the primary diagnosis of asthma (109, 28.3%). The list of the questions and the responses are detailed in table 3.3.

The t-test proved that there was no statistical significance between the total score and the gender of the healthcare provider, neither the institution type. The full comparisons are detailed in table 3.4.

The eta correlation between the total score and the specialty was moderate, 0.49, and 0.45, respectively. These results indicate that these variables contribute approximately 25% to the variability in the total score. The results of correlation are summarized in table 3.5.

The multivariate linear regression model had adjusted $R^2 = 0.3$. Two variables had significant contributions to the model: consultant level and specialists. The consultant had higher level of total score by 9 points compared to Family Medicine (b=9.3, p<0.001), and specialists had higher score by 4 points compared to Family Medicine (b=3.8, p=0.04).

Table 3.1 Baseline characteristics

Baseline characteristic	
Gender	N (%)
Male	257 (66.8)
Female	128 (33.2)
Age (mean, SD)	35.51 (±7.39)
Specialty	
Family Medicine	146 (37.9%)
General practitioner	145 (37.7%)
Consultant Respiratory	21 (5.5%)
Specialist Respiratory	73 (19.0%)
Institution	
Private sector	243 (63.1%)
Public hospital	142 (36.9%)

Table 3.2 Mean knowledge, attitude, practice, and total scores

Item	Mean (SD)
Knowledge score	5.01 (±2.79)
Knowledge score %	38.55 (±21.46)
Attitude score	3.51 (±2.06)
Attitude score %	43.86 (±25.80)
Practice score	4.86 (±2.29)
Practice score %	48.65 (±22.92)
Total score	13.38 (±5.87)
Total score %	43.18 (±18.95)

Table 3.3 Responses to questions

Domain/questions	Number of correct answers (%)
Knowledge	
1.Which statements regarding factors that contribute to the severity of asthma are false?	168 (43.6%)
2.Which of the following is false regarding the use of short-acting inhaled β2-agonists?	145 (37.7%)
3.Which of the following statements regarding spirometry is false?	120 (31.2%)
4.Which of the following is not a risk factor for death in an adult patient with asthma?	45 (11.7%)
5.Which of the following is not suggestive of asthma?	163 (42.3%)
6.Which of the following is not an inhaled steroid?	241 (62.6%)
7.Which of the following have not been shown to be associated with inhaled corticosteroids?	155 (40.3%)
8.Which of the following is not a direct cause of airway obstruction in asthma?	132 (34.3%)
9.Which of the following is false regarding the use of long-acting inhaled β2-agonists?	183 (47.5%)
10.Which of the following does not have anti-inflammatory properties?	202 (52.5%)
11.Which of the following statements regarding long term control of asthma is false?	27 (7.0%)
12.Patients with asthma may develop irreversible airflow obstruction because of:	182 (47.3%)
13.Which of the following statements regarding the use of inhaled corticosteroids is false?	166 (43.1%)
Attitude	
C14.Which of the following is not recommended to modify indoor allergens in the homes of asthmatic. patients?	202 (52.5%)
15.Which of the following is recommended for most patients presenting with an acute asthma exacerbation?	227 (59.0%)
16.Which of the following techniques for using inhalers is unacceptable?	140 (36.4%)
17.Which of the following best correlates with bronchial hyper responsiveness?	176 (45.7%)
18.Which of the following treatments is not recommended for most patients presenting with an acute asthma exacerbation?	152 (39.5%)
19.Which of the following medications is least indicated for long term control of asthma?	174 (45.2%)
20.For asthma patients without symptoms between attacks, which of the following statements regarding the long-term management is not correct?	86 (22.3%)
21.For a patient with Moderate Persistent asthma who is inadequately controlled on daily low dose inhaled steroids, which of the following regimens is not appropriate?	194 (50.4%)
Practice	
22.A 4 yo child, uses low dose inhaled corticosteroids (ICS) daily plus as needed inhaled SABA (Short-acting-beta2-agonist) to control asthma. This patient would be classified as:	250 (64.9%)
23.A 10 yo child, uses medium dose of ICS- formoterol as maintenance and reliever therapy (MART). This patient would be classified as:	273 (70.9%)
24.A 30 yo adult, uses high dose ICS-LABA (long-acting-beta2-agonist). This patient would be classified as:	213 (55.3%)
25.A 20 yo patient requires oral corticosteroids (OCS) and suffers from frequent exacerbations (≥ 2 /year).	227 (59.0%)
26.At which disease severity should anti-inflammatory medications be initiated?	206 (53.5%)
27.Which of the following data sets suggests an asthmatic patient at greatest risk of imminent respiratory failure?	184 (47.8%)
28.Which of the following data sets is most suggestive of asthma as a primary diagnosis? (Each value is % predicted)	109 (28.3%)
29.Which of the following is not consistent with Mild Persistent asthma?	121 (31.4%)
30.All of the following have been documented with patient education in the management of asthma except:	163 (42.3%)
31.Which of the following are necessary to diagnose asthma?	127 (33.0%)

Table 3.4 Comparing the Total score between factors with two levels (t-test)

Group	Mean total score	P-value
Gender		
Male	13.74	0.09
Female	12.67	
Institution:		
Public	13.65	0.49
Private	13.23	

Table 3.5 Correlation of total score with categorical variables*

Total score	
specialty	0.49

* Eta correlation was used

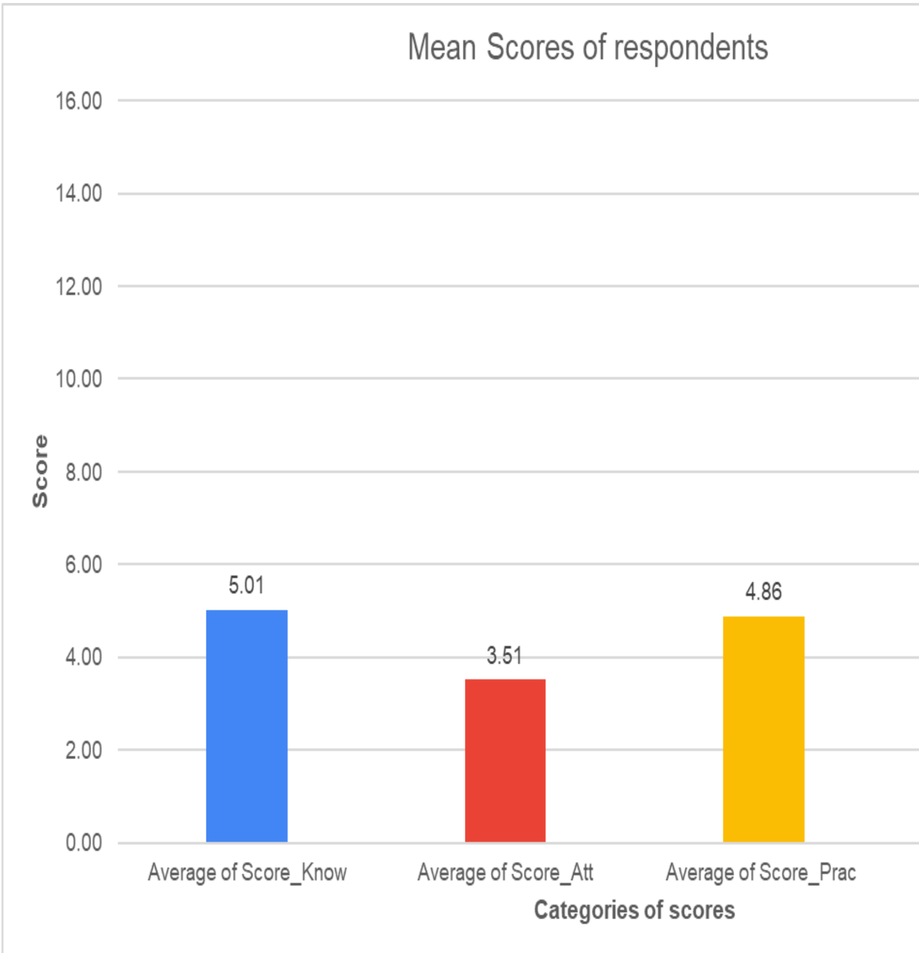


Figure 3.1: Average scores of the survey domain

1.5. Discussion

In this study, we aimed to explore the knowledge, attitude, and practice of the healthcare team at PHC in the Makkah region regarding the assessment and management of acute asthma. Unfortunately, the overall score of the questionnaire was 43.7%, and none of the scores from all three domains achieved 50%.

The respondents who were physicians and working in the private sector, achieved mean scores of 38.5%, 43.8%, and 48.6% for the knowledge, attitude, and practice domains respectively. For the knowledge domain, our results are better than those of Yousef et al.(Yousef et al., 2015) who found deficient knowledge about asthma among primary healthcare physicians in Al-Khobar City, Saudi Arabia (only 8% of their sample had good knowledge about asthma). However, our results are less than that of Assiri et al.,(Assiri et al., 2021) who found that 63.5% of PHC physicians had "good scores" in Aseer region, Saudia Arabia. This can be attributed to the level of training in our study compared to theirs. In Assiri et al(Assiri et al., 2021) study most of the participants were general practitioners (47.5%), specialists and consultants (52.5%); however, in our study, the participants were mostly Family Medicine (37.9%) and general practitioners (37.7%). This is obvious in our results as well, with consultants having higher level of total score by 9 points compared to Family Medicine ($b=9.3$, $p<0.001$), and specialists having higher score by 4 points compared to Family Medicine ($b=3.8$, $p=0.04$).

For the attitude, our participant's average score was 43.8%, highlighting a poor-to-average attitude. This comes close to Assiri et al(Assiri et al., 2021) results who found that 44% of PHC physicians in Asser region had positive attitude toward acute asthma management.

For the practice, the average score in our study was 48.6%. Assiri et al.(Assiri et al., 2021) found that the practice was "good" for 53.5% of their participants. This also can be attributed to the difference in the population and their levels of training and experience.

A cross sectional study included 698 general practitioners from Germany, The Netherlands, Norway, and Sweden, and 94 specialists from the Slovak Republic used a questionnaire to assess their knowledge and attitudes toward implementation of asthma management guidelines. German and Slovakian doctors seem to attach less importance to the inflammatory features of asthma than the doctors from the other three European countries with higher use of steroids and antibiotics and less depending on short acting bronchodilators during asthma exacerbations. (Lagerlov et al., 2000)

A systemic review addressed the impact of different interventions used to improve adherence to asthma management guidelines among health care providers included 68 studies found that decision support tools, feedback and audit, and clinical pharmacy support were most likely to improve provider adherence to asthma guidelines(Okelo et al., 2013)

Our study highlights significant implications for public health. The scores of the domains and the total score were less than 50% on average. This rings a bell for the need for more educational activities for healthcare professionals. Adoption of specialized asthma clinics, like the one in Oman, may be another solution for better educational and management purposes.

Our study covered most of the primary care centers in the Makkah region. We surveyed healthcare providers with different levels of specialties.

This study certainly has some limitations. The questionnaire was relatively lengthy, which may have introduced some sort of bias in the responses and led to a reduced level of knowledge, attitude and practice compared to other studies in Saudi Arabia.

Moreover, the sample size was not powered enough; however, the results may guide further research in the future.

Enhancing Primary Healthcare Workers' Knowledge of Asthma Management guidelines is crucial for improvement of asthma control. It should start by assessment of current knowledge gap among PHC providers and areas for improvement through Surveys and regular evaluation of health care personnel. comprehensive educational materials should be developed in collaboration with asthma experts and organizations. Updated concise local guidelines in form of infographics, charts and diagrams should be accessible in each PHC facility. Also providing training programs, webinars, and interactive workshops to deal with different case scenarios in interactive models to cover key topics on asthma diagnosis, treatment, and prevention. Involvement of Pharmaceutical Companies can provide additional support and Promote Collaboration in Asthma Management and outcomes Research. Evaluation and feedback mechanisms should be established to assess knowledge retention and application, with regular reporting and adaptation of educational materials.

1.6. Conclusion

This study has provided a critical insight into the current state of knowledge, attitude, and practices among primary healthcare providers in the Makkah region regarding the assessment and management of acute asthma. The findings indicate that there is a moderate level of understanding and application of asthma management principles among healthcare professionals in this region. With average scores across knowledge, attitude, and practice domains not surpassing 50%, it becomes evident that there is considerable room for improvement.

The results underscore the importance of ongoing education and training for healthcare providers in asthma management. This is particularly crucial given the chronic nature of asthma and its significant impact on patients' quality of life.

Enhancing the skills and knowledge of healthcare providers is essential to improve the quality of care for asthma patients and adhere more closely to established asthma management guidelines.

Future initiatives might include targeted training programs, more extensive use of decision support tools, and the establishment of specialized asthma clinics. These measures could not only bolster the confidence and competence of healthcare providers in managing asthma but also lead to better patient outcomes and more effective control of this widespread condition.

Despite the study's limitations, such as the potential response bias due to the questionnaire's length and the unpowered sample size, the findings lay a foundation for further research and action in this critical area of public health. By addressing these gaps in knowledge and practice, healthcare providers in the Makkah region can be better equipped to manage acute asthma effectively, ultimately contributing to improved health outcomes for patients suffering from this chronic disease.

Chapter four: Prescription pattern for Asthma medications: Exploring the Prescription Cost Analysis data in UK in 10 years (2011-2021)

4.1. Introduction

4.1.1. COVID-19 pandemic

In December 2019, an outbreak of pneumonia of unknown etiology was noticed in Wuhan, a city in Hubei Province of China (Chen et al., 2020). The patients presented mostly with symptoms of dry cough, dyspnoea, fever, and in severe cases with respiratory failure and multiple organ damage (Xu et al., 2020). Later on, the causative agent was identified by the Chinese Centre for Disease Control and Prevention as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on the 7th of January 2020 (Lu et al., 2020).

4.1.2. Asthma and COVID

The impact of COVID-19 pandemic on healthcare system during subsequent waves exceeded the immediate effect of viral morbidity and mortality to affect quality of care for other chronic conditions and elective procedures and resulted in psychological and economic burden. The continued disruption of supply chain resulted in resources restriction and critical shortfalls due to travel restrictions, giving priorities to critical care units treating COVD-19 patients and providing personal protective equipment PPEs(Ashley et al., 2022). A critical shortage in blood supply has also been reported (Wang et al., 2020b).

During the early months of the COVID-19 pandemic, there was a major concern regarding the huge need for asthma inhalers. In the United States, there was an increase in adherence to controller medications during March, 2020(Kaye et al., 2020). In UK, a surge in prescription of asthma medications was reported. There were 212.96% and 170.78% increase in prescriptions of Clenil Modulite and Fostair -the most frequently prescribed inhalers for asthma- in March 2020 (Bloom et al., 2021). A shortage has been reported by manufactures for certain inhalers during March 2020(Bloom et al., 2021). This coincided with a decrease in number of reported asthma exacerbations presenting to primary health care facilities(Shah et al., 2021). This could also be attributed to the public health message during COVID-19 pandemic which focuses on prevention, social distancing, wearing face masks and staying at home which resulted in reduced exposure to viral infection and also adherence of patients to their medications. Dhruve H et al had reported improved Overall adherence to ICS in 2020 in comparison to 2019 across England ($P < .001$), and increase in the proportion of patients meeting “good adherence” (≥75%) from 33.9% in 2019 to 42.0% in 2020 ($P < .001$) (Dhruve et al., 2022). Some authors suggest a false decrease in number of exacerbation due to the fear from presenting to health care facilities during the COVID-19 pandemic.

It has been reported that during this pandemic the number of admissions for common emergencies such as heart attack, stroke or asthma exacerbations has been decreased(Rosenbaum, 2020), this does not necessarily reflect lower incidence but may be due to less detection. Many studies have described the impact of delayed immunizations, elective surgeries and dental procedures, organ transplantation which can influence the type of procedure, recovery time and patient outcomes. The number of emergency visits has decreased by 40% in many communities across US (Hartnett et al., 2020) and the proportion of infectious disease–related visits was four times higher during the early pandemic period(Hartnett et al., 2020). There was a 23.7%-27.8% increase in visits for exacerbations of chronic medical conditions(DeLaroche et al., 2021). A CDC report identified about 300,000 excess deaths in the U.S. from January 26 through October 3, 2020, up to 60% of deaths are directly COVID-19 related while the remaining deaths may be attributed to delayed medical care and exacerbation of underlying chronic conditions(Rossen et al., 2020).

4.2. Aims

The aim of this study was to investigate the utilization trends of asthma medications between 2011 and 2021 in the four UK countries.

4.3. METHODS

4.3.1. Study Design

This analysis was a retrospective repeated cross-sectional national study using the publicly available Prescription Cost Analysis (PCA) datasets over 10-years from 2011 to 2021 in the four countries of United Kingdom: England, Scotland, Wales, and North Ireland.

4.3.2. Data sources:

All data were extracted from the NHS Prescription Cost Analysis (PCA) databases which provides details of the costs and volumes of all prescriptions dispensed in the community in the four countries.

Table 4.1. List of output classes and ingredients:

Single/Combined	Class	Ingredient
S	ICS	Beclomethasone [ICS]
S	ICS	Budesonide [ICS]
S	ICS	Ciclesonide [ICS]
S	ICS	Fluticasone [ICS]
S	ICS	Mometasone [ICS]
S	LABA	Formoterol [LABA]
S	LABA	Formoterol CAP [LABA]
S	LABA	Formoterol PWR [LABA]
S	LABA	Indacaterol [LABA]
S	LABA	Olodaterol [LABA]
S	LABA	Salmeterol [LABA]
S	LAMA	Aclidinium [LAMA]
S	LAMA	Tiotropium CAP [LAMA]
S	LAMA	Tiotropium SOLN[LAMA]
S	LAMA	Umeclidinium [LAMA]
S	MCS	Cromoglicate [MCS]
S	MCS	Nedocromil [MCS]
S	SABA	Salbutamol [SABA]
S	SABA	Terbutaline [SABA]
S	SAMA	Ipratropium [SAMA]

C	LABA+ICS	Fluticasone [ICS]+Salmeterol [LABA]
C	LABA+ICS	Formoterol [LABA]+Beclomethasone [ICS]
C	LABA+ICS	Formoterol [LABA]+Budesonide [ICS]
C	LABA+ICS	Formoterol [LABA]+Fluticasone [ICS]
C	LABA+ICS	Indacaterol [LABA]+Mometasone [ICS]
C	LABA+ICS	Vilanterol [LABA]+Fluticasone [ICS]
C	LABA+ICS+LAMA	Formoterol [LABA]+Beclomethasone [ICS]+Glycopyrronium [LAMA]
C	LABA+ICS+LAMA	Formoterol [LABA]+Budesonide [ICS]+Glycopyrronium [LAMA]
C	LABA+ICS+LAMA	Indacaterol [LABA]+Mometasone [ICS]+Glycopyrronium [LAMA]
C	LABA+ICS+LAMA	Vilanterol [LABA]+Fluticasone [ICS]+Umeclidinium [LAMA]
C	LABA+LAMA	Formoterol [LABA]+Aclidinium [LAMA]
C	LABA+LAMA	Formoterol [LABA]+Glycopyrronium [LAMA]
C	LABA+LAMA	Indacaterol [LABA]+Glycopyrronium [LAMA]
C	LABA+LAMA	Olodaterol [LABA]+Tiotropium [LAMA]
C	LABA+LAMA	Vilanterol [LABA]+Umeclidinium [LAMA]

***Check appendices for data cleaning and aggregation methods**

4.3.3. Study subjects.

Asthma generic medications available in the UK were grouped into five categories according to BNF classification into

Inhaled corticosteroids ICS

Long-Acting Beta 2 agonist LABA

Long-acting muscarinic antagonists LAMA

Short acting Beta agonists SABA

Mast cell stabilizers (MCs)

And their combination together

The combination process included the medicine's name, strength, quantity, cost, and formulation. Data from all four countries were extracted from 2011 to 2021. PCA datasets contain aggregated-level information on all dispensed asthma prescriptions in the United Kingdom primary care setting.

Utilization and prescribing patterns of inhalers were assessed using the prescription costs analysis (PCA) data.

Also, the population of each of the four countries was used to obtain an accurate comparison between four countries. This was the estimated population at the mid-year point in UK.

The total cost of all prescriptions was divided 12 and then divided by Mid-year population number according to offices of National statistics and then multiplied by 1000.

4.3.4. Study outcomes

The number of asthma prescriptions dispensed in the four countries and the cost of these items per 1000 inhabitants / year.

Defined Daily Doses (DDD):

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Secondary outcomes

The trends of dispensing asthma medications throughout the years

4.3.5. Ethical approval

Ethical approval was not required as this study used publicly available datasets in the United Kingdom. No participants were involved in the study so no informed consent was needed.

4.5. Results

4.5.1. Number of all items/100,000 inhabitant in the UK and each country

Table 4.2 represents the number of items of all asthma medications dispensed per 100,000 MYP (Measure of Prescribed Items) in the UK population over the period of 11 years from 2011 to 2021. The trend dispensing was increasing till 2016 then had a plateau phase till 2019. A peak was noticed in 2020 when it reached the maximum then started to decline towards the baseline in 2021. The highest number of items dispensed was in 2020 with 94,754.4 items per 100,000 MYP, while the lowest number was in 2011 with 83,833.9 items per 100,000 MYP. The relative and the absolute change and mean annual change.

Table 4.2. Items per 100K MYP = (Sum of Items/ MYP) x100000 for all classes in the UK

Year	Items per 100K MYP [UK]
2011	83833.9
2012	87226.9

2013	88130.8
2014	90992.5
2015	91797.1
2016	92746.6
2017	91612.0
2018	90831.8
2019	91069.6
2020	94754.4
2021	90764.7

Figure 4.1 represents the number of items of all classes of asthma medications per 100,000 MYP dispensed in England, Northern Ireland, Scotland, and Wales from the year 2011 to 2021. Wales had the highest number of items per 100,000 MYP followed by Northern Ireland while Scotland, and England had the lowest number of items throughout the years.

In 2011, the number of items per 100,000 MYP was highest in Wales (118,527.3), followed by Northern Ireland (88,424.1), Scotland (85,644.8), and England (81,494.9). However, in the subsequent years, there was inconsistent increase in England in number of items per 100,000 MYP, which increased from 81,494.9 in 2011 to 92,635.2 in 2020.

The trend in Wales also shows an increase from 118,527.3 in 2011 to 139,397.9 in 2020, which is the highest among all four countries in that year. Northern Ireland also shows a consistent increase, from 88,424.1 in 2011 to 108,020.5 in 2020. In contrast, Scotland shows a decline from 85,644.8 in 2011 to 81,880.7 in 2021.

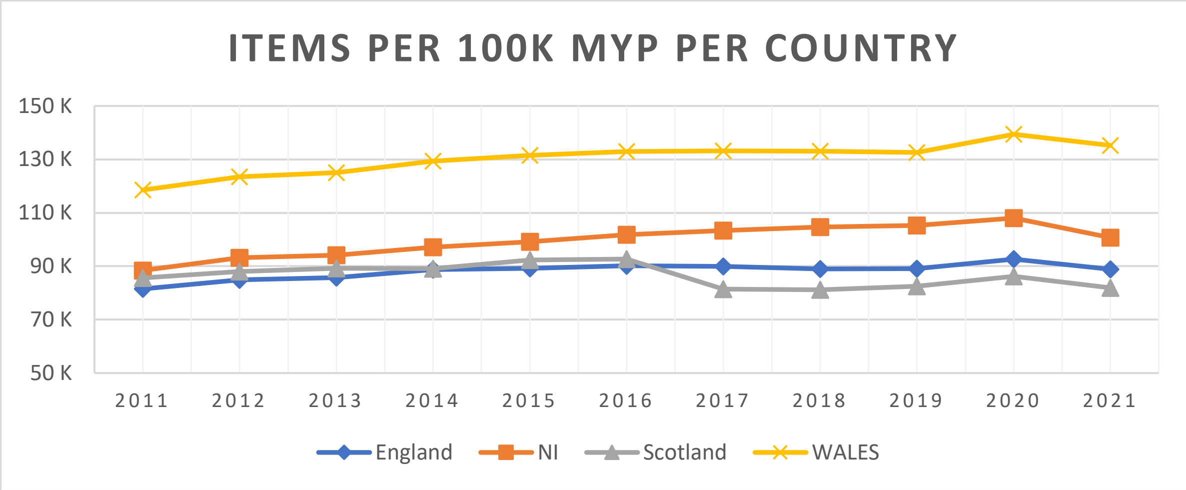


Figure 4.1: All items/100K MYP per each country

4.5.2. Number of items of ICS/100,000 inhabitant

Figure 4.2 shows the number of dispensed items of inhaled corticosteroids (ICS) per 100,000 MYP in England, Northern Ireland, Scotland, and Wales from 2011 to 2021. Overall, there is a gradual decrease in the number of dispensed ICS items in all countries throughout the years, except for a slight increase in 2020.

In 2011, Wales had the highest number of dispensed ICS items per 100,000 MYP, followed by England, Scotland, and Northern Ireland. However, there was a consecutive increase in trend of dispensing of ICS in Northen Ireland over time. By 2021, the dispensing in Scotland had the lowest number of dispensed ICS items, followed by England.

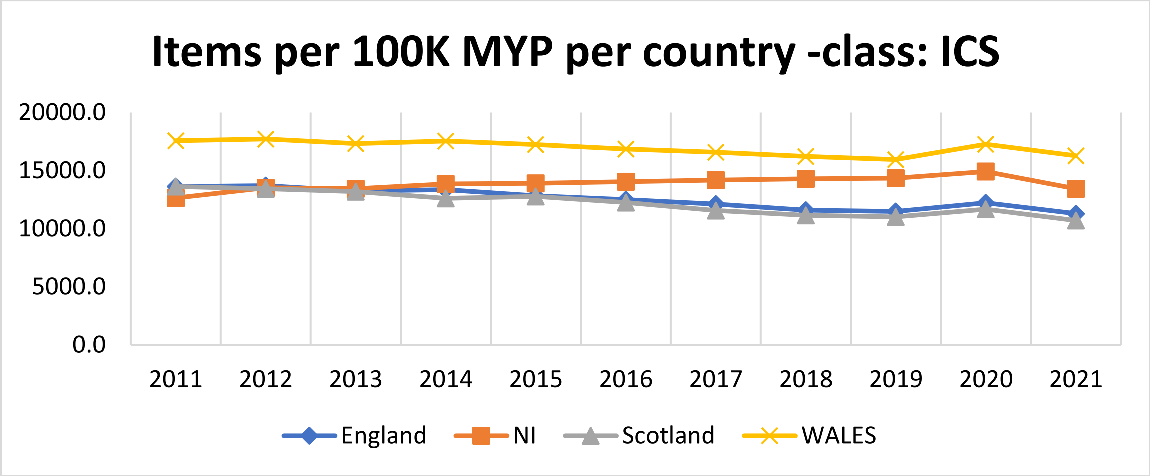


Figure 4.2: Dispensed items of ICS per 100,000 MYP in each country

4.5.3. Number of items of LABA/100,000 inhabitant

Figure 4.3 shows the number of LABA (Long-Acting Beta-Agonist) asthma medications dispensed per 100,000 population in England, Northern Ireland, Scotland, and Wales from 2011 to 2021. The data indicate that the usage of LABA medications was highest in Wales in all years, while Northern Ireland had the lowest usage. The usage of LABA medication has been decreasing in all four countries over the years.

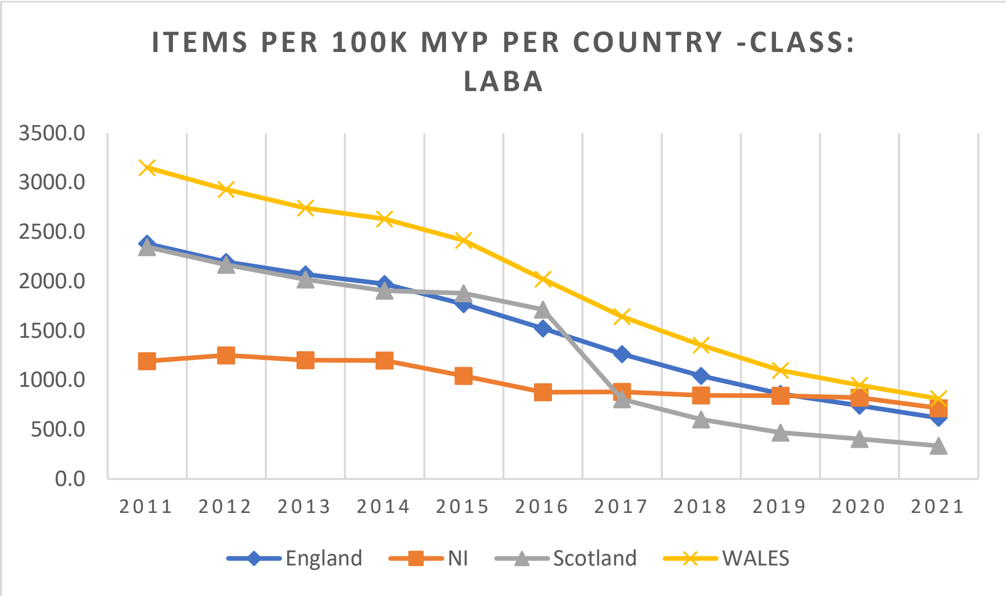


Figure 4.3: **Dispensed items of LABA per 100,000 MYP in each country**

4.5.4. Number of items of LABA+ICS /100,000 inhabitant

From Figure 4.4, we can see that the use of LABA+ICS combination has increased in all four countries over the years. In 2011, Wales had the highest use of LABA+ICS at 31493.2 items per 100K MYP, while England & Scotland had the lowest use at 19318.5 and 19748.4.

items per 100K MYP respectively. By 2021, Wales continued to have the highest use of LABA+ICS at 40,966.7 items per 100K MYP, followed by Northen Ireland at7 27552 items per 100K MYP.

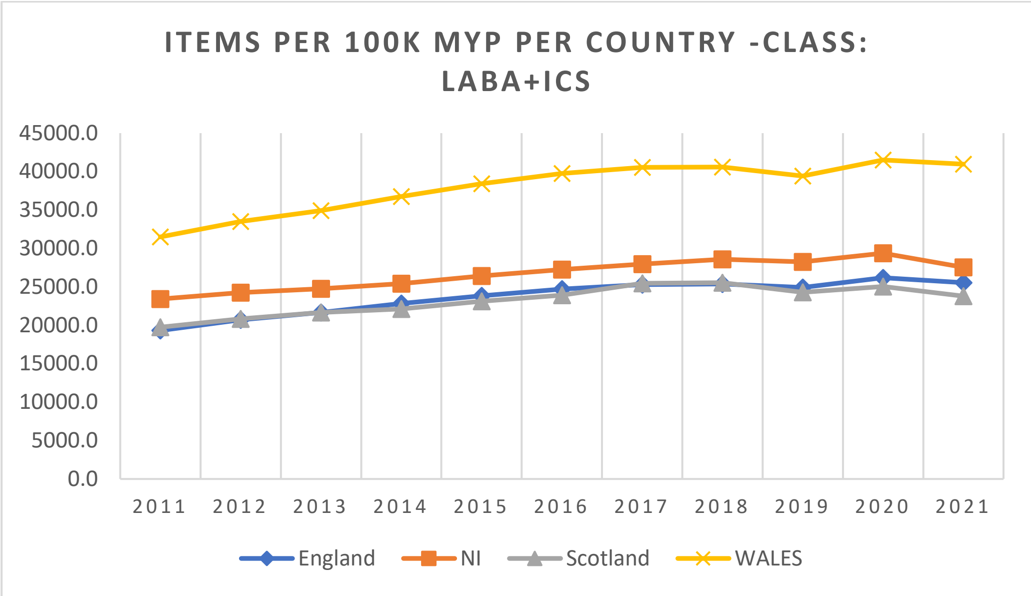


Figure 4.4: Dispensed items of LABA+ICS per 100,000 MYP in each country

4.5.5. number of items of SABA/100,000 inhabitant

From the data in figure 4.5, it can be observed that Wales had the highest number of SABA items per 100K MYP in all years, followed by Northern Ireland, Scotland, and England. There is a gradual increase in the number of SABA items per 100K MYP in all countries over the years. In 2021, the number of SABA items decreased in all countries compared to the previous year.

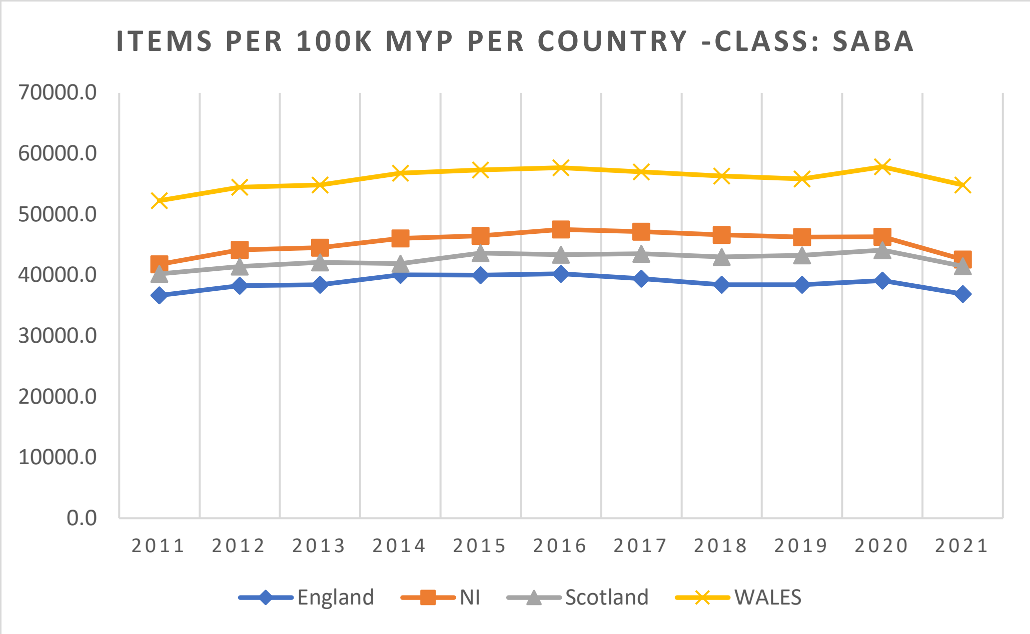
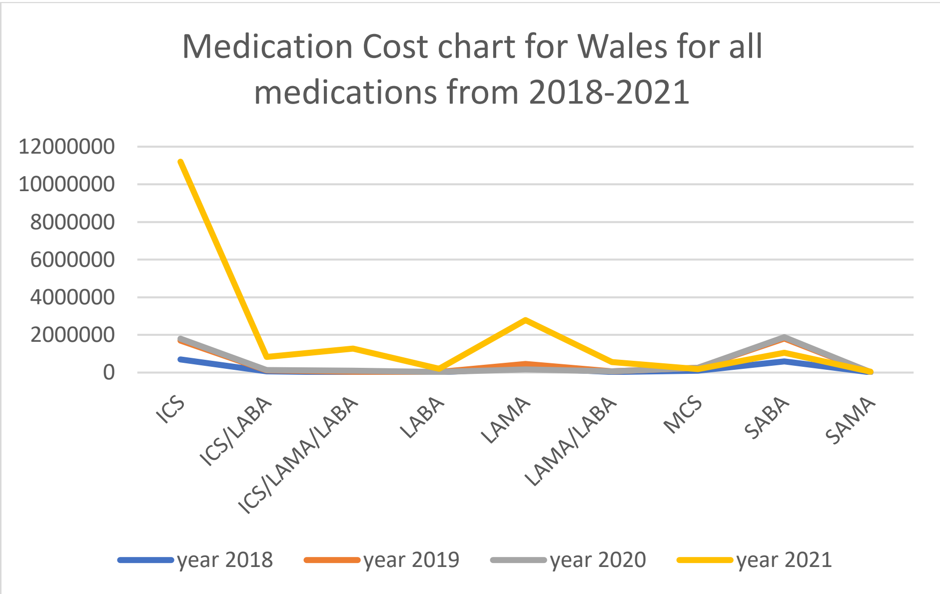
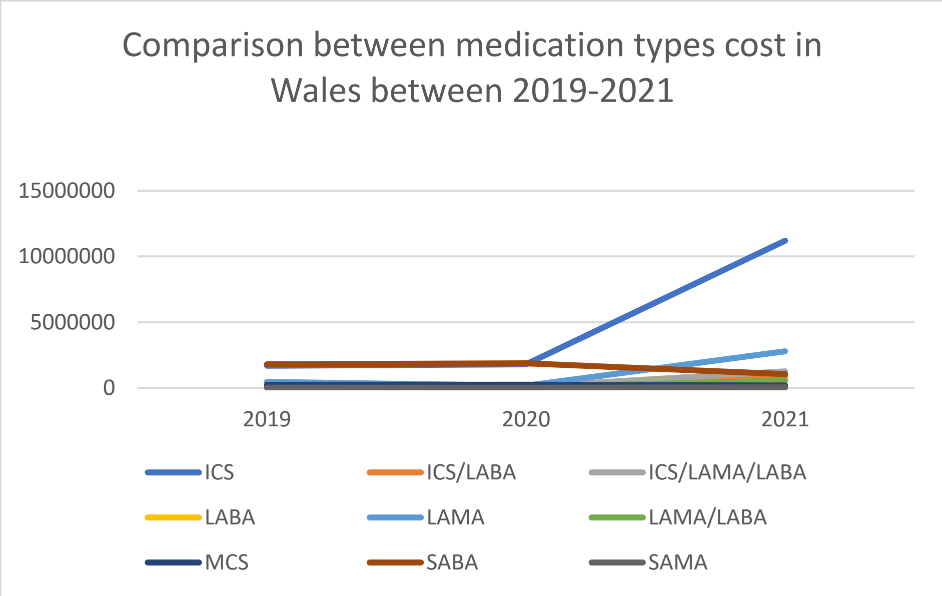


Figure 4.5 Dispensed items of SABA per 100,000 MYP in each country

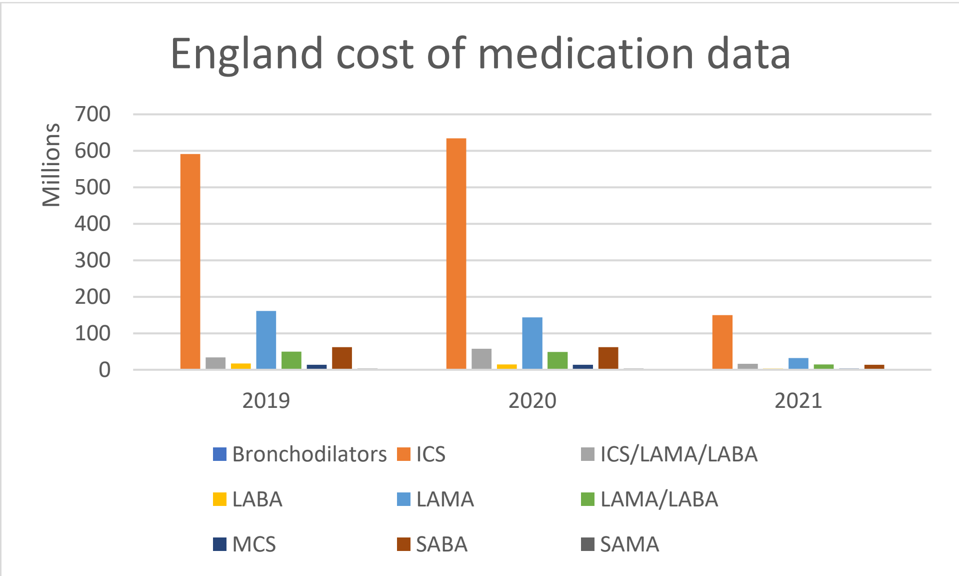
4.5.6. Cost of items dispensed.

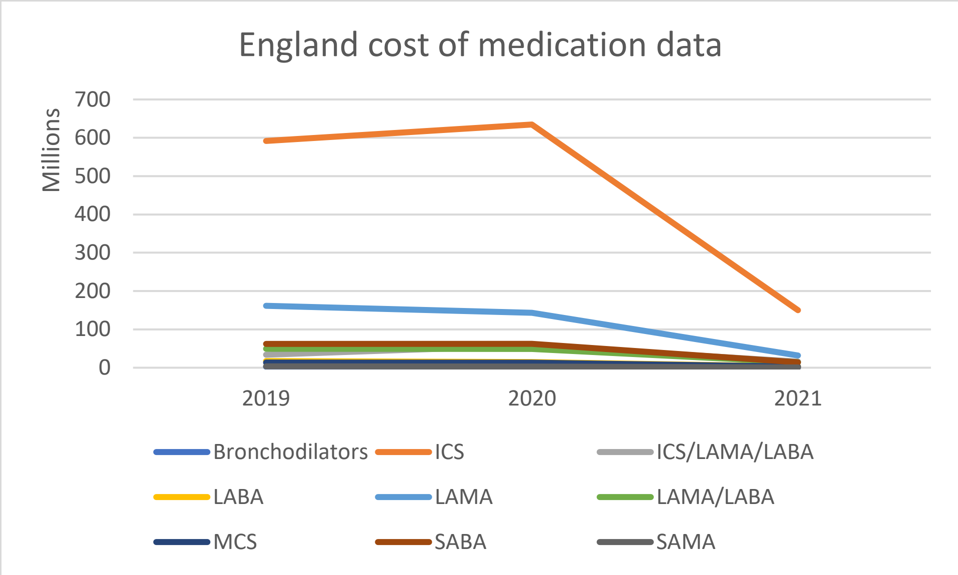
Appendix 4 summarize all the data related to cost of items for each country. Wales as an example is provided here. It's clear that ICS has the highest number of dispensed items and it represent 61% of the cost of the medications.



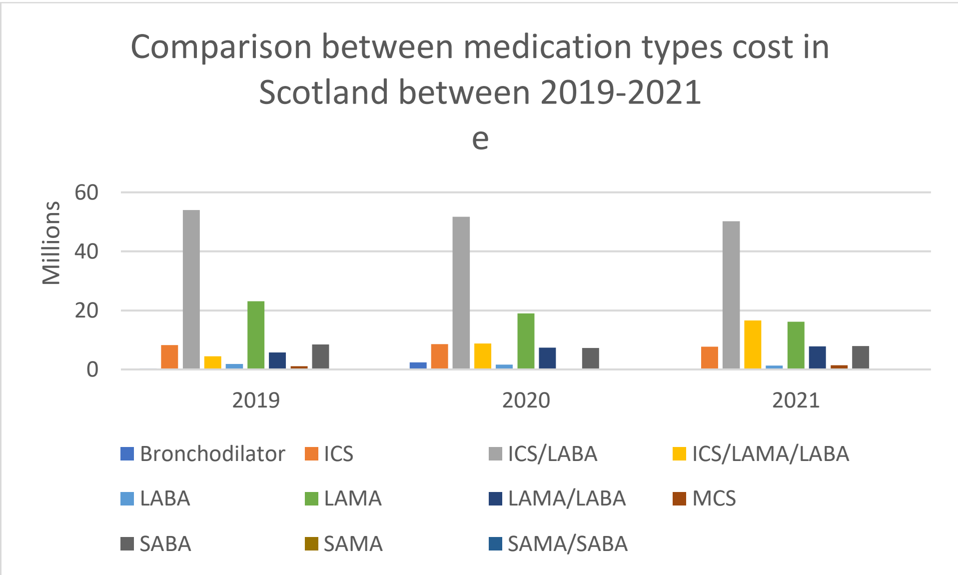


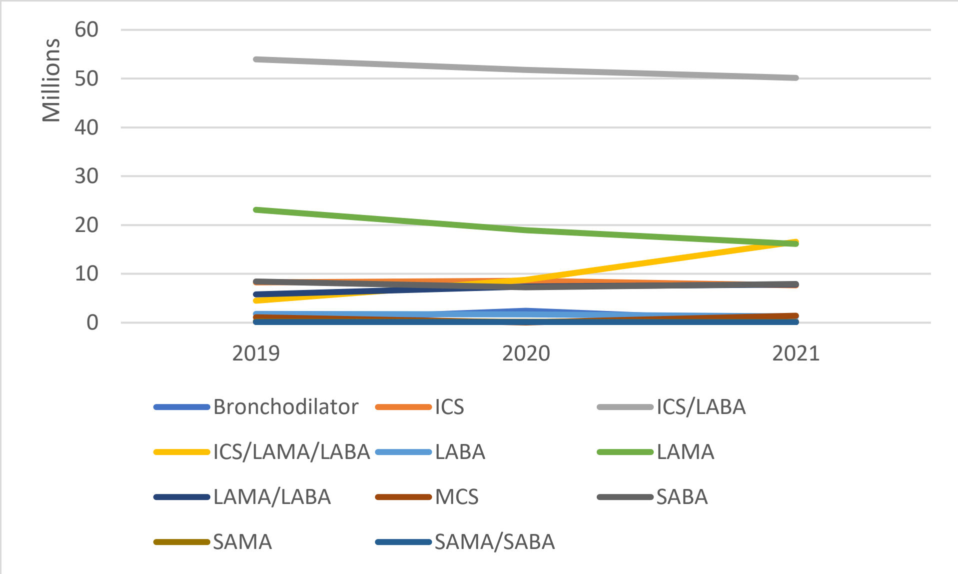
England had similar results to Wales in the ICS results as shown in the following figures.



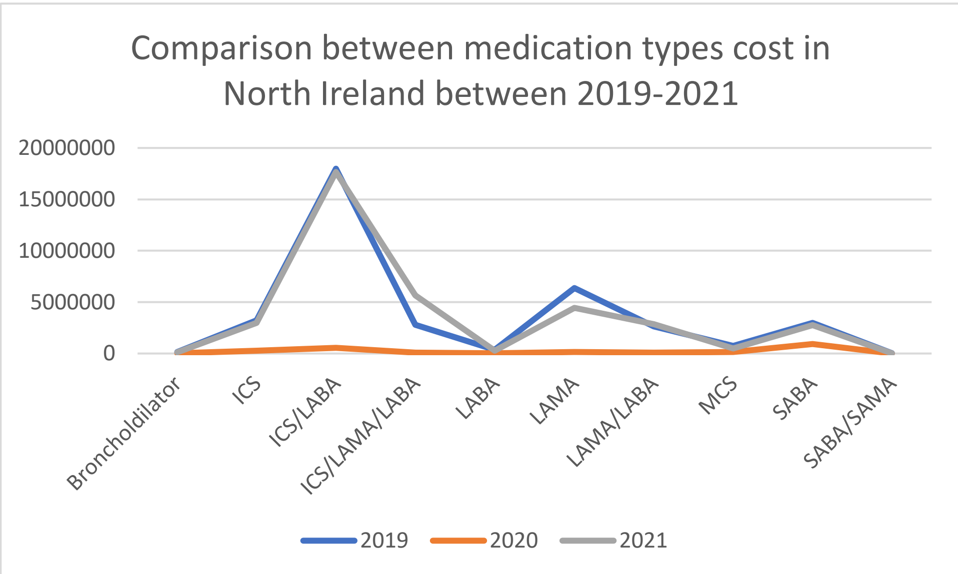


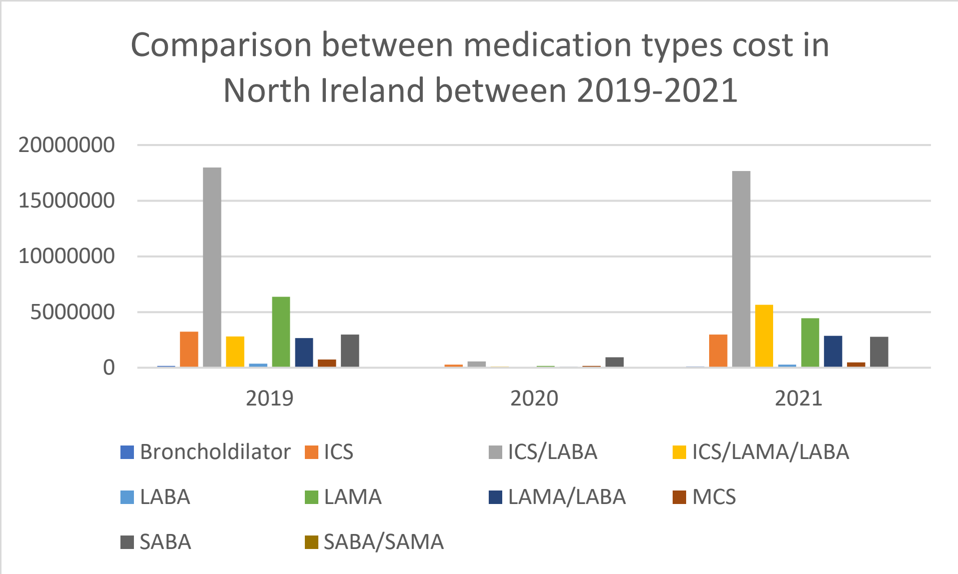
Scotland results showed that ICS/LABA was the highest cost throughout the years with almost 50 million pounds every year.





North Ireland had similar results to Scotland in the ICS/LABA category as shown in the following figures.





4.5.7. ARR and RRR

To calculate Absolute risk reduction and relative risk reduction we need the number of events, so we will consider the items as the number of events or cases and use the MYP as the population number. We will compare the 2021 to the 2011 data.

Table 4.3 Absolute risk reduction and relative risk reduction according to the medication class.

Medication Class	ARR (%)	RRR (%)
ICS	1.56	9.81
LABA	0.91	5.91
SABA	2.41	5.27
LABA+ICS	2.85	8.07
All Classes	4.35	5.19

The analysis of asthma medication utilization in the United Kingdom from 2011 to 2021 revealed significant findings in terms of the absolute risk reduction (ARR) and relative risk reduction (RRR). When combining data from all countries, the ARR ranged from 0.91% to 4.35% across different medication classes. The largest ARR was observed in the combined LABA+ICS class, indicating a reduction in asthma-related events or exacerbations by 2.85%. Similarly, the RRR ranged from 5.19% to 9.81%, with LABA+ICS showing the highest relative risk reduction. These results suggest that the utilization of asthma medications in the UK has contributed to a notable decrease in asthma-related events and improved outcomes over the studied period.

4.6. Discussion

Key Findings

The data suggests that the number of asthma medications dispensed has a consistent increase throughout the years in the UK and all four countries throughout the study period with a peak occurred in 2020. The reasons for such high levels could be due to the prevalence of asthma, and better accessibility to health care facilities. The prevalence of asthma among the UK population is estimated to be 12% (8 million individuals in 2009) according to The British Lung Foundation(British Lung Foundation (BLF), 2023). Asthma UK states that around 5.4 million people receive treatment for the disease and this number is expected to rise to 5.6 million by 2025 (British Lung Foundation (BLF), 2023). This increase in prevalence could partially explain the increase in the number of items dispensed over time. From 2004 to 2012 the estimated number of people diagnosed with asthma has an increase of under 3%(British Lung Foundation (BLF), 2023). Another cohort used UK electronic healthcare records from2006 to 2016 found the prevalence of asthma in the UK was 7.2% in 2006, gradually falling to 6.5% in 2016 (Bloom et al., 2019). the research has suggested asthma maybe considerably over-diagnosed and treated.

Wales consistently had the highest number of items per 100,000 MYP throughout the study period, which could be due to higher prevalence of asthma in this country. Moreover, Northern Ireland and Scotland also had a relatively higher number of items per 100,000 MYP compared to England. This could be due to factors such as different disease severity profiles of asthma cases, prescribing practices, patient compliance, socioeconomic status/deprivation , ethnicity, prevalence of active or passive smoking, , and air pollution (Alsallakh et al., 2021). We also should account for differences in definitions of diagnosis of asthma (i.e. lifetime symptoms suggestive of asthma and those with active, -and-treated asthma.) and different data source used across the UK nations(Mukherjee et al., 2016).

A peak was observed in 2020 which could be associated with the incidence of COVID-19 pandemic. In addition to of being at a higher risk of contracting COVID-19 infection and develop asthma exacerbations(Yang et al., 2020, Zhu et al., 2020b), the prescription pattern for asthma medications had changed during the lockdown period. A survey included 339 healthcare professionals treating asthma patients from 52 different countries reported that during lockdown period, about 80% of follow up consultations have been replaced by phone calls, and in about 70% of new patients, the diagnosis and prescription of inhalers was based only on clinical assessment without use of lung function tests (Eguiluz-Gracia et al., 2021). In the UK, the prescription of asthma inhalers was doubled at start of the COVID-19 lockdown and as a result inhaler deficiency has been reported (Bloom et al., 2021).

There was a decrease in the number of dispensed ICS and LABA items in all four countries. This could be compensated by the increasing use of ICS/LABA combination therapy. Another possibility is that alternative treatments such as biologic therapies which are becoming more commonly used, leading to a decrease in the use of ICS (Votto et al., 2021). Furthermore, the potential risks associated with the use of LABA medications, such as an increased risk of severe asthma exacerbations and deaths, have led to regulatory changes in the use of these medications (Chowdhury and Dal Pan, 2010, Wijesinghe et al., 2008). The decrease in usage could be an indication that healthcare professionals are adhering to these guidelines.

All countries have an increasing trend in the number of SABA items per 100K MYP which indicate increase in presentations with asthma exacerbations and the need of acute symptom control. An ecological study conducted between April 1999 and April 2020 using data extracted from the hospital episode statistics database in England and the patient episode database for Wales found that the hospital admissions rate for asthma increased by 46.1% over the study period(Alwafi et al., 2023). A previous study found that the ratio of salbutamol to inhaled corticosteroids prescription increased gradually in England from 2013 to 2017 as the ratio rose from 0.65 to 0.69(Gonem et al., 2019).

A parallel population-based cohort study compared inappropriate asthma therapy in the UK and France in 2007 and 2013 reported that UK adults were more frequently exposed to SABA overuse (⩾12 units)compared with those in France in both periods ($P<0.05$)(Belhassen et al., 2016).

There was a peak in dispensing SABA items in 2020 could be related to the COVID-19 pandemic, The decrease in SABA items in 2021 could be due to better asthma management and control of the pandemic.

It is interesting to note the variation in the number of dispensed ICS, LABA, SABA and ICS+LABA combinations items between the four countries. The reasons for this variation are not clear and may be related to differences in prescribing practices or patient populations. It may be worth investigating further to determine whether there are any underlying factors contributing to this variation.]. It is remarkable to demonstrate that type of medication changed over time, and national and international guidelines have also changed.

The findings from our analysis indicate that the use of asthma medications, particularly LABA+ICS, has been associated with a significant reduction in asthma-related events in the UK between 2011 and 2021. The observed ARR values demonstrate the absolute decrease in the risk of asthma events, with the combined LABA+ICS class showing the most substantial reduction. The RRR values highlight the relative effectiveness of these medications in reducing the risk of asthma-related events, with LABA+ICS again exhibiting the highest relative risk reduction. These results provide valuable insights into the impact of asthma medication utilization on asthma management and highlight the importance of optimizing treatment strategies to achieve better patient outcomes. However, further studies are warranted to explore potential factors influencing the observed reductions and to assess the long-term effects of these medications on asthma control and healthcare utilization.

Overall, the high number of asthma medications dispensed in the UK highlights the importance of effective asthma management practices and ensuring access to appropriate asthma treatments to reduce the burden of asthma on patients and the healthcare system.

Moreover, the improvement in awareness and diagnosis of asthma has led to more people being prescribed asthma medication. Healthcare professionals are now better equipped to identify asthma symptoms and prescribe appropriate medication to manage them. Additionally, improved access to healthcare services may have contributed to an increase in the number of items dispensed as more people are now able to seek medical attention and obtain medication when needed.

4.7. Strength and limitations

This study used resources that gave information on asthmatic dispensing medication in entire United Kingdom. More than one method was used, one of them was to use population to get accurate results as it adjusts for population increases, which gives better results than many other studies undertaken. The number of items were looked at and then was calculated/1000 inhabitants to accurately compare between different countries. Combination therapies were included in the data and all the relevant data was able to be collected.

A limitation of the study was that there was missing data about the prescription information, the exact diagnosis, and patients level data. No information was available on whether they were prescribed for acute, chronic or exacerbations.

4.8. Conclusion

In conclusion, it has been seen that asthma medication dispensing was affected by the pandemic. Most of the medication showed a decrease in dispensing and overall cost. However, ICS in all countries and ICS combination with LABA were increased. This might be because ICS is the first line of treatment in asthma guidelines.

The possible implications of this study's results could be an increase in cautionary prescribing hopefully leading to an improvement in optimised asthma treatment.

Overall, the increasing trend in the number of asthma medication items dispensed in the UK highlights the need for continued efforts to improve asthma management and reduce the burden of this condition on individuals and the healthcare system. This may involve increasing awareness of asthma, improving access to healthcare services, and ensuring that people with asthma have access to appropriate and effective medication.

Chapter five: Impact of lockdown during COVID-10 pandemic on the utilisation pattern of asthma medications in UK

Abstract:

Background: The COVID-19 pandemic prompted widespread lockdowns globally, drastically altering healthcare practices. This study explores how these lockdowns affected the utilization patterns of asthma medications in the UK.

Methods: A retrospective, observational study was conducted using the Prescription Cost Analysis datasets from the UK. The study focused on the prescription trends of asthma medications, including inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA), short-acting beta2 agonists (SABA), long-acting muscarinic antagonist (LAMA), and mast-cell stabilizers (MCS). The analysis compared dispensing data from January 2019 to February 2020 (pre-pandemic) with March to October 2020 (post-pandemic onset).

Results: The study revealed a significant increase in the dispensing of asthma medications during the lockdown period. Prescriptions for inhalers saw increases of 213% and 170.78%, respectively. The findings suggest a reflexive response from patients towards medication dispensing during emergencies, highlighting the need for better emergency preparedness in healthcare.

Conclusion: The COVID-19 lockdown significantly impacted the dispensation of asthma medications in the UK, with most drugs showing higher dispensing rates than in pre-lockdown periods. These findings underscore the need for further research to reassess dispensing behaviour and patient compliance with asthma treatment in the context of public health emergencies.

5.1. Introduction

In order to control the spread of COVID-19 in absence of vaccines or specific antivirals, the governments of many countries imposed a lockdown and self-quarantine to maintain social isolation. In UK, by 24th March 2020 the government has suspended all flights, closed schools, universities, and all public gatherings places and entertainment services, suspended all prayers in mosques and churches (Chang et al., 2020). The number of employees was reduced in non-vital works to encourage employees to work remotely and minimize contact and contamination of workplaces. A night curfew was imposed in many countries with suspension of all public transportation (Hassany et al., 2020). “Stay home, stay safe” campaign and adopting social distancing habits was encouraged on the social media to increase the public awareness of COVID-19 symptoms and preventive measures (Wilder-Smith and Freedman, 2020).

5.1.1. Impact on different medical aspects

The impact of COVID-19 pandemic and the following restrictions on healthcare systems exceeded the direct effect of viral morbidity and mortality to affect routine comprehensive care for chronic patients and elective procedures and resulted in psychological, social, and economic burden. The continued interruption of supply chain of medications and other medical equipment resulted in changes in drug prescription (figure 5.1), resources limitation and critical shortfalls. This was caused by travel restrictions and giving priorities to critical care units treating hospitalized COVD-19 patients (Halcomb et al., 2022). A critical shortage in blood components has also been reported (Wang et al., 2020b). Shortages of health professionals who are debuted in isolation hospitals and quarantined because of illness or exposure to COVID-19 cases affected the quality of provided care. Routine follow-up of outpatient clinics, elective surgeries and dental procedures were postponed. Relying on public transportation during lockdown periods affected accessibility to outpatient, and inpatient services. Application of telemedicine programs for follow up adversely affected clinical decision-making by limiting laboratory testing and physical examination.

5.1.2. Impacts of lockdown on patients with asthma: asthma exacerbations and medication use

In the UK, the prescription of asthma inhalers was doubled at start of the COVID-19 lockdown and as a result inhaler scarcity was reported (Bloom et al., 2021). There was a 52.5% , 44.2%, 17.3% and 12.9% increase in use of inhaled corticosteroids (ICS), short acting beta agonists (SABA), oral corticosteroids (OCS) and long acting beta agonists- inhaled corticosteroids combinations (LABA-ICS) respectively early during the pandemic (Bloom et al., 2021). There was a 213% increase in use of Clenil Modulite, the most commonly prescribed ICS and 170.78% increase in use of Fostair 100/6, the most commonly prescribed LABA-ICS in the UK. The peak of increase was reached in March 2020. Despite a reduction in the number of primary care visits during first 4 months of the pandemic, the number of ICS prescribed per appointment increased by 26% (Crook et al., 2022).

Analysis of English Prescribing Dataset comparing dispensing of asthma medications 14 months before the pandemic (from January 2019 to February 2020 and 8 months after the pandemic March to October 2020 (8 months after its onset) revealed a significant increase in use of salbutamol (P = 0.033) and ipratropium (P = 0.001) during March 2020 then continued to decrease gradually, however they did not returned to their pre-pandemic levels (Barrett and Barrett, 2021).

Many factors led to increase the requests of asthma medications including stockpiling; early ordering, multiple medication items prescribed by doctors (Ow et al., 2022). Patients reported adopting this shortage by starting stockpiling; ordering prescriptions early; try alternative prescriptions; requesting ‘emergency prescriptions’; and try ordering online and contacting drug manufacturers (Ow et al., 2022). Larger prescriptions of ICS corticosteroids were observed in younger patients of higher socioeconomic status, with milder asthma symptoms (Bloom et al., 2021). OCS orders were more in patients having one exacerbation during the past year, having COPD and using high dose of ICS(Bloom et al., 2021). Another factor that could be implicated in the increase in prescription, is the prevalence of virtual consultations through telemedicine which represent a challenge for the physician: with an absence of clinical examination and difficult confirmation of whether the right inhaler technique is used, the physician is usually under pressure for over prescription (Crook et al., 2022).

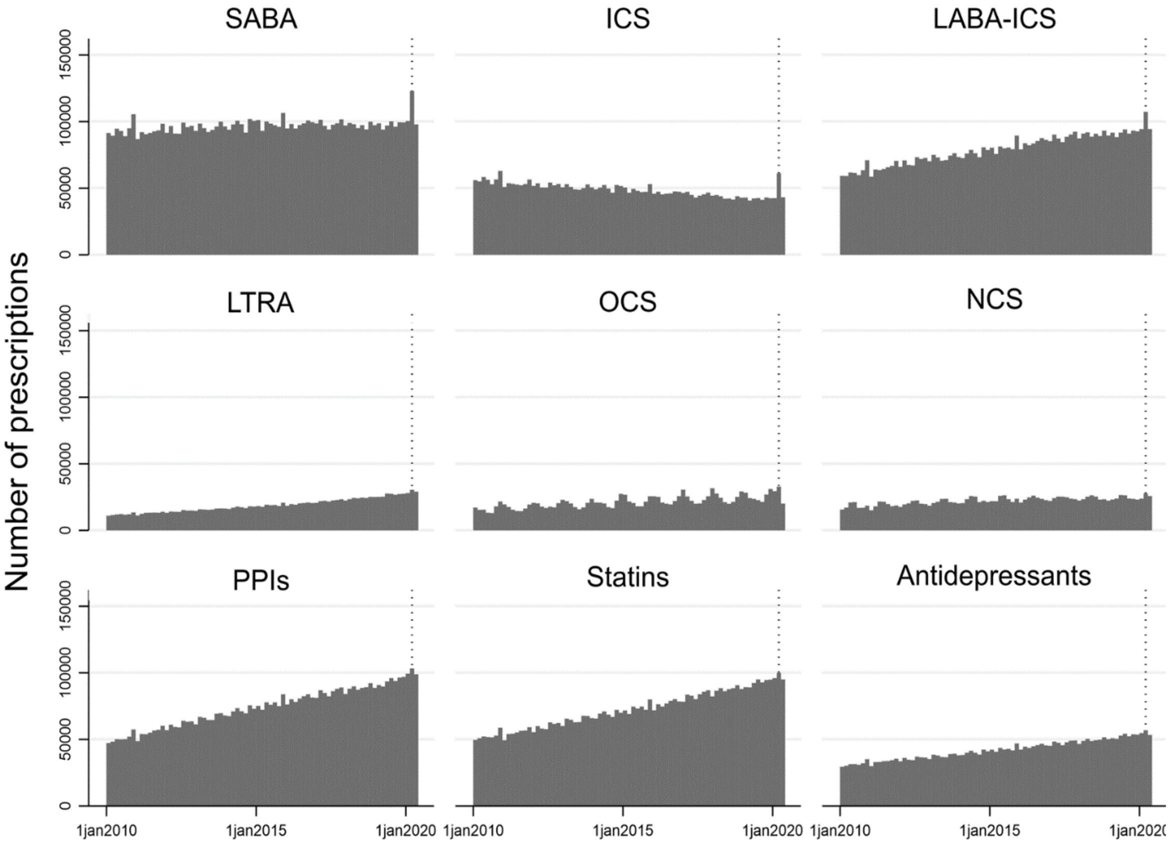


Figure (5.1): Prescription patterns of different drugs from 1st January 2010 until 1st June 2020 in UK(Bloom et al., 2021)

In Finland, prescription of antibiotics and asthma medications for children aged 0-5 years was decreased by 55.3% and 19.8%respectively during 2020 in comparison to 2019. This could be attributed to application of COVID-19 restrictions which decreased risk of URT infections(Haapanen et al., 2022).

The impact of COVID-19 pandemic and lockdown on the prescription and availability of asthma medications is not well studied. A change in patient behaviour regarding taking medications, self-management, adherence to drugs, and stockpiling of acute respiratory inhalers were also reported (Crook et al., 2022).

The aim of this study is to assess the impact of the coronavirus pandemic related lockdown on the dispensing of medications used in the management and control of respiratory symptoms of asthma in UK. Medications include inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA), short-acting beta2 agonists (SABA), long-acting muscarinic antagonist (LAMA), and mast-cell stabilizers (MCS).

5.2. Methods:

5.2.1. Study Design

This study was an observational, retrospective repeated cross-national study using the publicly available Prescription Cost Analysis (PCA) datasets in four countries of UK.

5.2.2. Data Source

Asthma generic medications available in Wales were grouped into categories according to BNF classification into

Inhaled corticosteroids ICS

Long-Acting Beta 2 agonist LABA

Long-acting muscarinic antagonists LAMA

Short acting Beta agonists SABA

Mast cell stabilizers MCs

And their combination together

The combination process included the medicine’s name, strength, quantity, cost, and formulation. Data from all four countries were extracted from 2019 to 2021. PCA datasets contain aggregated-level information on all dispensed asthma prescriptions in the United Kingdom primary care setting.

Utilization and prescribing patterns of inhalers were assessed using the prescription costs analysis (PCA) data compiled by the Information Services Division (ISD) of NHS in the four countries.

The total cost of all prescriptions was divided 12 and then divided by Mid-year population number according to offices of National statistics and then multiplied by 1000.

5.2.3. Study outcomes.

The impact of Covid 19 on dispensing asthma medication in UK

Secondary outcomes

The trends of dispensing asthma medications before and after Covid 19 lockdown

5.2.4. Data analysis

Statistical Analysis Plan for Segmented Regression Analysis

Objective: To assess the impact of the COVID-19 lockdown on the dispensing of asthma medications in the UK using segmented regression analysis.

Data Source:

- Prescription Cost Analysis (PCA) datasets from the UK.
- Timeframe: March 2019 (pre-pandemic) to March 2022 (post-pandemic).

Variables:

- Dependent Variables: Number of items dispensed per 1000 inhabitants per day, Defined Daily Dose (DDD) per 1000 inhabitants for each medication class (ICS, LABA, SABA, LAMA, MCS).
- Independent Variable: Time, segmented into pre-lockdown, lockdown, and post-lockdown periods.
- Control Variables: Medication class, country (England, Scotland, Northern Ireland, Wales).

Segmented Regression Analysis:

1. **Model Specification:**

- We will use Linear regression models for each medication class and country.
- We will Incorporate dummy variables to indicate time periods: pre-lockdown lockdown and post-lockdown.
- The lockdown period acts as an 'intervention' in this model.

2. **Model Estimation:**
    - Estimate baseline trends for each medication class and country before the intervention (lockdown).
    - Estimate changes in level (immediate effect) and slope (trend change) post-intervention.
    - Use interaction terms between time and period dummy variables to capture these changes.
3. **Statistical Tests:**
    - Use t-tests to assess the significance of changes in levels and slopes.
    - Report 95% confidence intervals for all estimates.
    - P-values less than 0.05 considered statistically significant.
4. **Model Checking:**
    - We check for autocorrelation and non-stationarity in residuals.
    - We apply appropriate transformations or differencing if necessary.
    - We will use graphical plots (scatter plots, time series plots) to visually inspect model fit and identify outliers or anomalies.
5. **Sensitivity Analysis (if applicable):**
    - We shall conduct sensitivity analysis to assess the robustness of findings, possibly by varying the definition of the lockdown period or excluding outlier observations.
6. **Reporting Results:**
    - We will report estimated changes in level and slope for each medication class in each country.
    - Interpret the results in the context of the COVID-19 lockdown, considering potential confounders and other relevant factors.
7. **Software:**
    - Analysis to be conducted using statistical software capable of time series analysis (R).

5.2.5. Ethical approval

Ethical approval was not required as this study used publicly available datasets in UK. No participants were involved in the study, so no informed consent was needed.

5.3. Results:

There was a peak increase for number of items dispensed per 1000 inhabitants per day as well as the DDD per 1000 inhabitants in almost all classes and all countries.

Regarding items dispensed per 1000 inhabitants per day, there was a significant decrease in the baseline trend in the number of LABA dispensed per 1000 inhabitants in England per day -0.62 (-1.11 to -0.127), p = 0.019, while there was a significant decrease in the baseline trend in the number of LAMA dispensed per 1000 inhabitants per day in NI and Wales -7.5 (-13.11 to -2), p = 0.012; -11.8 (-16.1 to -7.6), p < 0.001; respectively (Figure 5.2). Compared to the baseline, LAMA dispensing trend in Wales increased by 6 (0.33 to 11.75) items per 1000 in p = 0.046 (Figure 5.3). Regarding MCS dispensing in England the baseline trend decreased by -0.027 (-0.03 to -0.02) P < 0.001, the decrease was steeper in after the lockdown period compared to the after Covid-19 period -.18 (-0.27 to -0.09) P<0 .001 (Figure 5.4). Regarding the MCS dispensing in NI there was a significant increase in the dispensing trend after lockdown compared to the after covid-19 trend by 0.035 (0.014 to 0.056) P= 0.003.

Regarding the MCS dispensing in Wales there was a significant decrease in the dispensing trend at the baseline -0.014 (-0.025 to -0.0022) P= 0.026, the decrease was steeper in after the lockdown period compared to the after Covid-19 period -.29 (-0.44 to -0.14) P<0 .001.

Regarding the ICS dispensing in England there was a significant increase in the dispensing trend at the baseline 23.7 (8.4 to 39) P= 0.005. Same case was observed in NI and Wales 46.9 (16.1 t0 77.7) P= 0.006; 28 (7.4 to 48.6) p= 0.012; respectively, while there was a significant reduction in the despising trend in case of Scotland in the covid-19 period compared to the baseline -37.2 (-67.9 to -6.4) p = 0.024 (Figure

5.5).

Regarding the DDD per 1000 inhabitants there was a significant decrease in the baseline trend in case of England for LABA and LAMA-0.038 (-0.0716 to -0.0038) p= 0.037; -6.043 (-8.049 to -4.0379) p <0.001; respectively (Figure 5.6 and 5.7), while there was a significant increase in the baseline trend in case of England for MCS and ICS 0.732 (0.2567 to 1.2082) p = 0.005; 0.222 (0.0687 to 0.3744) p =0.007; respectively (Figure 5.8, 5.9). Furthermore, there was a significant decrease in the baseline trend in case of Scotland and Wales for -6.429 (-11.026 to -1.8317), p = 0.010; -11.812 (-15.7542 to -7.8692) p <0.001; respectively, while there was a significant increase in the baseline trend in case of Wales for MCS and ICS 0.771 (0.1863 to 1.3555), p = 0.015; 0.238 (0.0519 to 0.4249) p= 0.018; respectively (table 5.1).

Finally, there was a significant increase at the after-lockdown trend in case of England and Scotland for LABA 0.049 (0.0151 to 0.0838) p = 0.008; 0.029 (0.0088 to 0.0488) p = 0.008; respectively, while there was a significant decrease at the after-lockdown trend in case of Wales for LABA -0.042 (-0.076 to -0.0074) p = 0.023.

Table 5.1 Segmented Regression Table

	Estimate (95% CI)	P Value
Monthly number of items per 1000 inhabitants per day		
England LABA		
B1 Baseline trend	-0.617 (-1.107 to -0.1272)	0.01928
B2 After COVID-19	-1.909 (-11.2692 to 7.4511)	0.692086
B3 After lockdown	1.818 (-7.5323 to 11.1677)	0.705776
NI LABA		
B1 Baseline trend	-0.211 (-0.6753 to 0.254)	0.381082
B2 After COVID-19	-1.815 (-5.7714 to 2.1407)	0.375383
B3 After lockdown	1.748 (-2.1854 to 5.6809)	0.390474
Scotland LABA		
B1 Baseline trend	-0.389 (-1.0985 to 0.3197)	0.290106
B2 After COVID-19	-0.612 (-2.1002 to 0.8762)	0.426365
B3 After lockdown	0.538 (-0.8365 to 1.9117)	0.448981
Wales LABA		
B1 Baseline trend	-1.759 (-3.9872 to 0.469)	0.131917
B2 After COVID-19	0.831 (-1.4073 to 3.0702)	0.472143
B3 After lockdown	-1.551 (-8.1451 to 5.0438)	0.648109
England LAMA		
B1 Baseline trend	-2.951 (-7.1993 to 1.2978)	0.183241
B2 After COVID-19	-44.659 (-211.4365 to 122.1193)	0.603438
B3 After lockdown	43.597 (-123.3094 to 210.5044)	0.612308
NI LAMA		
B1 Baseline trend	-7.533 (-13.1105 to -1.955)	0.012651
B2 After COVID-19	-17.01 (-111.5035 to 77.4827)	0.726606
B3 After lockdown	17.918 (-76.4335 to 112.2698)	0.712267

	Estimate (95% CI)	P Value
Scotland LAMA		
B1 Baseline trend	-11.724 (-28.3027 to 4.8548)	0.17563
B2 After COVID-19	3.965 (-13.3929 to 21.3221)	0.657502
B3 After lockdown	2.915 (-3.1143 to 8.9449)	0.350648
Wales LAMA		
B1 Baseline trend	-11.835 (-16.053 to -7.6173)	5.13E-06
B2 After COVID-19	6.044 (0.3327 to 11.7547)	0.04646
B3 After lockdown	-17.317 (-52.3104 to 17.6773)	0.339613
England MCS		
B1 Baseline trend	-0.027 (-0.0335 to -0.0198)	1.43E-08
B2 After COVID-19	0.039 (-0.0086 to 0.086)	0.119103
B3 After lockdown	-0.177 (-0.2684 to -0.0859)	0.000626
NI MCS		
B1 Baseline trend	0.022 (-0.0314 to 0.0761)	0.42245
B2 After COVID-19	-0.05 (-0.1052 to 0.0046)	0.083489
B3 After lockdown	0.035 (0.014 to 0.0561)	0.002931
Scotland MCS		
B1 Baseline trend	0 (-0.0355 to 0.0351)	0.991106
B2 After COVID-19	-0.036 (-0.0744 to 0.0016)	0.070101
B3 After lockdown	-0.144 (-0.4425 to 0.155)	0.35295
Wales MCS		
B1 Baseline trend	-0.014 (-0.025 to -0.0022)	0.026165
B2 After COVID-19	0.058 (-0.0203 to 0.1367)	0.155961
B3 After lockdown	-0.293 (-0.4448 to -0.1421)	0.000634
England ICS		
B1 Baseline trend	23.679 (8.3791 to 38.9799)	0.00486
B2 After COVID-19	-105.851 (-252.6077 to 40.9047)	0.167422
B3 After lockdown	83.672 (-62.4736 to 229.8181)	0.270424
NI ICS		
B1 Baseline trend	46.886 (16.0891 to 77.6832)	0.005509
B2 After COVID-19	-249.553 (-837.9293 to 338.824)	0.412165
B3 After lockdown	213.339 (-374.3969 to 801.075)	0.482133
Scotland ICS		
B1 Baseline trend	17.37 (-4.3671 to 39.1076)	0.127455
B2 After COVID-19	-37.184 (-67.9248 to -6.4423)	0.024154
B3 After lockdown	31.32 (2.272 to 60.3675)	0.042728
Wales ICS		
B1 Baseline trend	28 (7.3722 to 48.6278)	0.012246
B2 After COVID-19	-89.882 (-216.0323 to 36.2686)	0.172493
B3 After lockdown	64.018 (-60.9014 to 188.9376)	0.322947
Monthly number of DDD dispensed per 1000 inhabitants		
England LABA		
B1 Baseline trend	-0.038 (-0.0716 to -0.0038)	0.037154
B2 After COVID-19	-0.033 (-0.081 to 0.0148)	0.185804
B3 After lockdown	0.049 (0.0151 to 0.0838)	0.008273
Scotland LABA		
B1 Baseline trend	0.067 (-0.2809 to 0.4145)	0.709044
B2 After COVID-19	-0.117 (-0.4654 to 0.2309)	0.514077
B3 After lockdown	0.029 (0.0088 to 0.0488)	0.008257
Wales LABA		
B1 Baseline trend	-0.171 (-0.3834 to 0.0422)	0.126324
B2 After COVID-19	0.146 (-0.0665 to 0.3595)	0.187441
B3 After lockdown	-0.042 (-0.076 to -0.0074)	0.023439
England LAMA		
B1 Baseline trend	-6.043 (-8.049 to -4.0379)	1.60E-06
B2 After COVID-19	-3.671 (-41.9868 to 34.6456)	0.852289
B3 After lockdown	5.795 (-32.4799 to 44.069)	0.768653
Scotland LAMA		
B1 Baseline trend	-6.429 (-11.026 to -1.8317)	0.010077
B2 After COVID-19	2.62 (-2.0846 to 7.3252)	0.283432
B3 After lockdown	1.813 (-3.9061 to 7.5312)	0.538989
Wales LAMA		
B1 Baseline trend	-11.812 (-15.7542 to -7.8692)	1.77E-06
B2 After COVID-19	9.12 (2.4835 to 15.756)	0.011308
B3 After lockdown	-2.467 (-8.1839 to 3.2506)	0.404253
England MCS		
B1 Baseline trend	0.732 (0.2567 to 1.2082)	0.005057
B2 After COVID-19	-3.944 (-13.033 to 5.1455)	0.401613

	Estimate (95% CI)	P Value
B3 After lockdown	3.296 (-5.783 to 12.3757)	0.48204
Scotland MCS		
B1 Baseline trend	0.468 (-0.3401 to 1.2752)	0.265252
B2 After COVID-19	-1.225 (-2.4496 to 0)	0.059047
B3 After lockdown	1.154 (0.0326 to 2.2758)	0.05243
Wales MCS		
B1 Baseline trend	0.771 (0.1863 to 1.3555)	0.01468
B2 After COVID-19	-5.949 (-17.1174 to 5.2192)	0.304545
B3 After lockdown	5.218 (-5.938 to 16.3743)	0.366354
England ICS		
B1 Baseline trend	0.222 (0.0687 to 0.3744)	0.007879
B2 After COVID-19	-1.919 (-4.8393 to 1.0017)	0.207385
B3 After lockdown	1.698 (-1.2196 to 4.6151)	0.262762
Scotland ICS		
B1 Baseline trend	0.172 (-0.0726 to 0.4161)	0.17823
B2 After COVID-19	-0.391 (-0.7178 to -0.0647)	0.025412
B3 After lockdown	0.344 (0.0178 to 0.6708)	0.047209
Wales ICS		
B1 Baseline trend	0.238 (0.0519 to 0.4249)	0.017693
B2 After COVID-19	-0.689 (-1.8295 to 0.4514)	0.245325
B3 After lockdown	0.46 (-0.6697 to 1.589)	0.431116

Figures

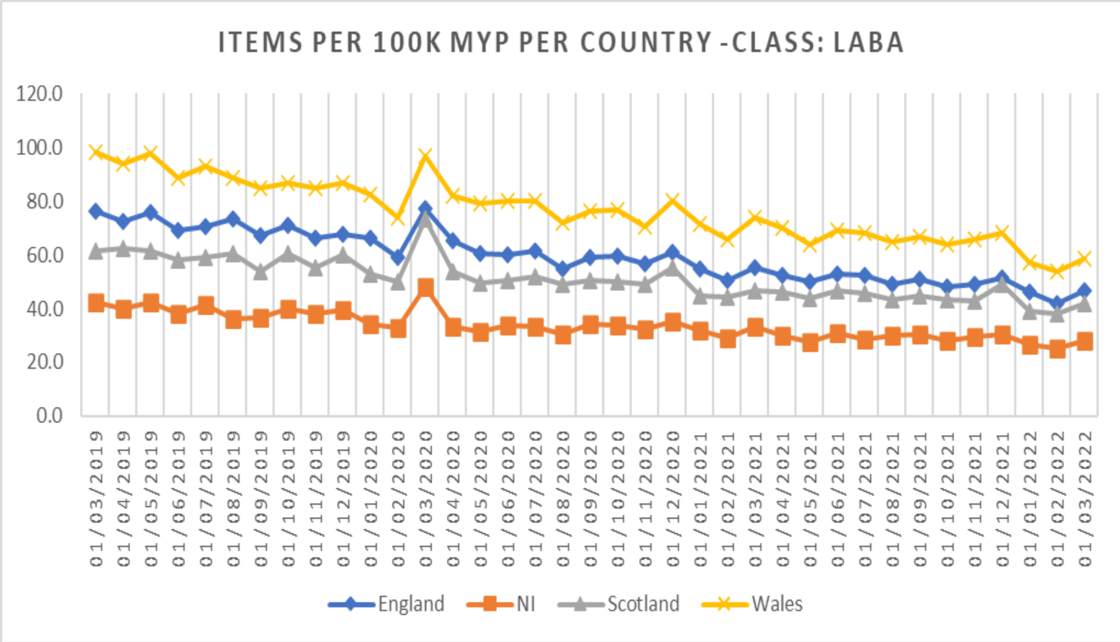


Figure 5.2 Items LABA

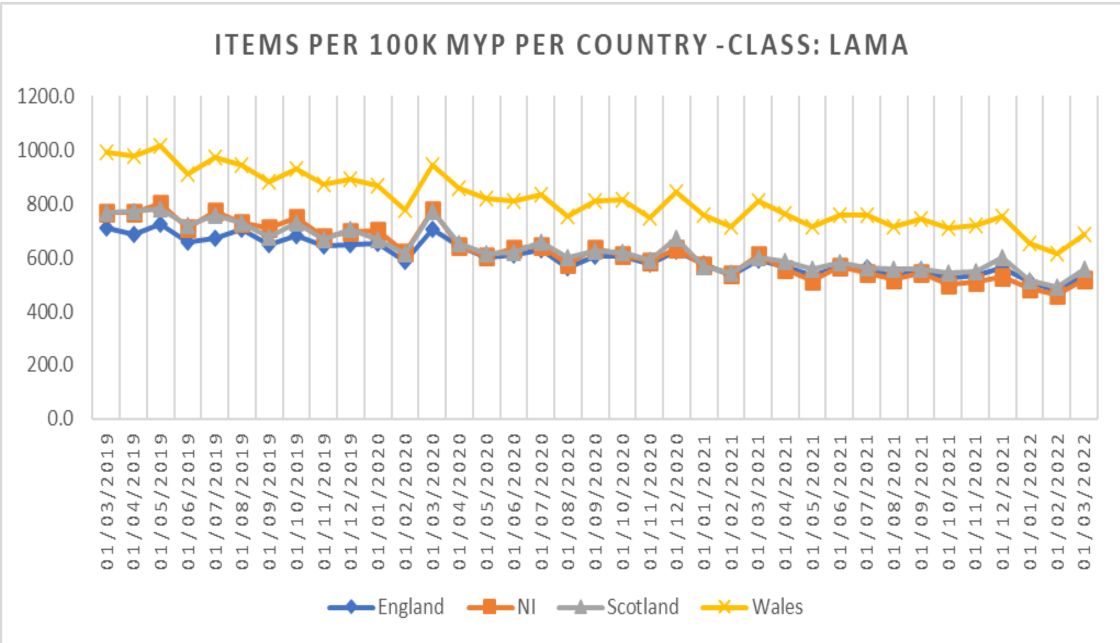


Figure 5.3 Items LAMA

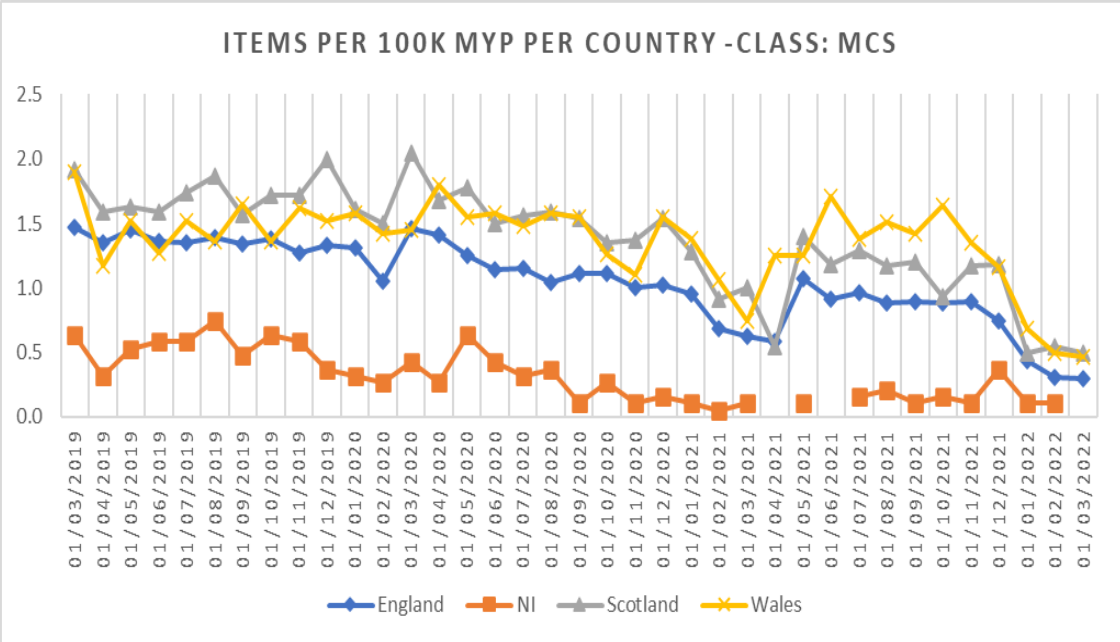


Figure 5.4 Items MCS

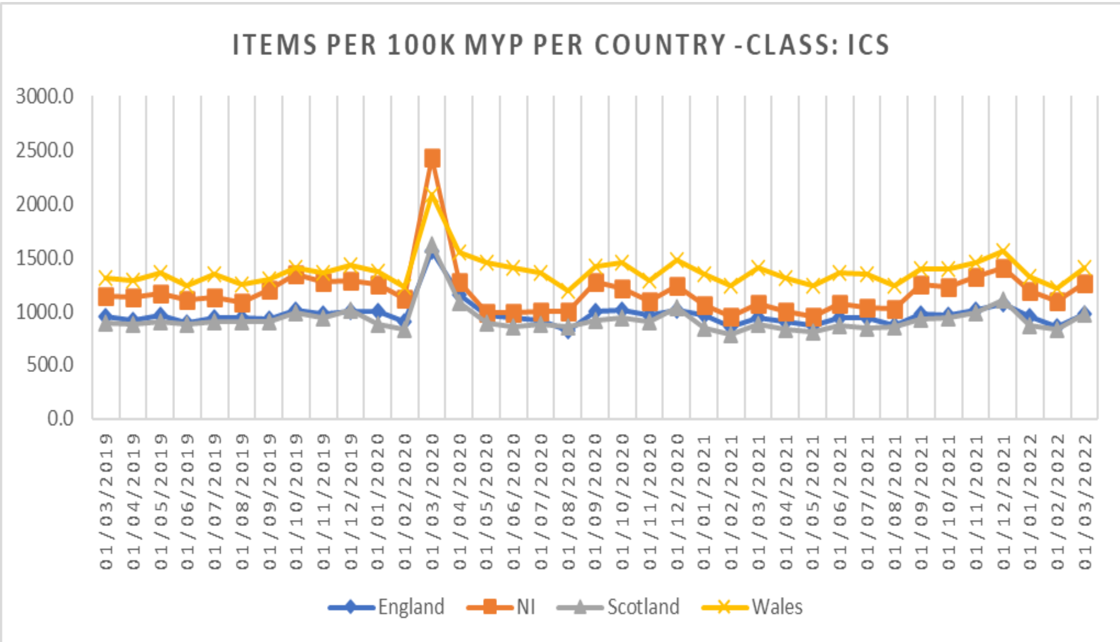


Figure 5.5 Items ICS

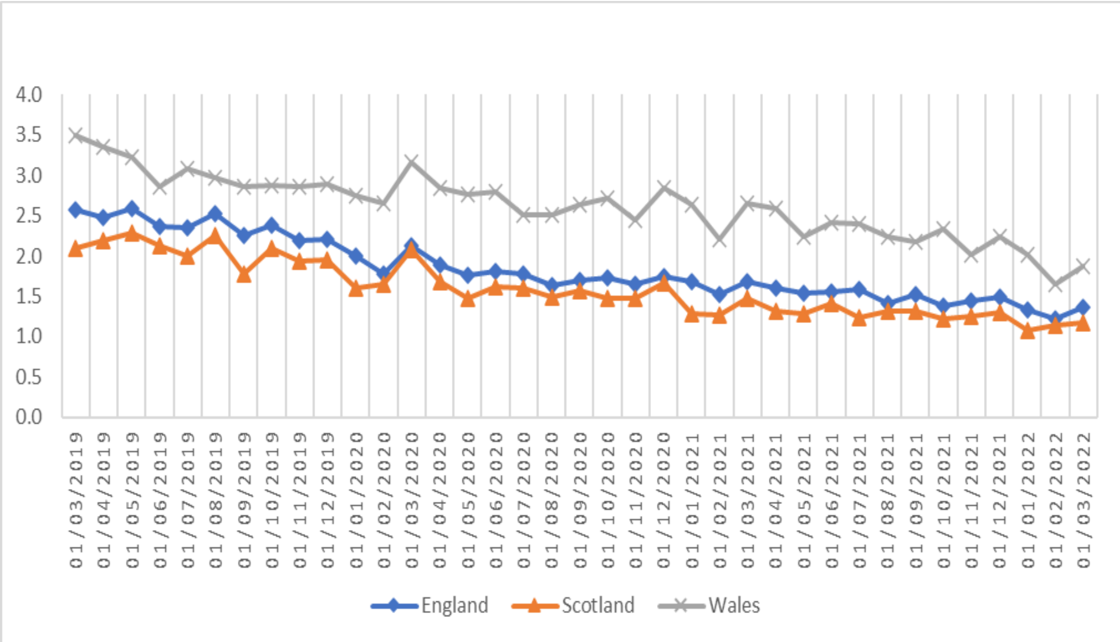


Figure 5.6 DDD LABA

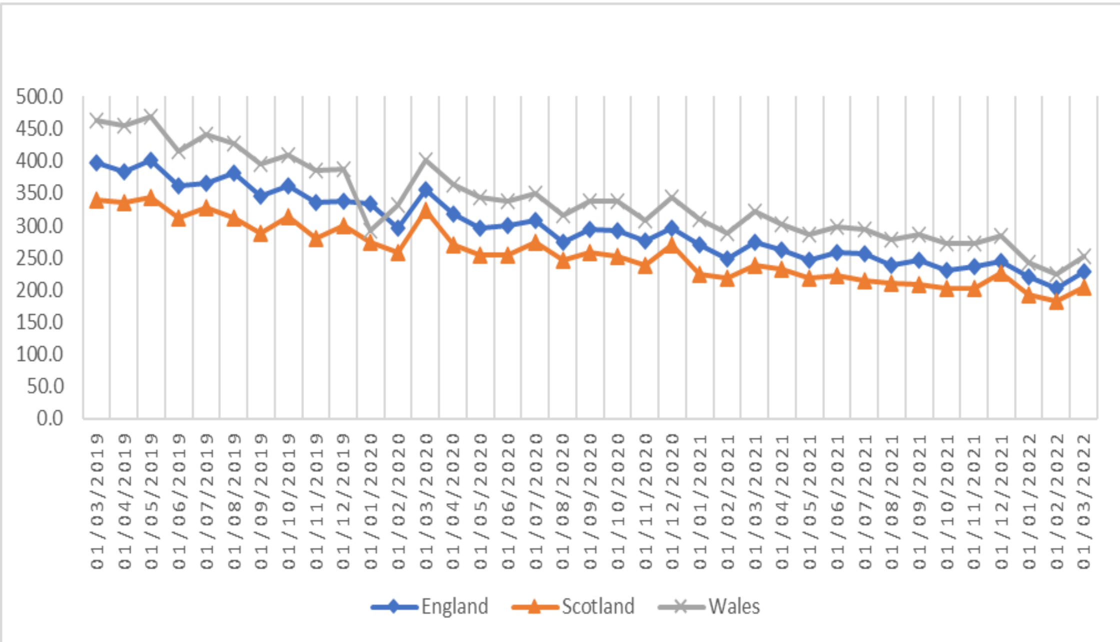


Figure 5.7 DDD LAMA

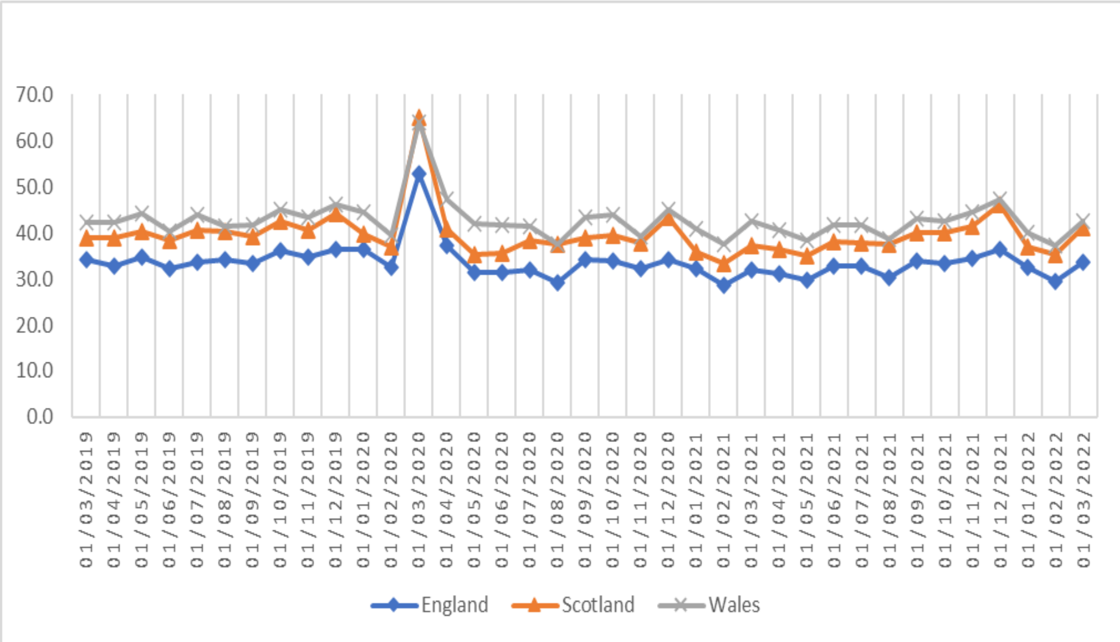


Figure 5.8 DDD MCS

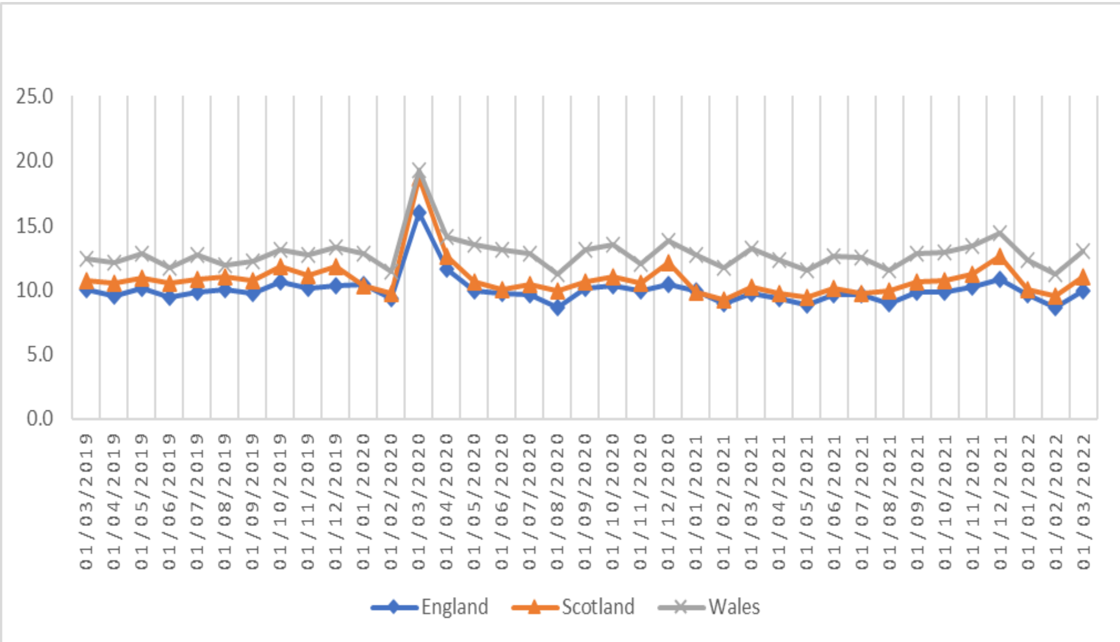


Figure 5.9 DDD ICS

5.4. Discussion:

Key findings:

The study investigated the dispensing trends of various drug classes in four countries, namely England, Scotland, Northern Ireland, and Wales. The results showed a peak increase in the number of items dispensed per 1000 inhabitants per day as well as the Defined Daily Dose (DDD) per 1000 inhabitants in almost all drug classes and countries. Specifically, there was a significant decrease in the baseline trend of the number of Long-Acting Beta-Agonists (LABA) dispensed per 1000 inhabitants in England per day and Long-Acting Muscarinic Antagonists (LAMA) dispensed per 1000 inhabitants per day in Northern Ireland and Wales.

In Wales, there was a significant increase in the LAMA dispensing trend compared to the baseline, while in England, there was a significant decrease in the baseline trend of Muscarinic Antagonists (MCS) dispensing after the lockdown period compared to the after Covid-19 period. On the other hand, there was a significant increase in the MCS dispensing trend after lockdown in Northern Ireland compared to the after Covid-19 trend. In Wales, there was a significant decrease in the dispensing trend of MCS after the lockdown period compared to the after Covid-19 period.

Regarding the dispensing trend of Inhaled Corticosteroids (ICS), there was a significant increase in the baseline trend of ICS dispensing in all four countries. However, there was a significant reduction in the dispensing trend of ICS in Scotland during the Covid-19 period compared to the baseline.

Regarding the DDD per 1000 inhabitants, the baseline trend of LABA and LAMA decreased significantly in England, while the baseline trend of MCS and ICS increased significantly in England. The baseline trend of LAMA and ICS decreased significantly in Scotland and Wales, respectively. Additionally, there was a significant increase in the baseline trend of MCS and ICS in Wales. Finally, there was a significant increase in the after-lockdown trend of LABA in England and Scotland, while there was a significant decrease in the after-lockdown trend of LABA in Wales.

In the UK, the prescription of asthma inhalers was doubled at start of the COVID-19 lockdown and as a result inhaler deficiency has been reported(Bloom et al., 2021). There was 52.5%, 44.2%, 17.3% and 12.9% increase in use of inhaled corticosteroids (ICS), short acting beta agonists (SABA), oral corticosteroids (OCS) and long-acting beta agonists- inhaled corticosteroids combinations (LABA-ICS) respectively early during the pandemic (Bloom et al., 2021). There was a 212.96% increase in use of Clenil Modulite, the most prescribed ICS and 170.78% increase in use of Fostair 100/6, the most commonly prescribed LABA-ICS in the UK. The peak of increase was reached in March 2020. Despite a reduction in the number of primary care visits during first 4 months of the pandemic, the number of ICS prescribed per appointment increased by 26% (Crook et al., 2022). In the week before lockdown, there was a spike increase in prescription of ICS by 121% and oral corticosteroid by 133% in Wales(Davies et al., 2021)

Analysis of English Prescribing Dataset comparing dispensing of asthma medications 14 months before the pandemic (from January 2019 to February 2020 and 8 months after the pandemic March to October 2020 (8 months after its onset) revealed a significant increase in use of salbutamol (P = 0.033) and ipratropium (P = 0.001) during March 2020 then continued to decrease gradually, however they did not returned to their pre-pandemic levels (Barrett and Barrett, 2021).

Another survey included 339 healthcare professionals treating asthma patients from 52 different countries reported that during lockdown period, about 80% of follow up consultations have been replaced by phone calls, and in about 70% of new patients, the diagnosis and prescription of inhalers was based only on clinical assessment without use of lung function tests (Eguiluz-Gracia et al., 2021).

Comparing the emergency admissions and deaths due to asthma over the first 18 weeks in 2020 with the national averages over 2015–2019 in Scotland and Wales revealed 36% pooled reduction in emergency admissions for asthma (incidence rate ratio, IRR: 0.64, 95% CI: 0.49 to 0.83, p value 0.001) across both countries and no significant change in asthma deaths (pooled IRR: 0.57, 95% CI: 0.17 to 1.94, p value 0.37)(Davies et al., 2021). This could be attributed to application of COVID-19 restrictions which decreased risk of URT infections and fear from attracting COVID-19 infection from health care facilities.

There was a significant increase in the dispensing trend of Inhaled Corticosteroids (ICS) in England, Northern Ireland (NI), and Wales during the study period. This increase in ICS dispensing trend contrasts with the trends observed for other medication classes such as Long-Acting Beta-Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA), which showed significant decreases in baseline trends for dispensing in certain regions like England and NI. The increase in ICS dispensing could be attributed to several factors, including changes in prescribing practices, increased awareness or diagnosis of respiratory conditions that warrant ICS use, or shifts in healthcare policies promoting the use of ICS for asthma or chronic obstructive pulmonary disease (COPD) management.

In conclusion, the study's findings suggest an overall increase in the dispensing trend of different drug classes across the four countries, with some variations in trends between countries and drug classes. These results showed the impact of the Covid-19 pandemic and lockdown measures on drug dispensing trends, which could inform future policies and interventions aimed at promoting appropriate prescribing practices. However, further research is needed to examine the impact of these trends on patient outcomes and health system costs.

Overall, these results suggest that while there was a general increase in the use of medication across the regions studied, there were also some notable variations in the trends for specific medications in certain regions. This may reflect differences in prescribing practices, regional healthcare needs, or other factors that warrant further investigation.

5.5. Strength and limitations:

To our knowledge, this is the first study addressing the cost of dispensing asthma medications for patients during the COVID-19 pandemic in UK. It highlighted the reflex action of patients towards dispensing in cases of emergency and pandemics. It also fire alarms for emergency preparedness procedures that should be incorporated in every field of medicine.

Limitations of the study included absence of patients’ level data, absent prescriptions, unknown indications for dispensing. For example, ICS have been incorporated in many protocols for COVID-19 treatment not necessarily for bronchial asthma treatment (Griesel et al., 2022). MCS has been used as a prophylaxis against COVID-19 vaccine induced anaphylaxis (Kazama, 2021).

Overall, while we can make some observations and speculate on potential impacts, it's difficult to directly determine the impact of COVID-19 lockdowns on asthma medication dispensation based solely on these results.

5.6. Future implications:

This study helps determine actions to be taken for emergency preparedness in cases with drug shortage. It helps prioritize the steps for drug dispensing during emergencies like lockdown periods.

5.7. Conclusion:

In conclusion, the lockdown period affected asthma medications dispensing, with most of the drugs showing higher dispensing rates than pre-lockdown periods. Further studies should follow to reassess the dispensing behaviour and patient compliance of asthma treatment.

REFERENCES

AI, T., YANG, Z., HOU, H., ZHAN, C., CHEN, C., LV, W., TAO, Q., SUN, Z. & XIA, L. 2020. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology,* 296**,** E32-e40.

AL-DAWOOD, K. 2001. Parental smoking and the risk of respiratory symptoms among schoolboys in Al-Khobar City, Saudi Arabia. *J Asthma,* 38**,** 149-54.

AL-MOAMARY, M. S., ALHAIDER, S. A., ALANGARI, A. A., AL GHOBAIN, M. O., ZEITOUNI, M. O., IDREES, M. M., ALANAZI, A. F., AL-HARBI, A. S., YOUSEF, A. A., ALORAINY, H. S. & AL-HAJJAJ, M. S. 2019. The Saudi Initiative for Asthma - 2019 Update: Guidelines for the diagnosis and management of asthma in adults and children. *Ann Thorac Med,* 14**,** 3-48.

AL-MOAMARY, M. S., ALHAIDER, S. A., IDREES, M. M., AL GHOBAIN, M. O., ZEITOUNI, M. O., AL-HARBI, A. S., YOUSEF, A. A., AL-MATAR, H., ALORAINY, H. S. & AL-HAJJAJ, M. S. 2016. The Saudi Initiative for Asthma-2016 update: Guidelines for the diagnosis and management of asthma in adults and children. *Annals of Thoracic Medicine,* 11**,** 3-42.

AL-ZAHRANI, A. M., AL-MUSHAYT, A. S., OTAIBI, M. F. & WYNE, A. H. 2014. Knowledge and attitude of Saudi mothers towards their preschool children's oral health. *Pak J Med Sci,* 30**,** 720-4.

AL DAWOOD, K. 2002. Risk factors associated with hospital emergency visits among asthmatic schoolboys in Saudi Arabia. *EMHJ-Eastern Mediterranean Health Journal, 8 (1), 31-41, 2002*.

AL FRAYH, A., AL NAHDI, M., BENER, A. & JAWADI, T. 1989. Epidemiology of asthma and allergic rhinitis in two coastal regions of Saudi Arabia. *Allergie et immunologie,* 21**,** 389-393.

AL FRAYH, A., SHAKOOR, Z., ELRAB, M. G. & HASNAIN, S. 2001. Increased prevalence of asthma in Saudi Arabia. *Annals of Allergy, Asthma & Immunology,* 86**,** 292-296.

ALATAWI, A. & ALSAYED, B. 2021. Assessment of Asthma Knowledge, Attitudes, and Practice among Health Professionals at Two Hospital Settings in Tabuk Region, Saudi Arabia. *Indian Journal of Forensic Medicine & Toxicology,* 15**,** 4646-4656.

ALBALAK, R., BRUCE, N., MCCRACKEN, J. P., SMITH, K. R. & DE GALLARDO, T. 2001. Indoor respirable particulate matter concentrations from an open fire, improved cookstove, and LPG/open fire combination in a rural Guatemalan community. *Environmental science & technology,* 35**,** 2650-2655.

ALKHAMIS, A. 2012. Health care system in Saudi Arabia: an overview. *East Mediterr Health J,* 18**,** 1078-9.

ALQAHTANI, J. M., ASAAD, A. M., AWADALLA, N. J. & MAHFOUZ, A. A. 2017. Environmental determinants of bronchial asthma among Saudi school children in Southwestern Saudi Arabia. *International journal of environmental research and public health,* 14**,** 22.

ALSAHN, B., ALZAHRANI, A., ALSAHMI, O., ALQUDHYBI, A. & ALSHAMRANI, A. 2017. Asthma control assessment using asthma control test among pediatric patients attending a tertiary care hospital in Saudi Arabia. *The Egyptian Journal of Hospital Medicine,* 68**,** 1215-1223.

ALSALLAKH, M. A., RODGERS, S. E., LYONS, R. A., SHEIKH, A. & DAVIES, G. A. 2021. Association of socioeconomic deprivation with asthma care, outcomes, and deaths in Wales: A 5-year national linked primary and secondary care cohort study. *PLoS medicine,* 18**,** e1003497.

ALSHEHRI, M. A., ABOLFOTOUH, M. A., SADEG, A., NAJJAR, Y., ASINDI, A. A., HARTHI, A., TRABULSI, H., FIFI, S. & FRAYH, A. 2000. Screening for asthma and associated risk factors among urban school boys in Abha city. *Saudi medical journal,* 21**,** 1048-1053.

ALWAFI, H., NASER, A. Y., ASHOOR, D. S., ALDHAHIR, A. M., ALQAHTANI, J. S., MINSHAWI, F., SALAWATI, E., SAMANNODI, M., DAIRI, M. S. & ALANSARI, A. K. 2023. Trends in hospital admissions and prescribing due to chronic obstructive pulmonary disease and asthma in England and Wales between 1999 and 2020: an ecological study. *BMC Pulmonary Medicine,* 23**,** 49.

ARKSEY, H. & O'MALLEY, L. 2005. Scoping studies: towards a methodological framework. *International journal of social research methodology,* 8**,** 19-32.

ASHLEY, C., HALCOMB, E., JAMES, S., CALMA, K., STEPHEN, C., MCINNES, S., MURSA, R. & WILLIAMS, A. 2022. The impact of COVID-19 on the delivery of care by Australian primary health care nurses. *Health & social care in the community,* 30**,** e2670-e2677.

ASHMORE, M. & DIMITROULOPOULOU, C. 2009. Personal exposure of children to air pollution. *Atmospheric Environment,* 43**,** 128-141.

ASSIRI, H. A., ALKHALDI, Y. M., ALSALEEM, S. A. & ALQARNI, H. M. 2021. Knowledge, attitude and practices of PHC physicians in Aseer region regarding management of acute asthma. *Journal of Family Medicine and Primary Care,* 10**,** 1882.

AUTRUP, H. 2010. Ambient air pollution and adverse health effects. *Procedia-Social and Behavioral Sciences,* 2**,** 7333-7338.

BARRETT, R. & BARRETT, R. 2021. Asthma and COPD medicines prescription-claims: A time-series analysis of England’s national prescriptions during the COVID-19 pandemic (Jan 2019 to Oct 2020). *Expert Review of Respiratory Medicine,* 15**,** 1605-1612.

BELHASSEN, M., NIBBER, A., VAN GANSE, E., RYAN, D., LANGLOIS, C., APPIAGYEI, F., SKINNER, D., LAFOREST, L., SORIANO, J. B. & PRICE, D. 2016. Inappropriate asthma therapy—a tale of two countries: a parallel population-based cohort study. *NPJ primary care respiratory medicine,* 26**,** 1-5.

BENER, A., AL-FRAYH, A., OZKARAGOZ, F. & AL-JAWADI, T. Q. 1993. Passive smoking effects on wheezy bronchitis. *Annals of Saudi Medicine,* 13**,** 222-225.

BERNARD, G. R., ARTIGAS, A., BRIGHAM, K. L., CARLET, J., FALKE, K., HUDSON, L., LAMY, M., LEGALL, J. R., MORRIS, A. & SPRAGG, R. 1994. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med,* 149**,** 818-24.

BINSAEED, A. A. 2014. Caregiver knowledge and its relationship to asthma control among children in Saudi Arabia. *J Asthma,* 51**,** 870-5.

BLAKE, K. V. 2017. Improving adherence to asthma medications: current knowledge and future perspectives. *Current opinion in pulmonary medicine,* 23**,** 62-70.

BLOOM, C., WONG, E., HICKMAN, K. & ELKIN, S. 2021. Influence of the first wave of COVID-19 on asthma inhaler prescriptions. *NPJ Prim Care Respir Med,* 31**,** 45.

BLOOM, C. I., SAGLANI, S., FEARY, J., JARVIS, D. & QUINT, J. K. 2019. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006-2016. *Eur Respir J,* 53**,** 1802130.

BOURDIN, A., GRAS, D., VACHIER, I. & CHANEZ, P. 2009. Upper airway x 1: allergic rhinitis and asthma: united disease through epithelial cells. *Thorax,* 64**,** 999-1004.

BRAUN, A., HUGGINS, F., KUBATOVA, A., WIRICK, S., MARICQ, M., MUN, B., MCDONALD, J., KELLY, K., SHAH, N. & HUFFMAN, G. 2008. Toward distinguishing woodsmoke and diesel exhaust in ambient particulate matter. *Environmental science & technology,* 42**,** 374-380.

BREYSSE, P. N., BUCKLEY, T. J., WILLIAMS, D. A., BECK, C. M., JO, S.-J., MERRIMAN, B., KANCHANARAKSA, S., SWARTZ, L. J., CALLAHAN, K. A. & BUTZ, A. M. 2005. Indoor

exposures to air pollutants and allergens in the homes of asthmatic children in inner-city Baltimore. *Environmental Research,* 98**,** 167-176.
BREYSSE, P. N., DIETTE, G. B., MATSUI, E. C., BUTZ, A. M., HANSEL, N. N. & MCCORMACK, M. C. 2010. Indoor air pollution and asthma in children. *Proceedings of the American Thoracic Society,* 7**,** 102-106.
BRITISH LUNG FOUNDATION (BLF) 2023. *Asthma statistics,* Scotland BFL. Available from: https://statistics.blf.org.uk/asthma.
BRUCE, N., PEREZ-PADILLA, R. & ALBALAK, R. 2000. Indoor air pollution in developing countries: a major environmental and public health challenge. *Bulletin of the World Health organization,* 78**,** 1078-1092.
BRUNEKREEF, B. 2010. The continuing challenge of air pollution. *Breathe,* 7**,** 13-14.
CARUSO, C., COLANTUONO, S., URBANI, S., HEFFLER, E., CANONICA, G. W., ANDRIOLLO, G., DI MICHELE, L., SCARLATA, S., ZENNARO, D. & RIGON, A. 2021. Real-life survey on severe asthma patients during COVID-19 lockdown in Italy. *Expert Review of Respiratory Medicine,* 15**,** 1057-1060.
CASTRO-RODRIGUEZ, J. A. & FORNO, E. 2020. Asthma and COVID-19 in children: A systematic review and call for data. *Pediatr Pulmonol,* 55**,** 2412-2418.
CHANG, L., YAN, Y. & WANG, L. 2020. Coronavirus Disease 2019: Coronaviruses and Blood Safety. *Transfus Med Rev,* 34**,** 75-80.
CHEN, N., ZHOU, M., DONG, X., QU, J., GONG, F., HAN, Y., QIU, Y., WANG, J., LIU, Y., WEI, Y., XIA, J., YU, T., ZHANG, X. & ZHANG, L. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet,* 395**,** 507-513.
CHENG, M. P., PAPENBURG, J., DESJARDINS, M., KANJILAL, S., QUACH, C., LIBMAN, M., DITTRICH, S. & YANSOUNI, C. P. 2020. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. *Ann Intern Med,* 172**,** 726-734.
CHENG, Y.-F., HSU, L.-N., YANG, K. D., YEH, S.-H. & SHU, S.-S. 2007. Outcomes of continuing education in the care of children with asthma for pediatric healthcare providers. *The journal of continuing education in nursing,* 38**,** 122-131.
CHHIBA, K. D., PATEL, G. B., VU, T. H. T., CHEN, M. M., GUO, A., KUDLATY, E., MAI, Q., YEH, C., MUHAMMAD, L. N., HARRIS, K. E., BOCHNER, B. S., GRAMMER, L. C., GREENBERGER, P. A., KALHAN, R., KUANG, F. L., SALTOUN, C. A., SCHLEIMER, R. P., STEVENS, W. W. & PETERS, A. T. 2020. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J Allergy Clin Immunol,* 146**,** 307-314.e4.
CHOI, Y. J., PARK, J. Y., LEE, H. S., SUH, J., SONG, J. Y., BYUN, M. K., CHO, J. H., KIM, H. J. & LEE, J. H. 2021. Effect of asthma and asthma medication on the prognosis of patients with COVID-19. *Eur Respir J,* 57**,** 2002226.
CHOWDHURY, B. A. & DAL PAN, G. 2010. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *New England Journal of Medicine,* 362**,** 1169-1171.
CHUDASAMA, Y. V., GILLIES, C. L., ZACCARDI, F., COLES, B., DAVIES, M. J., SEIDU, S. & KHUNTI, K. 2020. Impact of COVID-19 on routine care for chronic diseases: A global survey of views from healthcare professionals. *Diabetes Metab Syndr,* 14**,** 965-967.
COPERCHINI, F., CHIOVATO, L., CROCE, L., MAGRI, F. & ROTONDI, M. 2020. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev,* 53**,** 25-32.
CROOK, J., WEINMAN, J. & GUPTA, A. 2022. Changes in rates of prescriptions for inhaled corticosteroids during the COVID-19 pandemic. *Lancet Respir Med,* 10**,** 6-7.
DAVIES, G. A., ALSALLAKH, M. A., SIVAKUMARAN, S., VASILEIOU, E., LYONS, R. A., ROBERTSON, C. & SHEIKH, A. 2021. Impact of COVID-19 lockdown on emergency

asthma admissions and deaths: national interrupted time series analyses for Scotland and Wales. *Thorax,* 76**,** 867-873.
DELAROCHE, A. M., RODEAN, J., ARONSON, P. L., FLEEGLER, E. W., FLORIN, T. A., GOYAL, M., HIRSCH, A. W., JAIN, S., KORNBLITH, A. E., SILLS, M. R., WELLS, J. M. & NEUMAN, M. I. 2021. Pediatric Emergency Department Visits at US Children's Hospitals During the COVID-19 Pandemic. *Pediatrics,* 147**,** e2020039628.
DHARMAGE, S. C., PERRET, J. L. & CUSTOVIC, A. 2019. Epidemiology of Asthma in Children and Adults. *Front Pediatr,* 7**,** 246.
DHRUVE, H., D'ANCONA, G., HOLMES, S., DHARIWAL, J., NANZER, A. M. & JACKSON, D. J. 2022. Prescribing Patterns and Treatment Adherence in Patients with Asthma During the COVID-19 Pandemic. *J Allergy Clin Immunol Pract,* 10**,** 100-107.e2.
EGUILUZ-GRACIA, I., VAN DEN BERGE, M., BOCCABELLA, C., BONINI, M., CARUSO, C., COUTO, M., ERKEKOL, F., RUKHADZE, M., SANCHEZ-GARCIA, S. & DEL GIACCO, S. 2021. Real-life impact of COVID-19 pandemic lockdown on the management of pediatric and adult asthma: a survey by the EAACI Asthma Section. *Allergy,* 76**,** 2776-2784.
ELIZABETH, W., ALEX, J. W., KRISHNAN, B., SEB, B., CHRIS, B., CAROLINE, E. M., HELEN, J. C., AMIR, M., DAVID, E., PETER, I., JONATHAN, C., HELEN, I. M., BRIAN, M., LAURIE, T., IAN, J. D., CHRISTOPHER, T. R., ROHINI, M., ANGEL, W., RICHARD, G., DAVID, H., HARRIET, F., ANNA, S., RICHARD, C., JOHN, P., FRANK, H., SAM, H., RAF, P., STEPHEN, E., LIAM, S. & BEN, G. 2020. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *medRxiv,* 2020**,** 1-22.
ENILARI, O. & SINHA, S. 2019. The Global Impact of Asthma in Adult Populations. *Ann Glob Health,* 85.
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (ECDC) 2020. *Novel Coronavirus Disease 2019 (COVID-19) Pandemic: Increased Transmission in the EU/EEA and the UK-Sixth Update. Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK-sixth update,* Stockholm, ECDC.
FAN, H. F., HE, C. H., YIN, G. Q., QIN, Y., JIANG, N., LU, G. & LI, X. 2021. Frequency of asthma exacerbation in children during the coronavirus disease pandemic with strict mitigative countermeasures. *Pediatric pulmonology,* 56**,** 1455-1463.
FANG, Y., ZHANG, H., XIE, J., LIN, M., YING, L., PANG, P. & JI, W. 2020. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology,* 296**,** E115-e117.
FISHER, D. & HEYMANN, D. 2020. Q&A: The novel coronavirus outbreak causing COVID-19. *BMC Med,* 18**,** 57.
GASPAR-MARQUES, J., VAN ZELLER, M., CARREIRO-MARTINS, P. & CHAVES LOUREIRO, C. 2022. Severe asthma in the era of COVID-19: A narrative review. *Pulmonology,* 28**,** 34-43.
GHORANI-AZAM, A., RIAHI-ZANJANI, B. & BALALI-MOOD, M. 2016. Effects of air pollution on human health and practical measures for prevention in Iran. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences,* 21**,** 65.
GIACOMELLI, A., PEZZATI, L., CONTI, F., BERNACCHIA, D., SIANO, M., ORENI, L., RUSCONI, S., GERVASONI, C., RIDOLFO, A. L., RIZZARDINI, G., ANTINORI, S. & GALLI, M. 2020. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. *Clin Infect Dis,* 71**,** 889-890.
GLASZIOU, P., VANDENBROUCKE, J. P. & CHALMERS, I. 2004. Assessing the quality of research. *Bmj,* 328**,** 39-41.

GLOBAL INITIATIVE FOR ASTHMA (GINA) 2019. *Global strategy for asthma management and prevention,* Fontana, GINA. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf.

GLOBAL INITIATIVE FOR ASTHMA (GINA) 2022. *GINA Report, Global Strategy for Asthma Management and Prevention,* Fontana, GINA. Available from: https://ginasthma.org/gina-reports/.

GONEM, S., CUMELLA, A. & RICHARDSON, M. 2019. Asthma admission rates and patterns of salbutamol and inhaled corticosteroid prescribing in England from 2013 to 2017. *Thorax,* 74**,** 705-706.

GRIESEL, M., WAGNER, C., MIKOLAJEWSKA, A., STEGEMANN, M., FICHTNER, F., METZENDORF, M. I., NAIR, A. A., DANIEL, J., FISCHER, A. L. & SKOETZ, N. 2022. Inhaled corticosteroids for the treatment of COVID-19. *Cochrane Database Syst Rev,* 3**,** Cd015125.

GROSIOS, K., GAHAN, P. B. & BURBIDGE, J. 2010. Overview of healthcare in the UK. *Epma j,* 1**,** 529-34.

GUPTA, A., MADHAVAN, M. V., SEHGAL, K., NAIR, N., MAHAJAN, S., SEHRAWAT, T. S., BIKDELI, B. & AHLUWALIA, N. 2020. Extrapulmonary manifestations of COVID-19. *Nature medicine,* 26**,** 1017-1032.

HAAPANEN, M., RENKO, M., ARTAMA, M. & KUITUNEN, I. 2022. Systemic antibiotics and asthma medicines dispensed to 0– 12 year olds significantly decreased during the COVID-19 pandemic in 2020. *Acta Paediatrica,* 111**,** 376-382.

HALCOMB, E., FERNANDEZ, R., ASHLEY, C., MCINNES, S., STEPHEN, C., CALMA, K., MURSA, R., WILLIAMS, A. & JAMES, S. 2022. The impact of COVID-19 on primary health care delivery in Australia. *Journal of Advanced Nursing,* 78**,** 1327-1336.

HARTNETT, K. P., KITE-POWELL, A., DEVIES, J., COLETTA, M. A., BOEHMER, T. K., ADJEMIAN, J. & GUNDLAPALLI, A. V. 2020. Impact of the COVID-19 Pandemic on Emergency Department Visits - United States, January 1, 2019-May 30, 2020. *MMWR Morb Mortal Wkly Rep,* 69**,** 699-704.

HASSANY, M., ABDEL-RAZEK, W., ASEM, N., ABDALLAH, M. & ZAID, H. 2020. Estimation of COVID-19 burden in Egypt. *Lancet Infect Dis,* 20**,** 896-897.

HAZAN, G., FOX, C., EIDEN, E., ANDERSON, N., FRIGER, M. & HASPEL, J. 2022. Effect of the COVID-19 lockdown on asthma biological rhythms. *Journal of biological rhythms,* 37**,** 152-163.

HERSOUG, L.-G., HUSEMOEN, L. L. N., THOMSEN, S. F., SIGSGAARD, T., THUESEN, B. H. & LINNEBERG, A. 2010. Association of indoor air pollution with rhinitis symptoms, atopy and nitric oxide levels in exhaled air. *International archives of allergy and immunology,* 153**,** 403-412.

HIJAZI, N., ABALKHAIL, B. & SEATON, A. 1998. Asthma and respiratory symptoms in urban and rural Saudi Arabia. *European Respiratory Journal,* 12**,** 41-44.

HOPKINS, J. 2020. *Serology-based tests for COVID-19,* Baltimore, Johns Hopkins.

HORAK, F., DOBERER, D., EBER, E., HORAK, E., POHL, W., RIEDLER, J., SZÉPFALUSI, Z., WANTKE, F., ZACHARASIEWICZ, A. & STUDNICKA, M. 2016. Diagnosis and management of asthma - Statement on the 2015 GINA Guidelines. *Wien Klin Wochenschr,* 128**,** 541-54.

HU, Z., SONG, C., XU, C., JIN, G., CHEN, Y., XU, X., MA, H., CHEN, W., LIN, Y., ZHENG, Y., WANG, J., HU, Z., YI, Y. & SHEN, H. 2020. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci,* 63**,** 706-711.

HUANG, C., WANG, Y., LI, X., REN, L., ZHAO, J., HU, Y., ZHANG, L., FAN, G., XU, J., GU, X., CHENG, Z., YU, T., XIA, J., WEI, Y., WU, W., XIE, X., YIN, W., LI, H., LIU, M., XIAO, Y., GAO, H., GUO, L., XIE, J., WANG, G., JIANG, R., GAO, Z., JIN, Q., WANG, J. & CAO, B.

2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet,* 395**,** 497-506.

JIE, Y., ISA, Z. M., JIE, X., JU, Z. L. & ISMAIL, N. H. 2013. Urban vs. rural factors that affect adult asthma. *Rev Environ Contam Toxicol,* 226**,** 33-63.

KATTAN, M., GERGEN, P. J., EGGLESTON, P., VISNESS, C. M. & MITCHELL, H. E. 2007. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. *Journal of Allergy and Clinical Immunology,* 120**,** 618-624.

KAYE, L., THEYE, B., SMEENK, I., GONDALIA, R., BARRETT, M. A. & STEMPEL, D. A. 2020. Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. *J Allergy Clin Immunol Pract,* 8**,** 2384-2385.

KAZAMA, I. 2021. Potential prophylactic efficacy of mast cell stabilizers against COVID-19 vaccine-induced anaphylaxis. *Clin Mol Allergy,* 19**,** 25.

LAGERLOV, P., VENINGA, C., MUSKOVA, M., HUMMERS-PRADIER, E., LUNDBORG, C. S., ANDREW, M. & HAAIJER-RUSKAMP, F. 2000. Asthma management in five European countries: doctors' knowledge, attitudes and prescribing behaviour. Drug Education Project (DEP) group. *European Respiratory Journal,* 15**,** 25-29.

LAM, N. L., SMITH, K. R., GAUTHIER, A. & BATES, M. N. 2012. Kerosene: a review of household uses and their hazards in low-and middle-income countries. *Journal of Toxicology and Environmental Health, Part B,* 15**,** 396-432.

LEE, A., KINNEY, P., CHILLRUD, S. & JACK, D. 2015. A Systematic Review of Innate Immunomodulatory Effects of Household Air Pollution Secondary to the Burning of Biomass Fuels. *Ann Glob Health,* 81**,** 368-74.

LEGROS, G., HAVET, I., BRUCE, N., BONJOUR, S., RIJAL, K., TAKADA, M. & DORA, C. 2009. The energy access situation in developing countries: a review focusing on the least developed countries and Sub-Saharan Africa. *World Health Organization,* 142**,** 32.

LEMANSKE, R. F., JR. & BUSSE, W. W. 2010. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol,* 125**,** S95-102.

LEVAC, D., COLQUHOUN, H. & O'BRIEN, K. K. 2010. Scoping studies: advancing the methodology. *Implement Sci,* 5**,** 69.

LI, C., ZHAO, C., BAO, J., TANG, B., WANG, Y. & GU, B. 2020. Laboratory diagnosis of coronavirus disease-2019 (COVID-19). *Clin Chim Acta,* 510**,** 35-46.

LIM, S. S., VOS, T., FLAXMAN, A. D., DANAEI, G., SHIBUYA, K., ADAIR-ROHANI, H., ALMAZROA, M. A., AMANN, M., ANDERSON, H. R. & ANDREWS, K. G. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet,* 380**,** 2224-2260.

LIU, S., ZHOU, Y., WANG, X., WANG, D., LU, J., ZHENG, J., ZHONG, N. & RAN, P. 2007. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. *Thorax,* 62**,** 889-97.

LU, R., ZHAO, X., LI, J., NIU, P., YANG, B., WU, H., WANG, W., SONG, H., HUANG, B., ZHU, N., BI, Y., MA, X., ZHAN, F., WANG, L., HU, T., ZHOU, H., HU, Z., ZHOU, W., ZHAO, L., CHEN, J., MENG, Y., WANG, J., LIN, Y., YUAN, J., XIE, Z., MA, J., LIU, W. J., WANG, D., XU, W., HOLMES, E. C., GAO, G. F., WU, G., CHEN, W., SHI, W. & TAN, W. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet,* 395**,** 565-574.

MARTIN, W. J., HOLLINGSWORTH, J. W. & V., R. 2014. Household air pollution from cookstoves: Impacts on health and climate. *In:* PINKERTON, K. & ROM, W. (eds.) *Global Climate Change and Public Health.* New York: Springer.

MARTIN, W. J., RAMANATHAN, T. & RAMANATHAN, V. 2021. Household Air Pollution from Cookstoves: Impacts on Health and Climate. *In:* PINKERTON, K. E. & ROM, W. N.

(eds.) *Climate Change and Global Public Health.* Cham: Springer International Publishing.

MCCOY, K., SHADE, D. M., IRVIN, C. G., MASTRONARDE, J. G., HANANIA, N. A., CASTRO, M. & ANTHONISEN, N. R. 2006. Predicting episodes of poor asthma control in treated patients with asthma. *J Allergy Clin Immunol,* 118**,** 1226-33.

MELTZER, E. O., BUSSE, W. W., WENZEL, S. E., BELOZEROFF, V., WENG, H. H., FENG, J., CHON, Y., CHIOU, C. F., GLOBE, D. & LIN, S. L. 2011. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol,* 127**,** 167-72.

MIMS, J. W. 2015. *Asthma: definitions and pathophysiology. International forum of allergy & rhinology,* New York, Wiley Online Library.

MORAIS-ALMEIDA, M., PITÉ, H., AGUIAR, R., ANSOTEGUI, I. & BOUSQUET, J. 2020. Asthma and the Coronavirus Disease 2019 Pandemic: A Literature Review. *Int Arch Allergy Immunol,* 181**,** 680-688.

MORRIS, B. L., SHORT, M., BRIDGES, D., CRICHTON, M., VELANDER, F., RUSH, E., IFFLAND, B. & DUNCOMBE, R. 2022. Responding to student mental health challenges during and post-COVID-19. *Social Work Education,* 41**,** 1821-1838.

MUISER, S., GOSENS, R., VAN DEN BERGE, M. & KERSTJENS, H. A. M. 2022. Understanding the role of long-acting muscarinic antagonists in asthma treatment. *Ann Allergy Asthma Immunol,* 128**,** 352-360.

MUKHERJEE, M., STODDART, A., GUPTA, R. P., NWARU, B. I., FARR, A., HEAVEN, M., FITZSIMMONS, D., BANDYOPADHYAY, A., AFTAB, C. & SIMPSON, C. R. 2016. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC medicine,* 14**,** 1-15.

MUSHARRAFIEH, U., TAMIM, H., HOURY, R. & ALBUHAIRAN, F. 2020. A nationwide study of asthma correlates among adolescents in Saudi Arabia. *Asthma research and practice,* 6**,** 1-8.

MYERS, T. R. 2008. Guidelines for asthma management: a review and comparison of 5 current guidelines. *Respir Care,* 53**,** 751-69.

NAEHER, L. P., BRAUER, M., LIPSETT, M., ZELIKOFF, J. T., SIMPSON, C. D., KOENIG, J. Q. & SMITH, K. R. 2007. Woodsmoke health effects: a review. *Inhalation toxicology,* 19**,** 67-106.

NICI, L., DONNER, C., WOUTERS, E., ZUWALLACK, R., AMBROSINO, N., BOURBEAU, J., CARONE, M., CELLI, B., ENGELEN, M., FAHY, B., GARVEY, C., GOLDSTEIN, R., GOSSELINK, R., LAREAU, S., MACINTYRE, N., MALTAIS, F., MORGAN, M., O'DONNELL, D., PREFAULT, C., REARDON, J., ROCHESTER, C., SCHOLS, A., SINGH, S. & TROOSTERS, T. 2006. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med,* 173**,** 1390-413.

NWARU, B. I., EKSTRÖM, M., HASVOLD, P., WIKLUND, F., TELG, G. & JANSON, C. 2020. Overuse of short-acting β(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *The European respiratory journal,* 55**,** 1901872.

O'BYRNE, P., FABBRI, L. M., PAVORD, I. D., PAPI, A., PETRUZZELLI, S. & LANGE, P. 2019. Asthma progression and mortality: the role of inhaled corticosteroids. *The European respiratory journal,* 54**,** 1900491.

O'BYRNE, P. M., JENKINS, C. & BATEMAN, E. D. 2017. The paradoxes of asthma management: time for a new approach? *Eur Respir J,* 50**,** 1701103.

OKELO, S. O., BUTZ, A. M., SHARMA, R., DIETTE, G. B., PITTS, S. I., KING, T. M., LINN, S. T., REUBEN, M., CHELLADURAI, Y. & ROBINSON, K. A. 2013. Interventions to modify health care provider adherence to asthma guidelines: a systematic review. *Pediatrics,* 132**,** 517-534.

OLIVEIRA, M., SLEZAKOVA, K., DELERUE-MATOS, C., PEREIRA, M. C. & MORAIS, S. 2019. Children environmental exposure to particulate matter and polycyclic aromatic hydrocarbons and biomonitoring in school environments: A review on indoor and outdoor exposure levels, major sources and health impacts. *Environment international,* 124**,** 180-204.

OUR WORLD IN DATA (OWD) 2019. *Asthma prevalence,* Oxford, OWD.

OW, N. L., ATTALLA, S. S., DAVIES, G., GRIFFITHS, C. J. & DE SIMONI, A. 2022. Experiences and behaviours of patients with asthma requesting prescriptions from primary care during medication shortages linked to the COVID-19 lockdown: insights from a qualitative analysis of a UK asthma online community. *BJGP open,* 6**,** 1-11.

PAPI, A., BRIGHTLING, C., PEDERSEN, S. E. & REDDEL, H. K. 2018. Pathogenesis of asthma. *Lancet,* 391**,** 783-800.

PAULUHN, J. & MOHR, U. 2006. Mosquito coil smoke inhalation toxicity. Part II: subchronic nose-only inhalation study in rats. *J Appl Toxicol,* 26**,** 279-92.

PELLEGRINO, R., VIEGI, G., BRUSASCO, V., CRAPO, R. O., BURGOS, F., CASABURI, R., COATES, A., VAN DER GRINTEN, C. P., GUSTAFSSON, P., HANKINSON, J., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., MILLER, M. R., NAVAJAS, D., PEDERSEN, O. F. & WANGER, J. 2005. Interpretative strategies for lung function tests. *Eur Respir J,* 26**,** 948-68.

PÉREZ-PADILLA, R., SCHILMANN, A. & RIOJAS-RODRIGUEZ, H. 2010. Respiratory health effects of indoor air pollution. *The International Journal of Tuberculosis and Lung Disease,* 14**,** 1079-1086.

PETERS, M. D., GODFREY, C. M., MCINERNEY, P., SOARES, C. B., KHALIL, H. & PARKER, D. 2015. *The Joanna Briggs Institute reviewers' manual 2015: methodology for JBI scoping reviews,* South Australia, The Joanna Briggs Institute.

POKHREL, A. K., BATES, M. N., VERMA, S. C., JOSHI, H. S., SREERAMAREDDY, C. T. & SMITH, K. R. 2010. Tuberculosis and indoor biomass and kerosene use in Nepal: a case-control study. *Environ Health Perspect,* 118**,** 558-64.

QUIRCE, S., LEMIÈRE, C., DE BLAY, F., DEL POZO, V., GERTH VAN WIJK, R., MAESTRELLI, P., PAULI, G., PIGNATTI, P., RAULF-HEIMSOTH, M., SASTRE, J., STORAAS, T. & MOSCATO, G. 2010. Noninvasive methods for assessment of airway inflammation in occupational settings. *Allergy,* 65**,** 445-58.

REDDEL, H. K., FITZGERALD, J. M., BATEMAN, E. D., BACHARIER, L. B., BECKER, A., BRUSSELLE, G., BUHL, R., CRUZ, A. A. & FLEMING, L. 2019. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *The European respiratory journal,* 53**,** 1901046.

REHFUESS, E., MEHTA, S. & PRÜSS-USTÜN, A. 2006. Assessing household solid fuel use: multiple implications for the Millennium Development Goals. *Environ Health Perspect,* 114**,** 373-8.

ROSENBAUM, L. 2020. The untold toll—the pandemic's effects on patients without Covid-19. *New England Journal of Medicine,* 382**,** 2368-2371.

ROSIAS, P. P., DOMPELING, E., DENTENER, M. A., PENNINGS, H. J., HENDRIKS, H. J., VAN IERSEL, M. P. & JÖBSIS, Q. 2004. Childhood asthma: exhaled markers of airway inflammation, asthma control score, and lung function tests. *Pediatr Pulmonol,* 38**,** 107-14.

ROSSEN, L. M., BRANUM, A. M., AHMAD, F. B., SUTTON, P. & ANDERSON, R. N. 2020. Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity - United States, January 26-October 3, 2020. *MMWR Morb Mortal Wkly Rep,* 69**,** 1522-1527.

SAHU, K. K., MISHRA, A. K. & LAL, A. 2020. Comprehensive update on current outbreak of novel coronavirus infection (2019-nCoV). *Ann Transl Med,* 8**,** 393.

SCHATZ, M., ZEIGER, R. S., YANG, S. J., CHEN, W., CRAWFORD, W., SAJJAN, S. & ALLEN-RAMEY, F. 2012. The relationship of asthma impairment determined by psychometric tools to future asthma exacerbations. *Chest,* 141**,** 66-72.

SCHULTZE, A., WALKER, A. J., MACKENNA, B., MORTON, C. E., BHASKARAN, K., BROWN, J. P., RENTSCH, C. T., WILLIAMSON, E., DRYSDALE, H., CROKER, R., BACON, S., HULME, W., BATES, C., CURTIS, H. J., MEHRKAR, A., EVANS, D., INGLESBY, P., COCKBURN, J., MCDONALD, H. I., TOMLINSON, L., MATHUR, R., WING, K., WONG, A. Y. S., FORBES, H., PARRY, J., HESTER, F., HARPER, S., EVANS, S. J. W., QUINT, J., SMEETH, L., DOUGLAS, I. J. & GOLDACRE, B. 2020. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med,* 8**,** 1106-1120.

SHAH, S. A., QUINT, J. K., NWARU, B. I. & SHEIKH, A. 2021. Impact of COVID-19 national lockdown on asthma exacerbations: interrupted time-series analysis of English primary care data. *Thorax,* 76**,** 860-866.

SINHA, I. P., CALVERT, J., HICKMAN, K. C., HURST, J. R., MCMILLAN, V., QUINT, J. K., SINGH, S. J. & ROBERTS, C. M. 2019. National Asthma and COPD Audit Programme and the NHS Long Term Plan. *Lancet Respir Med,* 7**,** 841.

SMITH, K. R., BRUCE, N., BALAKRISHNAN, K., ADAIR-ROHANI, H., BALMES, J., CHAFE, Z., DHERANI, M., HOSGOOD, H. D., MEHTA, S. & POPE, D. 2014. Millions dead: how do we know and what does it mean? Methods used in the comparative risk assessment of household air pollution. *Annual review of public health,* 35**,** 185-206.

SPIRA-COHEN, A., CHEN, L. C., KENDALL, M., LALL, R. & THURSTON, G. D. 2011. Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. *Environ Health Perspect,* 119**,** 559-65.

STERN, C., JORDAN, Z. & MCARTHUR, A. 2014. Developing the review question and inclusion criteria. *Am J Nurs,* 114**,** 53-6.

SUBBARAO, P., MANDHANE, P. J. & SEARS, M. R. 2009. Asthma: epidemiology, etiology and risk factors. *Cmaj,* 181**,** E181-90.

SWEILEH, W. M., AL-JABI, S. W., ZYOUD, S. E. H. & SAWALHA, A. F. 2018. Outdoor air pollution and respiratory health: a bibliometric analysis of publications in peer-reviewed journals (1900–2017). *Multidisciplinary Respiratory Medicine,* 13**,** 1-12.

TOBÍAS, A., CARNERERO, C., RECHE, C., MASSAGUÉ, J., VIA, M., MINGUILLÓN, M. C., ALASTUEY, A. & QUEROL, X. 2020. Changes in air quality during the lockdown in Barcelona (Spain) one month into the SARS-CoV-2 epidemic. *Sci Total Environ,* 726**,** 138540.

TRIKAMJEE, T., COMBERIATI, P. & PETER, J. 2022. Pediatric asthma in developing countries: challenges and future directions. *Curr Opin Allergy Clin Immunol,* 22**,** 80-85.

VON SCHIRNDING, Y., BRUCE, N., SMITH, K., BALLARD-TREMEER, G., EZZATI, M. & LVOVSKY, K. 2002. *Addressing the impact of household energy and indoor air pollution on the health of poor: Implications for policy action and intervention measures,* Geneva, World Health Organization.

VOTTO, M., DE FILIPPO, M., LICARI, A., MARSEGLIA, A., DE AMICI, M. & MARSEGLIA, G. L. 2021. Biological therapies in children and adolescents with severe uncontrolled asthma: a practical review. *Biologics: Targets and Therapy***,** 133-142.

WALLACK, J. S. & RAMANATHAN, V. 2009. The other climate changers: Why black carbon and ozone also matter. *Foreign affairs,* 88**,** 105-113.

WANG, L., FOER, D., BATES, D. W., BOYCE, J. A. & ZHOU, L. 2020a. Risk factors for hospitalization, intensive care, and mortality among patients with asthma and COVID-19. *J Allergy Clin Immunol,* 146**,** 808-812.

WANG, Y., CHEN, J., CHEN, W., LIU, L., DONG, M., JI, J., HU, D. & ZHANG, N. 2021. Does Asthma Increase the Mortality of Patients with COVID-19?: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol,* 182**,** 76-82.

WANG, Y., HAN, W., PAN, L., WANG, C., LIU, Y., HU, W., ZHOU, H. & ZHENG, X. 2020b. Impact of COVID-19 on blood centres in Zhejiang province China. *Vox sanguinis,* 115**,** 502-506.

WENZEL, S. E. 2012. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med,* 18**,** 716-25.

WIJESINGHE, M., PERRIN, K., HARWOOD, M., WEATHERALL, M. & BEASLEY, R. 2008. The risk of asthma mortality with inhaled long acting β-agonists. *Postgraduate medical journal,* 84**,** 467-472.

WILDER-SMITH, A. & FREEDMAN, D. O. 2020. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J Travel Med,* 27**,** 1-4.

WOELFEL, R., CORMAN, V. M., GUGGEMOS, W., SEILMAIER, M., ZANGE, S., MUELLER, M. A., NIEMEYER, D., VOLLMAR, P., ROTHE, C. & HOELSCHER, M. 2020. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster. *MedRxiv,* 2020**,** 1-16.

WORLD HEALTH ORGANIZATION (WHO) 2002. *Health impact assessment of air pollution in the eight major Italian cities,* Geneva, WHO.

WORLD HEALTH ORGANIZATION (WHO) 2005. *Effects of air pollution on children's health and development: a review of the evidence,* Geneva, WHO.

WORLD HEALTH ORGANIZATION (WHO) 2006. *Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide, and sulfur dioxide,* Geneva, WHO.

WORLD HEALTH ORGANIZATION (WHO) 2018. *Air pollution and child health: prescribing clean air: summary,* Geneva, WHO.

WORLD HEALTH ORGANIZATION (WHO) 2020. *Diagnostic testing for SARS-CoV-2: interim guidance,* Geneva, WHO.

WORLD HEALTH ORGANIZATION (WHO) 2023. *Asthma,* Geneva, WHO.

XIE, X., ZHONG, Z., ZHAO, W., ZHENG, C., WANG, F. & LIU, J. 2020. Chest CT for typical coronavirus disease 2019 (COVID-19) pneumonia: relationship to negative RT-PCR testing. *Radiology,* 296**,** E41-E45.

XU, Z., SHI, L., WANG, Y., ZHANG, J., HUANG, L., ZHANG, C., LIU, S., ZHAO, P., LIU, H., ZHU, L., TAI, Y., BAI, C., GAO, T., SONG, J., XIA, P., DONG, J., ZHAO, J. & WANG, F. S. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med,* 8**,** 420-422.

YANG, J. M., KOH, H. Y., MOON, S. Y., YOO, I. K., HA, E. K., YOU, S., KIM, S. Y., YON, D. K. & LEE, S. W. 2020. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. *J Allergy Clin Immunol,* 146**,** 790-798.

YANG, Z., WANG, X., WAN, X. G., WANG, M. L., QIU, Z. H., CHEN, J. L., SHI, M. H., ZHANG, S. Y. & XIA, Y. L. 2022. Pediatric asthma control during the COVID-19 pandemic: A systematic review and meta-analysis. *Pediatric pulmonology,* 57**,** 20-25.

YEATTS, K. B., EL-SADIG, M., LEITH, D., KALSBEEK, W., AL-MASKARI, F., COUPER, D., FUNK, W. E., ZOUBEIDI, T., CHAN, R. L. & TRENT, C. B. 2012. Indoor air pollutants and health in the United Arab Emirates. *Environmental health perspectives,* 120**,** 687-694.

YOUSEF, H. A., KOURA, M. & YOUSEF, A. A. 2015. Knowledge about bronchial asthma management in primary health care physicians in Al-Khobar City, Saudi Arabia. *J Family Community Med,* 22**,** 1-7.

ZHANG, L., JIANG, Z., TONG, J., WANG, Z., HAN, Z. & ZHANG, J. 2010. Using charcoal as base material reduces mosquito coil emissions of toxins. *Indoor Air,* 20**,** 176-84.

ZHU, N., ZHANG, D., WANG, W., LI, X., YANG, B., SONG, J., ZHAO, X., HUANG, B., SHI, W., LU, R., NIU, P., ZHAN, F., MA, X., WANG, D., XU, W., WU, G., GAO, G. F. & TAN, W. 2020a. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med,* 382**,** 727-733.

ZHU, Z., HASEGAWA, K., MA, B., FUJIOGI, M., CAMARGO, C. A., JR. & LIANG, L. 2020b. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol,* 146**,** 327-329.e4.

Appendices

Appendix 1

Chapter Three

Asthma Management Questionnaire

Section A: Knowledge

1. Identify the false statements regarding factors contributing to asthma severity.
2. Identify the incorrect statement about the use of short-acting inhaled β2-agonists.
3. Which of these statements about spirometry is false?
4. Which of the following is not a risk factor for death in adult asthma patients?
5. Identify the option that is not indicative of asthma.
6. Which of the following is not an inhaled steroid?
7. Which effects have not been associated with inhaled corticosteroids?
8. Which is not a direct cause of airway obstruction in asthma?
9. Identify the false statement regarding long-acting inhaled β2-agonists.
10. Which of the following does not possess anti-inflammatory properties?
11. Identify the false statement regarding long-term control of asthma.
12. What can cause irreversible airflow obstruction in asthma patients?
13. Which statement about the use of inhaled corticosteroids is incorrect?

Section B: Attitude

14. Which method is not recommended for modifying indoor allergens for asthmatic patients?
15. What is recommended for most patients during an acute asthma exacerbation?
16. Which inhaler technique is considered unacceptable?
17. Which factor best correlates with bronchial hyper-responsiveness?
18. Which treatment is generally not advised for acute asthma exacerbations?
19. Which medication is least recommended for long-term control of asthma?
20. For asthma patients without symptoms between attacks, which long-term management statement is incorrect?
21. For a patient with moderately persistent asthma poorly controlled on low dose inhaled steroids, which treatment regimen is inappropriate?

Section C: Practice

22. Classify a 4-year-old child using low-dose inhaled corticosteroids (ICS) and as-needed inhaled SABA.
23. Classify a 10-year-old child using a medium dose of ICS-formoterol as maintenance and reliever therapy (MART).
24. Classify a 30-year-old adult using high-dose ICS-LABA.
25. How would you classify a 20-year-old requiring oral corticosteroids and experiencing frequent exacerbations?
26. At what disease severity should anti-inflammatory medications be initiated?
27. Which data set indicates an asthmatic patient at the highest risk of imminent respiratory failure?
28. Which data set most strongly suggests asthma as the primary diagnosis?
29. Which option is inconsistent with Mild Persistent asthma?
30. Which of the following is not documented as a benefit of patient education in asthma management?
31. What are the necessary criteria to diagnose asthma?

Appendix 2

Chapter 4

Data aggregation, calculations, and analysis:

The master table was added to a data model, to create the below measures:

a) Items per 100000 MYP per country = (∑ ([Dispensed Items country])/mean ([MYP country])) *100000

b) Items per 100000 MYP_UK= (∑ ([Dispensed Items country])/mean ([MYP UK])) *100000

c) DDD per year (single) = (Doses X strength X Quantity)/DDD value for that agent

d) DDD per year (combined) = (Doses X Quantity)/DDD value for that agent

e) DDD per 1000 inhabitant per day country =

((∑ ([DDD per year country]) /mean ([MYP country])) *1000)/365.

f) DDD per 1000 inhabitant per day UK = ((∑ ([DDD per year UK])/mean([MYPuk])) *1000)/365

g) total cost country year = ∑ ([cost country year])

h) total cost UK year = ∑ ([cost UK year])

The data model was summarized per class using PowerPivot table and charts.

Summary of the whole process

Asthma generic medications available in the UK were grouped into five categories according to BNF classification into

Inhaled corticosteroids ICS

Long-Acting Beta 2 agonist LABA

Long-acting muscarinic antagonists LAMA

Short acting Beta agonists SABA

Mast cell stabilizers (MCs)

And their combination together

The combination process included the medicine's name, strength, quantity, cost, and formulation. Data from all four countries were extracted from 2011 to 2021. PCA datasets contain aggregated-level information on all dispensed asthma prescriptions in the United Kingdom primary care setting.

Utilization and prescribing patterns of inhalers were assessed using the prescription costs analysis (PCA) data compiled by the Information Services Division (ISD) of NHS in the four countries.

Also, the population of each of the four countries was used to obtain an accurate comparison between four countries. This was the estimated population at the mid-year point in UK.

The total cost of all prescriptions was divided 12 and then divided by Mid-year population number according to offices of National statistics and then multiplied by 1000.

Appendix 3

Medication costs per country

England:

Year	class	Sum of Sum of Net Ingredient Cost (p)		Sum of Sum of Items Dispensed			
2018	Bronchodilator	107148979.9		329339			
2018	ICS	25542119492		8873624.8			
2018	ICS/LAMA/LABA	539144635		112790			
2018	LABA	832528401.4		263949.1			
2018	LAMA	7604116075		2495172			
2018	LAMA/LABA	1706288893		473240			
2018	MCS	232823978.8		1223527			
2018	SABA	2601954826		9245198			
2018	SAMA	172366868		187336			
2018	Grand Total	39338492150		23204175.9			
Year	**Class**	**Sum of Total cost (£)**	**% cost**	**Sum of Dispense**	**% items**	cost	items
2019	Bronchodilator	2460572.04	0.26%	739729	1%	3.642896	1.095174433
2019	ICS	591590139.3	63%	21126340	38%	875.8537	31.2777077
2019	ICS/LAMA/LABA	33719156.92	4%	697725	1%	49.92147	1.032987191
2019	LABA	17220476.68	2%	488384	1%	25.49505	0.723056242
2019	LAMA	161514269.7	17%	5059667	9%	239.1231	7.490875631
2019	LAMA/LABA	49396354.61	5%	1344445	2%	73.13168	1.990461089
2019	MCS	13434094.93	1%	3177057	6%	19.88928	4.70365715
2019	SABA	62064161.89	7%	22226525	40%	91.88647	32.90653999
2019	SAMA	3536749.1	0.38%	391977	1%	5.236184	0.580324942
		934935975.2	1	55251849			
Year		**Sum of Total Cost (GBP)**	**% cost**	**Sum of Total Ite**	**% items**	cost	items
2020	Bronchodilator	2249088.12	0.2%	695580	1%	3.314306	1.025022104
2020	ICS	634542768.4	64%	22699677	39%	935.0763	33.45074713
2020	ICS/LAMA/LABA	57660341	6%	1185691	2%	84.96956	1.747260536
2020	LABA	14888644.92	2%	422086	1%	21.94024	0.621995284
2020	LAMA	143185706.8	14%	4554629	8%	211.0016	6.71180224
2020	LAMA/LABA	57927779.29	6%	1569473	3%	85.36366	2.312810197
2020	MCS	13285064.68	1%	3587139	6%	19.57717	5.286087533
2020	SABA	63864914.68	6%	22719872	39%	94.11275	33.48050693
2020	SAMA	3120414.25	0.3%	333544	1%	4.598312	0.491517831
2020	Grand Total	990724722.1		57767691			
Year	**class**	**Sum of Sum of Net Ingredient Cost (£)**	**% cost**	**Sum of Sum of It**	**% items**	cost	items
2021	Bronchodilator	520025.12	0.22%	159571	1%	0.767137	0.235397954
2021	ICS	150037906.3	64%	5284786.6	40%	221.3348	7.796077935
2021	ICS/LABA	60.49	0.00%	3	0.00002%	8.92E-05	0.00000443
2021	ICS/LAMA/LABA	15937897.5	7%	326846	2%	23.51147	0.482160791
2021	LABA	3146700.441	1%	89551.8	1%	4.641989	0.13210615
2021	LAMA	31816804.7	14%	1018424	8%	46.93591	1.50237152
2021	LAMA/LABA	14188905.03	6%	383746	3%	20.93137	0.566099249
2021	MCS	2719732.28	1%	897455	7%	4.012129	1.323918949
2021	SABA	13954103.95	6%	5006398	38%	20.58499	7.38540114
2021	SAMA	667164.19	0.29%	70016	1%	0.984196	0.103287083
2021	Grand Total	232989300		13236797.4			

North Ireland

2018 NI	Sum of Count of QUANTITY	Sum of Sum of INGREDIENT COST (BEFORE DISCOUNT)
Broncholdilator	97	160856.806
ICS	288	3265217.725
ICS/LABA	254	20713102.21
ICS/LAMA/LABA	10	672422.504
LABA	119	445847.883
LAMA	110	7554270.637
LAMA/LABA	40	2152133.088
MCS	74	375793.025
SABA	184	3181394.599
SABA/SAMA	24	40922.142
Grand Total	1200	38561960.62

2019 NI	Sum of Sum o	% items	Sum of Sum of INGREDIENT COST (BEFORE DISCOUNT)	% cost		items	cost
Broncholdilator	2336268	4%	150137.488	0.40%		102.8088	6.606885
ICS	1318357	2%	3240410.705	9%		58.01504	142.5961
ICS/LABA	19112808	30%	17986753.61	48%		841.0699	791.5172
ICS/LAMA/LABA	4198799	7%	2800177.705	8%		184.7705	123.2234
LABA	89289	0.14%	355193.029	1%		3.929213	15.63047
LAMA	6750084	11%	6376636.835	17%		297.0412	280.6075
LAMA/LABA	2897007	5%	2647928.743	7%		127.4844	116.5236
MCS	5248651	8%	723235.713	2%		230.9698	31.82639
SABA	20795319	33%	2983383.658	8%		915.1097	131.2855
SABA/SAMA	82911	0.13%	32856.614	0.09%		3.648545	1.445874
Grand Total	62829493		37296714.1	1			

2020 NI	Sum of Sum o	% items	Sum of Sum of NUMBER PRESCRIPTION ITEMS	% cost		items	cost
Broncholdilator	127658.561	0.33%	31157	1%		5.610872	1.369418
ICS	3334259.841	8%	285600	12%		146.548	12.55274
ICS/LABA	18689052.92	48%	555546	24%		821.4246	24.41746
ICS/LAMA/LABA	4758619.368	12%	94894	4%		209.1517	4.170798
LABA	303634.924	1%	8087	0.35%		13.34542	0.355441
LAMA	5305189.21	14%	158756	7%		233.1746	6.977672
LAMA/LABA	2925701.829	7%	77788	3%		128.591	3.418952
MCS	675840.755	2%	151451	7%		29.70467	6.656602
SABA	3090404.185	8%	921926	40%		135.83	40.52066
SABA/SAMA	25311.853	0.06%	931	0.04%		1.112511	0.040919
Grand Total	39235673.44		2286136				

2021 NI	Sum of NUMB	% items	Sum of NGREDIENT COST (BEFORE DISCOUNT)	% cost		items	cost
bronchodilator	27490	1%	113027.173	0.30%		1.203738	4.949257
ICS	258649	12%	2982816.097	8%		11.32578	130.6122
ICS/LABA	522791	24%	17660991.22	47%		22.89208	773.3431
ICS/LAMA/LABA	113095	5%	5658862.896	15%		4.952227	247.7914
LABA	7101	0.33%	266384.157	1%		0.31094	11.66448
LAMA	135216	6%	4448435.839	12%		5.920866	194.789
LAMA/LABA	76582	4%	2863655.685	8%		3.353388	125.3943
MCS	151541	7%	482945.386	1%		6.635708	21.14731
SABA	846659	40%	2761525.732	7%		37.07368	120.9223
SABA/SAMA	794	0.04%	21226.517	0.06%		0.034768	0.929471
Grand Total	2139918	1	37259870.71	1			

Scotland

2018-2019 scot	Sum of Number of dispensed items	% items	Sum of Gross ingredient cost (£)	% cost	items		cost
Bronchodilator	63641	1%	316684.44	0.3%	5303.416667	0.970735	4.830482
ICS	603434	11%	8263244.2	8%	50286.16667	9.204358	126.0417
ICS/LABA	1369541	25%	53961411.34	50%	114128.4167	20.89001	823.0894
ICS/LAMA/LABA	76878	1%	4501442	4%	6406.5	1.172643	68.66183
LABA	46579	1%	1797691	2%	3881.583333	0.710483	27.42071
LAMA	582627	10%	23132003.77	21%	48552.25	8.886982	352.8393
LAMA/LABA	125946	2%	5797792.48	5%	10495.5	1.921092	88.43545
MCS	256421	5%	1137308.34	1%	21368.41667	3.911265	17.3477
SABA	2403329	43%	8438955.09	8%	200277.4167	36.65869	128.7219
SAMA	22448	0.4%	232025.9	0.2%	1870.666667	0.342406	3.53916
SAMA/SABA	3196	0.1%	127863.85	0.1%	266.3333333	0.04875	1.950345
Grand Total	5554040	1	107706422.4	1			

2019-2020 scot	Sum of Number of dispensed items	% items	Sum of Gross ingredient cost (£)	% cost			
ICS	638326	23%	8592236.89	9%	53193.83333	9.731766	130.9952
ICS/LABA	1365568	49%	51778762.11	54%	113797.3333	20.81912	789.4067
ICS/LAMA/LABA	141244	5%	8749278.5	9%	11770.33333	2.153372	133.3894
LAMA	483222	17%	18966192.47	20%	40268.5	7.367087	289.1541
LAMA/LABA	160603	6%	7376189.28	8%	13383.58333	2.448515	112.4556
MCS	1244	0.04%	42435.46	0.04%	103.6666667	0.018966	0.646961
SABA/SAMA	2632	0.09%	103680.56	0.11%	219.3333333	0.040127	1.580689
SAMA	16811	1%	174994.01	0.18%	1400.916667	0.256296	2.667917
Grand Total	2809650	1	95783769.28	1			

2020-2021 scot	Sum of Number of dispensed items	% items	Sum of Gross ingredient cost (£)	% cost			
Bronchodilator	54947	1%	263089.53	0.24%			
ICS	597088	11%	7655820.92	7%	49757.33333	9.079971	116.4228
ICS/LABA	1322438	24%	50157335.88	46%	110203.1667	20.11043	762.7471
ICS/LAMA/LABA	272621	5%	16581723.5	15%	22718.41667	4.145772	252.1598
LABA	33039	1%	1282262.45	1%	2753.25	0.502427	19.49948
LAMA	412331	8%	16139749.7	15%	34360.91667	6.270355	245.4386
LAMA/LABA	167457	3%	7818101.45	7%	13954.75	2.546534	118.8906
MCS	283801	5%	1427161.31	1%	23650.08333	4.315787	21.70297
SABA	2305145	42%	7940834.72	7%	192095.4167	35.05455	120.757
SAMA	14894	0.27%	146511.2	0.13%	1241.166667	0.226494	2.228009
SAMA/SABA	2077	0.04%	82398.64	0.08%	173.0833333	0.031585	1.253044
Grand Total	5465838	1	109494989.3	1			

Wales

						3,107,500
July to Dec 2018	Sum of Sum of Sum of Cost		Sum of Sum of Sum of Items			3,170,000
ICS	17417112.89		698313			3,153,000
ICS/LABA	1498858.5		60716			
ICS/LAMA/LABA	464046		10262			
LABA	653232.23		20599			
LAMA	7299129.37		253543			
LAMA/LABA	923323.22		27690			
MCS	163556.67		97980			
SABA	1506482.01		597153			
SAMA	143198.17		14259			
Grand Total	30068939.06		1780515			
2019	Sum of Sum of COST	% items	Sum of Sum of ITEMS	% cost	cost /1000 inh	ITEMS /1000 inh
ICS	43276434.07	61%	1696398	38%	1143.79	44.83555
ICS/LABA	3074197	4%	122999	3%	81.25058	3.250846
ICS/LAMA/LABA	2564935.5	4%	56583	1%	67.79087	1.49548
LABA	1106298.21	2%	34878	1%	29.2393	0.92182
LAMA	13348218.43	19%	462742	10%	352.7915	12.2302
LAMA/LABA	2087923.69	3%	62640	1%	55.18352	1.655566
MCS	943862.59	1%	246982	5%	24.94615	6.527698
SABA	4458774.99	6%	1807089	40%	117.8448	47.7611
SAMA	239061.61	0.3%	24251	1%	6.318364	0.64095
Grand Total	71099706.09	1	4514562	1		
2020	Sum of Sum of Items	% items	Sum of Sum of cost	% cost	items /1000 inh	cost /1000 inh
ICS	1804112	40%	45956342.88	67%	47.42671	1208.106
ICS/LABA	135014	3%	3422546	5%	3.549264	89.97229
ICS/LAMA/LABA	101542	2%	4606996	7%	2.669348	121.1093
LABA	30356	1%	959762.67	1%	0.798002	25.23035
LAMA	174528	4%	5476597.49	8%	4.588013	143.9694
LAMA/LABA	70412	2%	2351267.91	3%	1.850999	61.81041
MCS	250716	6%	840797.78	1%	6.590852	22.10299
SABA	1878389	42%	4720103.52	7%	49.37931	124.0826
SAMA	21282	0.5%	214138.6	0.3%	0.559464	5.629301
Grand Total	4466351		68548552.85	1		
Jan to March 20	Sum of Items	% items	Sum of Cost	% cost	items /1000 inh	cost /1000 inh
ICS	433888	39%	11200695.38	62%	46.54202	1201.469
ICS/LABA	32759	3%	836650.5	5%	3.513972	89.74529
ICS/LAMA/LABA	27862	3%	1265313	7%	2.988683	135.7268
LABA	6623	1%	208307.5	1%	0.710432	22.3446
LAMA	96870	9%	2789377.82	15%	10.39099	299.2092
LAMA/LABA	16872	2%	563352.87	3%	1.809815	60.42938
MCS	68548	6%	190221.34	1%	7.352963	20.40454
SABA	421859	38%	1056894.32	6%	45.2517	113.3703
SAMA	4645	0.4%	47583.4	0.3%	0.498257	5.104146
Grand Total	1109926	1	18158396.13	1		

Appendix 4 Ethical approval for the research

المملكة العربية السعودية
وزارة الصحة
المديرية العامة للشؤون الصحية
بصحة منطقة مكة المكرمة
اللجنة المحلية لأخلاقيات البحوث
بصحة منطقة مكة المكرمة
(H-02-K-076)
1439/4/28

وزارة الصحة
Ministry of Health

Institutional Review Board Opinion Letter

Date of Issue	11.10.2022
Research Title	Explore knowledge, attitude and practices of health team providing working at Primary Healthcare centers in Makkah region regarding assessment and management of acute asthma
Primary Investigator	Abdullah Saggah
IRB Number:	H-02-K-076-0922-808
Category of Approval	Approved (Expedite)

Dear MR. Abdullah Saggah,

This is to inform you that the above-mentioned proposal has been reviewed and discussed by IRB Committee and was approved according to ICH GCP guidelines. Please note that this letter is from research perspective only. You will still need to get permission from the head of research department in the Directorate of health affairs, Makkah Region to commence data collection and start your project.

We wish you all the best in your project and request you to keep the IRB informed of the progress on a regular basis, using the IRB log number shown in this letter.

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.

As a researcher, you are required to have a valid certification on protecting human research subject.
If you have further questions, feel free to contact me:

(research-makkah@moh.gov.sa).

DR.Nadir Hamza Motair

Chairman, Institutional Review Board (IRB), Makkah

INSTITUTIONAL REVIEW BOARD
APPROVAL
IRB

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