

**THE EPIDEMIOLOGY AND MANAGEMENT OF SCHOOL-  
AGE CHILDHOOD ASTHMA MANAGED IN PRIMARY  
CARE**

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Thesis submitted for degree of Doctor of Philosophy  
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## Declarations

### Declaration of originality

I, Zainab Khalaf, certify that this dissertation is my original work, and that any material included that is not my own has been correctly acknowledged.

Zainab Khalaf (03/11/2024)

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## Acknowledgments

As I bring this journey to a close, I am filled with deep gratitude for the incredible support, encouragement, and inspiration I've received from so many people.

First and foremost, my sincere and heartfelt thanks go to my supervisor, Dr. Chloe Bloom. Chloe, your guidance, patience, and unyielding encouragement made this entire PhD journey not only possible but deeply fulfilling. You saw my potential even when I doubted it, pushed me beyond my limits, and taught me to find joy in the challenges that research brings. I am incredibly grateful for your mentorship and friendship—qualities that transformed this experience into a period of growth and excitement. Thank you for always believing in me and walking this path by my side.

To my secondary supervisor, Dr. Sejal Saglani, thank you for your support throughout this journey. Your guidance and support helped me understand my work better, and I'm grateful for the insight you generously shared with me.

To the National Heart and Lung Institute (NHLI), thank you for funding my work.

To my daughter, Lulu—my inspiration and my light. Lulu, from the very beginning, this journey was ours together. I remember our conversations when you were so young yet wise beyond your years, talking through how this decision would shape us as a family. You have been my strength, my biggest cheerleader, and the reason I chose to pursue this dream. This work is dedicated to you, for your understanding, your patience, and your unconditional love. Thank you for reminding me every day why this journey matters.

To my family—especially my parents, sisters, brothers, nieces and nephews—thank you for your endless love and support. Mum and Dad, you laid the foundation of my dreams with your sacrifices. To my siblings, thank you for your encouragement, understanding, and for always being there to celebrate the highs and navigate the lows with me. A special thank you to Rayan for her non-stop support and the mental strength she provided me throughout this journey. To my colleagues, I am grateful for the support and shared moments that made this path easier and more enjoyable. Each of you has contributed to this achievement in meaningful ways, and I am deeply appreciative.

Finally, to my forever partner—thank you for your endless patience, encouragement, and support through every high and low.

To all of you, this achievement is shared. Thank you for making this journey possible and meaningful.

## Abstract

### Background

Asthma in school-age UK children is a condition that results in considerable healthcare burden and can significantly impact a child's quality of life. Although asthma care has evolved greatly, there are gaps in our knowledge of how age at diagnosis and different clinical practices affect asthma outcomes.

### Methods

I used data from the Clinical Practice Research Datalink, linked to the Hospital Episode Statistics and the Office of National Statistics, to form a cohort of children aged 5–16 years with asthma. Using logistic regression, inverse probability treatment weighting (IPTW), and a self-controlled case series design, my analysis focused on four primary objectives: (1) examining age-based differences in asthma characteristics, (2) determining factors contributing to exacerbation risks, (3) evaluating the national uptake of good clinical practice activities (GCPA) such as asthma reviews, management plans, and inhaler technique checks, and (4) assessing the effectiveness of these practices in reducing exacerbations.

### Results

My findings indicate differences in the characteristics of children based on the age of asthma diagnosis, including the prevalence of males, atopy, and obesity. Younger children experienced higher exacerbation rates than older ones. Other risk factors such as atopy, gender, socioeconomic deprivation, and obesity varied by age. Uptake of good clinical practice activities differed by age, deprivation, and body mass index. Notably, children receiving these activities had fewer exacerbations, especially when used together.

### Conclusion

Children's characteristics, exacerbation risk factors and asthma care differ according to the age their asthma was diagnosed. GCPA are very effective when used in conjunction at reducing asthma exacerbations in real-life clinical practice. These findings suggesting age-specific, comprehensive, guideline-based management would help to reduce asthma exacerbations in children. My results also highlight the need for targeted and equitable approaches to UK

asthma care, especially for younger children, obese children, and children from socioeconomically disadvantaged backgrounds.

## Dissemination

### **Publications arising from my thesis**

Khalaf Z, Bush A, Saglani S, Bloom C I, Influence of age on clinical characteristics, pharmacological management and exacerbations in children with asthma *Thorax* 2024;79:112-119.

Khalaf Z, Bush A, Saglani S, Bloom C I. Implementation and effectiveness of guideline-recommended clinical activities for children with asthma: population-based cohort. *Chest* December 2024.

### **Posters and oral presentation**

British Thoracic Society winter meeting, November 2022 (oral presentation)

Khalaf Z, Saglani S, Bloom C. S32 Characterising school-age children with asthma: English population-cohort study *Thorax* 2022;77:A23.

British Thoracic Society winter meeting, November 2023 (poster)

Z Khalaf, C Bloom, S Saglani. Inequality in the implementation of good clinical practice asthma activities among children in the UK

American Thoracic Society 2023 (poster)

Z. Khalaf, S. Saglani, and C.I. Bloom. The Impact of Routine Asthma Reviews: A UK Population-based Cohort (abstract). *Am J Respir Crit Care Med* 2024;209:A6158.

British Thoracic Society winter meeting, November 2024 (poster)

Z Khalaf, C Bloom, S Saglani. Real-world effectiveness of annual asthma reviews, asthma management plans, and inhaler technique checks in UK children with asthma

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## Abbreviations

A&E: Accident and Emergency

APC: Admitted Patient Care

BDR: Bronchodilator Reversibility

BMI: Body Mass Index

BTS: British Thoracic Society

BTS/SIGN: British Thoracic Society / Scottish Intercollegiate Guideline Network

CPRD: Clinical Practice Research Datalink

DM+D: Dictionary of Medicines and Devices

DPI: Dry Powder Inhalers

EHR: Electronic Healthcare Records

FENO: Fractional Exhaled Nitric Oxide

GAN: Global Asthma Network

GINA: Global Initiative for Asthma

GP: General Practitioner

GPRD: General Practice Research Database

HDM: House Dust Mite

HES: Hospital Episode Statistics

ICD-10: International Classification of Diseases, 10th Revision

ICS: Inhaled Corticosteroids

IMD: Index of Multiple Deprivation

IPTW: Inverse Probability Treatment Weighting

IRR: Incidence Rate Ratio

ISAAC: International Study of Asthma and Allergies in Childhood

LABA: Long-Acting Beta-2 Agonists

LSOA: Lower Layer Super Output Areas

LTRA: Leukotriene Receptor Antagonists

MDI: Metered Dose Inhalers

MHRA: Medicines and Healthcare Products Regulatory Agency

NCRAS: National Cancer Registration and Analysis Service

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NIHR: National Institute for Health and Care Research

NRAD: National Review of Asthma Deaths

OCS: Oral Corticosteroids

ONS: Office for National Statistics

OPCRD: Optimum Patient Care Research Database

PEF: Peak Expiratory Flow

QOF: Quality and Outcomes Framework

RCT: Randomized Controlled Trial

SABA: Short-Acting Beta-2 Agonists

SAIL: Secure Anonymised Information Linkage

SCCS: Self-Controlled Case Series

SIGN: Scottish Intercollegiate Guidelines Network

SNOMED CT: Systematized Nomenclature of Medicine–Clinical Terminology

## Ethics, Support, and Data Disclosure Statement

This research was funded by the National Heart and Lung Institute (NHLI) at Imperial College London. The views presented here are solely those of the author and do not necessarily reflect those of the NHLI.

The study uses data from the Clinical Practice Research Datalink (CPRD), provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and collected by the NHS. Protocol 20\_053 was approved by the Independent Scientific Advisory Committee (ISAC). Linked datasets, including mortality, socioeconomic, and secondary care data, were provided by NHS Digital for patients in England, with individual patients retaining the right to opt out.

The data supporting this research are available from CPRD under a licensed agreement and cannot be made publicly available by the authors. For licensing information, please contact CPRD (<http://www.cprd.com>).

# 1. Chapter 1: Introduction

## 1.1 Rationale for this research

Asthma is a common chronic respiratory disease affecting millions of children worldwide, with significant implications on quality of life, absence from school, healthcare use, and long-term health outcomes [1]. While asthma is well-recognized as a heterogeneous pathophysiological disease, the way it manifests in children can further vary depending on factors such as age at diagnosis, presence of comorbidities, and socioeconomic background of the child. Moreover, despite considerable progress in asthma management and treatment, disparities remain in how children receive and respond to care, particularly in terms of non-pharmacological interventions and self-management support.

The overarching objective of this thesis is to gain a better understanding of the characteristics of UK school-age children with asthma and how they are managed.

My first objective is to explore how the age of asthma diagnosis, within the broader age range of school-age (5-16 years), influences the characteristics and comorbidities of children. By categorising children into more granular age groups (5-8.9 years, 9-11.9 years, and 12-16 years), I seek to identify variations in baseline characteristics by age and assess differences in pharmacological management.

My second objective is to evaluate how age, and the age-associated differences in characteristics, effect a child's risk of experiencing an acute exacerbation.

My third objective is to assess the uptake of guideline-recommended good clinical practice activities, including asthma reviews, asthma management plans, inhaler technique checks, and influenza vaccinations. These activities are known to improve asthma outcomes when implemented correctly, yet there is some evidence suggesting that many adults do not receive them consistently, less is known about children. I seek to quantify gaps in care and identify risk factors for suboptimal management.

My last objective is to explore the effectiveness of these interventions, examining whether children who receive them experience fewer exacerbations. This will help to clarify which aspects of good clinical practice are most effective at improving long-term outcomes.

Overall, my thesis addresses critical gaps in understanding how the age of diagnosis and many aspects of asthma management impact asthma outcomes in children across the UK. Its findings will provide valuable insights for healthcare providers and policymakers in optimising asthma care and ensuring adequate access to guideline-recommended management for all children.

## 1.2 Background

### 1.2.1 Prevalence of childhood asthma

The global burden of asthma has been rising steadily over the past four decades, with the incidence of childhood asthma also increasing during this period. Currently, it is estimated that approximately 300 million people worldwide, including both children and adults, are living with asthma. Projections indicate that this number could rise to 400 million by 2025 [2]. However, the prevalence of asthma varies widely across different regions of the world [3], this variation could be due to the inconsistent definitions and diagnostic criteria used in various countries, or due to effects of the local environment and living conditions. Global analyses can teach us about potential risk factors and improve our broader understanding of asthma in the UK.

The landmark study addressing worldwide childhood asthma prevalence is the International Study of Asthma and Allergies in Childhood (ISAAC), which eventually became the Global Asthma Network (GAN) [4]. Launched in 1991, ISAAC utilised standardized questionnaires to gather data on asthma symptoms among children aged 6-14 years in 61 countries. The study was conducted in three phases. Phase I (1992-1996) aimed to measure the prevalence and severity of asthma and other allergic diseases in different populations and across various countries. The results of Phase I revealed variations in the prevalence of asthma symptoms, ranging from 20 to 60-fold between regions, suggesting a strong influence of environmental factors. Notably, the highest prevalence among adolescents was observed in the UK, where some centres reported rates as high as 32.2% [3].

Phase II (1998-2004) focused on investigating potential risk factors for asthma, such as environmental exposures and genetic predispositions. However, the methodology and scope of this phase were somewhat different, limiting direct comparisons with Phase I [3]. Phase III

(2000-2003) returned to the original methodology of Phase I, allowing researchers to assess changes in asthma prevalence over time. Phase III confirmed that asthma symptoms were on the rise in several low- and middle-income countries. This phase also reaffirmed the wide regional variability in prevalence, with English-speaking countries, including the UK, generally showing higher rates compared to other regions.

Recognising the need for updated and comparable data, the Global Asthma Network (GAN) [5] was established in 2012 as a continuation and expansion of ISAAC and used the same standardized study protocols as ISAAC. GAN Phase I (2015-2020) involved a large-scale survey that included school pupils aged 13-14 years (adolescents) and optionally aged 6-7 years (children) from centres across 44 countries, as well as an adult group [5]. The results highlighted several key findings. The overall prevalence of current asthma symptoms was 9.1% for children, 11.0% for adolescents, and 6.6% for adults. Again, the rates varied by region and income level. For instance, lower prevalences were generally observed in low- to lower-middle-income countries, while the highest prevalences were found in high-income countries. Comparatively, the prevalence rates observed in GAN were somewhat lower than those reported in ISAAC Phases I and III, particularly in English-speaking countries. However, the low- and middle-income countries, showed an increase in asthma prevalence, consistent with the trends observed in ISAAC Phase III [3]. Consistent across the decades and surveys has been the pattern of variability, underscoring the influence of environmental, socioeconomic, and healthcare factors on asthma prevalence.

While ISAAC and GAN relied on surveys of self-reported symptoms and diagnoses, several studies of asthma prevalence conducted in the UK since 2010, have instead leveraged available nationwide sources of accessible, routinely collected data. This type of data removes the risk of selection bias and recall bias that surveys suffer from, but they still rely on correct diagnoses by healthcare professionals, so may be biased by misclassification, particularly as these sources are often from primary care, not asthma specialists. Two of these studies addressed the prevalence of asthma in UK children. The first study used multiple sources of routine administrative and health and social care between 2010-2012 and found approximately 5.4 million people in the UK were receiving treatment for asthma, of which 1.1 million were children [6]. In a study using the Clinical Practice Research Datalink, from 2006-

2016, the authors only included those children with current asthma, defined as evidence of active asthma management in the last year. In this study they found around 8-10% of school-age children had current asthma. These estimates therefore are much lower than those reported from UK survey data, which were around 20% for the 6–7-year-olds and 25% for the 13–14-year-olds. This discrepancy perhaps evidences why it is important to use doctor-diagnosed asthma definitions rather than self-reported symptom-based ones. However, it may also reflect a degree of underdiagnosis of childhood asthma in the UK.

### 1.2.2 Asthma diagnosis

Asthma is a heterogeneous chronic respiratory condition characterised by chronic airway inflammation and hyper-responsiveness. Its symptoms—chest tightness, wheezing, coughing, and shortness of breath—vary greatly between individuals, as do the triggers and severity of the disease, making diagnosis particularly challenging. This challenge is compounded by the absence of a single diagnostic gold standard and inconsistencies in the clinical definition of childhood asthma, with nearly 60 different definitions cited across 122 studies [7].

Furthermore, diagnosis in children is particularly complex because the diagnostic criteria and methods used for adults may not be suitable for younger patients. The typical diagnostic process involves a thorough medical history, physical examination, and lung function tests such as spirometry, bronchodilator reversibility (BDR), and bronchial hyperresponsiveness tests [8-10]. In children, these tests can be less reliable, and guidelines frequently lack child-specific evidence [11]. For example, adult spirometry cut-offs may not appropriately reflect paediatric lung function, leading to potential misdiagnosis. Recognising these issues, a task force supported by the European Respiratory Society reviewed diagnostic standards for children aged 5–16 years. They advised against relying solely on clinical history or a single abnormal test, recommending that at least two tests (e.g., spirometry, BDR, or fractional exhaled nitric oxide, FENO) be abnormal before diagnosing asthma in children [11]. These recommendations aim to improve diagnostic accuracy and prevent inappropriate treatment, which is especially important since misdiagnosis can either delay necessary treatment or subject children to unnecessary therapies.

Despite these diagnostic tools, disparities in access to equipment and trained staff persist, particularly in primary care settings. This often limits the timely availability of essential tests

such as access to spirometry. Moreover, the onset of asthma symptoms can occur before age five years, complicating the diagnostic process, as spirometry is not suitable for this age group. Frequent reassessment of asthma diagnosis and treatment is essential to address the evolving nature of the disease, especially in children.

In the UK, we currently have two different guidelines, although they are at the tail end of the process of being amalgamated: British Thoracic Society / Scottish Intercollegiate Guideline Network (BTS/SIGN) and National Institute for Health and Care Excellence (NICE). In addition, many UK researchers and asthma specialists use the international Global Initiative for Asthma (GINA) guidelines [8-10]. Each present slightly varying diagnostic criteria, though they share similarities.

provides a comparison of these guidelines. The diagnostic tools include measures of expiratory variability and reversibility, including peak expiratory flow and spirometry. Such tests are also commonly used to monitor the progression of asthma in children, with objective testing recommended in cases of poor treatment response or diagnostic uncertainty [12].

The fractional exhaled nitric oxide (FeNO) test is used to detect airway inflammation. Once properly trained, healthcare staff can use FeNO in school-aged children, as it is quick and relatively easy to perform. However, the role of FeNO testing varies across guidelines and due to the costs of the machine, training and time to conduct the test, access to FeNO in primary care is very limited.

Despite our national guideline recommendations on how to diagnose one of the most prevalent childhood conditions, such testing is often only available in specialised care settings equipped with trained personnel. The COVID-19 pandemic has worsened these challenges by increasing diagnostic backlogs [13]. Proposed solutions include the recent creation of community diagnostic hubs. The issues around access to diagnostic tools likely contribute towards health disparities.

Table 1.1: Summary of diagnosis algorithms for childhood asthma, including national and international guidelines

| Guideline                                                                            | Year | Diagnostic Criteria                                                                                                               | Recommended Objective Testing                                                                                                                 | When to Refer to a Specialist                                                                                                                                | When to Consider Alternative Diagnoses                                                    | References |
|--------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------|
| National Institute for Health and Care Excellence (NICE, UK)                         | 2017 | Clinical history, suggestive examination, spirometry showing obstructive airflow, or FeNO $\geq 35$ ppb                           | Spirometry with bronchodilator reversibility or FeNO as first-line tests. Additional: PEF, bronchial challenge with histamine or methacholine | Children are unresponsive to treatment and/or unable to complete objective tests. Obstructive spirometry with negative bronchodilator reversibility and FeNO | Symptoms indicative of asthma but normal objective test results                           | [8]        |
| British Thoracic Society / Scottish Intercollegiate Guideline Network (BTS/SIGN, UK) | 2019 | Clinical history suggestive of asthma plus evidence of airflow variability using spirometry, PEF, or bronchodilator reversibility | Spirometry with bronchodilator reversibility. PEF monitoring for variation. FeNO considered in some cases                                     | Lack of improvement following initial treatments. Uncertain diagnosis. Severe or frequent exacerbations                                                      | Symptoms and history are not typical of asthma or if lung function tests are inconclusive | [10]       |
| Global Initiative for Asthma (GINA, international)                                   | 2021 | Clinical history indicating asthma, plus proof of variable expiratory airflow limitation                                          | Spirometry, PEF, exercise challenge, or bronchial challenge to assess lung                                                                    | Diagnostic uncertainty. Previous life-threatening asthma episodes. Poor                                                                                      | Atypical features or clinical examination findings (e.g., cardiac murmurs)                | [9]        |

|  |  |                                                               |                         |                                |  |  |
|--|--|---------------------------------------------------------------|-------------------------|--------------------------------|--|--|
|  |  | through<br>spirometry,<br>PEF, or positive<br>challenge tests | function<br>variability | or no response<br>to treatment |  |  |
|--|--|---------------------------------------------------------------|-------------------------|--------------------------------|--|--|

### 1.2.3 Age and asthma diagnosis

Studies have found that the characteristics and comorbidities associated with asthma can differ depending on the age at which the disease first presents [14-17]. However, much of the existing research has focused on comparing children with adults or examining the differences between 'early-onset' and 'late-onset' asthma [15-18], without specifically addressing the impact of age at diagnosis within the school-age range (typically 5-16 years) on asthma outcomes.

The age at which asthma first presents—whether during childhood or adulthood—can have an impact on the natural history and progression of the disease [14, 17]. In children, the timing of asthma onset is particularly critical, as it occurs during a period of rapid growth and development. These physiological and psychosocial changes can impact the pathophysiology of asthma, as well as the factors that influence its management [14, 17]. For instance, younger children may have different triggers for asthma exacerbations compared to older children, and their responses to treatment may also vary. Additionally, the developmental stage of the child may affect their ability to adhere to treatment regimens, which can further influence disease outcomes.

Although most children with asthma experience mild to moderate disease, many still face exacerbations that require medical intervention [19], such as the use of oral corticosteroids or hospitalisation. These exacerbations can have an impact on the child's quality of life and may contribute to long-term health issues if not properly managed. Despite the importance of understanding the factors that contribute to asthma exacerbations in children, real-world data on the incidence and risk factors for these events remain limited, particularly when stratified by age [16, 20]. Factors such as atopy and obesity have been proposed as potential risk factors for asthma exacerbations, but their roles may vary depending on the child's age and other contextual factors [21].

#### 1.2.4 Asthma exacerbations

Asthma exacerbations refer to acute episodes of worsening asthma symptoms, such as shortness of breath, wheezing, chest tightness and coughing that requires a change in the child's usual treatment [25].

##### 1.2.4.1 Exacerbation risk factors

There are several precipitators of asthma exacerbations, including seasonal changes that increase exposure to allergens in the spring and summer and increased exposure to respiratory viruses in the winter. Other factors such as poor adherence to inhaled corticosteroids, suboptimal inhaler technique, a history of previous exacerbations, exposure to cigarette exposure and pollution further increase the risk of an exacerbation [22, 23]. Therefore, a key factor in preventing exacerbations is ensuring children and their carers are educated on how to manage their asthma and prevent exacerbations, including on the importance of adherence and avoiding known triggers where possible. Studies show that patients who achieve 80% or more adherence to inhaled corticosteroids have the highest reduction in exacerbation risk [24]. Additionally, over-reliance on short-acting  $\beta$ 2-agonists (SABA) reliever medication is associated with an increased risk of exacerbations [25].

##### 1.2.4.2 Treatment of exacerbations

Exacerbations typically require rapid treatment, often with a short course of oral corticosteroids but sometimes hospital admission is necessitated. However, most exacerbations can be managed effectively in primary care settings. These interventions help control acute symptoms and prevent the exacerbation from worsening. Patients experiencing exacerbations can deteriorate rapidly, making continuous monitoring essential [26]. Regular assessment of peak expiratory flow and clinical examinations are required to evaluate the child's condition.

##### 1.2.4.3 Gaps in our knowledge on the management of exacerbations in children

A recent nationwide 7-year study found that many adults with frequent exacerbations were managed as having 'mild asthma,' while some adults without a history of asthma attacks were inappropriately treated with the highest doses of inhaled corticosteroids [27]. Longitudinal studies using real-world data from primary care have been instrumental in identifying areas for improvement in asthma management. However, there remains a gap in such research for school-aged children with asthma.

Although most children with asthma experience mild to moderate symptoms, a notable proportion still suffer from exacerbations that require medical intervention [19]. Exacerbations can negatively impact a child's quality of life, school attendance and may contribute to long-term health complications if not managed appropriately. Despite the importance of understanding the factors contributing to asthma exacerbations in children, real-world data on the incidence and risk factors for these events are limited, particularly when considering the age of the child [16, 20]. Proposed risk factors such as atopy and obesity may contribute to exacerbations, but their impact likely varies depending on the child's age and other contextual factors [21].

### 1.2.5 Pharmacological management of asthma in children

National asthma guidelines encompass both pharmacological and non-pharmacological good clinical practice activities with the goal of achieving good symptom control, maintaining normal activity levels, preventing absence from school, and minimising the risk of future asthma exacerbations [8-10]. The pharmacological approach to asthma management consists of two essential elements: maintenance therapy and reliever therapy (Table 1.2). Maintenance therapy forms the key element of asthma treatment, with the goal being to avoid the need for reliever medication. Maintenance therapies include inhaled corticosteroids, which are the first-line treatment aimed at long-term symptom control, while additional therapies like long-acting beta-2 agonists (LABA) and leukotriene receptor antagonists (LTRA, e.g., montelukast) can be added when control is inadequate [8-10]. More advanced options, including biologics, are reserved for severe cases under specialist care. On the other hand, reliever therapies, primarily SABAs, provide rapid relief during asthma attacks by relaxing airway muscles. Regular use of reliever therapy is used as an indicator of suboptimal asthma control and a need to increase maintenance medication. Oral corticosteroids are used for asthma exacerbations to reduce inflammation when local inhaled corticosteroids and relievers have been insufficient.

Table 1.2: Summary of maintenance and reliever therapies

| Therapy Type           | Treatment                                             | Recommended                                                                                                                                                      |
|------------------------|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Maintenance Therapies  | Inhaled Corticosteroids                               | First-line maintenance therapy in many guidelines; lowest effective dose should be used to minimise side effects, such as growth suppression and adrenal issues. |
|                        | Long-Acting Beta-2 Agonists                           | Add-on therapy when ICS and SABA are insufficient; provides bronchodilation for up to 12 hours.                                                                  |
|                        | Leukotriene Receptor Antagonists (e.g., Montelukast)  | Add-on therapy for poor symptom control with ICS and LABA; concerns include neuropsychiatric side effects (e.g., poor sleep, suicidal ideation).                 |
|                        | Long-Acting Muscarinic Antagonists (e.g., Tiotropium) | Add-on therapy for poor symptom control despite ICS and LABA use.                                                                                                |
|                        | Oral Theophylline                                     | Add-on therapy for uncontrolled symptoms; plasma monitoring required at treatment initiation and dose changes.                                                   |
|                        | Biologics                                             | Used under specialist care for those unresponsive to multiple therapies; can reduce attacks, improve lung function, and lower corticosteroid use.                |
| Reliever Therapies     | Short-Acting Beta-2 Agonists                          | First-line reliever in guidelines; bronchodilation lasts up to 4 hours, providing rapid relief by relaxing airway smooth muscles.                                |
| Exacerbation Treatment | Oral Corticosteroids                                  | Short-term use during attacks to reduce inflammation and ease symptoms; frequent use suggests poor control and should trigger a review of maintenance therapy.   |

All three key national and international guidelines follow a similar stepwise approach for pharmacological management, initiating treatment with inhaled corticosteroids as maintenance therapy (Table 1.3) [8-10].

However, despite their shared foundation, the guidelines differ in certain areas. In 2016, both the BTS/SIGN and GINA guidelines introduced a important change by recommending inhaled corticosteroids as the primary treatment for children with mild asthma, moving beyond the sole use of reliever medications [28]. For children over 5 years old who are not well controlled on inhaled corticosteroids alone, the BTS guidelines suggest adding a LABA, while NICE recommend LTRAs as the first-line add-on therapy [28].

A large UK study analysing primary care prescription data from 2006 to 2016 found that around 40% of children were not being prescribed inhaled corticosteroids [29]. Whether the 2016 updates regarding the use of inhaled corticosteroids have been fully implemented in primary care remains uncertain.

Guidelines also divide treatment by age, BTS/SIGN make recommendations for children 5-12 years and 13 years is included as adolescents and within the adult treatment guidelines. NICE make recommendations for children as aged 5-16 years old. GINA is similar to BTS/SIGN and applies 6-11 years age cut-off, above that age the young people are called adolescents and to be managed on the adult pathway.

Table 1.3: Summary of the pharmacological management in school-age children across the guidelines

| Guideline & age                     | Year | Stepwise Pharmacological Approach                                                                                                   | Inhaler Device Recommendations                                         | Add-on Therapy                                                                                                                                                                                                                                     |
|-------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NICE (UK),<br>5-16 years            | 2017 | If asthma symptoms more than twice a week or waken at night once a week or more, start with very low dose ICS.                      | Dry powder inhalers (DPI) or metered dose inhalers (MDI) with spacers. | Add in LTRA. If it is still not uncontrolled, consider stopping LTRA and add a LABA. If still uncontrolled consider a maintenance and reliever therapy (MART) regimen. If still uncontrolled increase ICS dose. Thereafter seek specialist advice. |
| BTS/SIGN (UK),<br>5-12 years        | 2019 | If asthma symptoms more than twice a week or woken at night once a week or more, start with very low dose ICS.                      | DPI or MDI with spacer.                                                | Add in LABA or LTRA. Still uncontrolled, increase ICS dose to low dose or add in LABA or LTRA. If no response to LABA consider stopping. Thereafter seek specialist advice.                                                                        |
| GINA (International),<br>6-11 years | 2023 | If asthma symptoms more than twice a week or woken at night once a week or more, start with low dose ICS whenever needing reliever. | DPI or MDI with spacer.                                                | Step up to regular low dose ICS. Still uncontrolled, choose between adding in LABA, medium dose ICS or very low dose MART.                                                                                                                         |

Inhaler device recommendations are consistent across the guidelines. All three suggest metered-dose inhalers (MDI) with spacers for younger children. Both GINA and BTS also suggest using face masks with spacers for younger children who may have difficulty with the standard device. For older children, dry powder inhalers (DPI) or MDIs with spacers are preferred, depending on the child's ability to use the device correctly [8-10].

For biological therapies, the guidelines converge on reserving these treatments for severe, persistent asthma that does not respond to standard therapies. This is a constantly evolving field that requires specialist asthma care.

#### 1.2.6 Good clinical practice activities

Managing asthma effectively goes beyond pharmacological treatments. Non-pharmacological management can include offering support to stop smoking (older children or household members), support for weight management in overweight children, education on asthma including supported self-management, medication adherence and trigger avoidance (indoor and outdoor, eg pollutants, allergens, air temperature and humidity[8-10] ). In addition, specific clinical practice activities that should be routinely offered to patients, also play a critical role in achieving long-term asthma control and preventing exacerbations. These activities I have termed in this thesis as 'good clinical practice activities' (GCPAs) and include the following asthma specific activities, asthma management plan, inhaler technique checks and scheduled annual asthma reviews, as well as annual influenza vaccination (Table 1.4).

Table 1.4: Summary of the good clinical practice activities and healthcare incentives across asthma national guidelines

| Guideline             | Year | Asthma Review                                                            | Inhaler Technique Check                                | Asthma Management Plan                                 | Influenza Vaccination                                       | QOF 2024                                                    |
|-----------------------|------|--------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| NICE (UK)             | 2017 | Annual; but more frequent if poorly controlled                           | Checked at every review                                | Personalized action plans recommended for all children | All primary school children, regardless of asthma diagnosis | QOF incentivise s reviews, inhaler checks, and action plans |
| BTS/SIGN (UK)         | 2019 | Annual; but more frequent if poorly controlled                           | Regular checks during reviews                          | Personalized action plans recommended for all children | Does not recommend vaccinating specifically for asthma      | Follows NICE; indirectly aligned with QOF incentive system  |
| GINA (Inter-national) | 2023 | Regular follow-ups, particularly for younger children; no time specified | Checked at every visit, especially in younger children | Written action plans advised to guide management       | Influenza vaccination if moderate to severe asthma          | No specific incentive, but emphasize s collaborati ve care  |

Currently it is unknown how often good clinical practice activities are conducted and how effective they are in real-life clinical practice. Audits and surveys of primary care practices in England and Scotland, as well as the United States and Canada, suggest asthma guidelines are frequently not adhered to [30-33]. There are several reasons postulated for the lack of implementation, including insufficient resources, unawareness of their potential benefit and lack of understanding [31, 32]. It is also likely that some patients are at greater risk of not

receiving these activities than others. For example, UK and US studies have shown differences in asthma management depending solely on where people reside, in relation to region or local healthcare infrastructure [33, 34].

A recent large-scale study, which evaluated the healthcare records of over 370,000 adults across the UK, found that less than one-third of asthma patients had received an annual asthma review, and fewer than 7% had been provided with a personalized asthma management plan[29] It is very likely the poor implementation in adults is reflected in children too. The National Review of Asthma Deaths (NRAD), published in 2014, investigated asthma-related deaths in the UK and found that many of the deaths were preventable. A key finding was the failure to comply with asthma management guidelines [35].

Poor inhaler technique will reduce corticosteroid absorption resulting in worse asthma control due to suboptimal treatment. Therefore, one would hypothesise that checking and correcting inadequate technique would improve asthma control and may prevent exacerbations. However, a Cochrane review of 29 randomised controlled trials, which included both adults and children, found that in fact most single interventions to improve inhaler technique did not ultimately result in a sustained improvement in clinical outcomes [36]. The concept that an isolated intervention has reduced effectiveness was also found in a Cochrane review of randomised controlled trials of asthma management plans in adults; this review concluded that management plans were most effective when used in conjunction with education and more intense clinical reviews [37].

In children, a 2006 Cochrane review of four randomised controlled trials of written asthma management plans found that children using symptom-based plans had a lower risk of exacerbations, but plans based on changes in peak flow readings only reduced the number of days of symptoms by a half day; there was no difference in school absenteeism, quality of life or symptoms [38]. However, a recent meta-review, synthesising evidence from 27 systematic reviews including 270 randomised controlled trials, which included adults and children, concluded that supported self-management reduces unscheduled care and improves asthma control [39]. Many of these trials though did not include children or were based on school interventions. We await the important findings from the IMPlimenting IMProved Asthma self-management as RouTine (IMP2ART) trial, a UK-wide cluster randomised implementation trial

that is testing a whole system implementation strategy that embeds supported asthma self-management in primary care. Critically, the trial includes children aged 5 years or older, as well as adults, and provides asthma management plan to patients, training for primary care staff and organisational support [39].

Viral infections are a common cause of exacerbations and influenza is a known contributor [36], therefore annual influenza vaccination may be expected to prevent exacerbations. However, randomised control trials have not shown concrete reduction in exacerbations, in adults or children, but there have been few trials and no trial for over two decades [40]. In contrast, more recent, quasi-experimental high-quality observational studies have found significant effectiveness [41]. Influenza vaccinations are recommended in the UK for all primary school children, regardless of asthma diagnosis or not, so offering an annual influenza vaccination should be part of their care. There has previously been concern over exacerbation of asthma due to the vaccination, but there is no evidence for this from studies [41].

#### 1.2.7 Implementation of good clinical practice activities in the UK

In 2004, the Quality and Outcomes Framework (QOF) was introduced in the UK to improve the quality of general practice. [42] The system is devised to financially incentivise primary care providers to provide certain activities and meet specific targets. QOF has been updated several times since 2004, some of these updates have included changes to the asthma QOF indicators. Unless the activity was coded for in the electronic medical records, the GP practice would not receive the points. There are currently four clinical asthma indicators, including prevalence (register of asthma patients), diagnosis (use of objective diagnostic tests), smoking (record active and passive exposure) and asthma management. Until 2020, the asthma 'ongoing management' QOF indicator included conducting an annual asthma review. This time period correlates with the dates that my data is available until. But at that time, the asthma review only had to include an assessment of asthma control using the Royal College of Physicians three asthma control questions.

Although my study does not cover data after 2020 it is worth noting that NHS England issued an update to the GP contract agreement in 2020 and the indicators were changed, including

the management indicator. To qualify for the full points, the asthma review should include an asthma review code, an asthma control test or asthma control questionnaire score, a record of the number of exacerbations and a written asthma management plan. The review should also include an inhaler technique assessment, but this does not need to be coded.

Additionally, it is worth mentioning that the system defines 'active' asthma patients—those eligible for review—differently from the denominator used in this thesis, as QOF includes only those with recent prescriptions or consultations for asthma. Understanding this distinction is important for interpreting the findings of this research, as the broader inclusion criteria in this study may capture a wider range of asthma patients than those meeting QOF eligibility.

Exception reporting within QOF allows practices to exclude certain patients from performance targets if, for example, they repeatedly fail to attend reviews. This can impact QOF recorded asthma care metrics, potentially leading to an underestimation of the proportion of children receiving asthma reviews. Additionally, QOF performance thresholds may influence clinical behaviour, as practices aiming to meet targets may prioritise coded entries over comprehensive clinical discussions [43]

The role of remote consultations in achieving QOF targets has also been explored. A study by Pinnock et al. (2007) highlighted that telephone-based asthma reviews were accessible and cost-effective but less comprehensive than in-person assessments [44]. This has implications for interpreting recorded asthma review data, particularly following the widespread adoption of remote consultations during the COVID-19 pandemic.

To be eligible for financial incentives, GPs must reach a threshold percentage of their asthma patients receiving these essential components of care (Table 1.5). These indicators carry varying points based on performance thresholds.

*Table 1.5:* : Summary of the asthma QOF indicators for 'ongoing management

| Indicator Code | Indicator Description | Points Available | Threshold (%) |
|----------------|-----------------------|------------------|---------------|
|                |                       |                  |               |

|                       |                                                                                                                                                                                                                                                                                                                                       |    |        |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--------|
| AST003<br>Before 2020 | The percentage of patients with asthma, on the register, who have had an asthma review in the preceding 12 months that includes an assessment of asthma control using the 3 RCP (Royal College of Physicians) questions                                                                                                               | 20 | 45–70% |
| AST007<br>From 2020   | The percentage of patients with asthma on the register, who have had an asthma review in the preceding 12 months that includes an assessment of asthma control using a validated asthma control questionnaire, a recording of the number of exacerbations, an assessment of inhaler technique and a written personalised action plan. | 20 | 45-70% |

In conclusion good clinical practice activities such as asthma reviews, inhaler technique checks, and asthma management plans are hypothesised to improve asthma outcomes through multiple mechanisms [45].

- Patient behaviour: Regular asthma reviews can reinforce adherence to preventer medications and improve symptom self-management [45].
- Clinician practice: Standardised assessments of inhaler technique and symptom control enable early identification of poorly controlled asthma.
- Healthcare system: Integration of structured asthma care within routine practice ensures equitable access to guideline-recommended management.

Data on these activities are recorded by different healthcare professionals and may be influenced by whether the intervention is incentivised under QOF. For instance, inhaler technique checks are encouraged during asthma reviews but are not specifically incentivised, potentially leading to variability in their documentation. In contrast, asthma reviews and management plans are part of QOF indicators, meaning their recording is more consistent [46].

Potential coding issues such as underreporting, coding variability and system limitation also need to be considered. Asthma management plans may be discussed during a consultation but not formally coded, leading to underestimation in the data. Similarly, influenza vaccination data may not always be linked to asthma management records, as vaccinations are recorded separately from asthma consultations.

By considering the mechanisms of change, the context of data collection, and potential coding issues, this thesis will aim to interpret primary care data with an awareness of how real-world clinical activity translates into research variables.

### 1.2.8 Translating Real-World Primary Care Activity into Research Data

Understanding how real-world primary healthcare activity translates into research data is crucial for interpreting the findings and recognising the inherent limitations of using electronic health records (EHRs). The way in which data is collected in primary care settings depends on a range of factors, including the structure of consultations, the professionals involved, and the coding systems used to document care. These factors can directly influence the completeness, accuracy, and applicability of the data available for research purposes.<sup>3</sup>

#### **Practice Organisation and Data Collection**

Primary care data is recorded by a range of healthcare professionals, including general practitioners (GPs), asthma nurses, and pharmacists. Each group has different responsibilities, workflows, and documentation habits, which inevitably shape the data that enters EHRs. Asthma nurses, for instance, are more likely to use structured templates during routine reviews, ensuring that key variables such as peak flow readings, medication adherence, and symptom control are systematically recorded [47]. In contrast, GPs managing acute exacerbations often focus on immediate clinical needs, meaning that essential details regarding long-term asthma management may not be captured in a structured manner [47].

#### **Differences in Routine and Unscheduled Consultations**

Routine asthma reviews, typically conducted by asthma nurses, are guided by electronic templates that prompt standardised data entry. These templates ensure that essential variables, such as inhaler technique assessments and adherence to self-management plans,

are systematically recorded [47]The structured nature of these consultations leads to more consistent and complete documentation, making them a valuable source of research data. However, while templates standardise care, they can also introduce rigidity, limiting the ability of clinicians to document nuanced clinical observations [48].

In contrast, unscheduled consultations for worsening asthma symptoms, usually handled by GPs, focus on immediate symptom relief rather than comprehensive data entry. As a result, key variables that are crucial for research—such as inhaler technique checks and long-term asthma control—may be omitted from these records [48].This variability in documentation practices presents a challenge when interpreting real-world data, as missing or inconsistently recorded variables can bias study findings.

### **Translating Primary Care Activity into Research Data**

The extent to which primary care activity is reflected in research data depends largely on the consistency and accuracy of documentation. While structured templates improve data completeness, they may not capture the complexity of patient interactions. On the other hand, free-text entries, which often contain rich clinical detail, may not be routinely included in research databases, such as CPRD, due to governance restrictions. This exclusion can result in loss of valuable contextual information that could otherwise improve the interpretability of the data [49].

From a research perspective, these limitations necessitate a critical approach to data interpretation. Variables extracted from EHRs must be assessed with an understanding of how and why they were recorded. Bias introduced by missing or systematically unrecorded data must be carefully considered, particularly when making inferences about clinical practices and patient outcomes.

While real-world data presents an invaluable opportunity for research purposes, researchers must acknowledge that EHRs are not designed for research but for clinical documentation. The fact of how different healthcare professionals interact with the system, how consultations are structured, and how data is prioritised must be factored into any analysis. As research methods evolve, integrating clinician-led validation of coding practices and ensuring up-to-date code lists will be essential for improving data reliability.

Despite these challenges, EHR data remains a powerful tool for investigating disease trends, treatment effectiveness, and healthcare utilisation. Continued advancements in coding systems, improvements in data linkage, and ongoing collaboration with clinicians will be key to maximising the research potential of primary care data in the future.

### 1.3 Aims

The overarching objective of my thesis is to get a broader understanding of the characteristics and management of UK school-age children with asthma and determine if the age asthma is diagnosed influences this. I will achieve this by characterising children by their age at diagnosis and describing their pharmacological management. I will then assess the uptake of non-pharmacological guideline-recommended good clinical practice activities and explore which children are less likely to receive these interventions. Lastly, I will determine how effective these good clinical practice activities are at reducing exacerbations in real-life clinical settings.

### 1.4 Objectives

1. Describe the characteristics and pharmacological asthma management of school-age children with asthma by their age of diagnosis, categorised into 5-8.9 years, 9-11.9 years and 12-16 years old.
2. Calculate the rate of future asthma exacerbations and determine the exacerbation risk factors, by their age of asthma diagnosis.
3. Measure the annual implementation of asthma reviews, asthma management plans, inhaler technique checks, and influenza vaccinations from 2007 to 2020, and identify which groups of children are less likely to receive them.
4. Determine the effectiveness of receiving an asthma review, asthma management plan or inhaler technique check, or receiving all three activities in the same GP practice visit.



## 2. Chapter 2: Data Sources and Variable Definitions

This chapter provides a comprehensive overview of the data types and sources utilised in subsequent chapters, including an ethical approval statement for their use. It also outlines the basic definitions of key variables derived from these data sources such as BMI (body mass index), IMD (Index of Multiple Deprivation) and asthma medication.

### 2.1. Electronic healthcare records

Patient records in primary care are nearly all held in digital formats, forming the core of the general practitioner's (GP) electronic healthcare records (EHR) [50]. EHR is an electronic system used by healthcare systems to collect and store patients' medical information, capturing a variety of patient-level variables over time and was designed to help manage clinical workflows and healthcare administration. EHR started in the UK in the 1980s and has progressively moved from paper to digital medical records. There are currently several different clinical software systems operating nationally but three systems dominate, these are EMIS Health, SystmOne (provided by The Phoenix Partnership; TPP) (which together cover more than 90% of England) and Vision (Cegedim Healthcare Solutions [51]).

There is growing interest in leveraging EHR for research purposes because of both its continuous expansion due to the ever-increasing digitalisation of healthcare and improvement in access. These factors were exponentiated as part of the UK's exemplary data response to the COVID-19 pandemic. As EHR provide real-world data, this enables certain advantages when measuring effectiveness that is not possible from the gold standard, randomised controlled trials (RCTs). In respiratory trials, approximately 90% of adult patients are not eligible and in trials involving airways drugs, inhaler technique and adherence is optimised, limiting the generalisability of trial findings [52, 53]. For example, high risk groups such as children and those from more socially deprived backgrounds, are unlikely to be included in RCTs.

Another advantage of EHR is the precise documentation of medications (including the exact date, dose and formulation), which is difficult (time consuming, costly, inaccurate) to obtain

by other means. Furthermore, EHR does not suffer from recall bias or error to remember the medication prescribed. For children with asthma, real-world data can therefore add a significant missing piece to the jigsaw trying to build up evidence around their management. Additionally, it encompasses nationwide generalisable data on clinical practices, whereas survey data is often limited by geographical pockets, patient demographics and willingness to engage.

However, a major disadvantage is that the routinely collected information is not generated for research purposes, thus often may miss critical variables or values required, limiting the type of research questions that can be answered with EHR. An example in asthma studies is the lack of recording in GP practices of spirometry for both children and adults, such that when it is missing it is not known if it was conducted outside of the GP practice and not recorded, or just not conducted at all.

In the UK, several sources harness GP digital data and provide it for a fee to researchers, including The Health Improvement Network (THIN), QResearch [54], Secure Anonymised Information Linkage (SAIL) Databank [55], Optimum Patient Care Research Database (OPCRD [56]) and the Clinical Practice Research Datalink (CPRD) [57]. Data is provided through the software suppliers, from GP practices that opt in (THIN, SAIL, QResearch, CPRD), or through contracts with individual GP practice level (OPCRD). The databases include information on patient demographics, diagnoses, tests, and treatments and can be linked with secondary data sources to provide a more complete picture of patient care, including Hospital Episode Statistics (HES) [58] the Office for National Statistics (ONS) and national cancer registries [59]. Data in these databases are de-identified to ensure patient confidentiality. For instance, in CPRD, data is de-identified at the practice level, meaning no identifiable information is uploaded to the research data server. When linkages are made, identifiable data is sent directly from the practice to NHS Digital, which handles the linkages. This data is then de-identified and sent to the CPRD research server.

This thesis will utilise data from CPRD, linked with HES, ONS, and socioeconomic data as appropriate. These data sources are described in more detail below.

### 2.1.1 Clinical Practice Research Datalink (CPRD)

In the 1980s a GP based in Essex set up a computer programme, with the help of information technology staff at a nearby shoe factory, to help manage his own GP practice [60]. This was turned in 1987 into the Value-Added Information Medical Product Ltd (VAMP) with the recruitment of other GP practices. Increasing GP practices allowed VAMP to access their data and eventually, the database was given to the Department of Health in 1993, becoming the General Practice Research Database (GPRD). In 2003 the Medicines and Healthcare Products Regulatory Agency (MHRA, known then as the Medicines Control Agency) took over the database [61]. They obtained individual patient linkage to HES, ONS, and the national cancer registry, to hugely increase the utility of the GPRD. Then in 2012 the MHRA, with support from the National Institute for Health and Care Research (NIHR) as part of the Department of Health and Social Care, launched the Clinical Practice Research Datalink (CPRD).

CPRD is now a real-world non-profit research service that supports both retrospective and prospective public health and clinical studies [57]. It collects anonymised patient data from GP practices across the UK using Vision and EMIS software systems. Due to differences in the structure and coding of the data between the two systems, the research database is released as a separate data offering. CPRD GOLD contains data from GP practices using Vision software, and CPRD Aurum contains data from GP practices in England using EMIS software. Today, CPRD is one of the world's largest longitudinal healthcare databases, broadly representative of the UK population in terms of age, sex, ethnicity, and BMI [61].

Data is collected monthly from general practices that have opted in at a practice level, including all patients, unless they individually opt-out [61]. Additionally, many practices in England have consented to link their data to secondary care data, mortality data and deprivation data, although each practice can revoke their consent at any time. As the patients are de-identified their primary care data must be individually linked to secondary sources by a trusted third party, NHS Digital [61, 62]. Patients are identified using a progressive algorithm matching NHS number, sex, date of birth, and postcode, ensuring accuracy by the number of concordant identifiers [62]. The correctly matched data is then de-identified and made available to researchers. Linkage datasets are released to CPRD and then researchers at discrete time points, dependent on NHS Digital.

Data linkages that are possible to the main primary care data include HES Admitted Patient Care, HES Accident & Emergency, HES Outpatients, HES Diagnostic Imaging Dataset, ONS mortality data, small area deprivation data (including Index of Multiple Deprivation, Townsend Deprivation Index, Rural-Urban classification) as well as more specific datasets such as COVID-19 virology data (from Public Health England), Intensive Care National Audit and Research Centre data on COVID-19 intensive care admissions, National Cancer Registration and Analysis Service datasets, and CPRD created linkages including Pregnancy Register and the Mother-and-Baby Link.

Only GP practices in England are eligible for secondary care data as HES only covers hospitals within NHS England. Therefore, the availability of linkage is dependent on where the software is used. CPRD Aurum receives data from GP practices using EMIS which is commonly used in England; thus, it has linkage for around 90% of its patients in the database. Whereas CPRD GOLD which receives data from GP practices using Vision software, often used outside of England, only has HES linkage for around 60% of the patients in the database [57]. It is possible to use both databases in one study, but they are separate entities, use different data files, cover different GP practices and locations and so should be considered and must be managed as two different data sources.

In this chapter and thesis, I have focussed on CPRD Aurum as this was the database I used for my studies.

#### *2.1.1.1 CPRD Aurum database*

Named after the Latin word for 'gold', CPRD Aurum was launched in October 2017 and has been available for research since 2018 [63]. CPRD Aurum due to its large coverage has quickly become a significant data source. GP practices using EMIS software and willingness to participate vary by region across England, with high numbers in Greater London and the West and South West of England ( ) [63].

As of June 2024, CPRD Aurum contained over 47 million patients, covering 24% of the UK population with over 16 million active (alive and currently registered) patients [64]. Table 2.1

reports the numbers of patients, GP practices and length of follow-up in the database in June 2024

Figure 2.1: CPRD Aurum population coverage and total patients by English region, September 2018.

Circles represent the total number of patients in CPRD Aurum in each region. Shading represents population coverage of current patients as a proportion of the total regional population. Source: Wolf, A., et al., Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International Journal of Epidemiology*, 2019. 48(6): p. 1740-1740g.

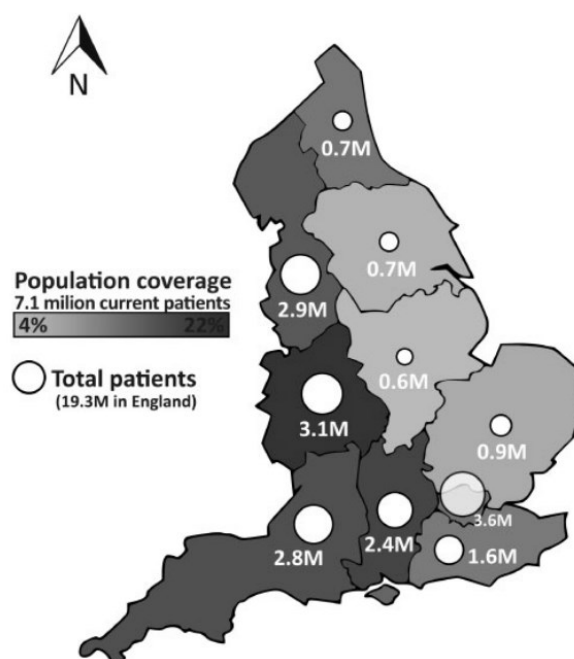


Table 2. 1: CPRD Aurum Metrics (June 2024).

| Metric                                                                                            | Coverage         |
|---------------------------------------------------------------------------------------------------|------------------|
| Total number of acceptable patients <sup>1</sup>                                                  | 47,766,944       |
| Current acceptable patients                                                                       | 16,227,262       |
| Percentage UK population coverage (current patients only) <sup>2,3</sup>                          | 24.2%            |
| Total patients eligible for linkage                                                               | 35,233,535       |
| Available follow-up time in years since 1st January 1995 (including transferred out and deceased) |                  |
| Mean (SD)                                                                                         | 8.7 (8.8)        |
| Median (IQR)                                                                                      | 5.2 (2.0 – 13.0) |
| Available follow-up time in years since 1st January 1995 (current patients only)                  |                  |
| Mean (SD)                                                                                         | 12.8 (10.4)      |
| Median (IQR)                                                                                      | 9.6 (3.3 – 22.2) |
| Total number of practices (current and historic)                                                  | 1,784            |
| Currently contributing practices                                                                  | 1,596            |
| Percentage coverage of UK general practices (currently contributing only)                         | 19.9%            |

<sup>1</sup> Permanent registration only. Over 93% of permanent registrations are deemed to have 'acceptable' data. <sup>2</sup> Currently contributing practices are those contributing to CPRD within

120 days of the database build being created.<sup>3</sup> Based on the latest UK population estimates from the Office of National Statistics. Source: Release Notes: CPRD Aurum June 2024. [64]

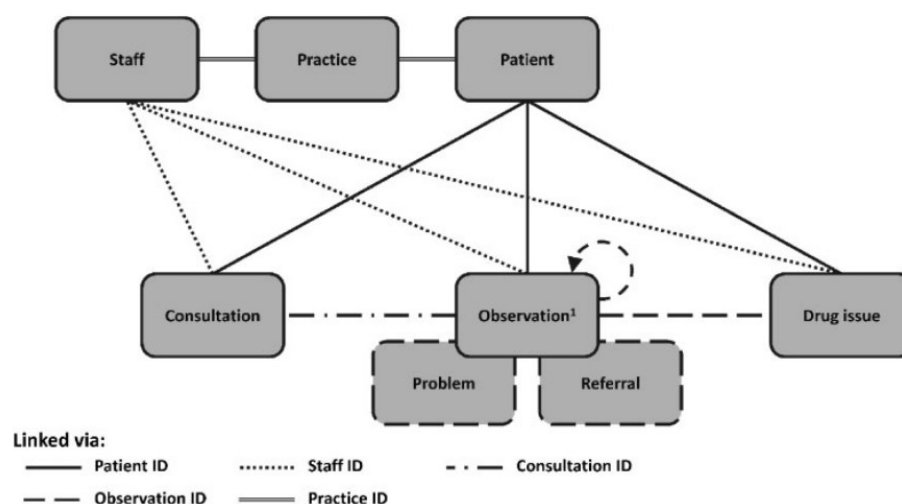
### 2.1.1.2 Structure of CPRD AURUM

The CPRD Aurum database is structured into eight separate files (Figure 2.2)

1. Practice File: Contains the region where the GP practice is located and the latest data collection date from that GP practice.
2. Staff File: Lists job categories for staff members.
3. Consultation File: Details types of consultations (e.g., phone, home visit) and links to observations and staff members involved.
4. Observation File: Includes medical history data including symptoms, clinical measurements, lab results, and diagnoses, as well as demographic information. This is all coded using Read codes and specific CPRD codes.
5. Referral File: Contains information on patient referrals to and from external care centres, most frequently from the practice to a secondary care provider.
6. Problem File: Details chronic conditions managed by GPs, grouping related clinical events.

Data in the referral and problem files are linked to the observation file and contain additional information for referral-type and problem-type observations.

Figure 2. 2: CPRD Aurum dataset structure.



Source: Wolf, A., et al., Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International Journal of Epidemiology*, 2019. 48(6): p. 1740-1740g.

#### *2.1.1.3 Ethical approval*

Access to CPRD data, including linked datasets, requires scientific and ethical approval through CPRD's Research Data Governance (RDG) Process. This rigorous process is provided by Expert Review Committees which consist of researchers, CPRD members and public members. Researchers must describe in detail their research questions, methods, data variables, outcomes, analysis plan, study limitations, dissemination plans, and any patient and public involvement, as well as provide a lay summary and technical summary that will be publicly available on their website. The assessment and approval process takes several months and often requires changes by the researchers to their protocols. The remit of the RDG is to ensure three broad principles are adhered to: public and professional trust, patient and public health benefit, and maintaining the integrity of the CPRD database asset. At later stages approved protocols can be amended, subject to RDG approval.

#### *2.1.1.4 Coding*

Different coding systems are used for different data sources. Primary care databases were coded across the UK using Read codes for clinical terms and GEMscript codes for medications. However, in 2018, NHS England changed to Systematized Nomenclature of Medicine–Clinical Terminology (SNOMED CT) codes for clinical terms and Dictionary of Medicines and Devices (DM+D) for prescription information [63]. SNOMED CT is a clinical terminology system that operates by a hierarchical ontological structure and is used in over 50 countries [65]. However, CPRD Aurum still contains both Read codes and SNOMED CT codes. In my PhD I have used Read codes as there are validated lists of Read codes for asthma, in addition, my dataset follow-up ended in 2020, therefore, Read codes were used for the majority of the study period. Read codes were developed in the 1980s and have been used in the NHS since 1985. There have been three major technical design changes, symbolised as Read version 1, Read version 2 and Read version 3 (also called Clinical Terms Version 3, CTV3). SNOMED CT is an amalgamation of CTV3 and an American coding system, SNOMED RT. However, many terms used by GP practices, and recorded by EMIS, do not yet have a SNOMED CT code, this was the third reason why I chose to use Read codes.

CPRD linked datasets integrate multiple coding systems (Table 2.2). HES Admitted Patient Care (APC) data and HES Outpatients use ICD-10 for diagnostic data and OPCS 4.6 for procedural

information. HES Accident and Emergency data utilise an A&E specific coding system from NHS England. The HES Diagnostic Imaging Dataset employs SNOMED-CT codes for tests. The ONS Death Registration data and the National Cancer Registration and Analysis Service (NCRAS) Cancer Registration data both use ICD-10, with NCRAS also employing the International Classification of Diseases for Oncology.

*Table 2. 2: CPRD-linked datasets and coding systems*

| Dataset                                    | Coding Systems Used                                                                                                                                   |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| HES Admitted Patient Care                  | Diagnostic data recorded using ICD-10.<br>Procedure information coded using the UK Office of Population, Census and Surveys classification (OPCS) 4.6 |
| HES Outpatient                             | Diagnostic data recorded using ICD-10                                                                                                                 |
| HES Accident and Emergency                 | Most diagnostic data recorded using an A&E specific coding system, that can be obtained from NHS England.                                             |
| HES Diagnostic Imaging                     | Diagnostic imaging tests recorded using SNOMED-CT codes (no diagnoses are recorded)                                                                   |
| ONS death registration                     | Cause of data recorded using ICD-10                                                                                                                   |
| NCRAS Cancer Registration                  | Cancer diagnoses are recorded using the International Classification of Diseases for Oncology which is mapped to ICD-10                               |
| NCRAS Systemic Anti-Cancer Therapy Dataset | Diagnostic data recorded using ICD-10                                                                                                                 |
| NCRAS National Radiotherapy Dataset        | Diagnostic data recorded using ICD-10                                                                                                                 |

To assist researchers, CPRD provides data dictionaries and code browsers to identify relevant codes in CPRD Aurum. The CPRD Aurum ‘Medical Dictionary’ contains information on all recorded medical observations, coded using a combination of SNOMED CT (UK edition) [66, 67], Read Version 2 and local EMIS Web codes [67]. The CPRD Aurum ‘Drug Dictionary’ contains information on drug and device prescriptions recorded in EMIS Web, coded using the Dictionary of Medicines and Devices (DM+D), which exists within the SNOMED CT terminological structure [67]. While practice staff can add additional information to patient records as free text, CPRD does not collect free text fields due to data governance concerns, as these may contain identifiable patient information [63].

### 2.1.1.5 Linkages used in my PhD

This section will highlight and elaborate on the specific linked data that was used throughout my thesis. The data sources I linked to are summarised in

Table 2.2.1.

Table 2. 3: Linked data used in my thesis

| <b>Table 2.2.1: Dataset</b>   | Relevance in my PhD                    | Coding Systems             |
|-------------------------------|----------------------------------------|----------------------------|
| HES Admitted Patient Care     | Dates of hospital admission for asthma | ICD-10                     |
| HES Accident and Emergency    | Date of A&E visits for asthma          | A&E specific coding system |
| ONS Death Registration Data   | Dates of asthma deaths                 | ICD-10                     |
| Index of Multiple Deprivation | Socioeconomic status for each child    | N/A                        |

#### **HES Admitted Patient Care**

HES Admitted Patient Care (APC) contains records of admissions to all hospitals under NHS England [58, 68]. It includes data on admission and discharge dates, diagnoses (primary diagnosis) and procedures undertaken. For each admission, the data is divided up by the different wards that the patient went to. Much of this information is administrative and not useful from a research perspective. The diagnoses and dates are the key information sources I used for my studies. For every admission, a patient may have several listed diagnoses, where the primary one is considered the main reason for the admission. However, for some patients, this distinction may not be possible if a patient is admitted for more than one condition. For exacerbations, I assumed that the primary HES diagnosis was the most robust piece of information to use. Diagnoses following the primary one can be included in the HES diagnosis list only because the patient is known to have that chronic condition, but the condition was not the reason for the admission. For example, asthma may be listed first as the admission was for an asthma exacerbation, but diabetes may be listed second as the child also has this condition, although it is not intimately related to the admission.

#### **HES Accident and Emergency**

HES Accident and Emergency (A&E) data includes information on accident and emergency records of patients in England. These records are a subset of national A&E data and are collected by NHS England to monitor the standard that 95% of patients attending A&E should be seen within four hours. The dataset therefore includes limited details about patients' attendance, diagnoses, treatments, and investigations [58, 69]. HES A&E diagnoses are much more limited than ICD-10 codes, for example COPD exacerbation is not coded but fortunately 'asthma' is used as a code. As with HES APC, this data relies on both the accuracy of the diagnosis by the treating clinician and the coding they used in the medical records. Therefore, although this dataset has some missing information it still provides relevant information and so was included in my studies.

### **ONS death registration data**

The ONS death registration data contains information on the date and causes of death using ICD-10 codes. Over half of deaths in the UK occur outside of hospital therefore HES data is insufficient, whereas ONS has nearly complete registration of England and Wales [70]. Furthermore, deaths are thought not to be accurately recorded in primary care datasets and do not offer a cause of death. The cause of death recorded in ONS is based on the death certificate written by the physician who attended in their last illness. The linked dataset includes the date of death, the derived underlying cause of death, and up to 15 additional direct and contributing causes of death as documented on the medical cause of death certificate [69]. Although the cause of death recorded by ONS is considered the gold standard, its accuracy may sometimes be uncertain due to inaccuracies of the death certificate. Additionally, there can be delays between the actual date of death and the issuance of the death certificate. [70], however, due to the young age of my cohort, there were very few deaths and there were no deaths from asthma.

### **Index of Multiple Deprivation**

The Index of Multiple Deprivation (IMD) is a composite measure of relative deprivation in England at the neighbourhood level, called the Lower Layer Super Output Areas (LSOA), and is calculated by the English government [71]. LSOA are small geographical areas developed

since the 2001 Census specifically to help determine deprivation indices; there are 32,482 LSOAs in England. IMD encompasses seven domains including income, employment, health, education, barriers to housing and services, living environment, and crime. Each domain contains multiple components within them, for example, distance to GP practice is one component within barriers to housing and services. IMD is calculated as a weighted sum of these seven domain indices, from which a relative ranking is applied. Although the choice of components and relative ranking is somewhat subjective, this still offers a good proxy for socioeconomic status. GP practice postcodes, or individual patient residence postcodes, are aligned at the LSOA level and linked to IMD by NHS Digital. IMD 2015, used in my PhD, was categorised into quintiles, from 'most deprived' to 'least deprived' from IMD data estimated in 2015.

#### *2.1.1.6 Strengths and Weaknesses of CPRD Data*

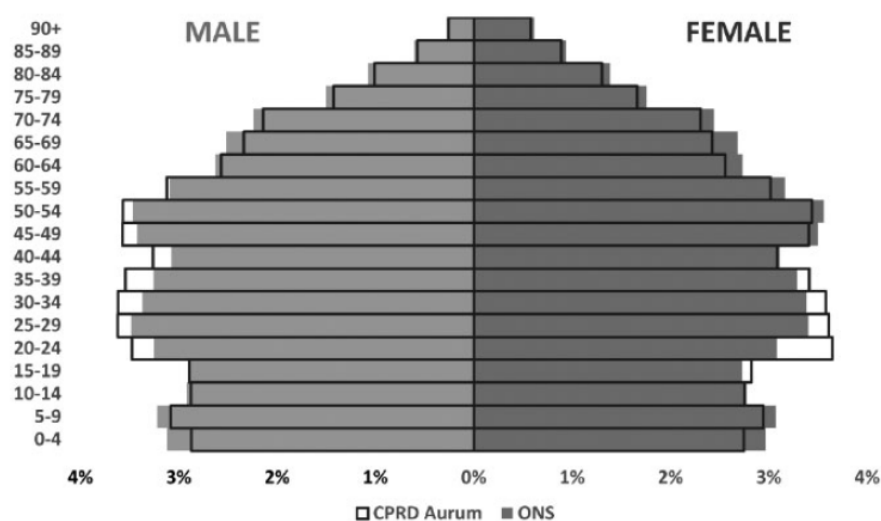
##### *Strengths*

**Data coverage:** CPRD is one of the largest longitudinal, datasets globally [61, 63]. Currently, patients in CPRD Aurum have a median prospective follow-up of 9.6 years for current patients and 5.2 years overall [64]. This provides large coverage in terms of the numbers of patients and length of follow-up.

**National representativeness:** CPRD Aurum and GOLD together represent over 20% coverage of GP practices in the UK. The CPRD population is broadly representative of the UK population in terms of major demographic variables [63]. In mid-2017, just after CPRD Aurum was first initiated, patients within the dataset had a similar spread by age and sex, including in children, as data nationwide published by ONS in the same year

). In 2018, the median IMD decile in CPRD Aurum was similar to the UK's median IMD decile, both were 5.3 which is therefore close to the median IMD decile of 5.

Figure 2. 3: Population representation for CPRD Aurum and ONS data



Based on mid-2017 ONS and mid-2017 CPRD Aurum. Source: Wolf, A., et al., Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International Journal of Epidemiology*, 2019. 48(6): p. 1740-1740g.

**Data quality:** Data quality in English general practice is supported by the Quality and Outcomes Framework, which incentivises GPs to record key data items such as smoking status [61]. CPRD provides criteria for patient acceptability and practice "up to standard" (UTS) time to help researchers select high-quality data. Additionally, CPRD performs extensive validation and quality assurance on GP data, including checks for data integrity, structure, and format [63]. The data quality relies on the accuracy of the diagnosis and in primary care, diagnoses such as childhood asthma suffer from multiple challenges including lack of a gold standard and a lack of diagnostic resources. However, external CPRD Aurum validation studies find a high positive predictive value for many diagnoses, and comparisons with other UK data sources are generally consistent [63].

**Extensive data linkages:** As discussed above, CPRD allows for the linkage of primary care data with secondary care datasets and other datasets, providing a comprehensive view of patient care pathways and outcomes[63].

### Weaknesses

**Missing data and variability in data recording:** In general practice, the variability in data recording and the completeness of the data can pose significant challenges, particularly concerning missing key data. For example, in my PhD, I am interested in body mass index (BMI) as this is a recognised risk factor for asthma severity [72]. To calculate BMI, I needed both the child's height and weight, and as children's height varies as they age, these need to be recorded nearby in time (unlike adults where a height only needs to be documented once). If one of these two values was missing, I could not calculate their BMI. Some GP practices directly document BMI, while others only document height, or only document the child's weight. This discrepancy and variability led to a huge amount of missing data in a basic childhood measurement. Understanding the missingness is also important and discussed later on, as systematic missingness will not cause bias, but if some children are more likely to have missing BMI than others this can bias estimates which may, or not, be amenable to statistical methods.

**Incomplete secondary care data:** Data from secondary care must be manually entered by GP practices so often remains incomplete in primary care records. Therefore, the ability to link to such data is critical. Although prescription data in primary care is very accurate, secondary care prescriptions and over-the-counter usage are not captured in CPRD even with linkage.

**Incorrect or inaccurate diagnoses:** Diagnoses are typically decided when the medical records include codes specific to that condition, in reverse, the absence of a specific code in a patient's record is usually taken to imply the absence of the related disease. However, there are situations where this may lead to misclassification: (i) if the patient does not report the condition, such as mild hay fever; (ii) when the diagnosis is made by specialist centres and not translated back to primary care (except in free text that is not recorded), such as uncommon genetic conditions where registries may be a more valuable data source (iii) when the disease has not yet been diagnosed, such as asthma in children where there can be delays in formally labelling a child with preschool wheeze as having asthma [29], or (iv) when there is no code for that condition, such as breathing pattern disorder (dysfunctional breathing pattern).

Additionally, the quality of the data for research purposes may not be consistent across the different GP practices and over time. The transition to SNOMED coding may further impact the consistency of the data [61, 63]. For instance, there are numerous Read codes for asthma,

and the number of codes has increased over the years. Some codes, like 'asthma' or 'annual asthma review,' are frequently used, while others, such as 'asthma symptom diary used,' are rare, with only a single practice recording such a code. Patients often may have several codes applied but equally a relevant code list must be carefully crafted to include all patients with asthma, especially if some patients do not frequently attend their GP practice for their asthma. It is also necessary to ensure codes that are not relevant to the disease diagnosis are not included in the code list, such as 'asthma in remission'. To ensure the code lists have a high positive predictive value, where possible, validated code lists should be used. However, data and coding are rapidly changing, and previously validated lists may miss out commonly applied codes. Another approach is to obtain the latest code list at the time of the data upload and review the list with clinicians, particularly primary care clinicians.

**Limited access to free text:** While practice staff can add free text to patient records, CPRD does not collect these fields due to data governance concerns. This exclusion may result in the loss of information. Secondary care data recorded by GPs can also be incomplete, although additional data linkages can help fill these gaps [63].

## 2.2 Variable definitions

This section provides an overview of how variables are identified within the CPRD database, specifically focusing on the process of identifying patients with asthma. It also covers how their demographic data and medical histories were determined.

### 2.2.1 Overview of code lists

Within the CPRD framework, Read codes were traditionally used to build these code lists. Read codes, a hierarchical classification system used by the NHS until 2020 [73], consist of alphanumeric characters that increase in specificity at each level. These codes are directly linked to CPRD-specific 'medcodes' which CPRD researchers used to identify the presence of conditions in individual patients. Each condition will include multiple different codes that may indicate that the patient has been diagnosed with that condition.

The process of creating a code list for each diagnosis involves generating terms and synonyms that describe a medical condition. One can then use the Medical Dictionary provided by CPRD to search for codes that match these terms. Once a list is generated it is then cross-checked with the results of any existing published code lists and shown to clinicians, to derive the most accurate and up-to-date code list [74].

### 2.2.2 Identifying the cohort of asthma patients using CPRD data

In my thesis, I adapted a previously validated list of asthma codes that was validated for adults diagnoses with asthma by their GP practice [49]. The codes were validated for use in CPRD GOLD and there has been no further validation since and no validation for use in CPRD Aurum. Therefore, I updated the code list and only included relevant asthma codes for CPRD Aurum. Two respiratory physicians reviewed the list. Finally, I compared my list to other open-source asthma codes to ensure I did not miss any codes [75]. To reduce the risk of misclassification I only included children with at least two asthma codes in their record within 2 years of cohort entry.

### 2.2.3 Identifying good clinical practice activities for asthma

I searched CPRD's medical dictionary to find all the relevant codes for each of the four good clinical practice activities: annual asthma review, asthma management plan, inhaler technique check, and influenza vaccination (Appendix 2). I also searched the product dictionary and vaccination dataset for influenza vaccination records (Appendix 3).

### 2.2.4 Creating variables for the children's characteristics

This section describes how demographics and clinical characteristics were defined for the studies.

#### **Age**

CPRD does not provide the day of birth for children under the age of sixteen years old to protect patient privacy. Instead, only the month and year of birth are recorded. I created a dummy day of birth for each child, for consistency I chose the 1st of the month for every child.

When categorising age into groups I used the categories, 5-11.9 years, and 12-15.9 years. I chose these based on the treatment recommendations in the national asthma management guidelines. To improve granularity, I further segmented the children into two equally sized age groups in the under 12 years category, 5-8.9 years and 9-11.9 years.

### **Gender**

CPRD have a 'gender' variable which is categorised as male, female, indeterminate, or not specified. For the purpose of this analysis, only individuals whose gender was identified as either male or female were included. I have kept the same term 'gender', and not used 'sex', as this is the name of the variable and only data provided by CPRD.

### **Atopy**

Conditions including hay fever (allergic rhinitis), eczema and food allergy were identified in children's electronic health records before their asthma diagnosis, using specific Read codes (Appendix 4). I derived these lists from CPRD's Medical Dictionary, asked two respiratory physicians to review them and checked other code repositories for similar lists. A child was considered to have received a code for one of these conditions if their records included at least one corresponding code; the absence of such a code indicated the non-presence of the condition. It is a limitation and expected that hay fever, particularly if mild, or even food allergies, may go unreported to the GP practice and therefore incorrectly reported as the child not having the condition. Searching using medications for hay fever did not increase the number of children labelled as having the condition, again to be expected as many children receive over-the-counter medication for hay fever. Comorbidities were categorised under three labels: 'atopy 1' for hay fever, pet allergies, or house dust mite allergies; 'atopy 2' for food or drug allergies; and 'eczema'.

### **BMI**

BMI was calculated using height and weight recorded within 12 months of each other. The formula used for calculating BMI was:

$$BMI = \frac{weight}{(height)^2}$$

Once BMI was calculated, children's growth and nutritional status were further evaluated using Z-scores. Using the 1990 WHO growth charts, which provide the mean ( $\mu$ ) and standard deviation ( $\sigma$ ) for children's BMI based on age and sex, I calculated Z-scores using:

$$Z = \frac{(BMI - \mu)}{\sigma}$$

After calculating the Z-score for a child's BMI, I interpreted the scores using percentiles and 1990 UK WHO cut-offs to categorise the child's nutritional and growth status [76]. I used following categorisation, obese was more than two Z-scores, overweight was greater than one Z-score and normal was less than one Z-score; where one Z-score indicates that a child is one standard deviation away from the average BMI for that age and sex.

### **Smoking**

Medical codes were used to ascertain two variables, active cigarette smoke status among adolescents aged 12-16 years, and passive cigarette smoke exposure across all age groups (Appendix 25 & **Appendix 6**). Smoking status was classified either as current or former smoker. If a smoking code was present in the child's records these children were categorised as exposed. If there was no code, these children were categorised as not smoking, although this will misclassify children that did not admit to smoking. It's important to note that while the accuracy of smoking prevalence data has previously been validated in adult populations by comparing primary care EHR with national surveys, such validations have not extended to the paediatric population [77]. Both smoking variables also rely on healthcare professionals asking these questions. Vaping data was not included in this analysis, as it only became more prevalent toward the end of the period under study and with very limited coding for vaping at that time.

### **Asthma medication**

To identify asthma medication, I began by importing and cleaning multiple Drug Issue data files. This involved reading in each file, retaining relevant variables (patid, pracid, issuedate, prodcodeid, dosageid, quantity, quantunitid, and duration), removing duplicates, and compressing the files for efficient storage. Due to the large volume of data the cohort was divided into six Drug Issue files. Therefore, the above steps had to be repeated for each Drug Issue file. I then appended the cleaned medication files together to create a single medication

dataset. To identify asthma-specific medications, I merged the medication dataset with a list of asthma drug codes. I created the code list of asthma medications by searching CPRD's Product Dictionary for asthma inhalers (inhaled corticosteroids, ICS, long-acting beta-agonists, LABA, short-acting beta-agonists, SABA) and oral medications, leukotriene receptor antagonists (LTRA) and oral prednisolone. As per the national asthma management guidelines, LABA and LTRA are defined as 'add-on' asthma medication. Within the drug code list I also separated the ICS by prescribed dose. I then standardised the ICS use across all the inhalers by equivalating the dose to beclomethasone for each inhaler, one by one. I achieved this by using Table 13 from the 2019 BTS/SIGN asthma guidelines and categorised doses into very low (<200mcg/day), low (200-400mcg/day), medium (400-800mcg/day) and high dose (>800mcg/day) [78]. The table incorporates the type of ICS, particle size and inhaler device into the equivalence calculation. Finally, I merged the asthma therapy data with my cohort and categorised the medication received in the year before the study start into, no treatment, reliever (SABA) only, very low ICS, very low ICS + add-on therapy, low ICS, low ICS + add-on therapy, medium ICS, medium ICS + add-on therapy, high ICS, and others. Children had to have at least one prescription of that inhaler to be categorised in that strata and were always categorised in the highest medication strata possible. Biologics are prescribed in secondary care only, therefore that information is not available in CPRD.

### **Respiratory symptoms**

Respiratory symptoms were assessed as binary variables based on whether they were reported to the GP practice including wheezing, chest tightness, cough, and breathlessness. Symptoms were classified using corresponding medical codes (Appendix 7, Appendix 8 & Appendix 8).

### **Asthma exacerbations**

I defined an asthma exacerbation as either a short course of oral corticosteroids (OCS) prescribed by the GP practice, an A&E visit for asthma, or a hospital admission for asthma. This definition is the most common one applied to observational studies using routinely collected healthcare data [29, 72].

A short course of OCS was defined as a prescription of a total of 200 mg or less. This is because there is accurate data on the dose of medication prescribed and number of tablets as this is

directly linked to the prescription. Whereas the data entry for the intended 'dose per day' is often missing or incorrectly entered. To obtain this I first created a file with OCS prescriptions by merging the Dose Issue files with the patient list and retaining matched records. Relevant variables such as patient ID, product code ID, quantity, issue date, and study dates were kept. This data was then merged with asthma medication codes to filter for OCS prescriptions. I kept only the highest dose for multiple prescriptions on the same day, assuming if the doses were the same, it was a rescue pack, and if different, the second was for weaning. I then used the description of each OCS to calculate the dose and multiple by the quantity variable.

Although corticosteroids are unlikely to be used for other conditions, to be sure of this, I investigated the proportion of children with asthma receiving a short course of oral corticosteroids on the day another steroid-managed condition was coded for. (e.g. inflammatory bowel disease). There were <0.5% of children with codes for another condition, therefore the assumption was made that all courses of corticosteroids were for an asthma exacerbation.

For A&E exacerbations, I merged the patient list with the HES A&E data file which contained the diagnostic code and date of the A&E visit. I then retained records with specific diagnostic codes (diagnosis "251") indicating asthma-related visits.

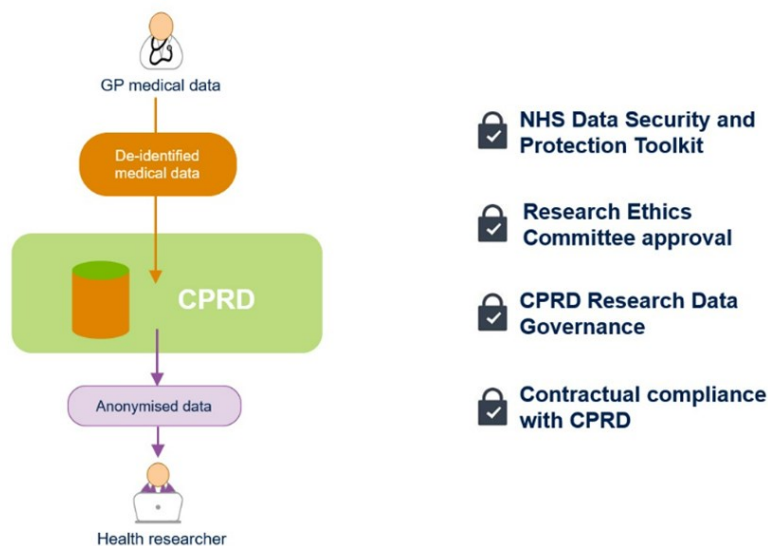
Hospital exacerbations were identified by merging the patient list with HES APC data, and filtering for asthma-related admissions using ICD-10 codes. The most commonly used ICD-10 code for asthma is J45 '*asthma*', and only in about one in ten times is the code for acute severe asthma applied, J46 '*status asthmaticus*'. Therefore, if J45 '*asthma*' is listed second in the HES diagnoses list, we cannot know if this was related to the hospital admission or not. For this reason, I defined hospital admission as only when '*asthma*' was listed first in the HES diagnosis list (ICD-10 J45 or J46).

Finally, I considered any exacerbation within 14 days of a previous one as being the same exacerbation and so merged exacerbations together that occurred in that time period, keeping only the date of the first exacerbation. The exacerbation could also be categorised as GP-managed, A&E or hospital-managed. I would have included deaths from asthma as part of the exacerbation definition, but during the study period, there were no asthma related deaths in my cohort.

## 2.3 Ethics approval

In clinical research, the requirement for approval of studies by research ethics committees is laid out in the Helsinki Declaration [79], most recently updated in 2013. CPRD ensures that all received anonymised data complies with the Information Commissioner's Office (ICO) anonymisation code of practice. The identity of patients and contributing GP practices is concealed. The data can only be used for public health research by researchers, and all requests to access the data are reviewed via the CPRD Research Data Governance (RDG) process to ensure the proposed research benefits patients and public health (**Error! Reference source not found.**) [80]. The protocol for this thesis was approved in 2020 by the previous ethics committee which existed before the RDG and was called the Independent Scientific Advisory Committee. My approved protocol is number 20\_053. Please also see my ethics and data sharing statement at the beginning of my thesis.

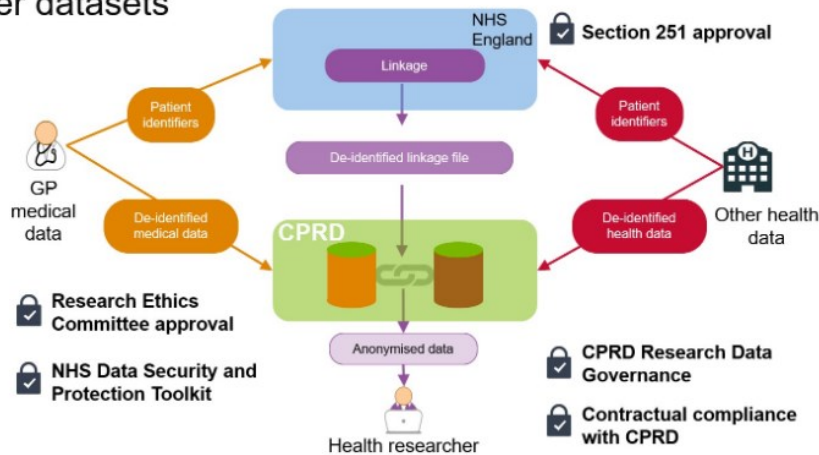
Figure 2. 4: Process and approvals required for providing anonymised data to researchers [80]



The ethics process and approval to link CPRD data with other data sources, as described earlier, additionally involves CPRD obtaining Section 251 regulatory support from the Health Research Authority Confidentiality Advisory Group and permission from GP practices ( ).

Figure 2. 5: Process and approvals required for linking primary care data to other data sets [80]

## Process and approvals required for linking primary care data to other datasets



## 2.4 Conclusion

A large part of using electronic healthcare records (EHR) is the time taken to clean the data and craft appropriate variables [81]. There were several potential constraints that I tried to minimise, including misclassification, selection bias and missingness to ensure methodological robustness. I achieved this through careful and often time-consuming data scanning, use of validated code lists, use of validated variable definitions, reviewing EHR literature, alongside discussion with my supervisors and other users of EHR data. Through this iterative process, I improved the robustness and generalisability of the asthma cohort drawn from the CPRD database and the variables I created to help answer my research questions and aims. However, there remain several limitations of the data, and these are discussed in each chapter, as appropriate.

## 3. Chapter 3: Influence of Age on Clinical Characteristics and Pharmacological Management

### 3.1. Introduction

Although age is recognised as an important factor in asthma, previous studies have focused on comparing asthma characteristics and comorbidities between, children and adults, or distinguishing early-onset asthma from late-onset asthma [14, 72, 82]. The more granular impact of age within the school-age range, 5 to 16 years, remains unexplored. However, this gap may be critical, as there are substantial growth and developmental changes that occur within this period. A common characteristic of children with asthma is atopy, which is also known to evolve as children age[83], but the effect of age-related atopy changes on childhood asthma has not previously been assessed in the general population. Other asthma-related characteristics known to change with age include sex, with a significant impact on asthma around the time of puberty[84], and body mass index, which tends to increase with age[84]. These characteristics that are known to change as a child ages and to influence the development of asthma, and its severity, may hence differ depending on the age at which a child's asthma develops.

The influence of age on the pharmacological management of childhood asthma is also not well understood, highlighted by the fact that asthma drug trials and guidelines rarely differentiate between adolescents and younger children [8, 9, 85]. National asthma guidelines include pharmacological and non-pharmacological recommendations, each follow a similar stepwise treatment plan for pharmacological management. However, the guidelines do differ in some respects. In 2016, while the BTS/SIGN guidelines followed GINA guidelines and introduced a major change for children with mild asthma but recommending prescribing an ICS alongside a reliever medication, NICE did not follow the same recommendation and continued to recommend only reliever medication [28]. In addition, for children over 5 years old, the add-on therapy for those not controlled on ICS alone would be either adding a LABA as recommended by BTS guidelines or a LTRA as recommended by NICE [28]. There are no recommendations on how pharmacological management may differ between children within the school-age range. A large UK study using primary care asthma medication prescriptions,

between 2006 and 2016, found that around 40% of school-age children were not prescribed an ICS [29]. Whether the 2016 guideline changes regarding ICS have since been implemented in primary care is currently unknown.

## 3.2 Objectives

**Objective 1:** Characterise school-age children by their demographics and comorbid conditions at the time of their asthma diagnosis, based on their age. Age categories will be 5-8.9, 9-11.9 and 12-16 years.

**Objective 2:** Describe the pharmacological management of asthma in these children using the same age categorisations.

**Objective 3:** Determine if SABA and ICS prescriptions changed over time, particularly after the change in the BTS/SIGN asthma guidelines in 2016.

## 3.2 Methods

### 3.2.1 Data source

The cohort was identified using electronic healthcare records from primary care, obtained from the Clinical Practice Research Datalink (CPRD), which was fully described in chapter 2. Data was individually linked to Hospital Episode Statistics and Office for National Statistics death data [63].

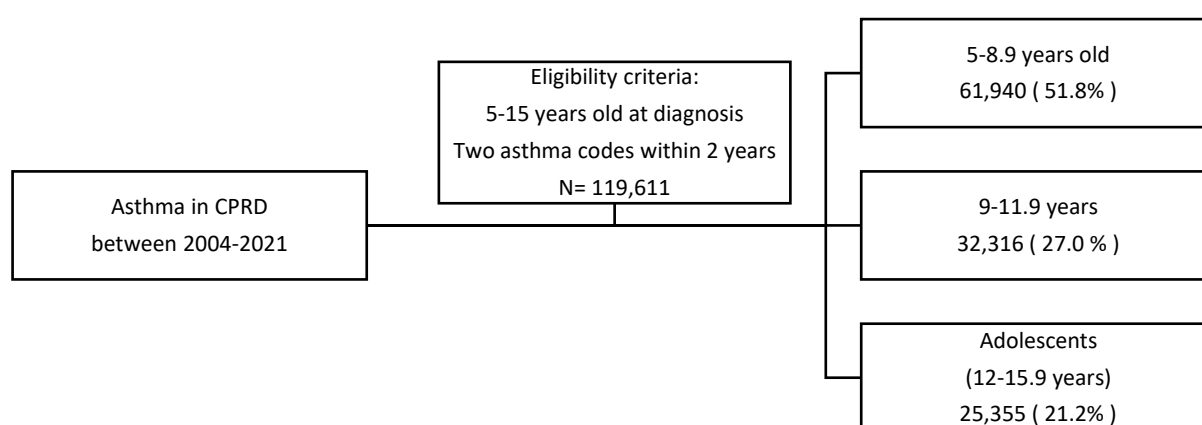
### 3.2.2 Study design and participants

The study population included children identified between January 2004 and January 2021. Children were included in the study if they were aged five to fifteen years old, had consistent registration with a CPRD-linked general practice, and met specific criteria for asthma diagnosis. To be eligible, each child needed two validated asthma codes recorded within two years and at least one year of data available before study entry, as well as one year of data following their diagnosis (**Error! Reference source not found.** and Appendix 1) [49]. The follow-up period was censored at the earliest of the following events: reaching the upper limit

of their age bracket, the study's conclusion on January 1, 2022, or the end of their data availability.

The date of asthma diagnosis was determined by the first recorded asthma code in the child's general practice records. Participants were grouped into age categories based on the UK asthma management guidelines [85], which classify children as those aged 5 to 12 years. We further subdivided these groups into ages 5 to 8.9 years and 9 to 11.9 years. Adolescents were defined as those aged 12 to 15.9 years. Only children with complete data from the date of their initial asthma diagnosis were included in the study.

Figure 3. 1: Flow chart of eligible cohort categorised into three age categories: CPRP= Clinical practice research datalink



### 3.3.3 Variables

This section will briefly define the variables used in this chapter; however, more comprehensive details about these variables and their definitions are described in Chapter 2.

**Demographic variables:** This included age, gender, BMI and IMD. Other variables included tobacco smoking and passive smoking.

**Atopy:** I included three atopy variables. One variable included children with codes for hay fever, pet allergy, and house dust mite allergy; these were included together in one variable to represent aeroallergen sensitisation. However, recognising that proof of sensitisation (IgE levels or skin prick tests) was not available and there was usually sparse documentation on the type of atopy, these were all put together into one variable. To recognise that sensitisation

data was unavailable, this proxy variable was not termed aeroallergen sensitisation but instead 'atopy 1'. Another atopy variable included children with codes for food or drug allergies; again, in recognition that these allergies was often not available, the proxy variable was called 'atopy 2'. The last atopy-related variable was eczema.

**Respiratory Symptoms:** Symptoms including cough, wheeze/chest tightness, and breathlessness were recorded in the year before diagnosis as binary variables.

**Asthma exacerbation:** Defined as GP-prescribed short course of oral corticosteroids, A&E visit or hospital admission for asthma. When used as covariates, these were categorised as 'pre-diagnosis', if occurred <30 days before diagnosis, 'around the time of diagnosis', if occurred from 30 days before and on the day of diagnosis.

**Asthma Medications:** Included short-acting beta-agonists (SABA), inhaled corticosteroids (ICS), and additional medications, long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA). ICS doses were categorized by 2019 SIGN/BTS guidelines, with tables for children under and over 12 years old. Doses correlate to, using budesonide equivalence, very low ( $\leq 200$   $\mu\text{g/day}$ ), low (200–400  $\mu\text{g/day}$ ), medium (>400–800  $\mu\text{g/day}$ ) or high ( $\geq 800$   $\mu\text{g/day}$ )

### 3.3.4 Analysis

This chapter includes a descriptive analysis of the children's characteristics at the time of their asthma diagnosis. Values are presented as percentages for categorical and binary variables and as medians with interquartile ranges for continuous variables.

To describe their pharmacological management, I used proportion of children prescribed each medication type. I chose not to use rates as these are harder to appreciate at a clinical level. As I used proportion, I therefore had to only include children with the same length of follow-up so I could compare the proportions between different groups of children. I calculated the percentage of children prescribed at least one asthma medication following diagnosis, using a fixed two-year follow-up period. Therefore, only children with a minimum of two years of follow-up data were included in this analysis. In addition, to determine how often the children were receiving ICS and SABA prescriptions, I calculated the total number of inhalers prescribed during the two-year period.

For objective 3 as I wished to compare use over time, I instead used rates of inhaler prescriptions. I calculated the average, annual rate of SABA and ICS prescriptions during the study period.

### 3.4 Results

#### 3.4.1 Patient characteristics by age group at the time of diagnosis (Table 3.9)

The study included a total of 119,611 children diagnosed with asthma. Most of the cohort, 61,940 (51.8%), were diagnosed between 5-8.9 years, while 32,316 (27.7%) were diagnosed between 9-11.9 years, and 25,355 (21.2%) during adolescence (**Error! Reference source not found.**). The average age at diagnosis was 6.8 years (SD = 1.2) in the youngest group, 10.4 years (SD = 0.9) in the middle group, and 13.7 years (SD = 1.7) in adolescents.

Gender distribution revealed large differences across age groups. In the youngest group, 36,514 (58.9%) were classified as male and 25,426 (41.1%) as female. In the 9-11.9 years age group, less children were classified as male with 17,868 (55.2%) and 14,448 (44.8%) classified as females. Among adolescents, as expected, this pattern reversed with the percentage classified as females higher than for males, 13,851 (54.7%) compared to 11,504 (45.3%) respectively.

BMI categories also varied across the groups. Overall, 52,668 (44.1%) of the cohort had a normal BMI, with 26,341 (42.5%) in the youngest group, 14,229 (44.0%) in the middle group, and 12,098 (47.7%) in adolescents. Being overweight and obese were more prevalent in older children, with 3,245 (12.8%) of adolescents being overweight compared to 4,419 (7.1%) of the youngest group, and 2,039 (8.0%) of adolescents being obese compared to 3,065 (4.9%) of the youngest group. Notably, BMI data was missing for 48,001 (40.1%) of participants, most frequently in the youngest group (28,115 or 45.5%).

Socioeconomic status, as indicated by the Index of Multiple Deprivation (IMD), showed a balanced distribution across groups. The most deprived (IMD 5) was represented by 28,631 (24.0%) of the total cohort, with similar distributions among the age groups: 15,204 (24.5%) in the youngest, 7,624 (23.6%) in the middle, and 5,803 (22.9%) in adolescents. The least deprived (IMD 1) accounted for 22,880 (19.1%) of the total, with slightly higher representation in the 9-11.9 years age group (6,420 or 19.9%).

Atopy 1 (hay fever, pet allergy, or house dust mite allergy) increased with age, diagnosed in 20,348 (17.1%) of the cohort, with 8,616 (14.0%) in the youngest group, 6,308 (19.6%) in the middle group, and 5,424 (21.4%) in adolescents.

Whereas eczema was most prevalent in the youngest age group with 23,108 (37.3%), declining to 10,651 (33.0%) in the 9-11.9 years old group and 7,055 (27.8%) in the adolescents.

Atopy 2 (food or drug allergies) were reported in 9,548 (8.0%) of the total cohort, with the highest prevalence in the youngest group at 5,561 (9.0%), and only 1,643 (6.5%) in the adolescents.

Passive smoking exposure was consistent across groups at approximately 2%, with 2,503 (2.1%) of the total cohort. Active smoking was reported by 4,225 (3.5%) of the total cohort, considerably more common in adolescents, 2,628 (10.4%), compared to 1,597 (5.0%) in the 9-11.9 group.

A small proportion of the cohort, 5,308 (4.4%), experienced an exacerbation around the time of their diagnosis (30 days before or on the day of diagnosis). Of these, 3,620 (3.0%) were GP-managed and 1,688 (1.4%) were hospital-managed. Both occurred more often in the younger children, 3.5% of the youngest had GP-managed and 1.9% had hospital-managed exacerbations and decreased with age.

### ***In the year preceding asthma diagnosis***

Breathlessness was reported by 8,650 (7.2%) of the cohort, with increasing prevalence in older groups, affecting 2,941 (11.6%) of adolescents. Wheeze or chest tightness was more common in the youngest group at 8,592 (13.9%), decreasing with age, only 9.5% of adolescents reported wheeze/chest tightness to their GP practice. Cough was reported by 41,767 (34.9%) of children, most prevalent in the youngest group at 24,703 (39.9%) but still of high prevalence even in adolescents, of whom just over a quarter reported cough (26.5%).

At least one short course of OCS was administered to 6,403 (5.3%) of the cohort before their formal documentation of their asthma diagnosis in their healthcare records, with the highest frequency of prescriptions in the youngest group at 4,269 (6.9%), and lowest in the adolescents, 777 (3.0%). Unscheduled hospital visits coded as asthma occurred in 1,542 (1.3%)

of the cohort, again most commonly in the youngest group at 1,134 (1.8%) and least common in the adolescents, 134 (1.2%).

Table 3. 1: Baseline characteristics and pre-diagnosis events by age groups

| CHARACTERISTICS                                       | Total<br>N (%)        | 5-8.9 years<br>N (%) | 9-11.9 years<br>N (%) | Adolescents<br>N (%) |
|-------------------------------------------------------|-----------------------|----------------------|-----------------------|----------------------|
| <b>TOTAL</b>                                          | N=119,611<br>(100.0%) | N=61,940<br>(51.8%)  | N=32,316<br>(27.7%)   | N=25,355 (21.2%)     |
| <b>Age at diagnosis (years)</b>                       | 9.7 (3.4)             | 6.8 (1.2)            | 10.4 (0.9)            | 13.7 (1.7)           |
| <b>Males</b>                                          | 65,886 (55.1%)        | 36,514 (58.9%)       | 17,868 (55.2%)        | 11,504 (45.3%)       |
| <b>Females</b>                                        | 53,725 (44.9%)        | 25,426 (41.1%)       | 14,448 (44.8%)        | 13,851 (54.7%)       |
| <b>BMI</b>                                            |                       |                      |                       |                      |
| Normal                                                | 52,668 (44.1%)        | 26,341 (42.5%)       | 14,229 (44.0%)        | 12,098 (47.7%)       |
| Overweight                                            | 11,367 (9.5%)         | 4,419 (7.1%)         | 3,703 (11.4%)         | 3,245 (12.8%)        |
| Obese                                                 | 7,575 (6.3%)          | 3,065 (4.9%)         | 2,471 (7.6%)          | 2,039 (8.0%)         |
| Missing                                               | 48,001 (40.1%)        | 28,115 (45.5%)       | 11,913 (37.0%)        | 7,973 (31.5%)        |
| <b>IMD (socioeconomic deprivation)</b>                |                       |                      |                       |                      |
| 1 (least deprived)                                    | 22,880 (19.1%)        | 11,548 (18.6%)       | 6,420 (19.9%)         | 4,912 (19.4%)        |
| 2                                                     | 21,567 (18.0%)        | 11,083 (17.9%)       | 5,757 (17.8%)         | 4,719 (18.6%)        |
| 3                                                     | 21,433 (17.9%)        | 10,962 (17.7%)       | 5,752 (17.8%)         | 4,719 (18.6%)        |
| 4                                                     | 25,100 (21.0%)        | 13,143 (21.2%)       | 6,763 (20.9%)         | 5,194 (20.5%)        |
| 5                                                     | 28,631 (24.0%)        | 15,204 (24.5%)       | 7,624 (23.6%)         | 5,803 (22.9%)        |
| <b>Atopy 1</b>                                        | 20,348 (17.1%)        | 8,616 (14.0%)        | 6,308 (19.6%)         | 5,424 (21.4%)        |
| <b>Eczema</b>                                         | 40,814 (34.1%)        | 23,108 (37.3%)       | 10,651 (33.0%)        | 7,055 (27.8%)        |
| <b>Atopy 2</b>                                        | 9,548 (8.0%)          | 5,561 (9.0%)         | 2,344 (7.3%)          | 1,643 (6.5%)         |
| <b>Passive smoking</b>                                | 2,503 (2.1%)          | 1,292 (2.1%)         | 726 (2.3%)            | 486 (2.0%)           |
| <b>Smoking</b>                                        | 4,225 (3.5%)          | NA                   | 1,597 (5.0%)          | 2,628 (10.4%)        |
| <b>Exacerbation at the time of diagnosis</b>          |                       |                      |                       |                      |
| No                                                    | 114,303 (95.6%)       | 58,560 (94.5%)       | 31,102 (96.0%)        | 24,641 (97.1%)       |
| GP managed exacerbation                               | 3,620 (3.0%)          | 2,178 (3.5%)         | 889 (2.7%)            | 553 (2.1%)           |
| Hospital managed exacerbation                         | 1,688 (1.4%)          | 1,202 (1.9%)         | 325 (1.0%)            | 161 (0.6%)           |
| <b>Reported symptoms in the year before diagnosis</b> |                       |                      |                       |                      |

|                                                   |                |                |                |               |
|---------------------------------------------------|----------------|----------------|----------------|---------------|
| Breathlessness                                    | 8,650 (7.2%)   | 2,954 (4.8%)   | 2,755 (8.5%)   | 2,941 (11.6%) |
| Wheeze/chest tightness                            | 14,532 (13.2%) | 8,592 (13.9%)  | 3,536 (11.0%)  | 2,404 (9.5%)  |
| Cough                                             | 41,767 (34.9%) | 24,703 (39.9%) | 10,347 (31.9%) | 6,717 (26.5%) |
| <b>Exacerbations in the year before diagnosis</b> |                |                |                |               |
| GP-managed ( $\geq 1$ )                           | 6,403 (5.3%)   | 4,269 (6.9%)   | 1,357 (4.2%)   | 777 (3.0%)    |
| Hospitalised                                      | 1,542 (1.3%)   | 1,134 (1.8%)   | 273 (0.8%)     | 134 (1.2%)    |

*BMI = body mass index, OCS = oral corticosteroids, IMD = Index of Multiple Deprivation, GP = general practitioner. Atopy 1 includes hay fever, allergy to pollen, pets of house dust mite. Atopy 2 includes food and drug allergies.*

### 3.4.2 Asthma medication in the first two years after diagnosis

#### 3.4.2.1 Proportion of children receiving each medication (Figure 3.7)

5-8.9 years age group: Most received asthma medication soon after their diagnosis. Very low-dose ICS was the most prescribed medication, 23,813 children (38.5%), followed by low-dose ICS, which was prescribed to 16,550 children (26.7%). Only 1,198 children (1.9%) of children received a prescription for medium-dose ICS. High-dose ICS was the least common therapy, used by only 105 children (0.2%).

SABA alone was prescribed to 7,869 children (12.7%). Only 0.1% were prescribed LTRA alone.

Some children were prescribed ICS plus an add-on asthma therapy, either LTRA or LABA. 4,409 children (7.1%) received a combination of very low-dose ICS with an add-on therapy. Low-dose ICS combined with an add-on was administered to 4,443 children (7.2%). 1,322 children (2.1%) received medium-dose ICS with an add-on.

Other therapies were reported in 583 children (0.9%) and only 1,648 (2.7%) did not receive any treatment.

9-11.9 years age group: Treatment patterns varied from the youngest age group in terms of the proportion receiving the lower doses of ICS. Very low-dose ICS was prescribed to 8,226 children (25.4%), but more children, 10,968 (33.9%) were prescribed low-dose ICS. Medium-

dose ICS was used by 1,247 children (3.9%). High-dose ICS was administered to only 152 children (0.5%).

SABA alone was used by 5,813 children (18.1%). Only 0.07% were prescribed LTRA alone.

Very low-dose ICS with an add-on was given to 1,231 children (3.8%), and low-dose ICS with an add-on to 2,341 children (7.2%). 1,214 children (3.8%) received medium-dose ICS with an add-on.

Other therapies were used in 242 children (0.7%) and 882 children (2.7%), did not receive any treatment.

Adolescent age group (12-15.9 years): In this group the prescription patterns shifted more towards higher doses. Low-dose ICS was the most frequently prescribed, with 9,189 children (36.2%) but very low-dose ICS was prescribed for 3,487 children (13.8%). Medium-dose ICS was used by 2,120 children (8.4%), and high-dose ICS was prescribed to 406 children (1.6%).

SABA alone was prescribed to 5,031 children (19.8%). Only 0.07% were prescribed LTRA alone.

Very low-dose ICS with an add-on was uncommon, with 517 children (2.0%) receiving this prescription. Low-dose ICS with an add-on was prescribed to 1,571 children (6.2%) and 1,997 children (7.9%) received medium-dose ICS with an add-on.

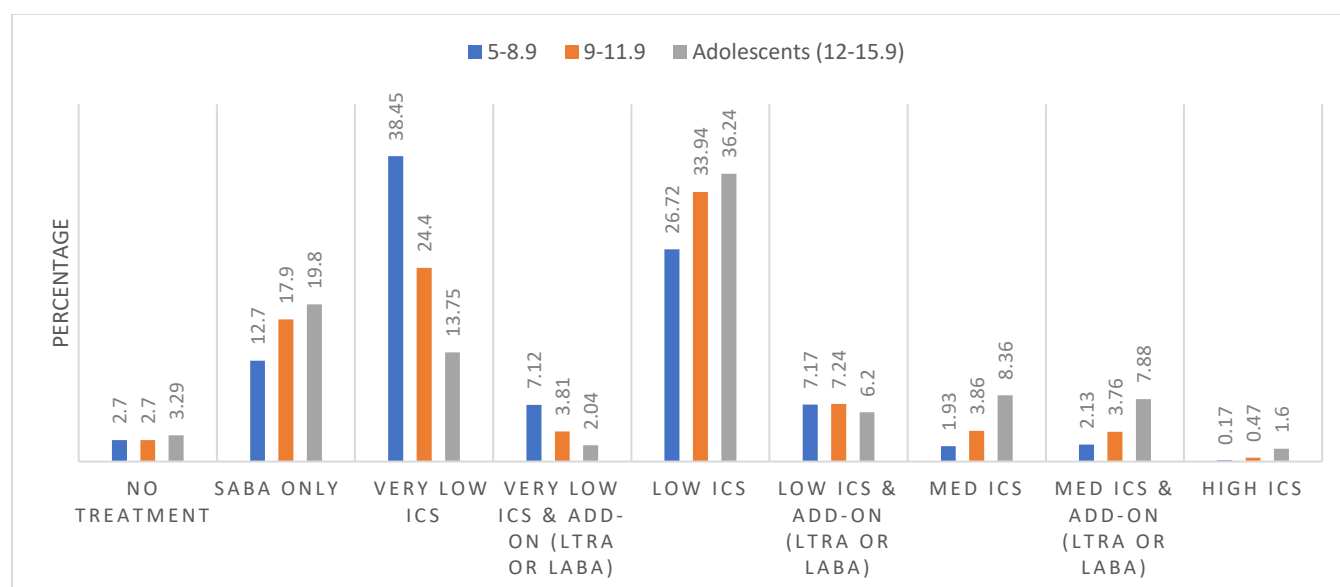
Other therapies were reported in 202 children (0.8%) and 835 children (3.3%), did not receive any treatment.

Across the whole cohort: Among children prescribed medium- or high-dose ICS, 58.2% received this higher dose as their first ever ICS prescription.

For those prescribed SABA inhalers, 64.5% were prescribed SABA either simultaneously with or after starting their ICS inhalers. 35.5% received a SABA inhaler on average of 124 days (IQR 37-312) before their ICS treatment.

For children with an exacerbation post-diagnosis, 21% had not been prescribed any ICS either before the event or within the first month following the exacerbation.

Figure 3. 2: Asthma medication within 2 years after diagnosis by age group



ICS = inhaled corticosteroids, LTRA = leukotriene receptor antagonists, LABA = long-acting beta-agonists, SABA = short-acting beta-agonists

### 3.4.2.2 Number of ICS inhalers prescribed

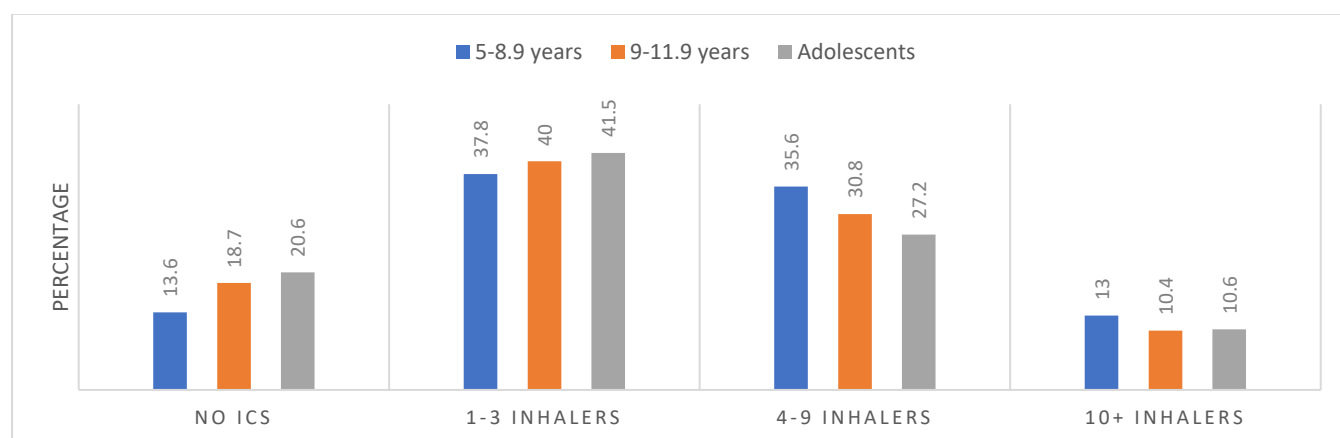
In all age groups, over one-third of children were prescribed 1-3 inhalers during the first two years after their asthma diagnosis, and around another third were prescribed 3-9 inhalers.

5-8.9 years age group: 8,440 children (13.6%) did not receive any ICS treatments within the two-year follow up period (figure 3.3). Of those prescribed ICS, most were prescribed 1-3 inhalers (23,439 children or 37.8%) or 4-9 inhalers (22,036 children or 33.6%) but some were prescribed 10 or more inhalers over the two years (8,025 children or 13.0%).

9-11.9 years age group: 6,050 children (18.7%) were not prescribed any ICS treatment (figure 3.3). Of those prescribed ICS, most were prescribed 1-3 inhalers (12,934 children or 40.0%) and 4-9 inhalers (9,966 children or 30.8%), while 3,366 children (10.4%) were prescribed 10 or more inhalers.

Adolescents group: Nearly a quarter of adolescents did not receive an ICS within two years of their diagnosis (5,228 children or 20.6% (figure 3.3). Of those prescribed ICS, most were prescribed 1-3 inhalers (10,534 children or 41.5%), though fewer received 4-9 inhalers (6,893 children or 27.2%) and 2,700 (10.6%) adolescents were prescribed 10 or more inhalers.

Figure 3. 3: Number of ICS prescriptions by age category



ICS = inhaled corticosteroids

### 3.4.2.3 Number of SABA inhalers prescribed

In all age groups, the majority of children were prescribed 1-3 inhalers during the study period.

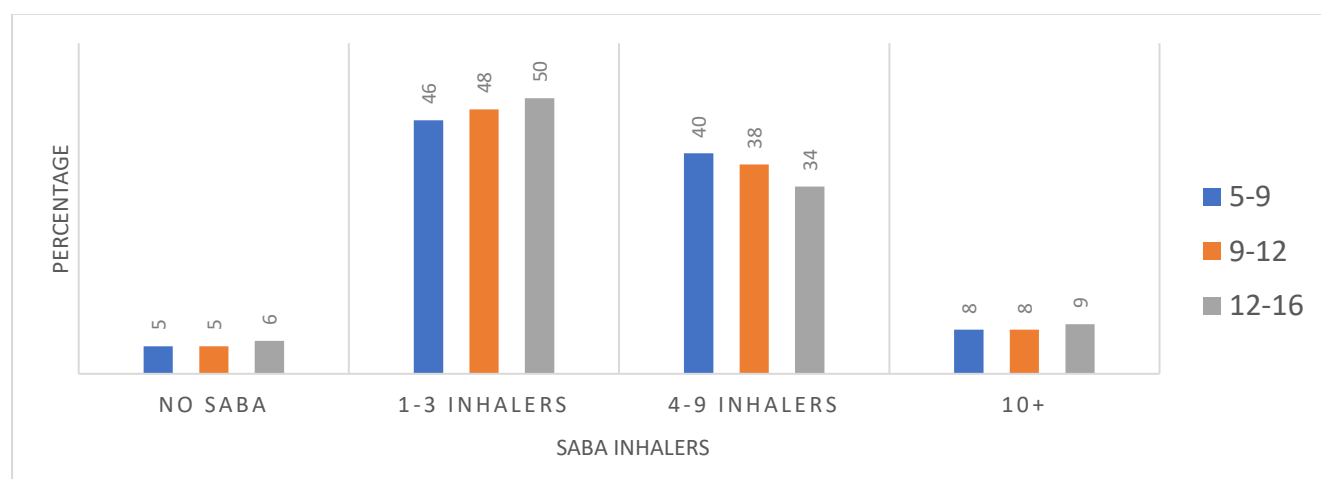
5-8.9 years age group: 5.34% (3,305 children) received no inhalers (Figure 3.4). The majority (46.2%, or 28,616 children) were prescribed 1-3 inhalers, while 39.91% (24,718 children) were given 4-9 inhalers. A smaller proportion, 8.56% (5,301 children), were prescribed 10 or more inhalers.

9-11.9 years age group: 5.26% (1,701 children) did not receive any inhalers (Figure 3.4). Most children, 47.84% (15,460), were prescribed 1-3 inhalers, while 38.35% (12,394) received 4-9 inhalers, and 8.54% (2,761) were prescribed 10 or more inhalers.

Adolescents group: 6.22% (1,577 children) did not receive any inhalers (Figure 3.4). A larger proportion, 50.53% (12,812 children), received 1-3 inhalers, while 34.3% (8,697 children) were prescribed 4-9 inhalers and 8.95% (2,269 children) were prescribed 10 or more.

Overall, across all groups, most children received between 1 and 3 inhalers (47.56%), followed by those prescribed 4-9 inhalers (38.30%), and a smaller proportion were prescribed 10 or more inhalers (8.64%). Only 5.5% of children did not receive any inhalers.

Figure 3. 4: Number of SABA prescriptions by age category

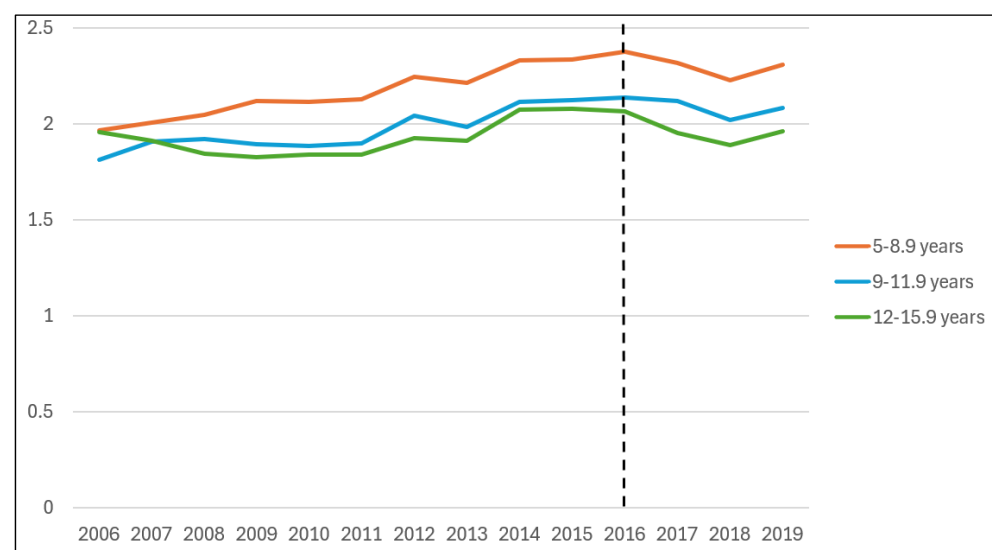


SABA = short-acting beta-agonists

#### 3.4.2.4: Annual rate of SABA prescriptions

SABA prescription rates have been slowly increasing since 2006, with the steepest rise in the youngest age group, which also had the overall highest annual average SABA rates (Figure 3.5). After the 2016 BTS/SIGN guideline update (to reduce reliance on SABA and promote the use of ICS as first-line treatment), the rates of SABA prescriptions started to fall.

Figure 3. 5: Annual average SABA prescription rate.



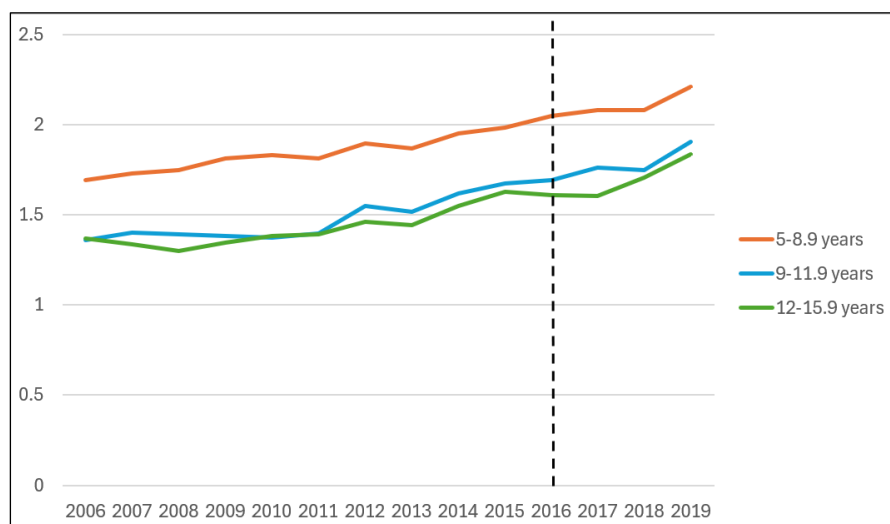
Dotted lined indicates year the guidelines changed.

#### 3.4.2.5: Annual rate of ICS prescriptions

There has been a steady increase in ICS prescriptions in all three age groups which continued to keep rising after the new guidelines were introduced (**Error! Reference source not found.**).

As seen before, the youngest group had the highest ICS prescription rate, which reached an average of 2 per child per year in 2016, as compared to 1.6-1.7 in the two older age groups.

Figure 3. 6: Annual average ICS prescription rate.



Dotted lined indicates year the guidelines changed.

### 3.4.2.6: Comparing children with and without a recorded BMI

As there was a large number of children with missing BMI, I wanted to compare them to those with a recorded BMI, to determine if there were factors explaining this phenomenon. There was a subtle difference in age between the two groups (Table 3.2). Children with missing BMI values were slightly younger, with a mean age of 8.7 years, compared to 9.6 years for those with a recorded BMI. But the two groups were very similar in terms of gender, socioeconomic status, atopy, smoking and exacerbation history and respiratory symptoms. There were minor differences in symptoms reporting, children without BMI reported breathless and wheeze slightly less often but reported cough slightly more often.

Overall, there were no clear factors from the variables included that explained why a large number of children did not have a documented BMI in their medical records.

Table 3. 2: Comparison of characteristics between the children with and without a recorded BMI

| Baseline Characteristics | Total   | Missing BMI | Recorded BMI |
|--------------------------|---------|-------------|--------------|
| Total                    | 119,611 | 48,001      | 71,610       |

|                                                    |               |              |              |
|----------------------------------------------------|---------------|--------------|--------------|
| <b>Age at diagnosis (years)</b>                    | 9.2 (3.0)     | 8.7 (2.9)    | 9.6 (3.0)    |
| <b>Gender</b>                                      |               |              |              |
| Male                                               | 65,886 (55%)  | 27,108 (56%) | 38,778 (54%) |
| Female                                             | 53,725 (45%)  | 20,893 (44%) | 32,832 (46%) |
| <b>Age category at diagnosis</b>                   |               |              |              |
| 5-8.9 years                                        | 61,940 (52%)  | 28,115 (59%) | 33,825 (47%) |
| 9-11.9 years                                       | 32,316 (27%)  | 11,913 (25%) | 20,403 (28%) |
| 12-16 years                                        | 25,355 (21%)  | 7,973 (17%)  | 17,382 (24%) |
| <b>IMD (socioeconomic deprivation)</b>             |               |              |              |
| 1 (Least deprived)                                 | 22,880 (19%)  | 9,750 (20%)  | 13,130 (18%) |
| 2                                                  | 21,567 (18%)  | 8,821 (18%)  | 12,746 (18%) |
| 3                                                  | 21,433 (18%)  | 8,744 (18%)  | 12,689 (18%) |
| 4                                                  | 25,100 (21%)  | 9,748 (20%)  | 15,352 (21%) |
| 5                                                  | 28,631 (24%)  | 10,938 (23%) | 17,693 (25%) |
| <b>Atopy 1</b>                                     | 20,348 (17%)  | 7,943 (17%)  | 12,405 (17%) |
| <b>Eczema</b>                                      | 40,814 (34%)  | 16,525 (34%) | 24,289 (34%) |
| <b>Atopy 2</b>                                     | 9,548 (8%)    | 3,627 (8%)   | 5,921 (8%)   |
| <b>Passive smoking</b>                             | 2,503 (2%)    | 879 (2%)     | 1,624 (2%)   |
| <b>Exacerbation at the time of diagnosis</b>       |               |              |              |
| None                                               | 114,303 (96%) | 45,895 (96%) | 68,408 (96%) |
| GP managed                                         | 3,620 (3%)    | 1,382 (3%)   | 2,238 (3%)   |
| Hospital managed                                   | 1,688 (1%)    | 724 (2%)     | 964 (1%)     |
| <b>Symptom reporting one year before diagnosis</b> |               |              |              |
| Breathlessness                                     | 8,650 (7%)    | 2,902 (6%)   | 5,748 (8%)   |
| Wheeze/chest tightness                             | 14,532 (12%)  | 5,315 (11%)  | 9,217 (13%)  |
| Cough                                              | 41,767 (35%)  | 17,157 (36%) | 24,610 (34%) |
| <b>Exacerbations in year before diagnosis</b>      |               |              |              |
| None                                               | 111,667 (93%) | 44,861 (93%) | 66,806 (93%) |
| GP managed                                         | 6,403 (5%)    | 2,529 (5%)   | 3,874 (5%)   |
| Hospital managed                                   | 1,541 (1%)    | 611 (1%)     | 930 (1%)     |

*BMI = body mass index, OCS = oral corticosteroids, IMD = Index of Multiple Deprivation, GP = general practitioner. Atopy 1 includes hay fever, allergy to pollen, pets of house dust mite. Atopy 2 includes food and drug allergies.*

### 3.5 Discussion

This chapter provides a comprehensive overview of the baseline characteristics and pharmacological management of a population-based cohort of school-aged children, categorised by three age groups, based broadly on the ages used in clinical guidelines for asthma management [85].

As expected, the prevalence of asthma was higher among boys in the younger age groups (5-12 years) but shifted towards a higher prevalence in girls during adolescence. This trend echoes findings from multiple other global and national studies reporting a shift in sex prevalence balance around the time of puberty [1, 16].

An increase in BMI was observed with age, with approximately 40% of children aged 12-15.9 years classified as overweight or obese, which aligns with national statistics across all UK children [86]. This is important as obesity, a modifiable risk factor, has been associated with an increased risk of developing asthma and higher rates of adverse outcomes, with some studies suggesting obese children have up to a one-third higher risk of developing asthma compared to non-obese children [87]. Therefore, it is of particular concern that around 40% of children did not have any BMI documented in their medical records, both for their asthma and their general health. The youngest children were least likely to have their weight documented, 45% of all children aged 5-9 years, presenting a missed opportunity to engage with families regarding education on healthy eating and exercise. Current guidelines suggest monitoring the height and weight of children with asthma but the new proposed NICE/BTS guidelines currently in consultation, suggest removing this aspect as *'Monitoring growth is part of management of all chronic childhood diseases.'* However, if children are not having this simple test recorded even when included in the guidelines of the most common chronic childhood disease, this number is sadly likely to fall further. With obesity a growing epidemic in children, removing this cost-effective, simple, clinical activity appears to be unnecessary and unwise.

Comorbidity of atopy including eczema and atopy 1 (aeroallergen sensitisation), were reported in around half of the children across all age groups at the time of diagnosis. The Global Asthma Network (GAN) phase I study, which reported prevalence rates for asthma, rhinoconjunctivitis and eczema found approximately one in ten children suffer with ever having diagnosis of asthma and similar proportion for rhinoconjunctivitis and eczema [88]. The prevalence of atopy in my study is much higher, likely reflecting the asthma population instead of all children, as the GAN study found there was a moderate to strong rank correlation between asthma prevalence and hay fever (0.29, CI 95% 0.23-0.69), and asthma and rhinoconjunctivitis (0.75, CI 95% 0.57-0.92) [88]. In my study atopy was reported before their asthma diagnosis, and there is some evidence suggesting that asthma may progress from the upper to the lower respiratory tract [89-92], potentially due to rhinitis-induced nasal dysfunction which can impair the nasal cavity's filtration, warming, and humidification functions, leading to bronchospasm and bronchial hyperresponsiveness [93-95].

A significant finding from a large UK study found that approximately 40% of UK children diagnosed with asthma were not prescribed an ICS, pointing towards potential suboptimal treatment [29]. The higher prevalence of ICS prescriptions in my cohort, around 80-85% of children, likely reflects the different variable definition that children had a two-year window in which to use an ICS, and it was within the first two years of diagnosis (the previous study could be at any time point and only included one year follow up). As per guideline recommendations [78], younger children should be prescribed lower doses of ICS, which is compatible with my findings that children in the youngest group were generally prescribed very low-dose ICS, whereas older children were more often prescribed low-dose ICS. However, it is concerning that so many children were prescribed ICS doses that are too high and that many were prescribed them as their first ICS dose, suggesting a possible lack of understanding regarding the differences in doses between children and adults in some GP practices. Interestingly, 20% of the oldest children were managed with SABA alone, indicating a deviation from ideal management practices as outlined in national guidelines [78]. However, ICS prescription rates have encouragingly been increasing year on year, particularly since the guidelines introduction, and SABA prescriptions appear to have at least plateaued. Yet one in five children managed only with reliever medication could still be considered as unacceptably high. The lack of ICS prescriptions in this group could be due to unawareness of guideline

recommendations by healthcare professionals, or due to patient preference and lack of education on the benefits of ICS use alongside reliever use.

Approximately one-third of children had reported a cough to their GP before being diagnosed with asthma. Less frequently documented symptoms included wheeze/chest tightness (slightly more than 10%) and breathlessness (slightly less than 10%). Some children received prescriptions for oral corticosteroids (OCS) or had unscheduled hospital visits for asthma, yet they did not have formal documentation of an asthma diagnosis in their primary care medical records. This issue of delayed diagnosis was particularly prevalent among the youngest children, with nearly 10% receiving OCS without an asthma diagnosis. Such delays in diagnosis could lead to inadequate management, such as the absence of regular reviews, structured asthma management plans, or relevant education, thereby missing critical opportunities to prevent further unnecessary OCS use. Notably, pre-diagnosis use of OCS emerged as a significant risk factor for future exacerbations, mirroring observations in adult populations [96, 97]. The apparent delay in diagnosis may be due to a reluctance to label children as having asthma. This was seen in a previous study where the label of asthma was increasingly not used over 10 years in healthcare records of children with wheeze under 5 years old[29].

Regarding smoking and passive smoking, these factors are well-documented risks for the development of asthma and exacerbation of its symptoms. Extensive research, including a comprehensive review of 79 prospective studies and a multi-national study from Europe and North America, has demonstrated the enduring impact of prenatal and postnatal tobacco smoke exposure on respiratory function in school-aged children [98, 99], significantly increasing the incidence of asthma by at least 20% [98]. Despite low recorded rates of passive smoking in my data, it is likely underreported due to the reluctance of families to disclose exposure and the lack of routine inquiries by healthcare providers. This study perhaps most usefully demonstrates the poor recording of such critical information in asthma care, as due to the high risk of misclassification interpretation of its frequency is somewhat limited.

### 3.6 Strength and limitations

While this analysis benefits from a large, unselected cohort that reflects real clinical practice, it is not without limitations many of which are inherent to most observational studies. One such limitation is the potential misclassification of asthma. To mitigate this, I included only

children who had been coded with asthma twice within two years. Despite these efforts, the absence of objective testing available to an average GP practice data might limit the robustness of the asthma diagnoses. Nevertheless, over 70% of the cohort had undergone some form of airflow measurement—primarily peak flow and to a lesser extent, spirometry—around the time of their diagnosis. Our reliance on patient and physician reports for allergy variables, coupled with limited data on whether sensitisation tests were performed, may have affected the reliability of these variables. For instance, it is likely hay fever was less commonly reported if the child had lower symptom burden. As discussed above, if a variable was not coded it was presumed not present, which may have led to misclassification, particularly for smoking, and comorbidities with milder symptoms. Passive smoking and smoking could also be subjected to social desirability bias, as well as relying on the healthcare professional to ask about these exposures.

Another limitation of this type of data is where values are missing or poorly recorded. Missingness was especially problematic for BMI, however, the lack of recording was in itself informative. The huge amount of missing data on recording of asthma control questionnaire scores, which may indicate the lack of use of such questionnaires, or the lack of recording, prevented the inclusion of these scores in the study. Due to the poor quality of ethnicity reporting in CPRD at the time of the data collection, I did not include this variable. Finally, while this study provides insights into the prescriptions written for asthma management, it doesn't confirm whether these prescriptions were dispensed or adhered to by patients. This limits the ability to fully understand the effectiveness of prescribed treatments and the level of asthma control as perceived by healthcare professionals. However, just the prescription itself informs us on the intended treatment.

CPRD Aurum does not include free text notes made by healthcare professionals or letters received by GPs from secondary care, which might contain crucial information. For example, written comments on the presence of milder exacerbations, that were not managed with a prescription of oral corticosteroids or unscheduled hospital visit were not able to be included. The A&E data was only collected by CPRD from 2015 onwards, leading to missing data on asthma exacerbation managed solely within A&E before 2015.

### 3.7 Conclusion

This chapter provides a comprehensive characterisation and management of the school-age asthma population in the UK at the time of diagnosis and two years after. I have shown that children's characteristics and management are influenced by the age of their asthma diagnosis. I also highlighted gaps in asthma management, particularly in the prescription practices of ICS and SABA.

Overall, the study underscores the importance of early diagnosis, effective weight management especially for the older age group, and tailored asthma care across different age groups. Addressing socioeconomic factors and improving data collection practices and simple interventions in primary care are important steps to improve asthma outcomes at a national level.

## 4. Chapter 4: Asthma Exacerbation Rates and Risk Factors

### 4.1. Introduction

Asthma remains a significant health challenge in the UK, particularly when compared to other countries. Young people aged 15-19 in the UK have the second-highest asthma-related mortality rate compared to other high-income countries, including Australia, USA and several European countries [100]. NHS England has reported that "the UK has one of the highest prevalence, emergency admission, and death rates for childhood asthma in Europe" [101]. While globally there has been a reduction in hospital admissions for children with asthma, these rates are still disproportionately high among minority ethnic groups and children living in socioeconomically deprived areas [2]. Alarming, in high income countries, children from the most deprived regions are nearly twice as likely to be hospitalized for asthma as those from the least deprived regions, highlighting disparities in healthcare access and outcomes [100]. Financially, asthma care imposes a significant burden on the healthcare system, with costs in England estimated at approximately £900 million annually year [102]. Asthma exacerbations not only place a strain on healthcare resources but also severely impact the quality of life for children and their families [21].

A recent nationwide UK study tracked a cohort of adults over seven years and revealed suboptimal levels of asthma management [72]. One-third of adult patients experienced asthma exacerbations during the study period. Among those exacerbating, half had a sporadic pattern with only one attack over seven years, while the other half experienced recurrent exacerbations with at least one annually [72]. Many adults who frequently experienced exacerbations were treated as having 'mild asthma,' receiving an inadequate level of asthma treatment. Conversely, some adults with no exacerbations were prescribed the highest doses of inhaled corticosteroids, which may have been unnecessary and potentially harmful [72]. The National Review of Asthma Deaths (NARD) reported that 58% of people who died from asthma exacerbations were being treated only as having mild or moderate asthma [34]. Put together, this suggests we often underestimate the degree of asthma severity some patients have. We have much less information regarding exacerbations during childhood, with little granularity on the differences across the age spectrum within school-age [16, 20]. Furthermore, we do not know the impact of some recognised risk factors such as atopy and

obesity within different age categories of school-age [21]. This chapter aims to address this gap by examining asthma exacerbation rates and associated risk factors across different age groups among school-aged children.

## 4.2 Objectives

Objective 1: Determine the incidence of asthma exacerbations by age at diagnosis, using the categories of 5-7.9 years, 8-11.9 years and 12-15.9 years.

Objective 2: Determine the risk factors associated with asthma exacerbations by age of diagnosis, using the same age categorisation as in Objective 1.

## 4.3 Methods

### 4.3.1 Data source

Data were provided by the Clinical Practice Research Datalink, which was described in Chapter 2. Data was individually linked to Hospital Episode Statistics and Office for National Statistics death data.

### 4.3.2 Study design and participants

For this chapter, I used the same cohort described in Chapter 3.

The inclusion criteria for the cohort are summarised as the following:

1. Children identified between January 2004 and January 2021.
2. Aged five years or older at the time of diagnosis.
3. Had two validated asthma codes recorded within a two-year period.
4. Had at least one year of follow-up data prior to study entry.
5. Had one year of follow-up data available post-diagnosis.

The follow-up period was censored at the earliest of the following events:

- Reaching the upper age limit,
- Study end date on January 1, 2022, or
- Data no longer being available.

Each child's asthma diagnosis date was based on the first recorded asthma code in their GP medical record. Participants were categorised by age according to UK asthma management guidelines [8-10], with children aged 5 to 12 years further subdivided into 5 to 8.9 years and 9 to 11.9 years, and adolescents defined as 12 to 15.9 years.

#### 4.3.3 Variables

This section outlines the key variables used in the study, with detailed definitions provided in Chapters 2 and 3.

**Demographic variables:** These included age, gender, BMI and IMD. Other variables included active tobacco smoking and passive smoke exposure

**Comorbidities:** Comorbidities were classified as 'atopy 1' (hay fever, pet allergy, house dust mite allergy), 'atopy 2' (food or drug allergies), and eczema, based on GP record codes. Conditions were considered present if coded before or at the time of their asthma diagnosis.

**Respiratory symptoms:** Symptoms including cough, wheeze/chest tightness, and breathlessness were recorded in the year before diagnosis as binary variables.

**Asthma exacerbation:** Defined as a GP-prescribed short course of oral corticosteroids, A&E visit or hospital admission for asthma. When used as covariates, these were categorised as 'pre-diagnosis', if occurred >30 days before diagnosis, and 'around the time of diagnosis', if occurred from 30 days before and on the day of diagnosis.

**Asthma medications:** Included short-acting beta-agonists (SABA), inhaled corticosteroids (ICS), and additional medications, long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA). ICS doses were categorized by 2019 SIGN/BTS guidelines, with tables for children under and over 12 years old. Doses correlate to, using budesonide equivalence, very low ( $\leq 200$   $\mu\text{g/day}$ ), low (200–400  $\mu\text{g/day}$ ), medium (>400–800  $\mu\text{g/day}$ ) or high ( $\geq 800$   $\mu\text{g/day}$ )

**Outcome:** First asthma exacerbation that occurred after their asthma diagnosis.

#### 4.3.4 Analysis

##### 4.3.4.1 *Descriptive analysis*

Exacerbations were described using incidence rates, Kaplan-Meier methodology and as proportions.

For incidence rates and Kaplan-Meier, I included all longitudinal data up until the censoring date which included their first exacerbation. As this was non-informative censoring, i.e., the reason a child stopped being part of the study was unrelated to their likelihood of having an asthma exacerbation, this prevented bias from censoring [103].

To calculate incidence rates, I divided the total number of exacerbations by the total person-years (time at risk of an exacerbation) for each age category within the cohort.

I applied Kaplan-Meier methodology to graphically display the cumulative probability of time to first exacerbation [104]. I used this approach as it assumes that censored children have the same chance of experiencing an asthma exacerbation as those who continue to be observed. Additionally, it presumes that the probability of an asthma exacerbation is the same for children who joined the study early as those who joined later. By following children only until their first exacerbation, I maintained these assumptions.

To calculate the proportion of children with at least one asthma exacerbation I only included children with the same fixed follow-up period (as I was no longer able to account for varying time of follow-up). I chose a two-year fixed period as this still included a large number of children and goes beyond just the first year after diagnosis. Although interesting to include a longer follow-up period, the number of eligible children that had sufficient data was reduced (by approximately 20%) and therefore would introduce a potential selection bias. In this analysis I also explored where the children's exacerbation was managed, primary care or hospital.

The reason I chose to look at both rates and proportions of exacerbations is that proportions are generally easier to comprehend as this is a more intuitive estimate, meaning my findings are more translatable to a wider audience. However, measuring rates meant I could include

all the children in the analysis (reducing selection bias and increasing the power). This was nicely demonstrated as this work has been published and NIHR Evidence has chosen the publication to report on [105, 106]. NIHR Evidence summarises studies to inform on decisions about health and care. The journalist could easily translate the proportions to a lay audience, but we had to find an easier way for lay people to understand rates.

#### 4.3.4.2 Statistical Analysis

To examine the association between the children's characteristics at asthma diagnosis and the first asthma exacerbation, I used multivariable Cox proportional hazards models. To determine if the proportional hazards assumption held true, I graphically checked the Schoenfeld residuals for each covariate using log-log plots to assess if the residuals were independent of time and were parallel between the exposed and unexposed.

The following variables were included in the multivariable Cox regression models as these were considered *a priori* to potentially be confounding. Two models were constructed:

- Model 1 included baseline characteristics (gender, age at diagnosis, IMD, BMI, smoking status, atopy 1, atopy 2, and eczema).
- Model 2 included additional covariates related to pre-diagnosis factors including symptoms, inhaler prescriptions and exacerbations either before diagnosis or at the time of diagnosis.

Only BMI had missing values, as all other clinical variables were presumed not present if there was no code. The BMI variable had over 30% missing therefore to deal with the large amount of missing data, I used a missingness strata label, i.e., I included children with missing values and noted missing as one of the BMI categories. This allowed the effect of having no BMI recorded also to be evaluated.

I conducted two sensitivity analyses. First, I conducted a complete case analysis to prevent selection bias, as there was so much missing data from BMI, I excluded the BMI variable completely from the models. Second, I repeated Model 2 and included all exacerbations during follow-up, not just the first exacerbation. To measure the association between the

children's characteristics and all exacerbations I used Cox proportional hazards model with an Andersen-Gill extension.

## 4.4 Results

### 4.4.1 Exacerbation incidence

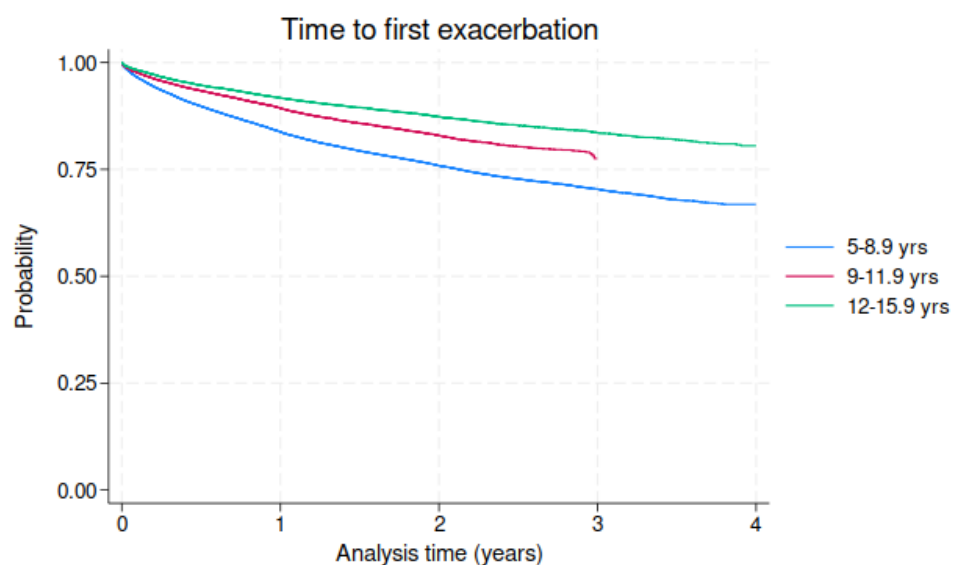
The highest rate of exacerbations was observed in the youngest age group (5-8.9 years), with an incidence rate of 1.61 per 10 person-years (95% CI: 1.58-1.63; Table 4.1). In the 9-11.9 years age group, the rate of exacerbations was 1.07 per 10 person-years (95% CI: 1.04-1.09). The lowest exacerbation rate was found in the adolescent group (12-15.9 years), with an incidence of 0.82 per 10 person-years (95% CI: 0.79-0.84).

*Table 4. 1: Rate of post-diagnosis exacerbations across the age groups*

| Age categories |                                   |              |                                   |             |                                   |
|----------------|-----------------------------------|--------------|-----------------------------------|-------------|-----------------------------------|
| 5-8.9 years    |                                   | 9-11.9 years |                                   | 12-16 years |                                   |
| N              | Rate per 10 person-years (95% CI) | N            | Rate per 10 person-years (95% CI) | N           | Rate per 10 person-years (95% CI) |
| 61,940         | 1.61<br>(1.58-1.63)               | 32,316       | 1.07<br>(1.04-1.09)               | 25,355      | 0.82<br>(0.79-0.84)               |

The Kaplan-Meier graph shows that the youngest children (5 - 8.9 years) had the shortest time to their first exacerbation, followed by the next youngest (9 - 11.9 years); Figure 4.1. For example, by 2 years after diagnosis, there was 25% probability that the youngest children in the cohort would have an asthma exacerbation but only a 13% probability that 12-15.9 years old would experience one. The median time to first exacerbation was greater than 4 years for all children as can be seen in the graph.

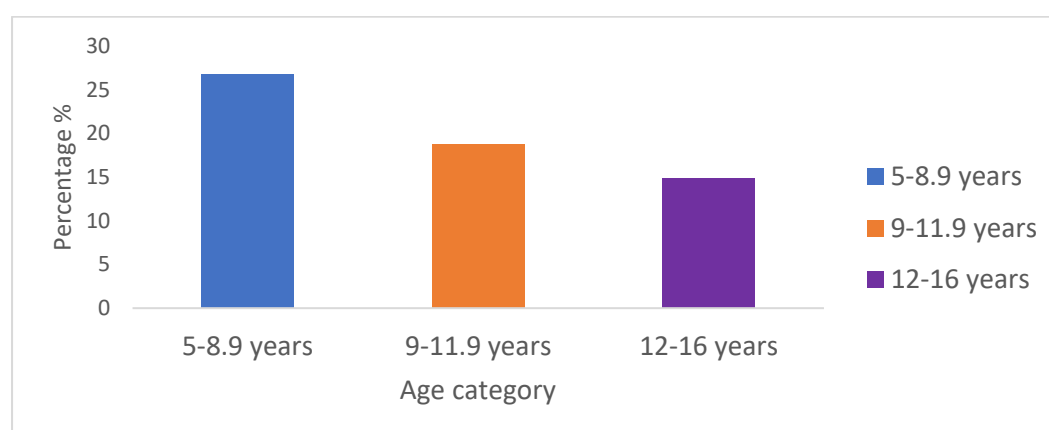
Figure 4. 1: Rate to first exacerbation by age group



#### 4.4.2 Proportion of children with an asthma exacerbation (fixed two-year follow-up)

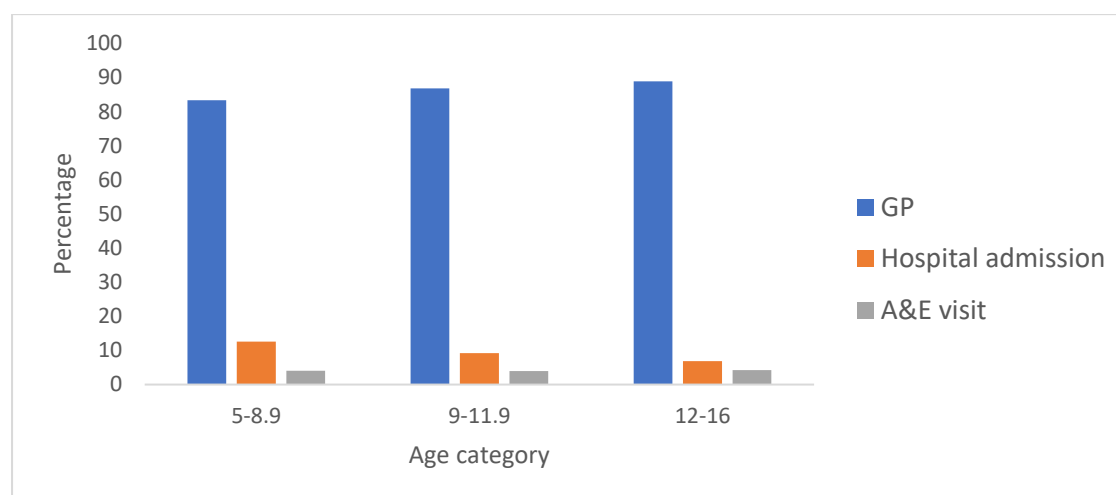
119,611 children had at least two years of follow-up. Of these children, 21.7% experienced an asthma exacerbation within the first two years after their diagnosis. Comparing across the age groups, the youngest children had the highest percentage experiencing at least one exacerbation 26.7% of 5-8.9 years old, followed by 18.7% of 9-11.9 years old, and 14.8% of 12-16 years old (**Error! Reference source not found.**)

Figure 4. 2: Bar graph showing the percentage of children with at least one asthma exacerbation in the first two years after diagnosis



At least 80% of all asthma exacerbations were treated in primary care, with a small percentage seen in A&E or admitted to hospital (Figure 4.14). The youngest children had the highest proportion of children admitted to hospital.

Figure 4. 3: Primary and secondary care received by age group.

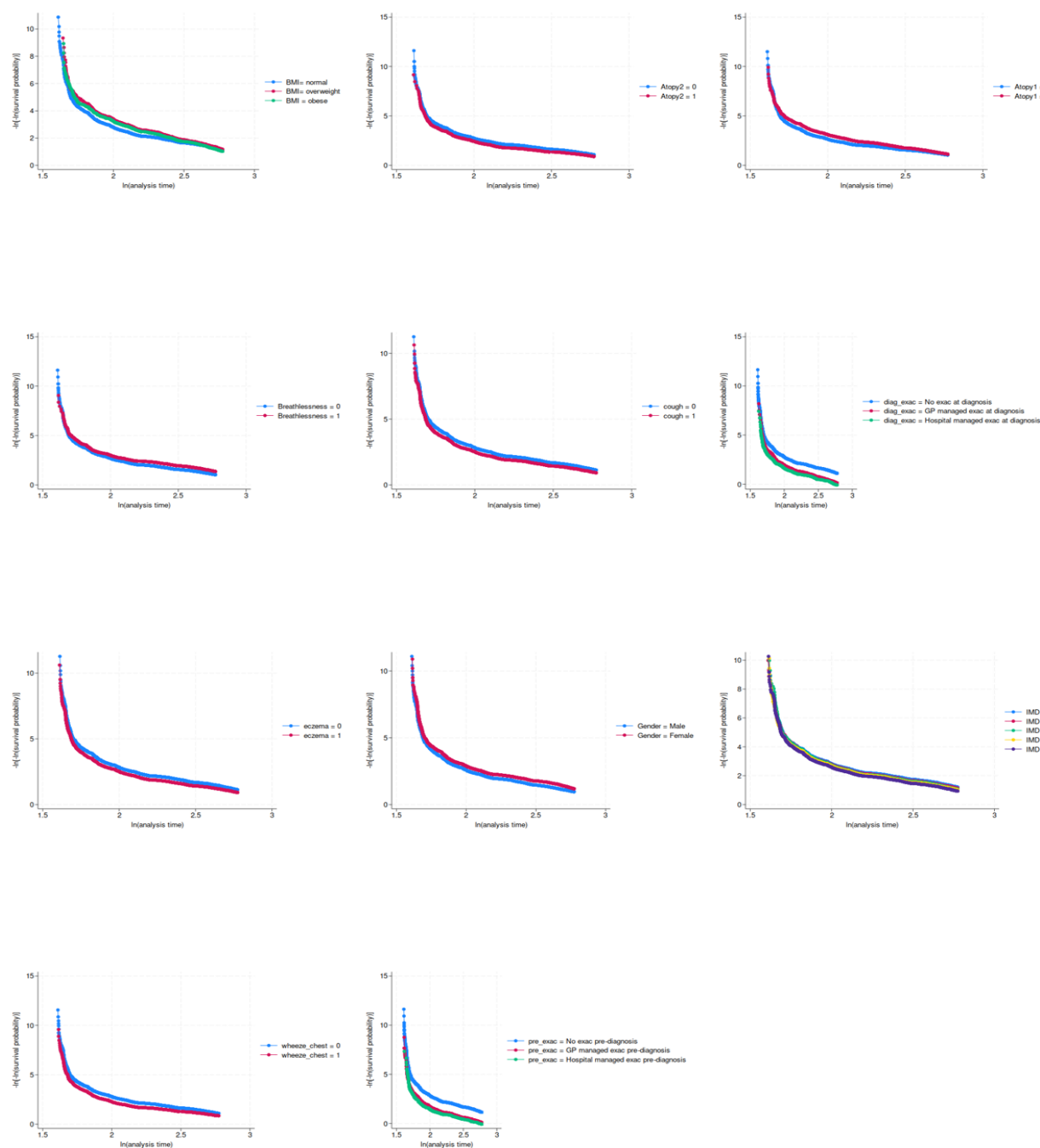


#### 4.4.3 Checking the models meet the proportional hazards assumptions

To ensure the validity of the Cox proportional hazards model, I assessed whether the proportional hazards assumption (that the hazard ratios between groups remain constant over time) held across the covariates (

). This was visually evaluated using log-log survival plots for age, gender, IMD, BMI, atopy1, atopy2, eczema, breathlessness, cough, wheeze, and exacerbation categories. All the plots exhibited parallel and closely aligned curves, indicating the assumption was not violated.

Figure 4. 4: Log-log plots to assess for proportional hazards



The plots are examined to check for closely aligned and parallel lines.

#### 4.4.3 Asthma exacerbation risk factors

##### 4.5.3.1 Events at diagnosis

The results here are reported from model 1 by each age category (**Error! Reference source not found., Error! Reference source not found. & Table 4.4).**

### **Age group: 5-11.9 years**

Several factors were associated with an increased risk of an exacerbation in the youngest children (**Error! Reference source not found., Error! Reference source not found.** & Table 4.4). Factors included socioeconomic deprivation, with children residing in the most deprived quintile associated with 20% increased risk (adjusted HR = 1.24, 95% CI: 1.16-1.34); eczema, which was associated with a 15% increased risk (adjusted HR = 1.15, 95% CI: 1.11-1.19); having atopy 2 (food and drug allergy), which was associated with a 19% increased risk (adjusted HR = 1.19, 95% CI: 1.12-1.26).

Factors associated with a decreased risk of having an exacerbation were being female (adjusted HR = 0.88, 95% CI: 0.85-0.91), older age at diagnosis (adjusted HR = 0.87 for each year, 95% CI: 0.88-0.96), having atopy 1 (hay fever/pet/HDM), adjusted HR = 0.94, 95% CI: 0.83-0.98) and reporting passive smoking (adjusted HR = 0.86, 95% CI: 0.76-0.90).

### **Age group: 9-11.9 years**

In children aged 8.9-11.9 years, socioeconomic deprivation, male gender, eczema and younger age showed similar associations as for the risk factors that were found in the youngest children (**Error! Reference source not found., Error! Reference source not found.** & Table 4.4). However, two additional risk factors in these older children were obesity (adjusted HR = 1.14, 95% CI: 1.02-1.28) and atopy 1 (adjusted HR = 1.10, 95% CI: 1.02-1.28).

Unexpectedly, reporting of active smoking by the child was associated with a decreased risk of having an exacerbation (adjusted HR = 0.926, 95% CI: 0.74-1.13)

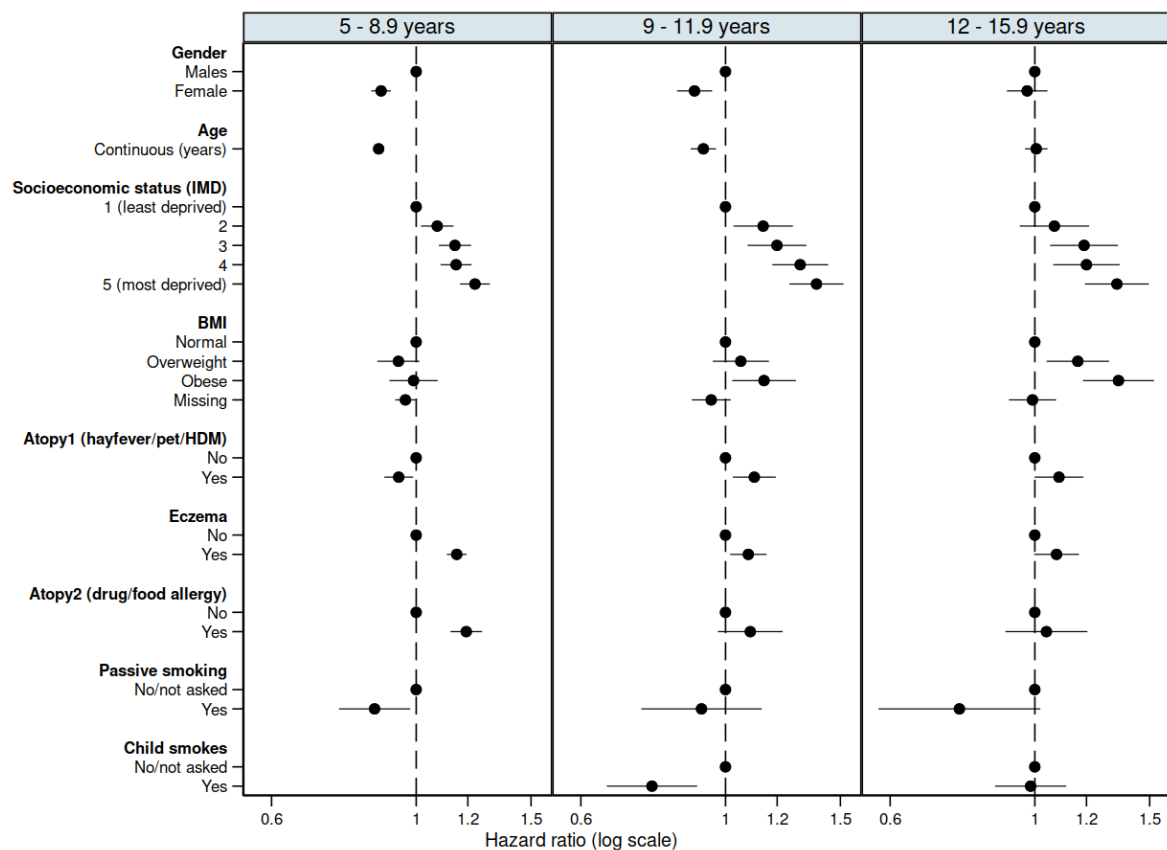
### **Adolescents (12-15.9 years)**

In adolescents, socioeconomic deprivation, atopy 1 (hay fever/pet/HDM) and eczema were again associated with an increased risk of asthma exacerbations (**Error! Reference source not found., Error! Reference source not found.** & Table 4.4). In this age group, being overweight was associated with 16% increased risk of exacerbations (adjusted HR = 1.16, 95% CI: 1.04-1.29), and obese adolescents had a 34% increased risk (adjusted HR = 1.34, 95% CI: 1.18-1.52). However, unlike in the younger children, gender and atopy 2 (food/drug allergy) were no longer associated with exacerbations.

## Comparison across age groups

The risk of exacerbations changed from being higher in younger male children to gender having no association by the time children reached adolescence. A similar pattern was seen with atopy 2 (drug/food allergy) and eczema. Whereas socioeconomic deprivation was consistently strongly associated, regardless of the child's age. Elevated BMI was only associated with an increased risk of exacerbations once children reached around 9 years old.

Figure 4. 5: : Forest plots showing the association between characteristics and first exacerbation by age (Model 1).



BMI=body mass index, IMD = Index of Multiple Deprivation. Atopy 1 indicates hay fever or allergy to pollen, house dust met or pets. Atopy 2 indicates food or drug allergy.

Table 4. 2: Table showing the association between characteristics and first exacerbation by age (multivariable analysis; Model 1).

|                         | 5-8.9 years old  |         |        |      | 9-11.9 years old |         |        |      | Adolescents |         |        |      |
|-------------------------|------------------|---------|--------|------|------------------|---------|--------|------|-------------|---------|--------|------|
|                         | Adj. HR          | p-value | 95% CI |      | Adj. HR          | p-value | 95% CI |      | Adj. HR     | p-value | 95% CI |      |
| <b>Female</b>           | 0.88             | <0.001  | 0.84   | 0.91 | 0.86             | <0.001  | 0.84   | 0.95 | 0.97        | 0.461   | 0.90   | 1.04 |
| <b>Age at diagnosis</b> | 0.87             | <0.001  | 0.85   | 0.89 | 0.92             | <0.01   | 0.88   | 0.96 | 1.07        | 0.810   | 0.96   | 1.04 |
| <b>IMD</b>              |                  |         |        |      |                  |         |        |      |             |         |        |      |
| 1                       | <i>Reference</i> |         |        |      |                  |         |        |      |             |         |        |      |
| 2                       | 1.07             | <0.01   | 1.02   | 1.1e | 1.14             | <0.01   | 1.02   | 1.26 | 1.07        | 0.260   | 0.94   | 1.21 |
| 3                       | 1.13             | 0.003   | 1.04   | 1.21 | 1.19             | <0.01   | 1.08   | 1.33 | 1.18        | <0.01   | 1.05   | 1.34 |
| 4                       | 1.21             | <0.001  | 1.12   | 1.31 | 1.30             | <0.001  | 1.23   | 1.40 | 1.20        | <0.01   | 1.06   | 1.49 |
| 5                       | 1.24             | <0.001  | 1.16   | 1.34 | 1.37             | <0.001  | 1.25   | 1.51 | 1.33        | <0.001  | 1.19   | 1.49 |
| <b>BMI</b>              |                  |         |        |      |                  |         |        |      |             |         |        |      |
| Normal                  | <i>Reference</i> |         |        |      |                  |         |        |      |             |         |        |      |
| Overweight              | 0.93             | 0.081   | 0.86   | 1.00 | 1.05             | 0.286   | 0.95   | 1.16 | 1.16        | <0.01   | 1.04   | 1.29 |
| Obese                   | 0.99             | 0.828   | 0.91   | 1.07 | 1.14             | <0.05   | 1.02   | 1.28 | 1.34        | <0.001  | 1.18   | 1.52 |
| Missing                 | 0.96             | <0.05   | 0.92   | 0.99 | 0.95             | 0.151   | 0.88   | 1.01 | 0.99        | 0.840   | 0.91   | 1.07 |
| <b>Atopy 1</b>          | 0.94             | <0.05   | 0.83   | 0.98 | 1.10             | <0.01   | 1.02   | 1.28 | 1.08        | 0.052   | 0.99   | 1.18 |
| <b>Eczema</b>           | 1.15             | <0.001  | 1.11   | 1.19 | 1.08             | <0.05   | 1.01   | 1.15 | 1.07        | 0.058   | 0.99   | 1.16 |
| <b>Atopy 2</b>          | 1.19             | <0.001  | 1.12   | 1.26 | 1.09             | 0.134   | 0.97   | 1.22 | 1.04        | 0.560   | 0.90   | 1.20 |
| <b>Passive smoking</b>  | 0.86             | <0.05   | 0.76   | 0.97 | 0.92             | 0.433   | 0.74   | 1.13 | 0.76        | 0.682   | 0.57   | 1.01 |
| <b>Active smoker</b>    | NA               | NA      | NA     | NA   | 0.77             | 0.001   | 0.66   | 0.91 | 0.98        | 0.820   | 0.87   | 1.12 |

Each variable shown is adjusted for all the other variables included in the table. Adj. HR = adjusted hazard ratio, BMI=body mass index, IMD = Index of Multiple Deprivation. Atopy 1 indicates hay fever or allergy to pollen, house dust met or pets. Atopy 2 indicates food or drug allergy.

#### 4.4.3.2 Events pre-diagnosis

The results here are reported from model 2 by each age category (**Error! Reference source not found.6, Error! Reference source not found.3** & Table 4.5).

##### Age group: 5-8.9 years

Several factors before diagnosis were associated with the risk of a post-diagnosis asthma exacerbation in the youngest children (**Error! Reference source not found.6, Error! Reference source not found.3** & Table 4.5). Respiratory symptoms such as breathlessness and wheeze reported to the GP practice were both associated with an increased risk (breathlessness, adjusted HR = 1.15, 95% CI: 1.07-1.24; wheeze adjusted HR = 1.16, 95% CI: 1.11-1.21). But experiencing an exacerbation before diagnosis had the strongest association, regardless of where the exacerbation was managed (GP-managed, HR = 2.00, 95% CI: 1.91-2.11; hospital-managed, adjusted HR = 2.15, 95% CI: 1.96-2.36). The prescription of ICS inhalers before diagnosis was associated with 23% increased risk for two ICS (95% CI: 1.14-1.33) and 20% increased risk for three or more ICS (95% CI: 1.14-1.34).

Adding in the additional variables into model 2, did not change the associations found with the covariates already included in the model from model 1.

##### Age group: 9-11.9 years

For children aged 9-11.9 years, the risk factors varied slightly (**Error! Reference source not found.6, Error! Reference source not found.3** & Table 4.5). Breathlessness in the year before diagnosis was associated with a decreased risk of exacerbation (adjusted HR = 0.83, 95% CI: 0.74-0.94), . However, having an exacerbation before diagnosis had the strongest association (GP-managed, adjusted HR = 2.45, 95% CI: 2.21-2.71; hospital-managed, adjusted HR = 2.49, 95% CI: 2.00-3.11). The prescription of two ICS inhalers prior to diagnosis was associated with a 11% increased risk (95% CI: 1.01-1.21) and three or more ICS prescriptions was associated with a 32% increased risk (95% CI: 1.21-1.51).

Adding in the additional variables into model 2, did not change the associations found with the covariates already included in the model from model 1.

##### Adolescents (12-15.9 years)

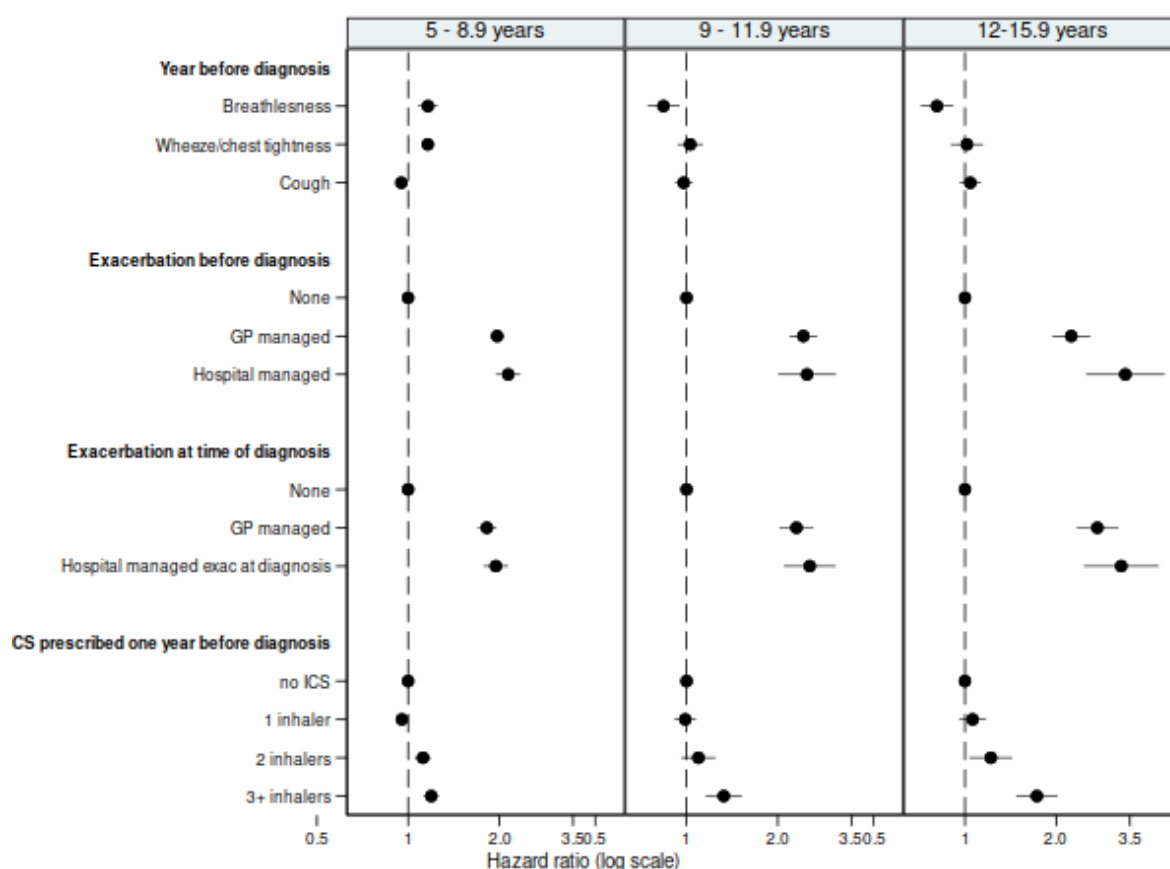
In adolescents, pre-diagnosis breathlessness was associated with reduced risk (adjusted HR = 0.80, 95% CI: 0.72-0.91), and previous exacerbations had the strongest association (GP-managed, adjusted HR = 2.27, 95% CI: 1.96-2.62; hospital-managed, adjusted HR = 3.38, 95% CI: 2.50-4.55; **Error! Reference source not found.**<sup>6</sup>, **Error! Reference source not found.**<sup>3</sup> & Table 4.5). ICS prescriptions prior to asthma diagnosis were also strongly associated with 20% increased risk with two ICS (95% CI: 1.12-1.38) and 71% increased risk with three or more (95% CI: 1.43-2.22).

Adding in the additional variables into model 2, did not change the associations found with the covariates already included in the model from model 1.

### **Comparison across age groups**

Across all age groups, the strongest risk factor for a future exacerbation was receiving treatment for an asthma exacerbation prior to their asthma diagnosis, regardless of whether GP-managed or hospital-managed. Multiple ICS prescriptions prior to diagnosis, which may suggest more severe asthma, were also associated with higher risk of a future exacerbation.

Figure 4. 6: Forest plots showing the association between characteristics and pre-diagnosis events and first exacerbation by age.



Model 2: includes all the variables in Model 1 and the additional variables shown in the plot. ICS=inhaled corticosteroids, GP=General practitioner.

Table 4. 3: Table showing the association between characteristics and pre-diagnosis events and first exacerbation by age (multivariable analysis; Model 2).

|                                                      | 5-8.9 years old |         |            | 9-11.9 years old |         |           | Adolescents |         |           |
|------------------------------------------------------|-----------------|---------|------------|------------------|---------|-----------|-------------|---------|-----------|
|                                                      | Adj. HR         | p-value | 95% CI     | Adj. HR          | p-value | 95% CI    | Adj. HR     | p-value | 95% CI    |
| <b>Respiratory symptoms in year before diagnosis</b> |                 |         |            |                  |         |           |             |         |           |
| Breathlessness                                       | 1.2             | <0.001  | 1.07- 1.24 | 0.8              | 0.004   | 0.74-0.94 | 0.8         | <0.001  | 0.72-0.91 |
| Wheeze                                               | 1.2             | <0.001  | 1.11- 1.21 | 1.0              | 0.573   | 0.93-1.13 | 1.0         | 0.755   | 0.91-1.15 |
| Cough                                                | 1.0             | 0.009   | 0.92- 0.99 | 1.0              | 0.488   | 0.91-1.04 | 1.0         | 0.335   | 0.95-1.12 |
| <b>Exacerbation in year before diagnosis</b>         |                 |         |            |                  |         |           |             |         |           |
| None                                                 | Reference       |         |            |                  |         |           |             |         |           |
| GP managed                                           | 2.0             | <0.001  | 1.91- 2.11 | 2.5              | <0.001  | 2.21-2.71 | 2.3         | <0.001  | 1.96-2.62 |
| Hospital managed                                     | 2.2             | <0.001  | 1.96- 2.36 | 2.5              | <0.001  | 2.00-3.11 | 3.4         | <0.001  | 2.50-4.55 |
| <b>Exacerbation at time of diagnosis</b>             |                 |         |            |                  |         |           |             |         |           |
| None                                                 | Reference       |         |            |                  |         |           |             |         |           |

|                                              |                  |        |            |     |        |           |     |        |           |
|----------------------------------------------|------------------|--------|------------|-----|--------|-----------|-----|--------|-----------|
| GP managed                                   | 1.8              | <0.001 | 1.70- 2.10 | 2.3 | <0.001 | 2.00-2.61 | 2.7 | <0.001 | 2.29-3.16 |
| Hospital managed                             | 1.9              | <0.001 | 1.76- 2.12 | 2.5 | <0.001 | 2.01-2.60 | 3.3 | <0.001 | 2.45-4.33 |
| <b>ICS inhalers in year before diagnosis</b> |                  |        |            |     |        |           |     |        |           |
| None                                         | <i>Reference</i> |        |            |     |        |           |     |        |           |
| 1 inhaler                                    | 1.0              | 0.41   | 0.97- 1.06 | 1.0 | 0.818  | 0.91-1.11 | 1.1 | 0.004  | 1.04-1.26 |
| 2 inhalers                                   | 1.2              | <0.001 | 1.14- 1.33 | 1.1 | 0.176  | 1.01-1.21 | 1.2 | <0.01  | 1.12-1.38 |
| 3+ inhalers                                  | 1.2              | <0.001 | 1.14- 1.34 | 1.3 | <0.005 | 1.21-1.51 | 1.7 | <0.001 | 1.43-2.22 |
| Age at diagnosis                             | 0.9              | <0.001 | 0.87- 0.91 | 0.9 | <0.005 | 0.90-0.98 | 1.0 | 0.447  | 0.94-1.05 |
| Female                                       | 0.9              | <0.001 | 0.86- 0.93 | 0.9 | 0.01   | 0.86-0.98 | 1.0 | 0.447  | 0.94-1.08 |
| <b>IMD</b>                                   |                  |        |            |     |        |           |     |        |           |
| 1                                            | <i>Reference</i> |        |            |     |        |           |     |        |           |
| 2                                            | 1.1              | 0.008  | 1.02- 1.14 | 1.1 | 0.027  | 1.01-1.25 | 1.1 | 0.201  | 1.00-1.20 |
| 3                                            | 1.1              | <0.001 | 1.08- 1.21 | 1.2 | <0.002 | 1.01-1.25 | 1.2 | 0.002  | 1.06-1.35 |
| 4                                            | 1.2              | <0.001 | 1.10- 1.23 | 1.3 | <0.001 | 1.15-1.40 | 1.2 | 0.003  | 1.06-1.34 |
| 5                                            | 1.2              | <0.001 | 1.11- 1.30 | 1.4 | <0.001 | 1.21-1.46 | 1.3 | <0.001 | 1.18-1.48 |
| <b>BMI</b>                                   |                  |        |            |     |        |           |     |        |           |
| Overweight                                   | 1.0              | 0.187  | 0.88- 1.02 | 1.1 | 0.245  | 0.90-1.21 | 1.2 | 0.008  | 1.04-1.29 |
| Obese                                        | 1.0              | 0.778  | 0.90- 1.07 | 1.2 | <0.01  | 1.03-1.29 | 1.3 | <0.001 | 1.04-1.48 |
| Missing                                      | 1.0              | 0.54   | 0.88-1.02  | 1.0 | 0.0254 | 0.96-1.17 | 1.0 | 0.99   | 0.91-1.08 |
| <b>Atopy 1</b>                               | 0.9              | 0.014  | 0.89-0.98  | 1.2 | 0.012  | 1.03-1.29 | 1.1 | 0.105  | 0.98-1.16 |
| <b>Eczema</b>                                | 1.1              | <0.001 | 1.08-1.16  | 1.1 | 0.071  | 0.99-1.13 | 1.1 | 0.113  | 0.98-1.16 |
| <b>Atopy 2</b>                               | 1.2              | <0.001 | 1.08- 1.22 | 1.1 | 0.276  | 0.96-1.19 | 1.0 | 0.676  | 0.89-1.20 |
| <b>Passive smoking</b>                       | 0.9              | 0.053  | 0.77-1.00  | 0.9 | 0.585  | 0.76-1.16 | 0.8 | 0.08   | 0.58-1.03 |
| <b>Smoker</b>                                | NA               | NA     | NA         | 0.8 | 0.002  | 0.66-0.91 | 1.0 | 0.755  | 0.86-1.11 |

Each variable shown is adjusted for all the other variables included in the table. Adj. HR = adjusted hazard ratio, BMI=body mass index, IMD = Index of Multiple Deprivation. Atopy 1 indicates hay fever or allergy to pollen, house dust mites or pets. Atopy 2 indicates food or drug allergy.

Table 4. 4: Univariable analysis of all the variables included in Model 1.

|               | 5-8.9 years old  |         |           | 8-11.9 years old |         |           | Adolescents |         |           |
|---------------|------------------|---------|-----------|------------------|---------|-----------|-------------|---------|-----------|
|               | Crude HR         | p-value | 95% CI    | Crude HR         | p-value | 95% CI    | Crude HR    | p-value | 95% CI    |
| <b>Female</b> | 0.9              | <0.001  | 0.85-0.91 | 0.9              | <0.001  | 0.83-0.94 | 1.0         | 0.397   | 0.90-1.04 |
| <b>Age</b>    | 0.9              | <0.001  | 0.81-0.90 | 0.9              | <0.001  | 0.87-0.96 | 1.0         | 0.775   | 0.96-1.04 |
| <b>IMD</b>    |                  |         |           |                  |         |           |             |         |           |
| 1             | <i>Reference</i> |         |           |                  |         |           |             |         |           |

|                        |                  |        |           |     |        |           |     |        |           |
|------------------------|------------------|--------|-----------|-----|--------|-----------|-----|--------|-----------|
| 2                      | 1.1              | <0.05  | 1.00-1.12 | 1.1 | 0.0014 | 1.02-1.26 | 1.1 | 0.233  | 0.95-1.21 |
| 3                      | 1.1              | <0.001 | 1.07-1.20 | 1.2 | 0.001  | 1.07-1.31 | 1.2 | <0.005 | 1.08-1.36 |
| 4                      | 1.1              | <0.001 | 1.07-1.21 | 1.3 | <0.001 | 1.21-1.41 | 1.2 | <0.001 | 1.21-1.51 |
| 5                      | 1.2              | <0.001 | 1.14-1.27 | 1.4 | <0.001 | 1.24-1.51 | 1.4 | <0.001 | 1.20-1.51 |
| <b>BMI</b>             |                  |        |           |     |        |           |     |        |           |
| Normal                 | <i>Reference</i> |        |           |     |        |           |     |        |           |
| Overweight             | 0.9              | 0.0215 | 0.85-0.98 | 1.0 | 0.2    | 0.90-1.20 | 1.2 | 0.004  | 1.05-1.31 |
| Obese                  | 1.0              | 0.666  | 0.90-1.06 | 1.2 | <0.05  | 1.01-1.30 | 1.4 | <0.001 | 1.22-1.57 |
| Missing                | 1.0              | 0.403  | 0.95-1.02 | 0.9 | 0.164  | 0.91-1.00 | 1.0 | 0.86   | 0.91-1.07 |
| <b>Atopy 1</b>         | 1.0              | 0.14   | 0.91-1.01 | 1.1 | 0.002  | 1.04-1.21 | 1.1 | 0.029  | 1.00-1.20 |
| <b>Eczema</b>          | 1.2              | <0.001 | 1.12-1.29 | 1.1 | 0.005  | 1.02-1.16 | 1.1 | 0.045  | 1.00-1.19 |
| <b>Atopy 2</b>         | 1.2              | <0.001 | 1.20-1.31 | 1.1 | 0.082  | 0.98-1.23 | 1.1 | 0.474  | 0.91-1.21 |
| <b>Passive smoking</b> | 0.9              | 0.029  | 0.76-0.98 | 0.9 | 0.585  | 0.76-1.21 | 0.8 | 0.115  | 0.59-1.05 |
| <b>Smoker</b>          | NA               | NA     | NA        | 0.8 | 0.004  | 0.67-0.92 | 1.0 | 0.947  | 0.88-1.13 |

HR = hazard ratio, BMI=body mass index, IMD = Index of Multiple Deprivation. Atopy 1 indicates hay fever or allergy to pollen, house dust met or pets. Atopy 2 indicates food or drug allergy.

Table 4. 5: Univariable analysis of all the variables included in Model 2.

|                                                           | 5-8.9 years old  |         |            | 9-11.9 years old |         |           | Adolescents |         |           |
|-----------------------------------------------------------|------------------|---------|------------|------------------|---------|-----------|-------------|---------|-----------|
|                                                           | Crude HR         | p-value | 95% CI     | Crude HR         | p-value | 95% CI    | Crude HR    | p-value | 95% CI    |
| <b>Respiratory symptoms one year before diagnosis</b>     |                  |         |            |                  |         |           |             |         |           |
| Dyspnoea                                                  | 1.1              | <0.001  | 1.04- 1.20 | 0.8              | 0.005   | 0.70-0.90 | 0.8         | <0.001  | 0.70-0.90 |
| Wheeze                                                    | 1.2              | <0.001  | 1.10- 1.31 | 1.1              | 0.564   | 0.90-1.10 | 1.0         | 0.804   | 0.96-1.12 |
| Cough                                                     | 1.1              | <0.001  | 1.02- 1.10 | 1.0              | 0.527   | 0.90-1.05 | 1.0         | 0.317   | 0.89-1.12 |
| <b>Exacerbation one year before diagnosis</b>             |                  |         |            |                  |         |           |             |         |           |
| None                                                      | <i>Reference</i> |         |            |                  |         |           |             |         |           |
| GP managed                                                | 2.1              | <0.001  | 1.96- 2.17 | 2.4              | <0.001  | 2.20-2.70 | 2.3         | <0.001  | 1.91-2.62 |
| Hospital managed                                          | 2.3              | <0.001  | 2.10- 2.47 | 2.5              | <0.001  | 2.20-3.00 | 3.4         | <0.001  | 2.52-4.61 |
| <b>Exacerbation at the time of diagnosis</b>              |                  |         |            |                  |         |           |             |         |           |
| None                                                      | <i>Reference</i> |         |            |                  |         |           |             |         |           |
| GP managed                                                | 1.8              | <0.001  | 1.70- 2.18 | 2.1              | <0.001  | 2.00-2.40 | 2.7         | <0.001  | 2.31-3.23 |
| Hospital managed                                          | 2.1              | <0.001  | 1.92- 2.16 | 2.5              | <0.001  | 2.10-3.10 | 3.3         | <0.001  | 2.52-4.44 |
| <b>ICS inhalers issued within a year before diagnosis</b> |                  |         |            |                  |         |           |             |         |           |
| None                                                      | <i>Reference</i> |         |            |                  |         |           |             |         |           |
| 1 inhaler                                                 | 1.1              | <0.001  | 0.92- 1.15 | 1.1              | <0.001  | 1.03-1.20 | 1.1         | 0.244   | 1.00-1.20 |
| 2 inhalers                                                | 1.2              | <0.001  | 1.12- 1.22 | 1.2              | <0.001  | 1.10-1.32 | 1.2         | <0.01   | 1.18-1.38 |
| 3+ inhalers                                               | 1.3              | <0.001  | 1.21- 1.43 | 1.5              | <0.001  | 1.30-1.60 | 1.7         | <0.001  | 1.51-2.12 |
| Age at diagnosis                                          | 0.9              | <0.001  | 0.80- 0.90 | 0.9              | <0.005  | 0.81-0.96 | 1.0         | 0.402   | 0.94-1.12 |
| Female                                                    | 0.9              | <0.001  | 0.80- 0.95 | 0.8              | <0.01   | 0.78-0.96 | 0.9         | 0.011   | 0.86-0.98 |
| <b>IMD</b>                                                |                  |         |            |                  |         |           |             |         |           |
| 1                                                         | <i>Reference</i> |         |            |                  |         |           |             |         |           |
| 2                                                         | 1.1              | <0.001  | 1.01- 1.10 | 1.1              | 0.021   | 1.05-1.30 | 1.1         | 0.211   | 1.03-1.22 |
| 3                                                         | 1.1              | <0.001  | 1.07- 1.20 | 1.2              | <0.005  | 1.10-1.31 | 1.2         | <0.001  | 1.12-1.41 |
| 4                                                         | 1.1              | <0.001  | 1.07- 1.20 | 1.3              | <0.001  | 1.22-1.38 | 1.2         | <0.001  | 1.12-1.42 |
| 5                                                         | 1.2              | <0.001  | 1.14- 1.27 | 1.4              | <0.001  | 1.24-1.50 | 1.3         | <0.001  | 1.21-1.47 |

| <b>BMI</b>             |                  |        |            |     |       |           |     |        |           |
|------------------------|------------------|--------|------------|-----|-------|-----------|-----|--------|-----------|
| Normal                 | <i>Reference</i> |        |            |     |       |           |     |        |           |
| Overweight             | 1.0              | 0.2    | 0.90- 1.02 | 1.1 | 0.205 | 0.90-1.22 | 1.1 | 0.005  | 1.03-1.31 |
| Obese                  | 1.0              | 0.77   | 0.90- 1.07 | 1.2 | 0.252 | 0.96-1.13 | 1.4 | <0.001 | 1.30-1.52 |
| Missing                | 1.0              | 0.677  | 0.90- 1.04 | 1.0 | 0.312 | 0.82-1.08 | 1.0 | 0.422  | 0.91-1.12 |
| <b>Atopy 1</b>         | 0.9              | <0.001 | 0.88- 0.98 | 1.0 | <0.05 | 1.03-1.29 | 1.1 | 0.178  | 0.99-1.20 |
| <b>Eczema</b>          | 1.2              | <0.001 | 1.03- 1.30 | 1.1 | 0.064 | 1.02-1.19 | 1.1 | 0.646  | 0.99-1.21 |
| <b>Atopy 2</b>         | 1.2              | <0.001 | 1.10- 1.29 | 1.1 | 0.297 | 0.91-1.24 | 1.1 | 0.676  | 0.92-1.21 |
| <b>Passive smoking</b> | 0.9              | <0.001 | 0.82- 0.99 | 0.9 | 0.61  | 0.82-1.22 | 0.9 | 0.483  | 0.76-1.14 |
| <b>Smoker</b>          | NA               | NA     | NA         | 0.8 | <0.05 | 0.70-0.90 | 1.0 | 0.755  | 0.90-1.10 |

*HR = hazard ratio, BMI=body mass index, IMD = Index of Multiple Deprivation. Atopy 1 indicates hay fever or allergy to pollen, house dust met or pets. Atopy 2 indicates food or drug allergy*

#### 4.4.4 Sensitivity analysis

##### 4.4.4.1: Excluding the BMI variable

Excluding BMI from the models made negligible difference to the effect estimates of the association between multiple demographic and clinical characteristics and first asthma exacerbation, after formal asthma diagnosis, across the three age groups (Figure 4.7 & 4.8).

Figure 4. 7: Sensitivity analysis, excluding BMI from Model 1.

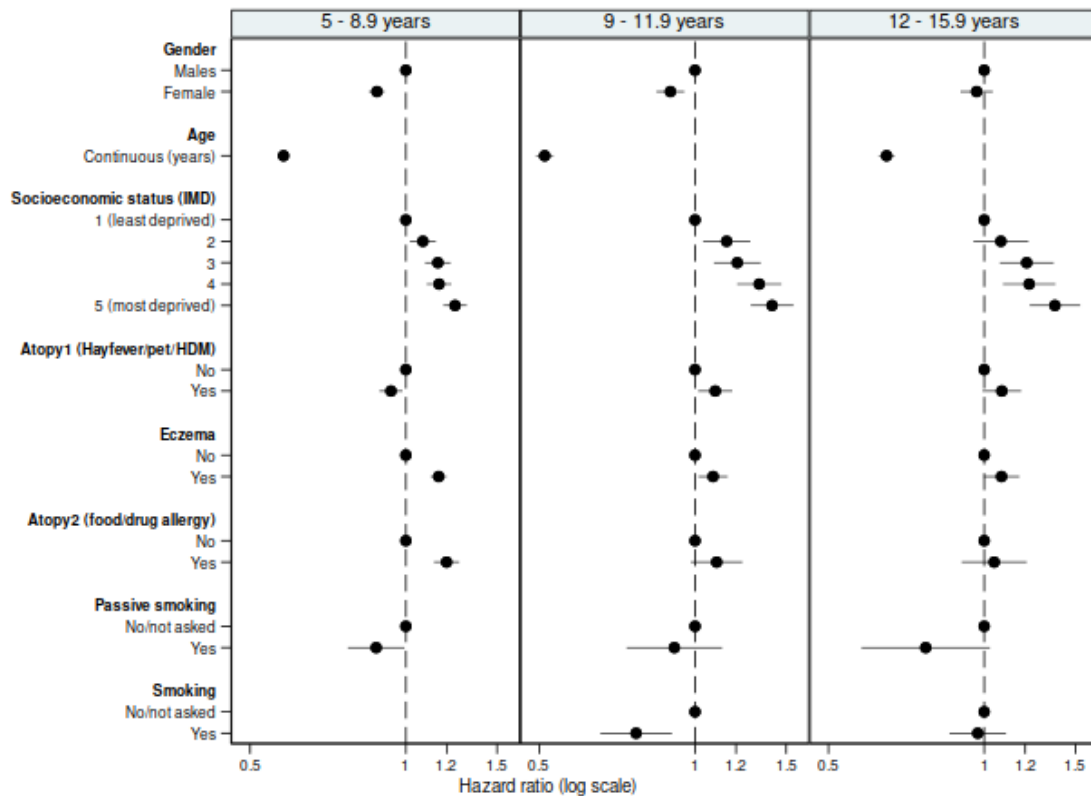
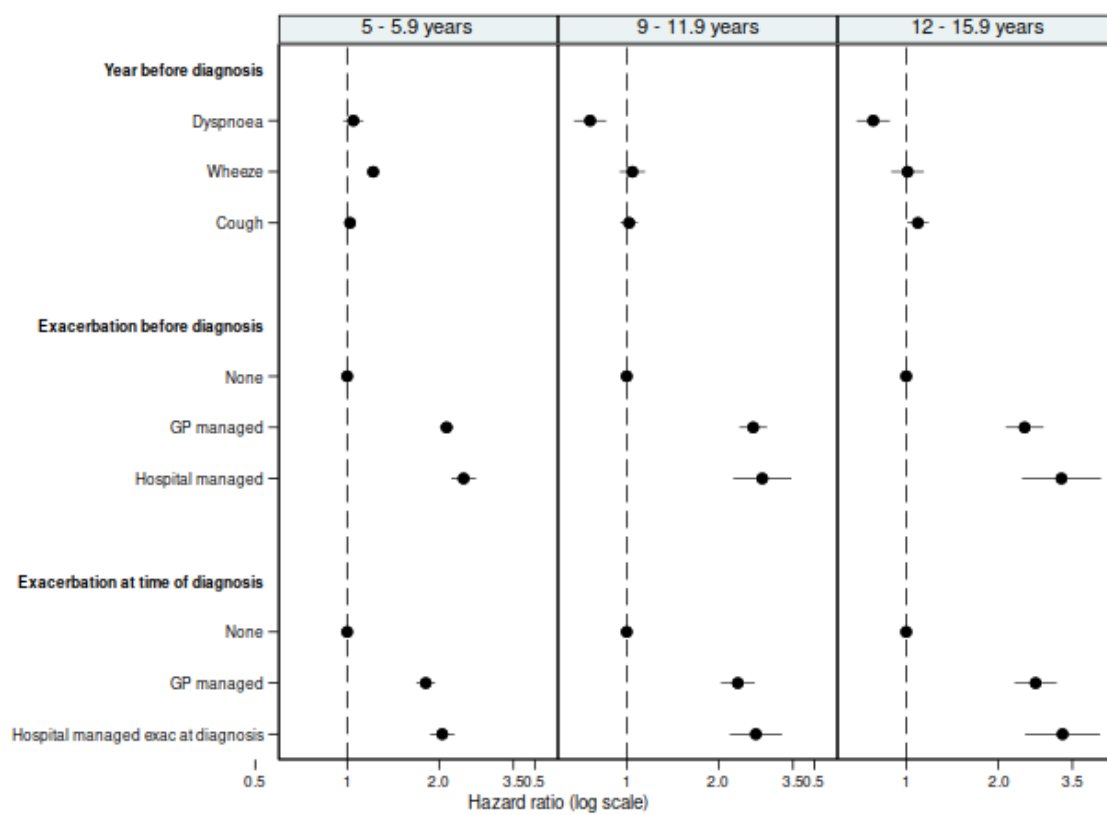


Figure 4. 8: Sensitivity analysis, excluding BMI from Model 2.



#### 4.4.4.2: Including all exacerbations, not just the first exacerbation

Including all exacerbations made little difference to the risk factors and factors associated with reduced risk of an exacerbation (Figure 4.9 & Figure 4.10).:

Figure 4. 9: Multivariable analysis including all exacerbations, Model 1.

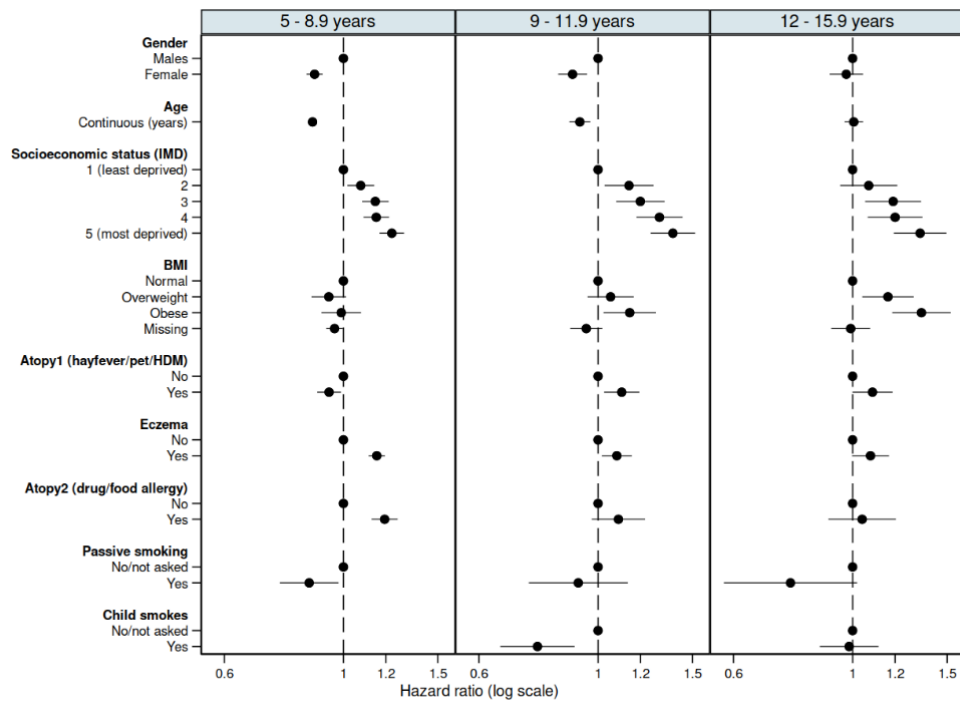
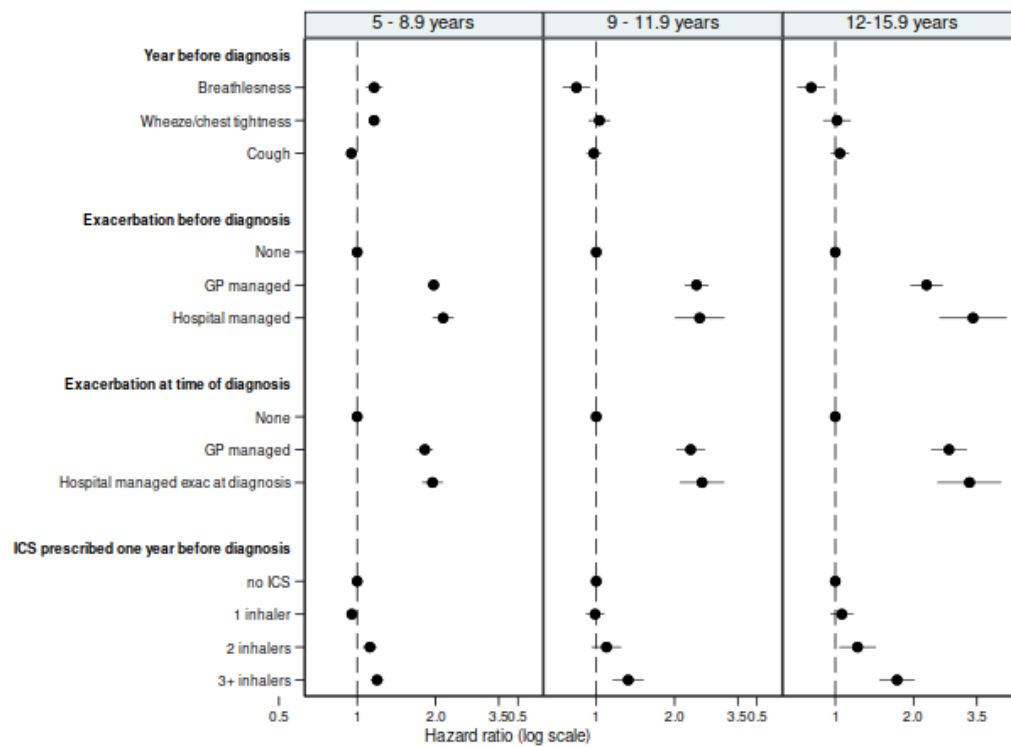


Figure 4. 10: Multivariable analysis including all exacerbations, Model 2.



## 4.5 Discussion

This chapter aimed to identify patterns and risk factors associated with asthma exacerbations in school-aged children using a more granular age approach than has previously been explored and found exacerbation rates and risk factors were dependent on age, within the broader school-age label. Exacerbations rates were highest among the youngest children, aged 5-8.9 years, approximately 3-4 times higher than in the older children. This difference in exacerbation rates could be due to several factors, including a more immature respiratory system in the younger children, age-related differences in atopic sensitisation, or age-related difficulties in adhering to treatment regimens [83, 107].

I also found different factors were associated with exacerbations, depending on age. In children aged 5 to 9 years, male gender, eczema, atopy 2 (related to food or drug allergies), dyspnoea, and wheezing were associated with a greater risk of exacerbation. Whereas for those aged 9 years and older, obesity, overweight, or history of atopy 1 (related to hay fever, pet, or house dust mite allergies) were key risk factors. Some characteristics were found to be risk factors for all children, regardless of age. These included socioeconomic deprivation, having an exacerbation before receiving a formal diagnosis of asthma in their GP records, having an exacerbation at the time of diagnosis, and receiving a prescription for ICS before formal diagnosis. Previous exacerbations having a strong association with future exacerbations, echoes findings from multiple studies in both adults and smaller paediatric populations [27, 108, 109].

The lack of a formal diagnosis within the GP practice, even after the child had received asthma treatment either for an exacerbation or ICS, is a missed opportunity for intervention, including education for the families, and may have contributed towards the increased risk of future exacerbations. Some of the exacerbations were managed within secondary care, through hospital admissions or A&E visits, and perhaps this vital piece of information was not adequately transferred to the child's GP practice. But other times children received a short course of corticosteroids that was not for any other condition, suggesting it was for presumed asthma, although not formally labelled as so. The reticence to label preschool children with asthma has grown over the last decade or so, as seen in a previous UK study [29].

Interestingly, our findings suggest that the presence of aeroallergen sensitisation (using the proxy variable atopy 1) was not a strong risk factor for exacerbations, until the children reached at least 9 years old. In contrast, food and drug allergies were found to be strongly associated in the youngest age group, increasing the risk by approximately 20%, but not in children over 9 years old. Food allergies are common in younger children and their prevalence appears to be steadily increasing in the UK [110]. Several studies have suggested they are a risk factor for both asthma development in young children, and worsening asthma control and exacerbations in children across all ages [111]. Previous studies did not separate children into ages within the school-age boundaries and my study indicates that food allergies are not associated with exacerbations as children grow older. This age-related change in association could also be related to reduced prevalence in older children, that food allergy becomes relatively more common in females with age [110], or increased mis- or under-diagnosis in primary care medical records as children age [110]. Atopy/allergic disease is an established risk factor for asthma exacerbations in childhood asthma, and from a systematic review of over 68 observational studies, was found to be associated with a moderately increased risk [21]. A better understanding of allergen sensitisation could improve predictions of exacerbation risk, but machine learning approaches using data from well characterised birth cohorts with a wealth of sensitisation data has revealed the highly complex relationship between atopy and asthma [83].

Another well recognised exacerbation risk factor in childhood asthma is sex. I found, as multiple other studies have shown, that male gender is associated with an increased risk of exacerbations until around puberty, where there is little difference in risk between females and males [112]. These differences may be related to a multitude of factors, including changes in sex hormone levels, genetics, epigenetics, and potential interactions with environmental factors [110, 113].

Socioeconomic deprivation, a potentially modifiable risk factor, was strongly associated with exacerbations in all children, regardless of age. This effect may be due to a combination of factors such as reduced access to healthcare, increased reliance on unscheduled asthma care, increased exposure to environmental pollutants, poorer health literature and higher levels of stress [114-117]. However, the variable, index of multiple deprivation, used to represent the child's socioeconomic deprivation is based on their postcode and therefore may not accurately

represent that household if the postcode includes households of different levels of deprivation.

In addition, I found elevated BMI to be strongly associated with exacerbations as children increase in age, such that by adolescence overweight children had around 20% increased risk and obese children had 30% increased risk. As discussed in Chapter 3, elevated BMI is a modifiable risk factor and its role as a significant exacerbation risk factor suggests that weight management should be a key consideration in asthma care, especially in older children.

There was an association, although a weak one of around 10% increase between symptoms in the youngest children and exacerbations. Yet this differed in the older children, where symptoms were either not associated (wheeze and cough) or appeared to be associated with a slightly reduced risk of an exacerbation (breathlessness). It is not easy to explain this but could be that breathlessness and cough are non-specific symptoms, that are common in many conditions so are not good markers, alone, of uncontrolled asthma. Whereas wheeze, which was most prevalent in the younger children (14% as shown in Chapter 3), is more specific to airways disease, of which asthma is the most common in children. Wheeze that is reported to and documented by the GP practice suggests it is either a more severe episode or occurring more frequently, and thus more likely to be suggestive of worse asthma control. Frequent reporting of wheeze episodes to GP practices in preschool children, under 5 years old, has been shown to be associated with an increased risk of developing childhood asthma [112].

I included the variables for smoking, both passive smoking and active smoking by the child, as these are known critical risk factors for asthma exacerbations [118]. The results are surprising, in that presence of either of these appeared to be protective. But, as I showed in the previous chapter, it is likely there was high level of missing information, so these findings are at high risk of bias. However, one explanation of the 'protective' effect found, could be that families that chose to report the smoke exposure were aware of the potential negative impact so tried actively to mitigate other triggers for exacerbations, or ensure their child had good adherence to their ICS, or their child was not exposed to the cigarette smoke. Therefore, the main conclusion for these covariates is that healthcare professionals should be more attuned to this potential modifiable risk factor, including directly asking families about smoke exposure and educating them on the risk. Asking about smoke is now one of the QOF indicators, yet this

study shows at the time of study, this variable was still rarely reported; additionally, information on vaping may be critical and should be included in routine data collection.

## 4.6 Limitations

Most of the limitations and the strengths have already been discussed in the Strengths and Limitations section in Chapter 3 as I used the same data source and cohort. The limitations already discussed included potential misclassification of the exposure and covariates, and issues of missing values and variables. Here, I will only describe additional limitations, particular to this analysis, so as not to repeat the limitations in section 3.6.

I did not have access to pollution data, which is a potential exacerbation risk factor. Although including a marker for socioeconomic deprivation may have accounted somewhat for this, it would have been insufficient, leading to residual confounding. For example, as mentioned above, IMD is based on the child's postcode which may not accurately represent the child, nor can it account for their individual indoor and outdoor pollution exposure. Additionally, we could not assess the effect of pollution as a risk factor. This is an area for future work and dedicated pollution studies.

## 4.7 Conclusion

In this chapter I have shown that the youngest children are at greatest risk of asthma exacerbations and that this risk is lowest in the adolescent period. I have determined factors that are strongly associated with exacerbations in all children, including socioeconomic deprivation and receiving treatment for an asthma exacerbation or multiple ICS prescriptions, prior to formal diagnosis of their asthma in the GP practice medical records. However, several factors were unique to each age group, showing the need to manage children in a more granular way and not assume homogeneity across the school-age. These risk factors included gender, the type of atopy the child had, elevated BMI, and respiratory symptoms. This disparity in exacerbation rates and risk factors across the school-age is not currently

acknowledged in the UK asthma management guidelines but could help to direct asthma care in a more personalised manner.

## 5. Chapter 5: Prevalence and Disparities in the Delivery of Good Clinical Practice Activities in Children

### 5.1. Introduction

All national and international asthma guidelines recommend a stepwise approach to pharmacological management. The steps have been displayed in a relatively simple and easy-to-follow pictogram, including in the BTS/SIGN guidelines, which aid its broad application in asthma care across the UK. But beyond pharmacological management, national guidelines also recommend the implementation of good clinical practice activities, in a bid to improve asthma outcomes and reduce exacerbations [8, 9, 85]. These activities, as discussed earlier, may include adherence monitoring, inhaler technique education, scheduled dedicated asthma reviews, education on trigger avoidance, and provision of an asthma management plan. For aid of writing my findings and describing my work, in conjunction with my assessors and supervisors, we chose the term ‘good clinical activity practices’ to describe these non-pharmacological activities that patients should optimally receive as part of their asthma care. In chapters 5 and 6, I focus on good clinical practice activities that are routinely documented in medical records.

### 5.2. Objectives

**Objective 1:** Determine the national prevalence of the implementation of four good clinical practice activities, annual asthma review, asthma management plan, inhaler technique check and influenza vaccination.

**Objective 2:** Determine which children were less likely to receive an annual asthma review, asthma management plan and inhaler technique check.

Due to the low numbers in my dataset of children documented as receiving influenza vaccination and therefore high risk of selection bias, I did not assess the risk factors associated with its vaccination uptake.

## 5.3. Methods

### 5.3.1 Data source

Data were provided by the Clinical Practice Research Datalink, which was described in chapter 2. Data was individually linked to Hospital Episode Statistics and Office for National Statistics death data (13).

### 5.3.2 Study design and participants

The study population included children (5-16 years old) identified between January 2004 to January 2021 from the CPRD database, who had at least two asthma codes within two years, a minimum of 12 months of data before entering the study, and at least 12 months of follow-up data after their first asthma code. Follow-up started from their asthma diagnosis which was defined as their first recorded asthma code. Follow-up was censored at the earliest of the end of the study period as per the protocol (1<sup>st</sup> January 2022), the date the child left the GP practice, the date of death, or date of their 18<sup>th</sup> birthday.

### 5.3.3 Variables

**Outcomes:** The annual prevalence of receiving an asthma review, asthma management plan, inhaler technique check, and influenza vaccination (objective 1). The relative risk of receiving an asthma review, asthma management plan, and inhaler technique check (objective 2).

**Covariates:** Demographic variables included age, gender, BMI, IMD, and smoking status (please see earlier chapter 2 for methods on their derivation).

In the year before cohort entry, the prevalence of respiratory symptoms was determined as binary reporting to GP practice (yes/no) for wheeze/chest tightness, cough, or breathlessness using the codes listed in (Appendices 7, 8, and 9).

Reported comorbidities were categorized into 'atopy 1,' 'atopy 2,' and eczema, based on the child receiving a relevant code in their medical record. Atopy 1 included hay fever, pet allergy,

or house dust mite (HDM) allergy, while atopy 2 encompassed food or drug allergies (Appendix 4).

An asthma exacerbation was defined as described in detail in the earlier chapter 2 (but in summary it is a short course of oral corticosteroids, unscheduled A&E or hospital admission for asthma).

Asthma medications included short-acting beta-agonists (SABA), inhaled corticosteroids (ICS), and add-on medications such as long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA)

#### 5.4.4 Analysis

**Descriptive analysis:** Annual prevalence of each good clinical practice activity was calculated by dividing the number of children receiving at least one good clinical practice activity by the number of children with a complete year of data. The annual prevalence was calculated for each 12-months after their asthma diagnosis, reaching a maximum of a possible 12 years for those children aged 5 years old at the start of the cohort.

**Statistical analysis:** To determine the risk factors associated with receiving or not receiving each good clinical practice activity, I first had to decide which time period to assess this in. For the primary analysis, I chose the second year after their asthma diagnosis. This was because I assessed baseline characteristics as risk factors for receiving a good clinical practice activity, some of which are features of their asthma, therefore children had to have at least one year after their asthma diagnosis to accumulate relevant information (eg ICS use). I could have assessed the period further away from their asthma diagnosis, but this would reduce the number of children able to be included (due to loss from follow-up). I applied three separate multivariable logistic regression models, one for each of the good clinical practice activities. Due to the low prevalence of influenza vaccine uptake in the database this was not assessed as would have provided biased estimates. The three models were each adjusted for age, gender, IMD, BMI, atopy 1, atopy 2, eczema, smoking status, and in the year before diagnosis: respiratory symptoms, exacerbations, and asthma medication use.

Only BMI had missing values, as all other clinical variables were presumed not present if there was no code. To deal with the large amount of missing data in the statistical analysis, and to enable the ability to assess the effect of missing BMI on receiving good clinical practice activities, I used a missingness strata label, i.e., I included children with missing values and noted that as one of the BMI categories. This allows the effect of having no BMI to be assessed.

### **Sensitivity analyses**

- (i) Here I wished to evaluate the effects of assessing the risk of receiving good clinical practice activities over a long time period. In the main analysis above, I evaluated it over a one year period. But in this sensitivity analysis, a period of 3 years was applied. As this was a longer period, I applied multinomial multivariable logistic regression and categorised good clinical practice activity frequency in the first three years after asthma diagnosis as three outcomes: never occurring, occurring just once, or occurring in at least two out of the three years. This helped to determine if some risk factors varied depending on how frequently the good clinical practice activities were provided. In the main analysis the outcome was binary, good clinical practice activity occurred, or did not.
- (ii) Considering the missingness of BMI data. It is unlikely that BMI was missing at random, as it was likely influenced by factors such as the willingness of some children (or permission of their families) to measure the children's weight and height, and the willingness of GP practices to spend the time to measure and record children's BMI. However, as shown in Chapter 3, I could not find discernible differences in the characteristics, between children with recorded BMI values and those without a BMI value. Data are said to be *missing not at random* (MNAR) if the value of the unobserved variable itself predicts missingness. In this case, the children with high BMIs were most likely not to have one recorded, due to various reasons, such as not attending regular check-ups or avoiding measurements due to discomfort with their weight. Missing data require different approaches depending on the pattern of missingness [119, 120], when data are *missing completely at random* (this means the data is truly randomly missing, MCAR), analysing only the complete cases (termed 'complete case analysis') will not result in biased results. However, the sample size may be reduced (by 40% in

this study), leading to reduced precision in the effect estimate. In contrast, conducting a complete case analysis if data is considered to be *missing at random* (missingness is dependent on other variables in the study, e.g. age if older children more likely to have missing values, MAR) or MNAR can lead to biased estimates.

BMI data in electronic health care records is thought to be MAR, or MNAR. Therefore, we did not use complete case analysis. Instead, we used two approaches both of which include all children so there is no loss of sample size. First, using a 'missing' strata, so identifying children with missing data as a specific category – this was applied in our main analysis. Second, using the statistical method, multiple imputation, which derives plausible BMI values for those missing by using the child's observed values in other variables. We then compared our effect estimates using these two different approaches.

Multiple imputation uses regression models to predict the missing BMI values and incorporates uncertainty through an iterative approach. I used STATA's *mi impute* package which uses the chained equations method, the most commonly applied MI method. I created 10 sets of imputations for the missing BMI values, each of which had a slightly different value due to randomness. To reduce the bias and increase the efficiency of the imputed values, I included 'auxiliary' variables in the imputation regression models. Auxiliary variables are variables that are correlated with the missing value or thought to be associated with the missingness. My chosen auxiliary variables were age, gender, GP practice, asthma treatment, asthma exacerbations, good clinical practice activity implementation, smoking history and atopy. Finally, to combine the values for each child from the 10 datasets, I pooled them using Rubin's rule [121]. The imputed values, coefficients and standards errors, were then included in the sensitivity models.

- (iii) To determine any clustering effect that may occur from individual GP practices, I conducted three mixed-effect, multivariable logistic regression models with each GP practice as the random effect.

## 5.4. Results

#### 5.4.1 Prevalence of receiving good clinical care activities (figure 5.1)

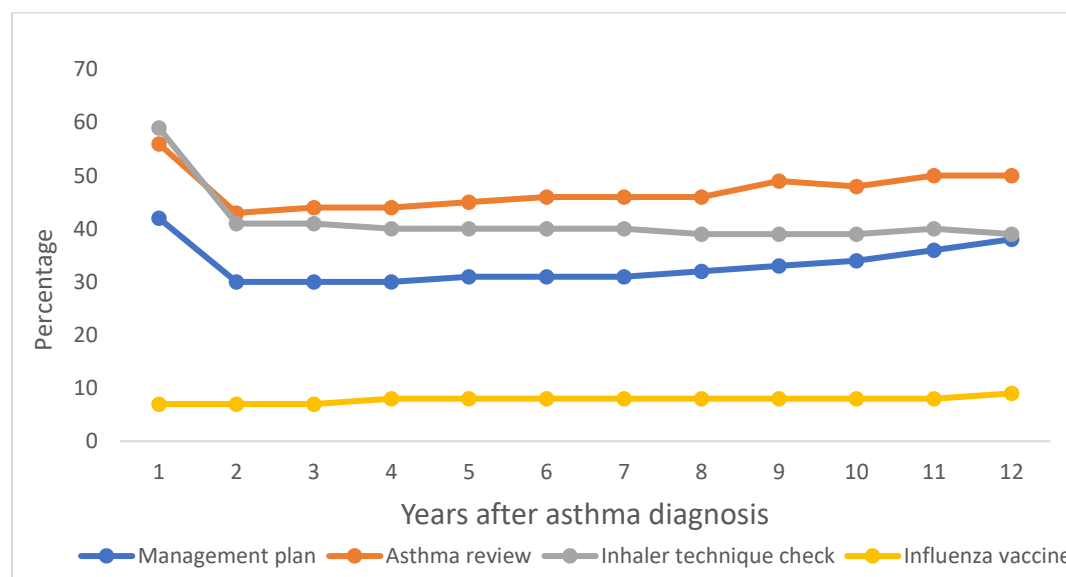
126,483 children were eligible for the study. In the first year after asthma diagnosis, 56% of these children received an asthma review, decreasing to 44-50% in subsequent years. 42% were given an asthma management plan in the first year after asthma diagnosis but this dropped to 30-38% in later years. Inhaler technique checks were reported for 59% of the children during the first year after diagnosis, but this also decreased to 39-41% in later years.

The uptake of the influenza vaccine through their GP practice was very low, with only about 7% of children documented to receive one.

Additionally, in the first year after diagnosis, 11,457 children (9%) received two key asthma care processes in the same consultation, which could be an asthma review and management plan, or review and inhaler technique check, or management plan and inhaler technique check. Only 10,035 children (8%) received all three essential asthma care processes in a single

consultation. The proportion receiving these in the second year were a little lower, 8% receiving two and 7% receiving all three.

Figure 5. 1: Annual prevalence of receiving each good clinical practice activities according to years since asthma diagnosis



#### 5.4.2 Description of cohorts used to assess the factors associated with good clinical practice activity implementation

Children who received at least one good clinical practice activity were similar to each other by most, but not all, baseline characteristics from those children who did not receive any good clinical practice activities (Table 5.1).

Children receiving good clinical practice activities were around 1 year older and included more males. Around half of those with a good clinical practice activity had a normal BMI as compared to only a quarter of those with no good clinical practice activity. All other variables were similar between those receiving or not receiving a good clinical practice activity, including atopy, IMD, symptoms, SABA use, and exacerbations.

Table 5. 1: Description of baseline characteristics of the children included in the cohorts to assess the factors associated with good clinical practice activities implementation, shown by type of good clinical practice activities received, or not.

|       | All children     | Asthma review  | Inhaler technique check | Management plan | No activity    |
|-------|------------------|----------------|-------------------------|-----------------|----------------|
| Total | 126,483 (100.0%) | 72,001 (56.9%) | 76,309 (60.3%)          | 54,484 (43.0%)  | 29,008 (22.9%) |

|                                   |               |               |              |              |              |
|-----------------------------------|---------------|---------------|--------------|--------------|--------------|
| <b>Age, mean (SD) years</b>       | 9.7 (3.4)     | 9.8 (3.4)     | 9.9 (3.4)    | 9.7 (3.4)    | 8.4(3.3)     |
| <b>Males</b>                      | 68,229 (54%)  | 38,490 (53%)  | 40,587 (53%) | 29,073 (53%) | 12,847 (44%) |
| <b>BMI</b>                        |               |               |              |              |              |
| Normal                            | 56,006 (44%)  | 36,143 (50%)  | 40,141 (53%) | 30,086 (55%) | 7,668 (26%)  |
| Overweight                        | 12,291 (10%)  | 7,899 (11%)   | 8,702 (11%)  | 6,515 (12%)  | 1,707 (6%)   |
| Obese                             | 8,252 (7%)    | 5,123 (7%)    | 5,649 (7%)   | 4,284 (8%)   | 1,272 (4%)   |
| Unknown                           | 49,934 (39%)  | 22,836 (32%)  | 21,817 (29%) | 13,599 (25%) | 18,361 (63%) |
| <b>IMD (socioeconomic status)</b> |               |               |              |              |              |
| 1 (least deprived)                | 24,071 (19%)  | 14,346 (20%)  | 14,565(19%)  | 9,903 (18%)  | 5,349 (18%)  |
| 2                                 | 22,755 (18%)  | 13,343 (18%)  | 13,873(18%)  | 9,689 (18%)  | 5,078 (17%)  |
| 3                                 | 22,690 (18%)  | 12,927 (56%)  | 13,672(18%)  | 9,533 (17%)  | 5,234 (18%)  |
| 4                                 | 26,587 (21%)  | 14,387 (20%)  | 15,814(21%)  | 11,713 (21%) | 6,302 (22%)  |
| 5                                 | 30,380 (24%)  | 16,998 (24%)  | 18,385 (24%) | 13,646 (25%) | 7,045 (24%)  |
| <b>Atopy 1</b>                    | 21,813 (17%)  | 12,456 (17%)  | 13,211 (17%) | 9,537 (18%)  | 4,850 (17%)  |
| <b>Eczema</b>                     | 42,459 (34%)  | 24,496 (34%)  | 25,298 (33%) | 18,856 (35%) | 9,853 (34%)  |
| <b>Atopy 2</b>                    | 9,975 (8%)    | 5,669 (8%)    | 5,784 (8%)   | 4,509 (8%)   | 2,424 (8%)   |
| <b>Events in the year before</b>  |               |               |              |              |              |
| Dyspnoea                          | 9,499 (8%)    | 5,783 (8%)    | 6,272 (8%)   | 4,495 (8%)   | 1,705 (6%)   |
| Wheeze                            | 15,148 (12%)  | 9,314 (13%)   | 9,860 (13%)  | 7,610 (14%)  | 2,757 (10%)  |
| Cough                             | 43,571 (34%)  | 25,725 (36%)  | 27,671 (36%) | 18,850 (35%) | 8,744 (30%)  |
| <b>ICS inhaler prescriptions</b>  |               |               |              |              |              |
| None                              | 90,083(71%)   | 48,971 (68%)  | 52,681(69 %) | 36,706 (71%) | 22,586(78%)  |
| 1-3                               | 32,553 (26%)  | 20,608 (29%)  | 21,262 (28%) | 15,972 (29%) | 5,661 (20%)  |
| 4-9                               | 3,605 (3%)    | 2,284 (3%)    | 2,242 (3%)   | 1,701 (3%)   | 700 (2%)     |
| 10+                               | 242 (0.19%)   | 22,701 (0.19) | 124 (0.16)   | 105(0.19%)   | 242(0.19%)   |
| <b>SABA inhaler prescriptions</b> |               |               |              |              |              |
| None                              | 49,370 (39%)  | 25,201 (35%)  | 26,792 (35%) | 18,353 (34%) | 14,443 (49%) |
| 1-3                               | 69,218 (55%)  | 41,933 (58%)  | 44,637 (58%) | 32,370 (59%) | 13,008(45%)  |
| 4-9                               | 7,327 (5%)    | 4,537 (6%)    | 4,545 (6%)   | 3,497 (6%)   | 1,425 (5%)   |
| 10+                               | 568 (1%)      | 330 (1%)      | 335 (1%)     | 265 (1%)     | 132 (1%)     |
| <b>Exacerbations</b>              |               |               |              |              |              |
| None                              | 118,272 (94%) | 67,180 (94%)  | 71,399 (94%) | 50,677 (93%) | 27,098 (94%) |
| GP managed                        | 6,625 (5%)    | 3,926 (5%)    | 4,053 (5%)   | 3,067 (6%)   | 1,484 (5%)   |
| Hospital managed                  | 1,586 (1%)    | 895 (1%)      | 857 (1%)     | 740 (1%)     | 426 (1%)     |

#### 5.4.3 Association between baseline characteristics and the risk of receiving a good clinical practice activities

##### Annual asthma review

Older children were more likely to receive an asthma review, with children aged 9-11.9 years having 10% higher odds (OR 1.10, 95% CI: 1.07-1.13), and those aged 12-16 years having 14% higher odds (OR 1.14, 95% CI: 1.10-1.18), as compared to the youngest group, aged 5-8.9 years (Figure 5.2).

Children residing in more deprived areas were less likely to receive an asthma review. Specifically, as compared to the least deprived, IMD 1, each increasing IMD had a lower odds of having an annual asthma review: IMD 2, OR = 0.95 (95% CI: 0.91-0.98), IMD 3 = 0.89 (95% CI: 0.85-0.92), IMD 4 = 0.78 (95% CI: 0.75-0.80), and IMD 5 = 0.84 (95% CI: 0.81-0.87; Figure 5.2).

Atopy 1 (pollen/pet/HDM allergy) and atopy 2 (food/drug allergies) were associated with a minor relative decrease in odds of 4% (95% CI: 0.93-0.99) and 5% (95% CI: 0.90-0.98) of receiving an asthma review, respectively (Figure 5.2). Whereas children with eczema had 4% higher odds (95% CI: 1.10-1.06) of receiving an asthma review than those without eczema.

Passive smoking also showed a negative association with 10% reduced odds (95% CI: 0.83-0.98) of receiving a review as compared to those not documented as exposed to cigarette smoke (Figure 5.2). Although it is notable the total numbers of children with this documented were very low.

Obese children had 8% lower odds of receiving an asthma review (OR 0.92, 95% CI: 0.87-0.96) but there was no significant association with overweight children. Children with no recorded BMI anywhere in their medical records had the lowest odds of receiving a review, 53% lower than children with a normal BMI (OR 0.47, 95% CI: 0.46-0.48; Figure 5.2).

Past exacerbations in the year prior, were not associated with an increased odds of receiving an asthma review (Figure 5.2).

However, the presence of respiratory symptoms, wheeze/chest tightness, and breathlessness, but not cough, were associated with receiving an asthma review (wheeze: OR 1.10, 95% CI: 1.07-1.10; cough: OR 1.05, 95% CI: 1.02-1.08; breathlessness: OR 1.07, 95% CI 1.03-1.12; (Figure 5.2).

Being prescribed ICS, was also strongly associated with receiving an asthma review. As compared to not being prescribed ICS, there was 23% increased odds (95% CI: 1.18-1.26) with

1-3 inhalers in the year before, and 27% increased odds (95% CI: 1.18-1.36) with 4-9 inhalers (Figure 5.2).

After adjusting for all relevant factors, including symptoms and ICS, there was no significant association between the number of SABA prescriptions and the risk of receiving an asthma review (Figure 5.2).

### **Asthma management plan**

Only the oldest children (12-16 years) had a slightly reduced association with receiving an asthma management plan (OR 0.96, 95% CI: 0.93-0.99) as compared to the youngest age group (Figure 5.2).

On the other hand, children from the most deprived areas (IMD 5 and IMD 4) were more likely to receive a management plan, with an OR of 1.14 (95% CI: 1.10-1.18) and OR of 1.10 (95% CI: 1.06-1.14), respectively (Figure 5.2).

Passive smoking was not associated with receiving an asthma management plan (Figure 5.2).

Only having eczema, not atopy 1 or atopy 2, was associated with receiving an asthma management plan (eczema: OR 1.06, 95% CI: 1.04-1.06; (Figure 5.2).

Again, obese children had lower odds of receiving a management plan (OR 0.92, CI: 0.88-0.97) and the lowest odds, 68% lower, occurred for those children without a recorded BMI (95% CI: 0.32-0.33; Figure 5.2).

Hospital-managed exacerbations was also positively associated with receiving a management plan, (OR 1.13, 95% CI: 1.02-1.22), but GP-managed ones were not (Figure 5.2).

Reporting of wheeze and breathlessness, but not cough, was associated with receiving an asthma management plan (wheeze: OR 1.28, 95% CI: 1.24-1.33; cough: OR 0.90, 95% CI 0.88-0.92; breathlessness: OR 1.07, 95% CI 1.02-1.12), as found for the two other good clinical practice activities (Figure 5.2).

Lastly, similar for the two other good clinical practice activities, 1-3 ICS inhalers were associated with increased odds of receiving a management plan (OR 1.18, 95% CI 1.16-1.23; Figure 5.2).

SABA inhaler use was again not significantly associated with management plan provision ( $p < 0.05$ ; Figure 5.2).

### **Inhaler technique check**

Higher age was significantly associated with receiving an inhaler technique check. Children aged 9-11.9 years, and 12-15.9 years had relatively higher odds, with an odds ratio of 1.23 (95% CI: 1.20-1.27) and 1.25 (95% CI: 1.22-1.29) respectively, as compared to the youngest children, aged 5-8.9 years (Figure 5.2).

Children from the most deprived areas (IMD 4 and IMD 5) had lower odds of receiving an inhaler technique check, with an odds ratio of 0.92 (95% CI: 0.88-0.95) and 0.95 (95% CI: 0.91-0.98) respectively (Figure 5.2). But there was no significant difference between the highest three relative categories of social deprivation, IMD 1-3 ( $p > 0.05$ ).

Passive smoking increased the odds of receiving inhaler technique checks by 70% (95% CI: 1.60-1.92).

Having atopy 1 (pollen/pet/HDM allergy), eczema, and atopy 2 (food/drug allergies) were associated with a decreased odds of receiving inhaler technique checks by 5% (95% CI: 0.93-0.98), 4% (95% CI: 0.93-0.99) and 12% (95% CI: 0.84-0.91), respectively (Figure 5.2).

Obesity and unrecorded BMI were again associated with a reduced association as compared to normal BMI, with 16% reduced odds (95% CI: 0.80-0.88) and 69% reduced odds (95% CI: 0.30-0.32), respectively (Figure 5.2).

Hospital-managed exacerbations decreased the odds by 22% (95% CI: 0.72-0.84), although GP-managed exacerbations were not associated with receiving an inhaler technique check (Figure 5.2).

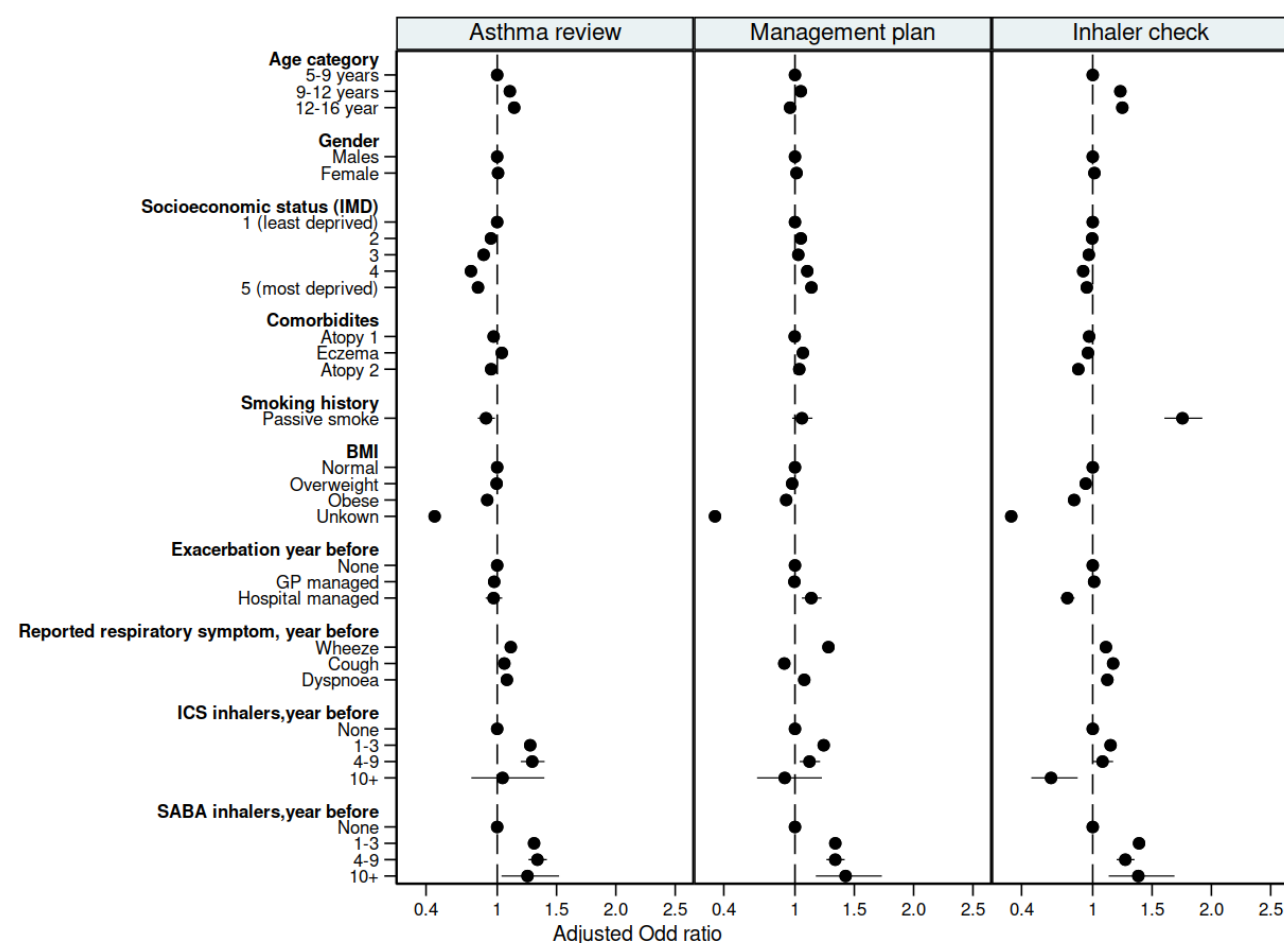
Reported respiratory symptoms increased the odds of receiving an inhaler technique check by around 10-15% for each symptom (wheeze: OR 1.11, 95% CI 1.07-1.16; cough: OR 1.16, 95% CI 1.07-1.17; breathlessness: OR 1.12, 95% CI 1.07-1.17) (Figure 5.2).

In terms of inhaler prescriptions, 1-3 ICS prescriptions in the year before, as compared to no inhaler prescriptions, had higher odds of receiving an inhaler technique check (1-3 ICS: OR

1.10, 95% CI: 1.07-1.14). However, children with 10 or more ICS prescriptions were at significantly lower odds, of 30%, of receiving an inhaler technique check (95% CI: 0.67-0.72; Figure 5.2).

SABA use of up to 3 inhalers was associated with receiving inhaler technique checks (1-3 SABA: OR 1.11, 95% CI: 1.04-1.19) but 10 or more inhaler prescriptions were not (Figure 5.2).

Figure 5. 2: Association between baseline characteristics and receiving each good clinical practice activity (multivariable analysis, all shown variables were included in the models)



#### 5.5.4 Sensitivity analysis

I conducted three sensitivity analyses, all showing negligible differences from the main analysis.

The first sensitivity analyses included evaluating the annual prevalence of the good clinical practice activities, over 3 years after diagnosis, instead of just the first year (Table 5.2, Table 5.3 & Table 5.4). In the second sensitivity analysis I imputed BMI where there were missing values (

5.3). In the third sensitivity analysis, I used mixed logistic regression to account for GP practice clustering (**Error! Reference source not found.**).

*Table 5. 2: : Annual asthma review: multinomial multivariable logistic regression model showing the association between each baseline characteristic and frequency of receiving the good clinical practice activity (once, or 2-3 times) within three years after asthm*

|                                   | 1 annual asthma review in 3 years |         |             | 2-3 annual asthma reviews in 3 years |         |             |
|-----------------------------------|-----------------------------------|---------|-------------|--------------------------------------|---------|-------------|
|                                   | Adjusted OR                       | p-value | 95% CI      | Adjusted OR                          | p-value | 95% CI      |
| <b>Gender</b>                     |                                   |         |             |                                      |         |             |
| Female                            | 0.98                              | 0.43    | (0.93-1.03) | 0.97                                 | 0.17    | (0.92-1.01) |
| <b>Age category (years)</b>       |                                   |         |             |                                      |         |             |
| 5-8.9                             | <i>Reference</i>                  |         |             |                                      |         |             |
| 9-11.9                            | 1.32                              | <0.001  | (1.25-1.4)  | 1.36                                 | <0.001  | (1.29-1.44) |
| 12-16                             | 2.32                              | <0.001  | (2.13-2.53) | 2.63                                 | <0.001  | (2.42-2.86) |
| <b>IMD (socioeconomic status)</b> |                                   |         |             |                                      |         |             |
| 1 (least deprived)                | <i>Reference</i>                  |         |             |                                      |         |             |
| 2                                 | 0.92                              | 0.05    | (0.85-1)    | 0.86                                 | <0.001  | (0.8-0.93)  |
| 3                                 | 0.95                              | 0.18    | (0.87-1.03) | 0.83                                 | <0.001  | (0.77-0.89) |
| 4                                 | 0.89                              | 0.01    | (0.83-0.97) | 0.7                                  | <0.001  | (0.65-0.76) |
| 5                                 | 0.94                              | 0.09    | (0.87-1.01) | 0.74                                 | <0.001  | (0.69-0.8)  |
| <b>Atopy 1</b>                    | 1.05                              | 0.14    | (0.98-1.12) | 1.09                                 | 0.01    | (1.02-1.16) |
| <b>Eczema</b>                     | 0.96                              | 0.14    | (0.91-1.01) | 1.01                                 | 0.76    | (0.96-1.06) |
| <b>Atopy 2</b>                    | 1.07                              | 0.14    | (0.98-1.18) | 1.01                                 | 0.91    | (0.92-1.1)  |
| <b>Passive smoking</b>            | 0.91                              | 0.28    | (0.77-1.08) | 0.91                                 | 0.27    | (0.78-1.07) |
| <b>BMI</b>                        |                                   |         |             |                                      |         |             |
| Normal                            | <i>Reference</i>                  |         |             |                                      |         |             |
| Overweight                        | 1.08                              | 0.15    | (0.97-1.21) | 0.99                                 | 0.82    | (0.89-1.1)  |
| Obese                             | 1.23                              | <0.001  | (1.08-1.41) | 0.98                                 | 0.77    | (0.86-1.11) |
| unknown                           | 0.62                              | <0.001  | (0.59-0.66) | 0.37                                 | <0.001  | (0.35-0.38) |
| <b>Year before study start</b>    |                                   |         |             |                                      |         |             |

| <b>Exacerbations</b>                 |                  |        |              |      |        |              |
|--------------------------------------|------------------|--------|--------------|------|--------|--------------|
| None                                 | <i>Reference</i> |        |              |      |        |              |
| GP managed                           | 1.07             | 0.138  | (0.97-1.17)  | 1.05 | 0.213  | (1.00-1.17)  |
| Hospital managed                     | 1.06             | 0.46   | (0.90-1.24)  | 0.97 | 0.735  | (0.83-1.13)  |
| <b>Reported respiratory symptoms</b> |                  |        |              |      |        |              |
| Wheeze                               | 1.04             | 0.290  | (0.96-1.13)  | 1.08 | 0.039  | (1.00-1.17)  |
| Cough                                | 1.06             | 0.025  | (1.00-1.11)  | 1.21 | <0.001 | (1.15-1.27)  |
| Dyspnoea                             | 0.99             | 0.868  | (0.889-1.10) | 1.14 | 0.012  | (1.02-1.266) |
| <b>ICS inhalers</b>                  |                  |        |              |      |        |              |
| None                                 | <i>Reference</i> |        |              |      |        |              |
| 1-3                                  |                  |        |              |      |        |              |
| 4-10                                 | 1.68             | <0.001 | (1.56-1.81)  | 3.18 | <0.001 | (2.96-3.42)  |
| 10+                                  | 1.14             | <0.001 | (1.04-1.24)  | 2.46 | <0.001 | (2.27-2.67)  |
| <b>SABA inhalers</b>                 |                  |        |              |      |        |              |
| None                                 | <i>Reference</i> |        |              |      |        |              |
| 1-3                                  |                  |        |              |      |        |              |
| 4-9                                  | 1.18             | <0.001 | (1.11-1.25)  | 1.59 | <0.001 | (1.51-1.69)  |
| 10+                                  | 1.42             | <0.001 | (1.3-1.55)   | 1.86 | <0.001 | (1.71-2.01)  |

Table 5. 3: : Inhaler technique check: multinomial multivariable logistic regression model showing the association between each baseline characteristic and frequency of receiving the good clinical practice activity (once, or 2-3 times) within three years after as

|                                   | 1 Inhaler check in 3 years |         |             | 2-3 Inhaler check in 3 years |         |             |
|-----------------------------------|----------------------------|---------|-------------|------------------------------|---------|-------------|
|                                   | Adjusted OR                | p-value | 95% CI      | Adjusted OR                  | p-value | 95% CI      |
| <b>Gender</b>                     |                            |         |             |                              |         |             |
| Female                            | 0.98                       | 0.38    | (0.93-1.03) | 0.98                         | 0.39    | (0.93-1.03) |
| <b>Age category (years)</b>       |                            |         |             |                              |         |             |
| 5-8.9                             | Reference                  |         |             |                              |         |             |
| 9-11.9                            | 1.42                       | <0.001  | (1.33-1.51) | 1.49                         | <0.001  | (1.40-1.59) |
| 12-16                             | 2.3                        | <0.001  | (2.10-2.52) | 2.58                         | <0.001  | (2.35-2.83) |
| <b>IMD (socioeconomic status)</b> |                            |         |             |                              |         |             |
| 1 (least deprived)                | Reference                  |         |             |                              |         |             |
| 2                                 | 0.95                       | 0.21    | (0.87-1.03) | 0.92                         | 0.04    | (0.84-1.00) |
| 3                                 | 0.92                       | 0.05    | (0.85-1.00) | 0.83                         | <0.001  | (0.76-0.90) |
| 4                                 | 0.92                       | 0.06    | (0.85-1.00) | 0.78                         | <0.001  | (0.72-0.85) |
| 5                                 | 0.9                        | 0.01    | (0.83-0.97) | 0.76                         | <0.001  | (0.70-0.82) |
| <b>Atopy 1</b>                    | 1.03                       | 0.4     | (0.96-1.11) | 1.06                         | 0.13    | (0.98-1.13) |
| <b>Eczema</b>                     | 0.97                       | 0.23    | (0.92-1.02) | 0.96                         | 0.12    | (0.91-1.01) |
| <b>Atopy 2</b>                    | 0.91                       | 0.05    | (0.83-1.00) | 0.86                         | <0.001  | (0.78-0.95) |
| <b>Passive smoking</b>            | 1.35                       | <0.001  | (1.11-1.65) | 1.53                         | <0.001  | (1.26-1.87) |
| <b>BMI</b>                        |                            |         |             |                              |         |             |
| Normal                            | Reference                  |         |             |                              |         |             |
| Overweight                        | 1.01                       | 0.83    | (0.89-1.15) | 0.89                         | 0.07    | (0.79-1.01) |
| Obese                             | 0.96                       | 0.57    | (0.83-1.11) | 0.73                         | <0.001  | (0.63-0.84) |
| unknown                           | 0.38                       | <0.001  | (0.36-0.4.) | 0.19                         | <0.001  | (0.18-0.21) |
| <b>Year before study start</b>    |                            |         |             |                              |         |             |
| <b>Exacerbations</b>              |                            |         |             |                              |         |             |
| None                              | Reference                  |         |             |                              |         |             |
| GP managed                        | 1.04                       | 0.348   | (0.94-1.15) | 1.00                         | 0.984   | 0.90-1.10)  |

|                                      |                  |        |             |      |        |            |
|--------------------------------------|------------------|--------|-------------|------|--------|------------|
| Hospital managed                     | 0.80             | 0.008  | (0.68-0.94) | 0.64 | <0.001 | 0.55-0.75) |
| <b>Reported respiratory symptoms</b> |                  |        |             |      |        |            |
| Wheeze                               | 1.16             | 0.001  | (1.06-1.27) | 1.2  | <0.001 | 1.10-1.31) |
| Cough                                | 1.12             | <0.001 | (1.06-1.18) | 1.21 | <0.001 | 1.14-1.27) |
| Dyspnoea                             | 1.11             | 0.08   | (0.98-1.24) | 1.24 | <0.001 | 1.10-1.39) |
| <b>ICS inhalers</b>                  |                  |        |             |      |        |            |
| None                                 | <i>Reference</i> |        |             |      |        |            |
| 1-3                                  | 1.58             | <0.001 | (1.47-1.69) | 1.93 | <0.001 | 1.78-2.08) |
| 4-9                                  | 1.81             | <0.001 | (1.67-1.96) | 3.94 | <0.001 | 3.64-4.27) |
| 10+                                  | 1.68             | <0.001 | (1.52-1.85) | 5.07 | <0.001 | 4.58-5.60) |
| <b>SABA inhalers</b>                 |                  |        |             |      |        |            |
| None                                 | <i>Reference</i> |        |             |      |        |            |
| 0-3                                  | 1.12             | <0.001 | (1.06-1.27) | 1.26 | <0.001 | 1.10-1.31) |
| 4-10                                 | 1.19             | <0.001 | (1.12-1.27) | 1.63 | <0.001 | 1.53-1.73) |
| 10+ inhalers                         | 1.32             | <0.001 | (1.21-1.45) | 1.83 | <0.001 | 1.68-2.00) |

Table 5. 4: Asthma management plan: multinomial multivariable logistic regression model showing the association between each baseline characteristic and frequency of receiving the good clinical practice activity (once, or 2-3 times) within three years after asthma

|                                   | 1 management plan in 3 years |         |             | 2-3 management plans in 3 years |         |             |
|-----------------------------------|------------------------------|---------|-------------|---------------------------------|---------|-------------|
|                                   | Adjusted OR                  | p-value | 95% CI      | Adjusted OR                     | p-value | 95% CI      |
| <b>Gender</b>                     |                              |         |             |                                 |         |             |
| Female                            | 0.96                         | 0.11    | (0.92-1.01) | 0.97                            | 0.16    | (0.92-1.01) |
| <b>Age category (years)</b>       |                              |         |             |                                 |         |             |
| 5-8.9                             | <i>Reference</i>             |         |             |                                 |         |             |
| 9-11.9                            | 1.37                         | <0.001  | (1.3-1.45)  | 1.40                            | <0.001  | (1.32-1.48) |
| 12-16                             | 2.63                         | <0.001  | (2.43-2.86) | 2.68                            | <0.001  | (2.47-2.92) |
| <b>IMD (socioeconomic status)</b> |                              |         |             |                                 |         |             |
| 1 (least deprived)                | <i>Reference</i>             |         |             |                                 |         |             |
| 2                                 | 1.04                         | 0.33    | (0.96-1.12) | 1.03                            | 0.38    | (0.96-1.12) |
| 3                                 | 0.96                         | 0.24    | (0.89-1.03) | 0.95                            | 0.22    | (0.88-1.03) |
| 4                                 | 1.01                         | 0.86    | (0.94-1.08) | 1.01                            | 0.85    | (0.94-1.08) |
| 5                                 | 1.02                         | 0.65    | (0.95-1.09) | 1.06                            | 0.13    | (0.98-1.13) |
| <b>Atopy 1</b>                    | 1.04                         | 0.17    | (0.98-1.11) | 1.04                            | 0.18    | (0.98-1.11) |
| <b>Eczema</b>                     | 0.97                         | 0.19    | (0.92-1.02) | 1.00                            | 0.98    | (0.95-1.05) |
| <b>Atopy 2</b>                    | 0.98                         | 0.66    | (0.9-1.07)  | 0.98                            | 0.65    | (0.9-1.07)  |
| <b>Passive smoking</b>            | 1.12                         | 0.16    | (0.95-1.32) | 0.97                            | 0.73    | (0.82-1.15) |
| <b>BMI</b>                        |                              |         |             |                                 |         |             |
| Normal                            | <i>Reference</i>             |         |             |                                 |         |             |
| Overweight                        | 1.06                         | 0.28    | (0.96-1.17) | 0.99                            | 0.85    | (0.9-1.09)  |
| Obese                             | 1.02                         | 0.79    | (0.9-1.14)  | 0.87                            | 0.02    | (0.77-0.97) |
| Unknown                           | 0.47                         | <0.001  | (0.45-0.49) | 0.25                            | <0.001  | (0.24-0.27) |
| <b>Year before study start</b>    |                              |         |             |                                 |         |             |
| <b>Exacerbations</b>              |                              |         |             |                                 |         |             |
| None                              | <i>Reference</i>             |         |             |                                 |         |             |

|                                      |                  |        |             |      |        |             |
|--------------------------------------|------------------|--------|-------------|------|--------|-------------|
| GP managed                           | 1.08             | 0.066  | (0.99-1.17) | 1.02 | 0.558  | (0.94-1.11) |
| Hospital managed                     | 0.91             | 0.222  | (0.79-1.05) | 0.90 | 0.191  | (0.78-1.04) |
| <b>Reported respiratory symptoms</b> |                  |        |             |      |        |             |
| Wheeze                               | 1.38             | 0.001  | (1.05-1.22) | 1.25 | <0.001 | (1.16-1.35) |
| Cough                                | 0.95             | 0.071  | (0.91-1.00) | 0.97 | 0.405  | (0.93-1.02) |
| Dyspnoea                             | 1.01             | 0.719  | (0.92-1.12) | 1.11 | 0.043  | (1.00-1.22) |
| <b>ICS inhalers</b>                  |                  |        |             |      |        |             |
| None                                 | <i>Reference</i> |        |             |      |        |             |
| 1-3                                  | 1.59             | <0.001 | (1.48-1.70) | 1.87 | <0.001 | (1.73-2.02) |
| 4-10                                 | 1.67             | <0.001 | (1.55-1.79) | 3.12 | <0.001 | (2.88-3.37) |
| 10+                                  | 1.55             | <0.001 | (1.42-1.69) | 3.67 | <0.001 | (3.34-4.03) |
| <b>SABA inhalers</b>                 |                  |        |             |      |        |             |
| None                                 | <i>Reference</i> |        |             |      |        |             |
| 1-3                                  | 1.6              | <0.001 | (1.49-1.72) | 2.88 | <0.001 | (2.66-3.11) |
| 4-9                                  | 1.88             | <0.001 | (1.67-2.11) | 1.91 | <0.001 | (1.67-2.19) |
| 10+                                  | 1.28             | <0.001 | (1.18-1.39) | 2.58 | <0.001 | (2.36-2.81) |

Figure 5. 3: Imputing BMI values: three forest plots showing the association between children's baseline characteristics and receiving each good clinical practice activity. The models used imputed BMI values and were adjusted for all baseline variables.

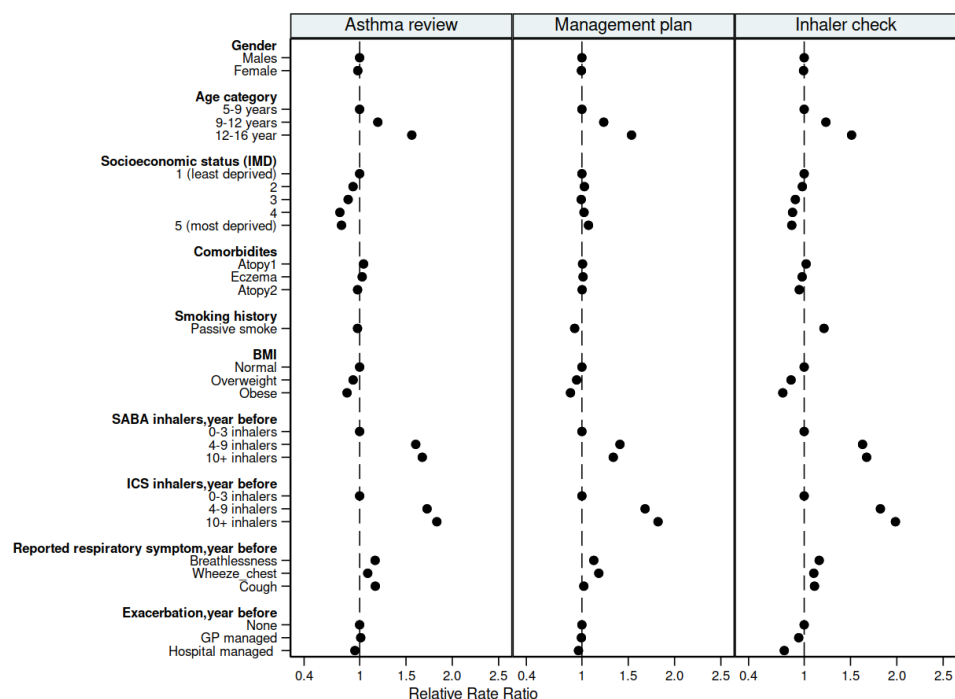
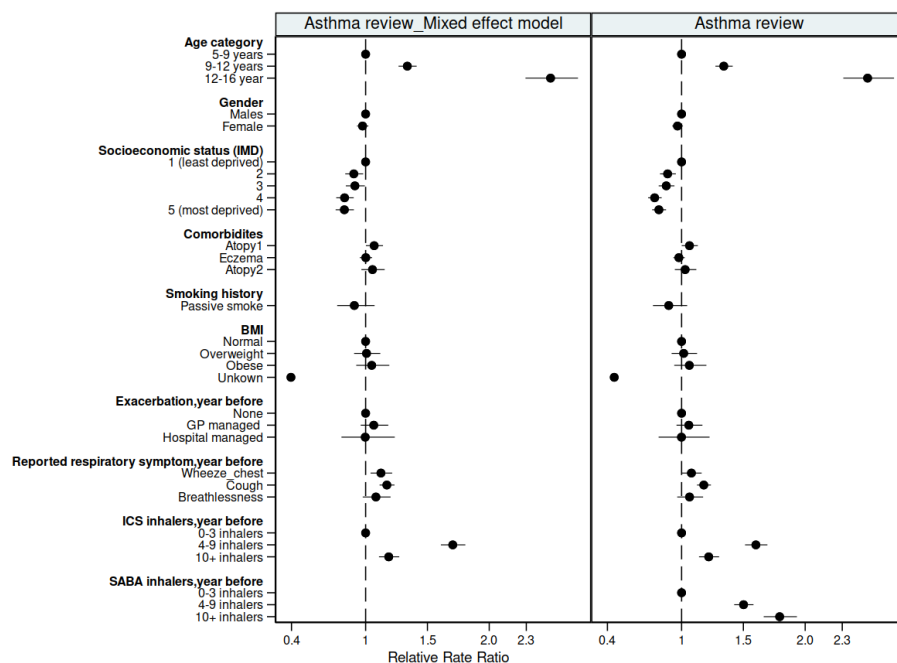


Figure 5. 4: Assessing potential clustering effect by GP practice: comparison of the asthma review model, with and without mixed effects.



## 5.5 Discussion

I have shown that around half (41%-64% depending on which good clinical practice activity of UK school-age children with asthma did not receive a good clinical practice activity as recommended by national and international guidelines. Furthermore, it appeared that less than one in ten children received all three together in one consultation. A higher proportion received them in the first year of diagnosis, but thereafter the proportion dropped for all good clinical practice activities. Although this has not been addressed as comprehensively in other studies, medical record audits and questionnaires of primary care practices from the UK and North America, suggest suboptimal implementation of asthma guideline recommendations is commonplace [30-33].

It is notable that the percentage of children who received an annual asthma review meets the 45% minimum threshold required for English primary care practices to qualify for financial incentives under the NHS's Quality Outcomes Framework (QOF) [42]. My findings in children, are very similar to the proportion of UK adults receiving annual asthma reviews, further supporting the concept that this proportion is related to QOF [29]. This correlation raises concerns that the financial incentives may be driving practices to meet only the minimum care standards rather than striving for optimal patient outcomes. Additionally, asthma management plans and inhaler technique checks, which are not directly incentivised financially, were received by a smaller proportion of children, approximately 30-40%. This discrepancy underlines potential shortcomings in the UK's financial reward system for managing chronic conditions, which appears to influence the delivery of care in ways that might not necessarily align with patient needs. The lack of specificity in the threshold requirements could further exacerbate healthcare disparities, as they do not define which children should benefit from these critical clinical activities, potentially leaving the most vulnerable patients without essential care [42, 122].

Very small numbers of children were recorded as receiving an influenza vaccine. However, this low uptake is probably related to a higher uptake of influenza vaccines through school vaccination programmes, or even local pharmacies, without this information being translated back into NHS primary care records. I therefore concluded that this dataset is not suitable for assessing influenza uptake and did not explore this further.

I also investigated the factors related to receiving good clinical practice activities. I found that the children most at risk of not receiving them were also those most at risk of poor asthma control or asthma exacerbations. This included younger children who, as my study has shown (chapter 4), are at the greatest risk of exacerbations. It is unclear why younger children would be less likely to receive them but perhaps this is poor perception on the behalf of healthcare professionals believing younger children do not benefit as much. In fact, understanding of asthma by the caregiver, including how to use inhalers, spacers, how to self-manage, is critical at an early age and may ensure better management throughout childhood [123].

Another group of children less likely to receive good clinical practice activities were children residing in more deprived areas. In general, in the UK, childhood poverty is associated with poorer access to healthcare, delayed treatment and worse outcomes [124]. This study appears to show an example of this, in that children with asthma living in more deprived areas were at greater risk of not receiving optimal asthma care and were at greater risk of experiencing an asthma exacerbation (see Chapter 4) which may lead to reduced school attendance [125]. In the UK, NHS England reports that “The UK has one of the highest prevalence, emergency admission and death rates for childhood asthma in Europe” [126]. Although there is a general observed decrease in hospitalisation rates among children, they remain elevated among low socioeconomic status and minority populations [127]. This is partly due to difficulties in accessing primary care services as reported by the Office for National Statistics, relying on emergency care instead of primary care services [128]. According to a recent Health Foundation report, poorer areas in England are missing out on funding and additional primary care staff, because the greater health needs of their populations are not adequately considered in current funding arrangements [129]. With childhood poverty increasing in the UK [130], my nationwide study further highlights this issue particularly as asthma is the most prevalent childhood chronic condition [131]. There are many relatively simple, modifiable risk factors in asthma care, but these first require healthcare engagement.

Children that were obese were at risk of not receiving all three good clinical practice activities. Obesity is highly prevalent in children with asthma, especially in those with more severe asthma [105, 132]. Obese children tend to experience more asthma symptoms, more frequent and severe exacerbations, a diminished response to various asthma medications, and a lower

quality of life [133], which should necessitate more comprehensive management strategies and these are the children we should be targeting to need more asthma reviews, not less.

Yet, it was the children with no recorded BMI in their medical records that were at the greatest risk of not receiving any of the activities, a staggering approximate 70% lower odds. As discussed above, we found the absence of BMI recording for around 40% of the children. This is particularly alarming given that it is a known, modifiable, risk factor for worse asthma outcomes [105]. The absence could be attributed to a variety of factors, including a potential lack of engagement with healthcare services by caregivers, or a lack of healthcare understanding of the importance of BMI in asthma. The lack of recording itself appears to be a marker for suboptimal asthma healthcare. Even though, as shown in my earlier Chapter 3, I found no differences between the group of children with recorded BMI and those without, despite efforts to understand the reasons for missing BMI data. This suggests that the absence of BMI records may not be related to specific child characteristics. It could instead reflect differences in healthcare provision at a practice level, however on accounting for each GP practice (in the clustering sensitivity analysis) this did not affect the estimates. Therefore, it could be specifically related to individual healthcare professionals which I could not account for or measure in this data due to the lack of granularity at the individual clinical level. For example, respiratory-trained practice nurses may be more aware that BMI is a risk factor for poor asthma control and take the time to measure and record it, equally, they may be more likely to conduct good clinical practice activities. Recording of BMI, a standardised, quick and cheap monitoring tool for children's health, may be a proxy for the level of asthma care (or all medical care) received by the child.

Unfortunately, the scores of validated asthma control questionnaires were rarely recorded in the dataset. However, it was notable that children that reported symptoms to their GP practice or had prescriptions of ICS and SABA, generally had higher odds of receiving a good clinical practice activity. As these variables are often used as markers of asthma control, reassuringly these findings suggest poorer asthma control was associated with receiving a good clinical practice activity.

## 5.6 Strengths and limitations

The strengths of this study include the use of a large cohort of children, representing real clinical practice and generalisability to the UK population. Furthermore, I believe this is the first nationwide assessment of these three asthma clinical practices in children. The use of routinely recorded data meant that the study did not suffer from recall or selection bias, however, I therefore also did not have data on non-routinely recorded variables such as lung function, asthma control scores, medication adherence, asthma education, school attendance and quality of the good clinical practice activities provided. Due to the dates of the study, it is likely most good clinical practice activities were provided in person and activities were rarely coded as being via telephone or not in person. For this reason, I could not investigate the effect of remote consultations, as compared to in-person activities. I also had missing values for some variables, particularly BMI. As a sensitivity analysis, I used multiple imputations and found negligible differences in the estimates, suggesting that the missing data did not significantly impact the results. Additionally, I did not have information on children's ethnicity, although this is now available in CPRD data, at the time reliable ethnicity data was not available. I was unable to evaluate outcomes other than exacerbations due to the nature of the data available to us, as I did not have questionnaire data on asthma control, school absenteeism, or quality of life. However, the proxies for asthma control of symptoms and inhaler prescriptions did suggest worse control was associated with implementation of good clinical practice activities.

## 5.7 Conclusion

In this chapter, I utilised nationwide data from real-life clinical practices to assess the implementation of guideline-recommended good clinical practice activities for childhood asthma. Nearly half of school-aged children with asthma did not appear to receive one of the good clinical practice activities I investigated, and only 8% were recorded as receiving all three activities in one consultation. The proportion of children receiving good clinical practice activities was higher in the first year after diagnosis but declined thereafter. This study highlighted significant disparities in the implementation of asthma guidelines. The financial incentives under the NHS's Quality Outcomes Framework may drive practices to meet only

minimum care standards, leaving more vulnerable groups at risk of not receiving adequate care. These groups include younger children, those from more deprived areas, children with missing BMI values (that may signify a more general lack of healthcare engagement from either the provider or the caregiver), and children with excessive inhaler prescription rates. This study underscores the importance of enhancing healthcare engagement to address these disparities and improve asthma outcomes for all children.

## 6. Chapter 6: Effectiveness of guideline-recommended good clinical practice activities

### 6.1. Introduction

In my previous chapter, I investigated the annual prevalence of the implementation of good clinical practice activities. These activities, which are advocated by national guidelines, include scheduled asthma reviews, asthma management plans and inhaler technique checks [8, 9, 85]. As discussed in Chapter 1, there is evidence from RCTs that some of these activities are effective in certain settings, for example, asthma management plans provided within a supportive framework[39], while standalone inhaler technique checks may not be effective [36]. However, many of these RCTs did not include children. In this study I therefore sought to understand how effective these activities are for school-age children when implemented within everyday clinical practice and which children are most likely to benefit. Interestingly, the BTS/SIGN asthma management guidelines only comment that as there is no evidence of harm from asthma reviews, they continue to recommend them [78]. Therefore, if there is no patient benefit from such blanket activities, it could be argued that the cost-effectiveness and resource allocation of these practices should be evaluated.

### 6.2. Objectives

I sought to evaluate the effectiveness of three good clinical practice activities: annual asthma review, asthma management plan, and checking patients' inhaler technique.

I sought to examine the effectiveness of these activities as a standalone clinical practice as well as their combined impact on patient outcomes in a real-world clinical setting.

To assess effectiveness in this setting, I chose the outcome of asthma exacerbations. Although it would be valuable to also assess their effect on asthma control, this was not possible with the data source available to me (as discussed further in the limitations section).

## 6.3. Methods

### 6.3.1. Data source

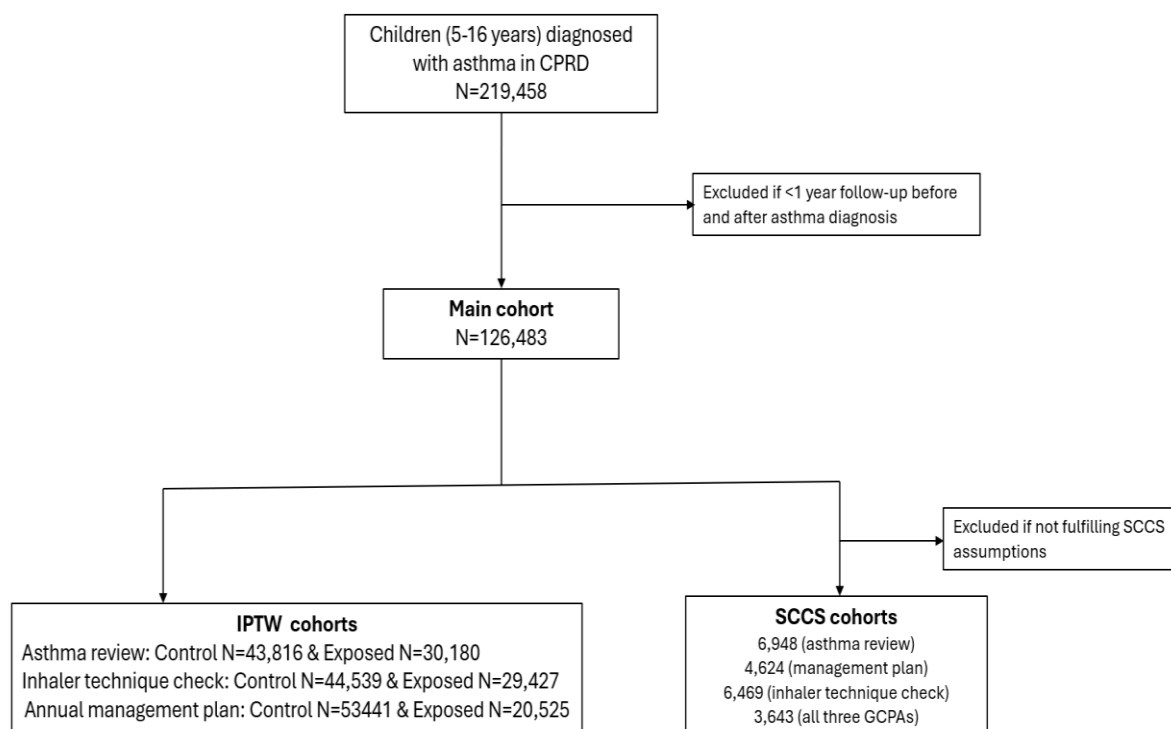
Data were collected from the Clinical Practice Research Datalink (CPRD), details of which are described in Chapter 2. These data were then linked with Hospital Episode Statistics, providing admissions data, and mortality data from the Office for National Statistics

### 6.3.2 Study design and participants

The identification of the cohort is described in detail in the previous chapter. In brief, the study population included children aged 5-16 years old, between 2004 and 2021, with  $\geq 2$  asthma codes recorded and  $\geq 12$  months of follow-up data. Each child entered the cohort on the day their asthma was diagnosed (i.e. their first asthma code) and exited at the earliest of leaving the GP practice, their 18th birthday, or death.

To assess the effect of good clinical practice activities on asthma exacerbations, I used two methodological approaches, (i) a self-controlled case series and (ii) a longitudinal cohort with inverse probability treatment weighting. Using two different methods, each with different biases, is often termed triangulation [134]. The benefit of triangulation is that if both approaches report the same result, this provides a more robust and reliable finding. On the other hand, if they do not report the same finding, this points towards a limitation of one, or both, of the methodological approaches for that research question.

Figure 6. 1: Flow chart for the cohort selection



SCCS=Self-Controlled Case series, IPTW= Inverse Probability of Treatment Weighting

**Cohort design (method 1):** The first methodological approach is a traditional longitudinal cohort design. I created three cohorts, one for each good clinical practice activity. Within each cohort, the exposed group included children who received an asthma review, management plan or inhaler technique check in the second year after their diagnosis. The date of the instigation of the good clinical practice activity was the study start date.

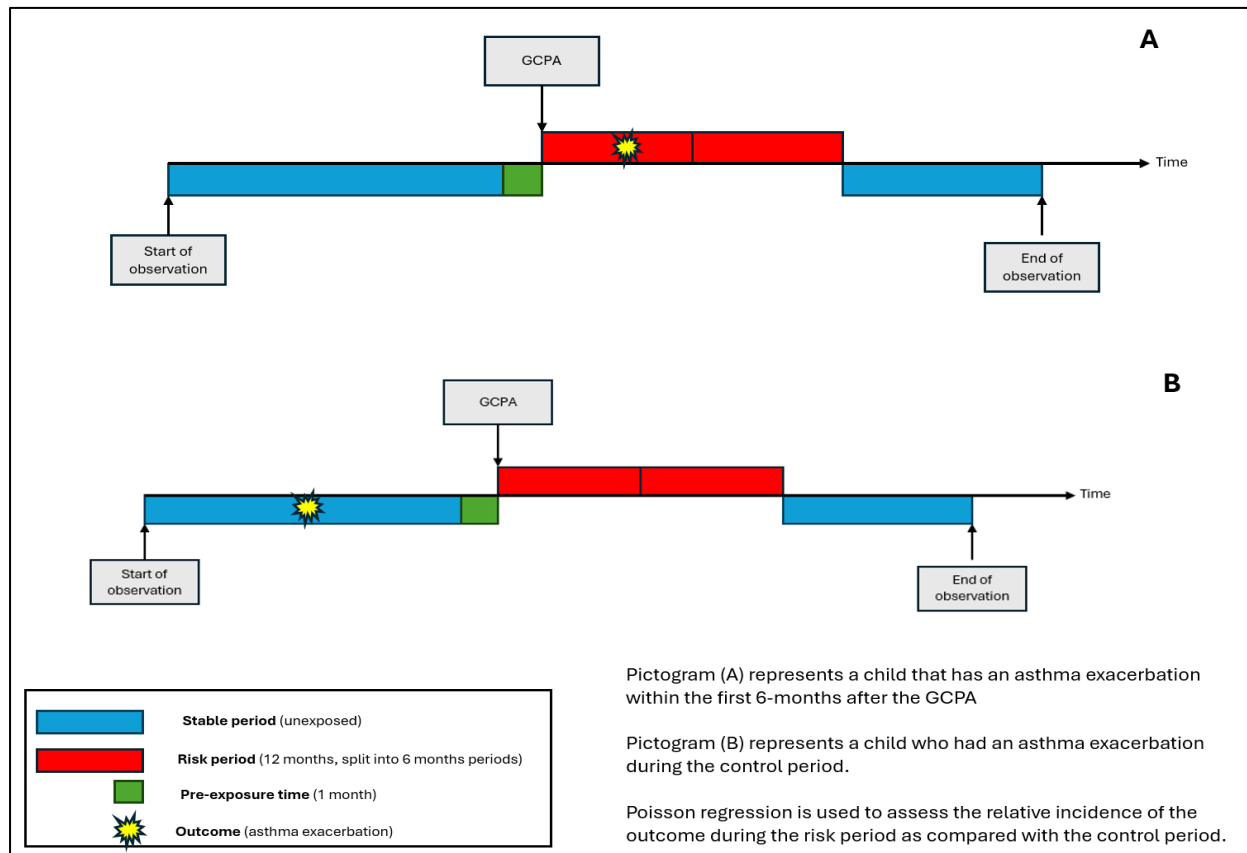
I chose the second year after diagnosis to assess the effectiveness of good clinical practice activities because looking several years after diagnosis could be at higher risk of bias (including confounding from previous good clinical practice activities). The good clinical practice activity occurring in the first year may provide spurious estimates as the good clinical practice activities were often documented as occurring on the day of their asthma diagnosis. Furthermore, I wished to see the effect of good clinical practice activities on children with a more established period of living with their asthma.

The control group consisted of children who did not receive good clinical practice activity in the second year after diagnosis, with their follow-up start date set at 18 months post-diagnosis. The choice of 18 months was based on my calculation of the mean time for children to receive their second asthma review, which was 18 months after diagnosis.

**Self-controlled case series (method 2):** For my second methodological approach, I used a self-controlled case series (SCCS) design (figure 6.2). The SCCS method offers a unique advantage by completely removing confounding that is constant throughout the observation period, such as genetics, socioeconomic status, and healthcare behaviour [135, 136]. This is achieved because each child serves as their own control. Statistical analysis is then applied to compare the number of outcome events before and after the exposure in each individual. In this type of design, only those that were exposed (received the good clinical practice activity) and experienced the outcome (asthma exacerbation) are included.

To ensure valid and unbiased estimates in the SCCS design, several key assumptions must be met [135]. First, recurrences of the outcome (asthma exacerbations) should be independent. To adhere to this, only the first exacerbation for each child was included. Second, the occurrence of the outcome should not alter the probability of subsequent exposures. To control for this, a 'pre-exposure period' was employed. In this study, a 31-day pre-exposure period was used, recognising that an asthma exacerbation could lead to the provision of a good clinical practice activity. This pre-exposure period is then ignored in the analysis, such that any exacerbations occurring during this period do not contribute towards the final estimate, as they likely led to the implementation of the good clinical practice activity. Including these events could bias the estimates towards suggesting effectiveness, but incorrectly excluding (if they did not lead to a good clinical practice activity) will only reduce the precision of the estimate. For this reason, I used 31 days as a sufficient pre-exposure period, i.e. a realistic time within which an exacerbation-related good clinical practice activity would be made. A good clinical practice activity that occurred on the day of an exacerbation were also excluded within the pre-exposure period. Third, the outcome itself should not shorten the observation period; for example, an asthma-related death, which fortunately did not occur in this cohort, would end the observation period prematurely.

Figure 6. 2: Self case-control series study design



GCPA=Good Clinical Practice Activity

### 6.3.3. Variables

**Outcome:** An asthma exacerbation was defined as a short course of oral corticosteroids, asthma-related A&E visit, or hospital admission for asthma (ICD-10 codes J45 and J46).

**Variables:** The demographic variables considered were BMI, socioeconomic deprivation (IMD) and smoking status (derived as previously described).

Reported comorbidities were categorized into 'atopy 1,' 'atopy 2,' and eczema, based on relevant medical record codes. Atopy 1 included hay fever, pet allergy, or house dust mite allergy, while atopy 2 included food or drug allergies (Appendix 4).

Asthma medications evaluated included short-acting beta-agonists (SABA), inhaled corticosteroids (ICS), and add-on medications such as long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA).

In the year before cohort entry, the prevalence of respiratory symptoms was assessed as a binary variable based on GP practice reports (yes/no) for wheeze/chest tightness, cough, or breathlessness, using the codes listed in Appendices 7,8 and 9.

#### 6.4.4 Analysis

##### **Descriptive analysis**

The children included in the IPTW and SCCS models were described by the variables listed above, using total number and percentage for categorical variables, and mean and standard deviation, or median and interquartile range, for continuous variables.

##### **Statistical Analysis**

Two statistical methods were used to estimate the association between each good clinical practice activity and asthma exacerbations, depending on the design.

Inverse probability treatment weighting (IPTW) was applied to the cohort design. IPTW is a method used in observational studies to try to replicate, as best as possible, the balance of confounders that occurs in RCTs. IPTW aims to mimic the random allocation of the treatment in an RCT by assigning each child a propensity score. This score quantifies the likelihood of a child having received the intervention (e.g. an asthma review) based on observable baseline characteristics. IPTW creates a pseudo-population where treatment assignment is independent of observed confounders, aiming for unbiased comparison of outcomes between unexposed and exposed groups [137].

**IPTW method:** To determine the probability of receiving the good clinical practice activity I used logistic regression and included the following variables in the model: sex, BMI, year of birth, age at the time of diagnosis, passive smoking, atopy variables, respiratory symptoms, number of inhalers (ICS and SABA) and exacerbation history in the year before the study start. These variables were chosen as they could be potential confounders or major risk factors for an asthma exacerbation. To obtain the propensity score I took the inverse of the probability score.

Two key assumptions of IPTW are (i) all significant confounders are included in the logistic regression model to derive the probability score, and (ii) every individual has a non-zero

probability of receiving the treatment [138]. All children met the second assumption, and I discuss the limitations of the study in respect of the first assumption below.

After applying IPTW, I applied balance diagnostics to ensure there was sufficient balance of each covariate between the exposed and unexposed groups. First, I measured the mean standardized difference for each covariate, before and after applying weighting. The mean standardised difference is the difference in means, in units of the pooled standard deviation, and is not influenced by sample size [139]. Second, I visualised the propensity scores of the exposed and unexposed on the same graph, after weighting, to determine the region of common support (overlap of scores) as inferences can only be made where the groups have similar scores.

Once the balance was confirmed I used proportional Cox regression to estimate the association between each good clinical practice activity and the first asthma exacerbation within the following 12 months. I used five models, one for each of the three activities, one for children who received at least two good clinical practice activities in the same consultation, and one for when children received three good clinical practice activities in the same consultation.

I intended to conduct stratified analyses for all three good clinical practice activities to determine if there were modifiers of the association between each good clinical practice activity and asthma exacerbations. All the good clinical practice activity models were to be stratified by the following binary variables age (above or below 12 years old), gender (male or female), inhaler use (SABA and ICS: no inhalers prescribed or at least one, in the year before), and asthma exacerbations (none or at least one, in the year before). However, it was clear after conducting the stratified analysis for just one good clinical practice activity, asthma review, that the models were biased.

To further investigate the bias in the model, I ran two sensitivity analyses. First, I only analysed the first 3 months of time after an asthma review, and separately, the first 6 months after an asthma review. Second, I ran the models categorising the exacerbation outcome into GP-managed and hospital-managed (admission or A&E) exacerbations and then analysed these outcomes in separate models.

**SCCS design:** The SCCS design is described above. I had four SCCS models, one for each of the three good clinical practice activities and one for children that had received all three good clinical practice activities during the same consultation. To estimate the association between each good clinical practice activity and asthma exacerbations I applied fixed-effect conditional Poisson to derive incidence rate ratios (IRR), comparing the control period (12 months before the good clinical practice activity; excluding the 31-day pre-exposure period) and the risk period (12 months after the good clinical practice activity. To examine for longitudinal effects, the risk period was segmented into two periods, 0-181 days, and 182-365 days after good clinical practice activity. As the design does not account for time-varying confounding, models were adjusted for age.

## 6.5 Results

### *6.5.1. Characteristics of the children in the two methods*

Multiple different analysis cohorts were drawn from the main cohort (Figure 6.1). These included five IPTW-cohorts. One cohort for each good clinical practice activity as a standalone intervention, one cohort for children with two good clinical practice activity (any two of the three) in the same consultation, and one cohort for children with three good clinical practice activity in the same consultation.

Additionally, four SCCS cohorts were formed (one for each good clinical practice activity and one for three good clinical practice activities in the same consultation). The SCCS design is such that these cohorts are smaller in sample size because to satisfy the assumptions of the SCCS design, each child must have had the exposure and the outcome at some point during the observation period. The observation period was maximum of two years, 12 months before the good clinical practice activity and a maximum of 12 months after.

Not all of these cohorts are described below, due to their similarity and thus repetitiveness of information.

- For the IPTW-cohort, only the asthma review cohort is described below in the written results and by bar graphs; but the tables for all three main IPTW-cohorts are included in the thesis.

- For the SCCS, all three cohorts were described that contained children having one of each good clinical practice activity.

#### 6.5.1.1. Characteristics of the children in the asthma review IPTW-cohort

The IPTW-cohort for annual asthma review included 73,996 children, 30,180 were exposed (had an asthma review) and 43,816 were controls (no good clinical practice activity) (Figure 6.1).

#### **Baseline characteristics**

The average age at diagnosis was 8.8 years (SD 2.7) for exposed and 8.7 years (SD 2.7) for the controls. Gender distribution between the exposed and controls was identical, with 56% males and 44% females in both groups (Figure 6.3).

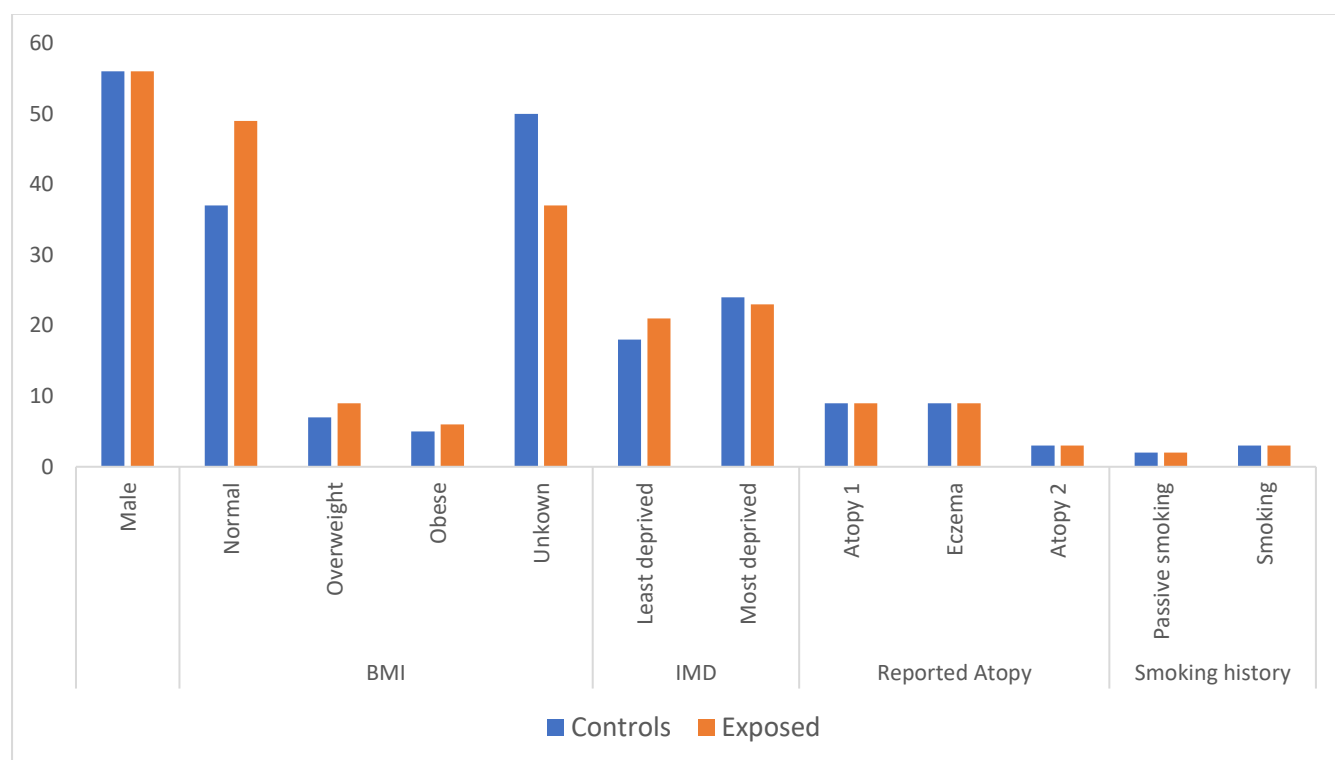
42% of the total cohort had a normal BMI, with the exposed group having a higher proportion of children with a normal BMI (49%) compared to the control group (37%). The prevalence of overweight children was slightly higher in the exposed group (9%) than in the control group (7%), and the obese category was similar across both groups (5% in the control and 6% in the exposed). Notably, a higher percentage of BMI data was unknown in the control group (50%) compared to the exposed group (37%).

IMD (socioeconomic status), was similar across both groups, with minor variations: the exposed group had slightly more children in the last deprived (21% vs. 18%) and slightly fewer in the most deprived (23% vs. 24%) categories (Figure 6.3).

Health characteristics showed that the presence of atopy (7%) and eczema (7%) was consistent across both groups, while atopy 2 was reported in 2% of both groups (Figure 6.3).

Smoking and passive smoking exposure were also similar, affecting 3% and 2% of the children, respectively, in both groups (Figure 6.3)

Figure 6. 3: Characteristics of the IPTW-cohort for asthma review at cohort entry.



IMD= index of multiple deprivation, BMI=body mass index, Atopy 1 receiving a code for allergic rhinitis, or allergy to pets, pollen or house dust mites, Atopy 2 receiving a code for 'food/drug allergy.

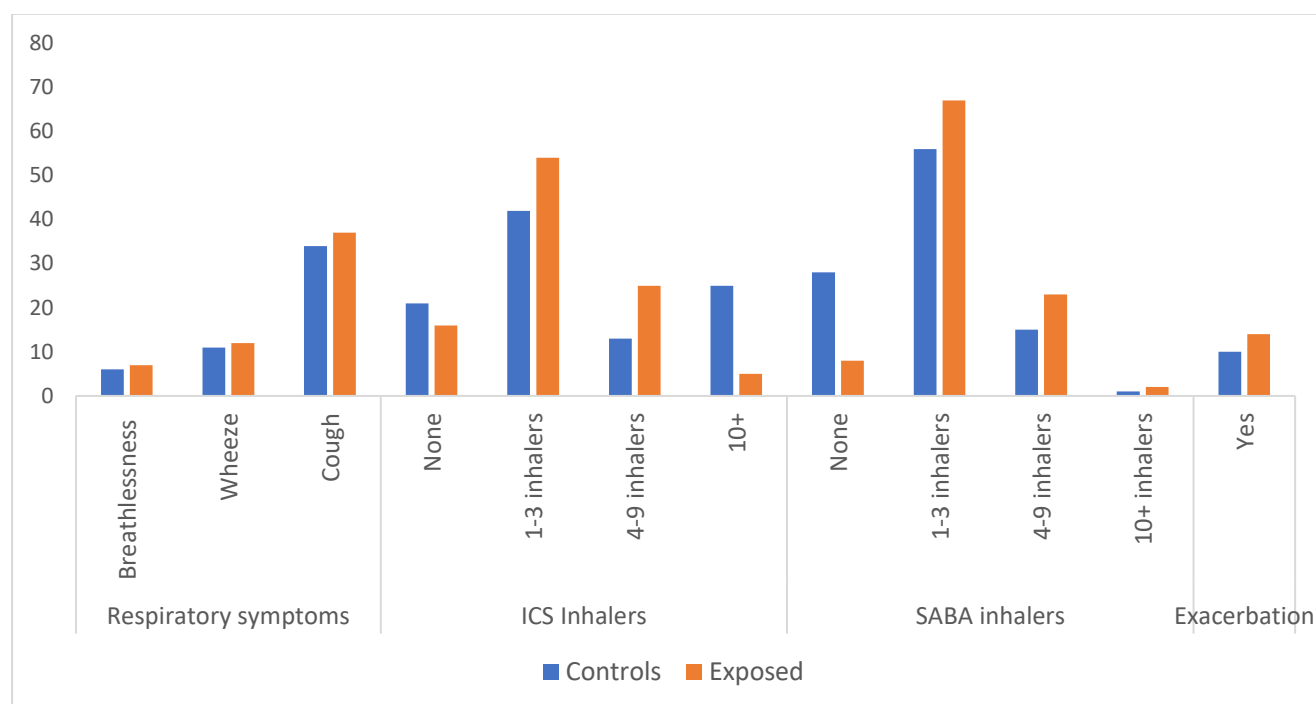
### Variables measured one year before cohort entry

The exposed group reported a higher prevalence of breathlessness (4% vs. 2%), wheeze/chest tightness (10% vs. 3%), and cough (23% vs. 16%) (Figure 6.4).

Inhaler use differed, with the exposed group showing higher use of 1-3 inhalers (56% vs. 42%) and 4-9 inhalers (20% vs. 13%). While the control group had more children with no ICS inhalers (44% vs. 21%) and more children with 10+ inhalers (2% in both groups). SABA inhaler use was higher in the exposed group for 1-3 inhalers (68% vs. 56%) and 4-9 inhalers (21% vs. 15%) (Figure 6.4).

Number of children with exacerbations were slightly higher in the exposed than in the controls (14% vs. 10%) (Figure 6.4)

Figure 6. 4: Asthma characteristics of the IPTW-cohort for asthma review

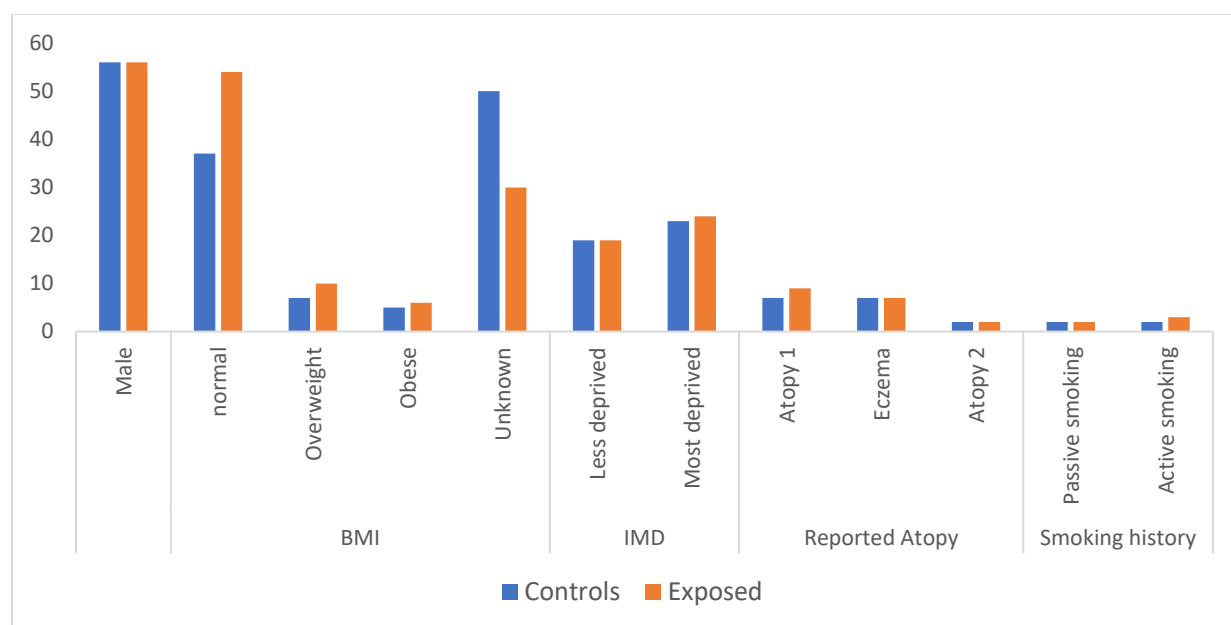


ICS=inhaled corticosteroids, SABA=short-acting beta-agonist

#### 6.5.1.2. Characteristics of the children in the asthma management plan IPTW-cohort

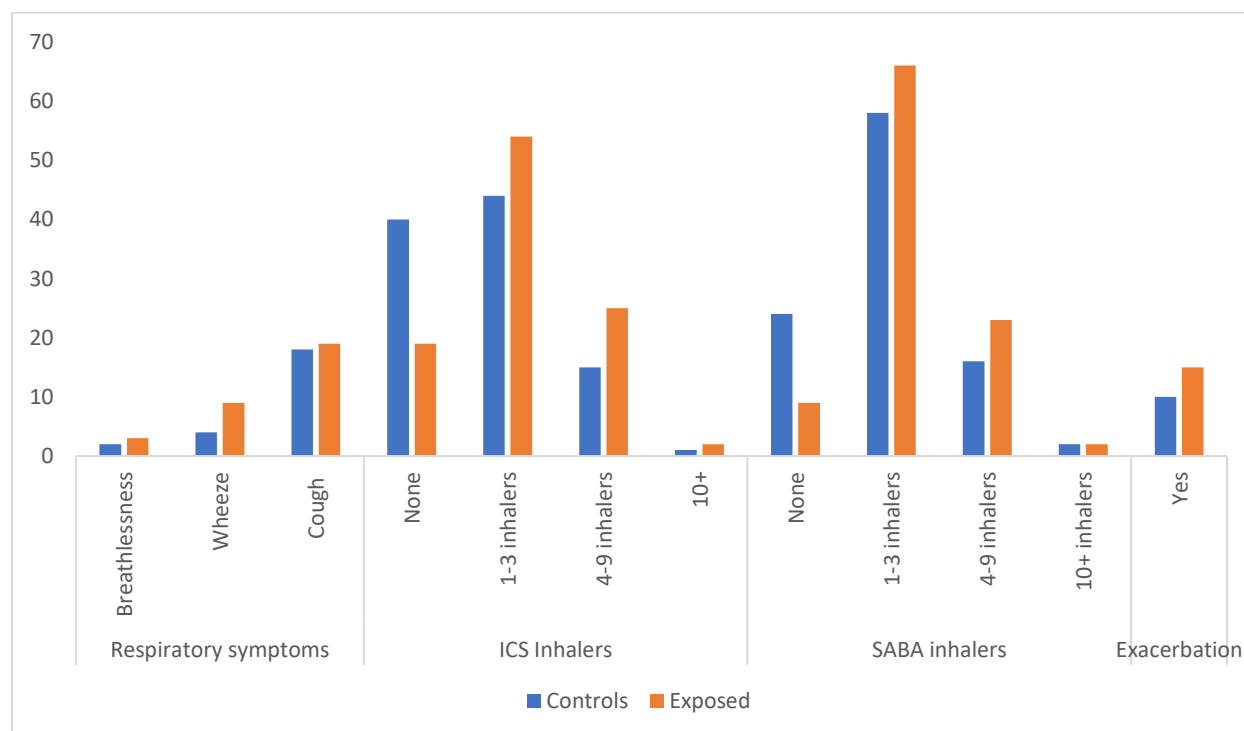
As described above, the IPTW cohorts were very similar to each other, so I have not described each again in detail. The baseline characteristics and variables in the year before cohort entry are shown for the asthma management plan cohort in figure 6.5.

Figure 6. 5: Characteristics of the IPTW-cohort for asthma management plan at cohort entry.



IMD= index of multiple deprivation, BMI=body mass index, Atopy 1 receiving a code for allergic rhinitis, or allergy to pets, pollen or house dust mites, Atopy 2 receiving a code for 'food/drug allergy.

Figure 6. 6: Asthma characteristics of the IPTW-cohort for management plan

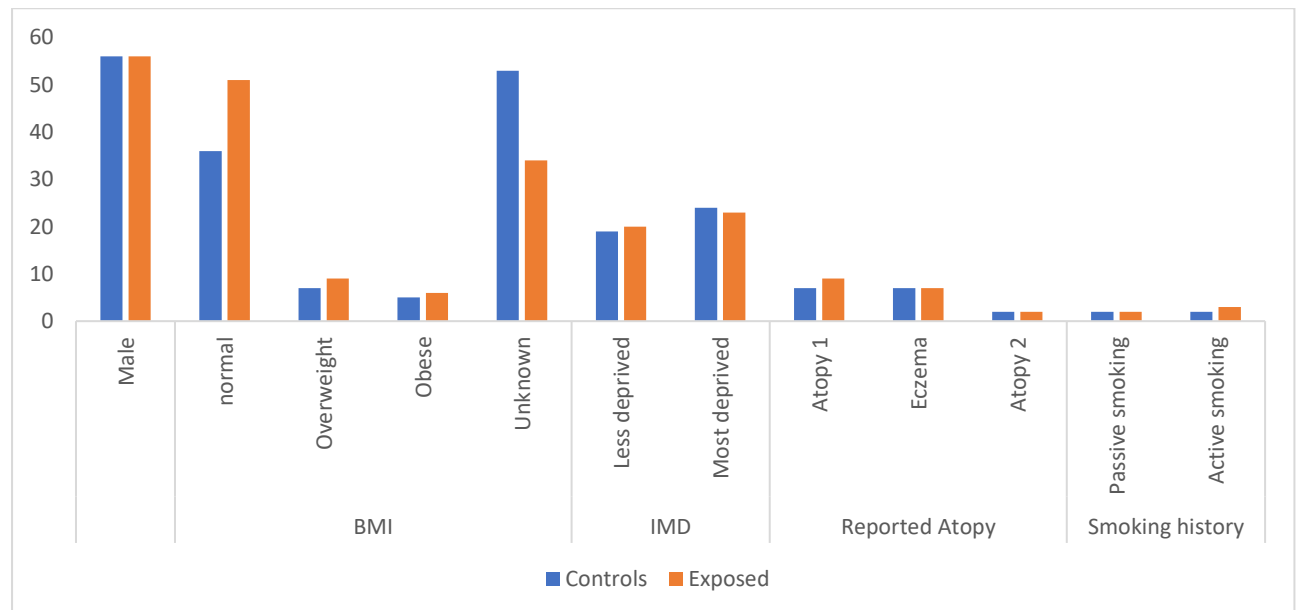


ICS=inhaled corticosteroids, SABA=short-acting beta-agonist. IMD= index of multiple deprivation, BMI=body mass index, Atopy 1 receiving a code for allergic rhinitis, or allergy to pets, pollen or house dust mites, Atopy 2 receiving a code for 'food/drug allergy.

### 6.5.1.3. Characteristics of the children in the inhaler technique check IPTW-cohort

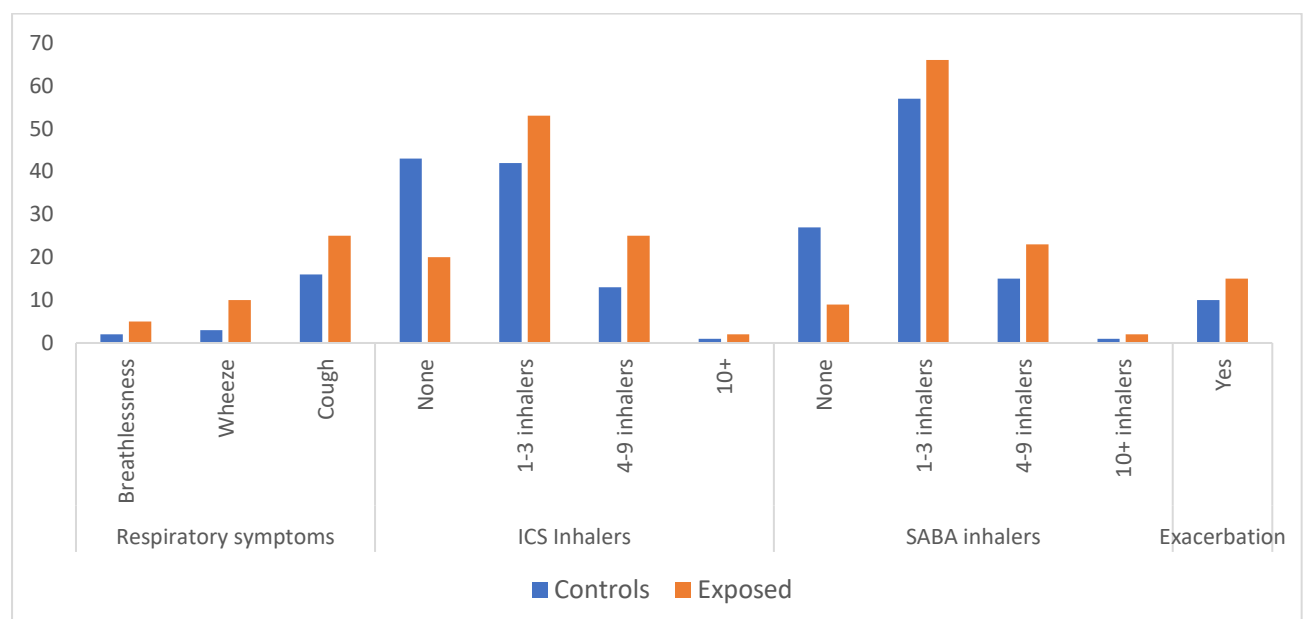
As described above, the IPTW cohorts were very similar to each other, so I have not described each again in detail. The baseline characteristics and variables in the year before cohort entry are shown for the inhaler technique cohort in figure 6.6.

Figure 6. 7: : Characteristics of the IPTW-cohort for inhaler technique checks at cohort entry



IMD= index of multiple deprivation, BMI=body mass index, Atopy 1 receiving a code for allergic rhinitis, or allergy to pets, pollen or house dust mites, Atopy 2 receiving a code for 'food/drug allergy.

Figure 6. 8: Asthma characteristics for IPTW-cohort for inhaler technique checks



*ICS=inhaled corticosteroids, SABA=short-acting beta-agonist*

#### 6.5.1.4. Comparing characteristics of the children in the IPTW-cohorts and those not able to be included in the IPTW-cohorts

In each of the IPTW-cohorts, some children were not included from the main cohort. These children were those that had one of the good clinical practice activities not being assessed in that analysis. For example, in the asthma review IPTW-cohort, children that had a management plan were not included in the exposed or controls. There were only minor differences in the characteristics of the children not included as those included as exposed.

#### 6.5.1.5. Characteristics of the children in the SCCS cohorts

The number of eligible children for the three SCCS cohorts for each good clinical practice activity was 6,948 for asthma reviews, 6,469 for inhaler technique checks, and 4,624 for asthma management plans (Table 6.1). Due to the nature of the design, each child must have had both the exposure and the outcome to be included in the SCCS cohort, the cohort is therefore not representative of the study population of UK children with asthma (showing some similarity to the concept of a case-control design as the design purposely selects cases).

The average age at diagnosis and gender was the same for each SCCS cohort, 6.3 years and 57%, respectively (Table 6.1).

Again, BMI was found to be missing for high numbers of children, 29% in the asthma review and inhaler technique check cohort, and 32% in the asthma management plan cohort. The proportion of children that were overweight and obese was relatively low, with overweight children constituting 5-6% and obese children 3-4% across all three SCCS cohorts (Table 6.1).

In terms of IMD (socioeconomic status), there was a fairly even spread across the quintiles, with 16-22% per IMD category, but the highest percentage was in the most deprived category (25-27%) for all three SCCS cohorts (Table 6.1).

Health characteristics revealed that 23% of children in the asthma review cohort, 37% in the inhaler technique check cohort, and 37% in the asthma management plan cohort had documented atopy 1. Eczema prevalence was highest in the asthma management plan cohort (47%), followed by inhaler technique checks (45%) and asthma reviews (39%). Atopy 2 was present in 11-17% of the children, with the highest percentage in the asthma management plan cohort (Table 6.1).

Passive smoking exposure was reported by 4-8% of the children (Table 6.1).

Reported symptoms varied considerably, with breathlessness affecting 6-17%, wheeze/chest tightness affecting 14-37%, and cough affecting 24-76% of the children across the cohorts (Table 6.1).

Most children (81%) in the asthma review SCCS cohort were prescribed at least one ICS inhaler, but the proportion was lower in the inhaler technique check cohort (65%) and asthma management plan cohort (68%). For SABA inhaler prescriptions, 48% were prescribed 1-3 inhalers in the asthma review SCCS cohort but around 60% in the other two cohorts, inhaler technique check cohort, and asthma management plan. Some children (15-18%) were prescribed 4-9 inhalers, and very few (1-2%) received prescriptions for 10 or more SABA inhalers (Table 6.1).

Table 6. 1: Descriptive analysis for the SCCS cohort for each activity

|                                                               | <b>Asthma review<br/>N (%)</b> | <b>Inhaler technique<br/>check<br/>N (%)</b> | <b>Asthma<br/>management plan<br/>N (%)</b> |
|---------------------------------------------------------------|--------------------------------|----------------------------------------------|---------------------------------------------|
| <b>Total</b>                                                  | 6,948                          | 6,469                                        | 4,624                                       |
| <b>Age of diagnosis,<br/>years, mean (SD)</b>                 | 6.3 (3.6)                      | 6.3 (3.5)                                    | 6.2 (3.5)                                   |
| <b>Males</b>                                                  | 3,975 (57%)                    | 3,692 (57%)                                  | 2,622 (57%)                                 |
| <b>BMI</b>                                                    |                                |                                              |                                             |
| Normal                                                        | 2,020 (29%)                    | 1,870 (29%)                                  | 1,485 (32%)                                 |
| Overweight                                                    | 372 (5%)                       | 347 (5%)                                     | 262 (6%)                                    |
| Obese                                                         | 218 (3%)                       | 236 (4%)                                     | 166 (4%)                                    |
| Unknown                                                       | 4,338 (62%)                    | 4,016 (62%)                                  | 2,711 (59%)                                 |
| <b>IMD (socioeconomic status)</b>                             |                                |                                              |                                             |
| 1                                                             | 1,247 (18%)                    | 1,119 (17%)                                  | 724 (16%)                                   |
| 2                                                             | 1,250 (18%)                    | 1,114 (17%)                                  | 776 (17%)                                   |
| 3                                                             | 1,241 (18%)                    | 1,114 (17%)                                  | 813 (18%)                                   |
| 4                                                             | 1,458 (21%)                    | 1,441 (22%)                                  | 1,027 (22%)                                 |
| 5 (Most deprived)                                             | 1,737 (25%)                    | 1,663 (26%)                                  | 1,271 (27%)                                 |
| <b>Atopy 1</b>                                                | 1,565 (23%)                    | 2,404 (37%)                                  | 1,693 (37%)                                 |
| <b>Eczema</b>                                                 | 2,688 (39%)                    | 2,930 (45%)                                  | 2,172 (47%)                                 |
| <b>Atopy 2</b>                                                | 773 (11%)                      | 1,008 (16%)                                  | 772 (17%)                                   |
| <b>Passive smoking</b>                                        | 294 (4%)                       | 514 (8%)                                     | 325 (7%)                                    |
| <b>In the year before the good clinical practice activity</b> |                                |                                              |                                             |
| <b>Reported respiratory symptoms</b>                          |                                |                                              |                                             |
| Breathlessness                                                | 441 (6%)                       | 1,121 (17%)                                  | 798 (17%)                                   |
| Wheeze/chest tightness                                        | 978 (14%)                      | 2,275 (35%)                                  | 1,708 (37%)                                 |

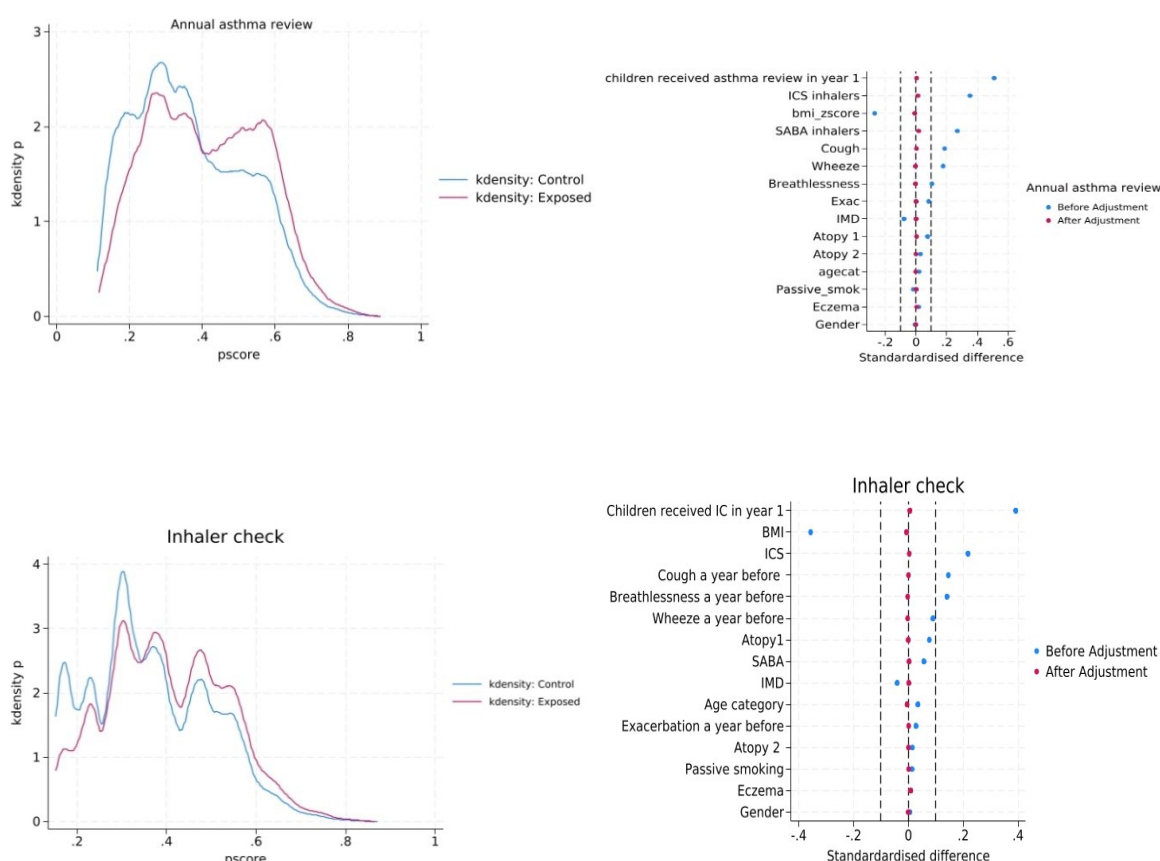
|                      |             |             |             |
|----------------------|-------------|-------------|-------------|
| Cough                | 1,695 (24%) | 4,923 (76%) | 3,514 (76%) |
| <b>SABA inhalers</b> |             |             |             |
| None                 | 2,425 (35%) | 1,213 (19%) | 821 (18%)   |
| 1-3 inhalers         | 3,363 (48%) | 3,947 (61%) | 2,848 (62%) |
| 4-9 inhalers         | 1,068 (15%) | 1,191 (18%) | 871 (19%)   |
| 10+                  | 92 (1%)     | 118 (2%)    | 84 (2%)     |
| <b>ICS inhalers</b>  |             |             |             |
| None                 | 1,318 (19%) | 2,289 (35%) | 1,502 (32%) |
| 1-3 inhalers         | 4,250 (61%) | 3,103 (48%) | 2,284 (49%) |
| 4-9 inhalers         | 1,267 (18%) | 987 (15%)   | 759 (16%)   |
| 10+ inhalers         | 113 (2%)    | 90 (1%)     | 79 (2%)     |

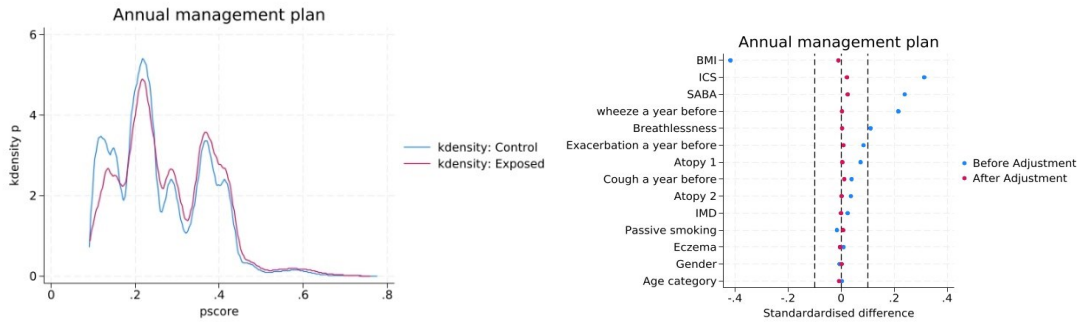
## 6.5.2. Association between each good clinical practice activity and asthma exacerbations (IPTW-cohort)

### Balance diagnostics

I first compared the distribution of the propensity score, and standardised difference of the covariates, between the exposed and controls, after applying weighting. The density plots show nearly complete overlap between the exposed and controls post-adjustment, indicating good balance, for all three IPTW-cohorts (**Error! Reference source not found.**). The standardized differences plot confirms that the difference for most covariates was within the acceptable threshold of 0.1 after adjustment, for all three IPTW cohorts.

Figure 6. 9: : Balance diagnostics: comparing the distribution graphically and the measured standardised differences plots for each covariate





## Main results

In the crude analysis, an annual asthma review appeared to be significantly associated with experiencing an asthma exacerbation in the following 12 months (HR = 1.20, 95% CI: 1.10-1.20,  $p < 0.005$ ) (Table 6.2). In the weighted model, this association was no longer present (HR = 1.04, 95% CI: 0.99-1.1,  $p = 0.102$ ).

In the crude analysis, an inhaler technique check was significantly associated with asthma exacerbations (HR = 1.09, 95% CI: 1.04-1.15,  $p < 0.005$ ) (Table 6.2). In the weighted model, this association was no longer present (HR = 0.95, 95% CI: 0.91-1.00,  $p = 0.371$ ).

In the crude analysis, an asthma management plan was significantly associated with asthma exacerbations (HR = 1.10, 95% CI: 1.05-1.17,  $p < 0.05$ ) (Table 6.2). In the weighted model, this association was no longer present (HR = 1.04, 95% CI: 0.99-1.10,  $p = 0.1121$ ).

In the IPTW-cohort only including children with at least two activities in the same consultation, there was again no association found between having the activities and future asthma exacerbation risk (HR = 0.99, 95% CI: 0.85-1.14,  $p = 0.925$ ) (Table 6.2).

For those receiving all three activities in the same consultation, although not significant, there was a slight reduction in the risk (HR = 0.91, 95% CI: 0.79-1.07,  $p = 0.242$ ) (Table 6.2).

In summary, none of the models, after accounting for confounding, appeared to find a significant association between good clinical practice activity implementation and asthma exacerbation risk in the following 12 months.

Table 6. 2: Association between each good clinical practice activity as standalone, or used in conjunction, and having an asthma exacerbation in the following 12 months

|                                                                                   |                 | Hazard Ratio | 95% CI    | p-value |
|-----------------------------------------------------------------------------------|-----------------|--------------|-----------|---------|
| <b>Asthma review (N=73,966)</b>                                                   |                 |              |           |         |
|                                                                                   | <b>Crude</b>    | 1.20         | 1.10-1.20 | <0.001  |
|                                                                                   | <b>Weighted</b> | 1.04         | 0.99-1.10 | 0.102   |
| <b>Inhaler technique check (N=73,966)</b>                                         |                 |              |           |         |
|                                                                                   | <b>Crude</b>    | 1.09         | 1.04-1.15 | <0.001  |
|                                                                                   | <b>Weighted</b> | 0.95         | 0.91-1.00 | 0.371   |
| <b>Asthma management plan (N=73,966)</b>                                          |                 |              |           |         |
|                                                                                   | <b>Crude</b>    | 1.10         | 1.05-1.17 | <0.05   |
|                                                                                   | <b>Weighted</b> | 1.04         | 0.99-1.10 | 0.121   |
| <b>Two good clinical practice activities in the same consultation (N=2,232)</b>   |                 |              |           |         |
|                                                                                   | <b>Crude</b>    | 0.90         | 0.79-1.14 | 0.105   |
|                                                                                   | <b>Weighted</b> | 0.99         | 0.85-1.14 | 0.925   |
| <b>Three good clinical practice activities in the same consultation (N=2,023)</b> |                 |              |           |         |
|                                                                                   | <b>Crude</b>    | 0.92         | 0.79-1.05 | 0.231   |
|                                                                                   | <b>Weighted</b> | 0.91         | 0.79-1.07 | 0.242   |

### 6.5.3. Stratifying the asthma review model (IPTW-cohort)

As shown in Table 6.3, I stratified the main model to determine if certain characteristics were associated with the effectiveness of the annual asthma review. These characteristics included gender, age, exacerbations and inhaler prescriptions.

The stratified analysis showed no discernible difference in the risk of a future asthma exacerbation associated with asthma reviews, in any of the variables assessed, i.e., the association was the same for children by age, gender, and those children that were or were not prescribed ICS or SABA.

However, when stratifying by exacerbations, it appeared that children with a history of exacerbations were at a significantly greater risk of having a future exacerbation if they received an asthma review. Clearly, this is not possible, as an asthma review cannot be causally associated with an asthma exacerbation. This is discussed below in more detail.

Due to this clear spurious finding from the IPTW approach, at this point I did not continue to use this method.

*Table 6. 3: Stratified analyses for the asthma review IPTW-cohort*

| <b>Covariates</b>    | <b>Category</b> | <b>OR (95% CI)</b> | <b>p-value</b> |
|----------------------|-----------------|--------------------|----------------|
| <b>Gender</b>        | Male            | 0.92 (0.85-0.99)   | 0.930          |
|                      | Female          | 0.91 (0.84-0.99)   | 0.208          |
| <b>Age Category</b>  | 5-11.9 years    | 0.93 (0.90-0.98)   | <0.001         |
|                      | 12-15.9 years   | 0.88 (0.86-0.92)   | <0.001         |
| <b>Exacerbation</b>  | None            | 0.81 (0.77-0.85)   | 0.030          |
|                      | Yes             | 1.10 (1.04-1.35)   | <0.001         |
| <b>SABA Inhalers</b> | None            | 0.94 (0.90-0.97)   | <0.001         |
|                      | Yes             | 0.97 (0.91-1.01)   | 0.005          |
| <b>ICS Inhalers</b>  | None            | 0.94 (0.91-0.98)   | 0.020          |
|                      | Yes             | 0.96 (0.91-0.99)   | 0.005          |

#### 6.5.4. Sensitivity analyses: asthma review IPTW-cohort

To determine if the spurious finding was related to measuring when the exacerbation occurred. I ran a sensitivity analysis changing the time period after the asthma review in which to assess exacerbations. I investigated if there was a difference in effect estimates looking 3, 6 and 12 months after the asthma review (Table 6.4).

I found that the risk of exacerbations appeared to be highest in the first months after the asthma review (3 months: weighted-HR = 1.19, 95% CI: 1.07-1.3,  $p < 0.005$ ); 6 months: weighted-HR = 1.07, 95% CI: 1.005-1.15,  $p = 0.033$ ).

Next, I investigated if the spurious finding was related to the severity of exacerbation. In this model, I only included hospital-managed exacerbations. This effect estimate was even higher (weighted HR = 1.30, 95% CI: 1.03-1.66,  $p = 0.02$ ).

Both these findings further corroborated that the model suffered from bias, as it is not possible that an asthma review causes 20% increased risk of an asthma exacerbation within 3 months of the review, and 30% increased risk of having a hospitalised asthma exacerbation.

Table 6. 4: Sensitivity analyses of the asthma review IPTW-cohort

|                               |          | Hazard Ratio | 95% CI    | p-value |
|-------------------------------|----------|--------------|-----------|---------|
| <b>3-month follow-up</b>      | Crude    | 1.30         | 1.25-1.47 | <0.001  |
|                               | Weighted | 1.19         | 1.07-1.30 | <0.001  |
| <b>6-month follow-up</b>      | Crude    | 1.19         | 1.12-1.27 | <0.001  |
|                               | Weighted | 1.07         | 1.00-1.15 | 0.033   |
| <b>Hospital exacerbations</b> | Crude    | 1.50         | 1.20-1.90 | <0.001  |
|                               | Weighted | 1.30         | 1.03-1.66 | 0.020   |

#### 6.5.5. Association between each good clinical practice activity and asthma exacerbations (SCCS design)

To remove confounding that does not change over time, such as healthcare behaviour, and is able to minimise confounding by indication, I used a different methodological approach, the SCCS design as described above. Furthermore, because the model does not need to include time-invariant variables that one would traditionally adjust for, there is no risk of misclassification bias from these variables.

Standalone annual asthma reviews were associated with a 9% significant decrease in exacerbations during the first six months (0-180 days: IRR=0.92, 95% CI 0.85-1.00, p=0.034) but not thereafter (181-365 days: IRR=0.93, 95% CI 0.83-1.03, p=0.161).

Standalone inhaler technique checks did not show a significant decrease in exacerbations, although there was a small non-significant decrease (0-180 days: IRR=0.92, 95% CI 0.84-1.00, p=0.065; 181-365 days: IRR=0.92, 95% CI 0.82-1.03, p=0.174).

In contrast, standalone provision of an asthma management plan was associated with an approximate 15% significant decrease in exacerbations, persistent across the 12 months after

the activity (0-180 days: IRR=0.87, 95% CI 0.79-0.96,  $p<0.01$ ; 181-365 days: IRR=0.83, 95% CI 0.73-0.95,  $p<0.01$ ).

Provision of all three good clinical practice activities, during the same consultation, was associated with an approximate 30% decrease in exacerbations, persistent across the 12 months after the activities (0-180 days: IRR=0.76, 95% CI 0.68-0.85,  $p<0.0001$ ; 181-365 days: IRR=0.69, 95% CI 0.60-0.81,  $p<0.0001$ ).

*Table 6. 5: Association between good clinical practice activities and asthma exacerbations (SCCS)*

|                                             | Exposure period (days) | Events (n) | Age adjusted IRR | 95% CI    | p-value |
|---------------------------------------------|------------------------|------------|------------------|-----------|---------|
| Asthma review                               | 1-180                  | 2522       | 0.92             | 0.85-0.99 | 0.034   |
|                                             | 181-365                | 1324       | 0.93             | 0.83-1.03 | 0.161   |
| Inhaler check                               | 1-180                  | 2337       | 0.92             | 0.84-1.00 | 0.065   |
|                                             | 181-365                | 1211       | 0.92             | 0.82-1.03 | 0.174   |
| Management plan                             | 1-180                  | 1653       | 0.87             | 0.79-0.96 | <0.01   |
|                                             | 181-365                | 849        | 0.83             | 0.73-0.95 | <0.01   |
| All three good clinical practice activities | 1-180                  | 1187       | 0.76             | 0.68-0.85 | <0.0001 |
|                                             | 181-365                | 611        | 0.69             | 0.60-0.81 | <0.0001 |

## 6.4. Discussion

In this chapter, I sought to provide an insight into the real-world effectiveness of guideline-recommended good clinical practice activities. In particular, there is a lack of studies regarding the effectiveness of annual asthma reviews for children. To try to answer this question, initially I used a cohort design and to minimise potential confounding I weighted each child based on the probability of receiving the good clinical practice activity. Propensity score methodology aims to, as near as possible, replicate a randomised controlled trial using observational data, in that it aims to balance the confounders at baseline between the exposed and unexposed [137]. However, if the variables included to derive the propensity score are misclassified (for

example, cigarette smoke exposure), or there is missing information (for example, I could only include reported respiratory symptoms), or there is missing confounders altogether (for example, I did not have information on asthma control, or how well the good clinical practice activity was provided), this may provide a biased probability score. Specifically, indication bias, can also provide spurious estimates. Indication bias (also known as confounding by indication) would occur if the children who were more likely to have the outcome, were also more likely to be exposed. In this study this may occur, as children the clinicians feel may exacerbate are potentially also the children more frequently offered an annual review and/or more frequently take up the offer of an annual review. One way to deal with confounding by indication is to compare two possible exposures, i.e., an active comparator design [140], but there is no alternative to the exposure of a good clinical practice activities, the only alternative is 'usual care'.

It is notable that after applying the weighting, much of the confounding was reduced as the crude and weighted estimates differed considerably. However, there still appeared to be bias, because when I stratified by exacerbation history, an implausible and counterintuitive association was found, that asthma reviews were associated with exacerbations. Unless the person conducting the review caused the child to have an exacerbation, this association must be spurious and cannot be a causal association.

To overcome this issue, I used an alternative methodological approach that can mitigate this type of confounding as per my original statistical plan which included applying a triangulation approach, where two different methods are applied, each with different biases [134]. The self-controlled case series (SCCS) method, inherently controls for time-invariant confounding by comparing individuals to themselves over different time periods [136]. Therefore time-invariant confounding that is hard to measure such as healthcare behaviour is no longer an issue. I also included a pre-exposure period, this period occurred just before the good clinical practice activity was implemented. The pre-exposure period is intentionally not included in the analysis. This period is added to avoid violating a key assumption of the SCCS model, that the outcome should not affect subsequent exposures. Therefore, if an exacerbation occurred in that pre-exposure period, it was not measured, and so would not bias the effect estimate. If a child had an exacerbation that meant the GP instigated an annual review, this exacerbation would not therefore be included. As primary care appointments are made in short periods,

having a 31-day pre-exposure period should be sufficient to prevent this violation of the model assumptions.

The SCCS analysis showed that standalone annual asthma reviews were associated with a small (9%) decrease only in the first six months, but this was not sustained for the full year until the next annual review. There is very little evidence regarding asthma reviews in children. Three randomised controlled studies (1999-2004, two from Australia and one from the UK) found there was no benefit from primary care asthma clinics in terms of hospitalizations, medication utilization, or overall quality of life; but only one trial included children [141]. Yet, a more recent, real-world cohort study of 5,656 children from the US, found a significant association between well-child-care visits and a reduction in asthma exacerbations [141]. The well-childcare visits could vary between practices but were designed to include an assessment of asthma control, education, and self-management support. The visits are therefore more comprehensive than the UK's annual asthma review, which only specifies a review of asthma control [142]. Of note, similar to my findings from the previous chapter 5, the US study found that children at the greatest risk of exacerbations were least likely to attend the well-childcare visits [142]. UK asthma management guidelines comment that as there is no evidence of harm from asthma reviews, they continue to recommend them [85]. Here, we provide for the first time, evidence that reviews in UK clinical practice can even reduce the most troublesome asthma outcome, asthma exacerbations.

Standalone asthma management plans appeared to be more effective than asthma reviews and were associated with a 15% decrease in exacerbations across one year. It is probable though that the management plans were in fact provided alongside a review of the child's asthma, but this was not specifically coded. A huge meta-review of 27 systematic reviews and 13 updated randomised controlled trials (including both adults and children) found that supported self-management reduces hospitalisation and improves asthma control and quality of life [39]. For most trials this included three elements, education, a management plan, and professional review; trials were additionally maximally effective when encompassing proactive long-term asthma care.

Unfortunately, standalone inhaler technique checks did not appear to be effective. This finding using real life clinical practice data is in keeping with the conclusion of a large Cochrane review

of 29 trials of singular inhaler technique interventions. This review found that interventions did not lead to sustained improvement in clinical outcomes [143]. However, my data show that provision of all three good clinical practice activities during the same consultation was associated with an approximate 30% decrease in exacerbations, persistent across the 12 months after the activities. Analysis of randomised controlled trials, also report much greater improvement in asthma outcomes for children when interventions are delivered as a comprehensive package, including regular professional review, patient education, and supported self-management [39, 144].

Altogether, our real-world evidence, along with findings from randomised controlled trials, suggests that asthma outcomes improve significantly when interventions are delivered as a comprehensive package. This includes regular professional reviews, patient education, and supported self-management. However, trials often do not mirror day-to-day clinical practice or real-life behaviours. Many asthma patients are either ineligible for trials or, choose not to participate, additionally the optimally controlled trial conditions differ from typical practice [53]. Importantly, trials often underrepresent individuals from lower socioeconomic backgrounds and certain ethnicities, whereas our real-world data includes a broader population, potentially capturing a wider range of patient experiences.

This inclusivity indicates that the benefits we observed might be even greater if those from lower socioeconomic groups had more frequent good clinical practice activities, suggesting that our results could, in fact, underestimate the full potential of these interventions. The agreement between our population-level clinical practice data and randomised trial outcomes strongly supports current guideline recommendations and underscores areas for further advocacy to improve asthma management across diverse populations

## 6.5. Limitations

One key limitation is the potential for selection bias, as children who received and had documented records of all three good clinical practice activities may have been reviewed by healthcare professionals with a specialist interest in respiratory care. This information was not available in the dataset, so we were unable to assess the impact of specialist involvement on outcomes. However, as nearly half the children had good clinical practice activities it is unlikely they all had specialist interest in respiratory care. Furthermore, we lacked detailed

information on the nature of each intervention. For example, some asthma reviews may have included inhaler technique checks while others did not, or some inhaler technique checks may have been suboptimal and rushed. As with all research I could only measure the effectiveness of the good clinical practice activity in children that received one, but it may be those children that did not would have benefitted the most from that interaction with a healthcare professional. Lastly, in this dataset I was only able to look at exacerbations as an outcome, but it would be important to see the effect on asthma control and other important asthma-related outcomes, such as school absenteeism and quality of life.

## 6.6. Conclusion

In this chapter, I explored the real-world effectiveness of guideline-recommended good clinical practice activities for asthma management in children using the process of triangulation, I found that my first method, a longitudinal cohort with IPTW, was unable to sufficiently mitigate confounding and thus provided biased estimates. Instead, I used a SCCS design. By this approach, I was able to determine that standalone asthma reviews and management plans could reduce the risk of future exacerbations in the next year, but these activities showed a much greater magnitude of effect when combined in one consultation, alongside an inhaler technique check. These findings using real-life clinical practice data paralleled those from randomised control trials and show their value in a UK primary care setting.

## 7. Chapter 7: Discussion

### 7.1 Introduction

The overarching objective of my PhD was to provide an understanding of UK school-age children with asthma, in terms of their characteristics and management, and determine if children across the UK are receiving optimal care, as recommended by national guidelines. This final chapter summarises and briefly discusses again my key findings, as well as the strength and limitations.

The specific objectives of my thesis were

1. Describe the characteristics and pharmacological asthma management of school-age children with asthma by their age of diagnosis, categorised into 5-8.9 years, 9-11.9 years and 12-16 years old.
2. Calculate the rate of future asthma exacerbations and determine the exacerbation risk factors, by their age of asthma diagnosis.
3. Measure the annual implementation of asthma reviews, asthma management plans, inhaler technique checks, and influenza vaccinations from 2007 to 2020, and identify which groups of children are less likely to receive them.
4. Determine the effectiveness of receiving an asthma review, asthma management plan or inhaler technique check, or receiving all three activities in the same GP practice visit.

### 7.2 Overview of Key Findings

#### 7.2.1 Characteristics of UK children with asthma (*chapter 3; objective 1*)

In this generalisable UK cohort, there was considerable heterogeneity in the characteristics related to age at the time of asthma diagnosis. These observed age-specific differences are

supported by developmental asthma studies, which suggest that asthma can present differently across age groups due to the dynamic nature of physiological and immunological changes as children grow. For instance, lung development and immune response maturation during childhood and adolescence can influence asthma severity, with younger children having less mature immune systems that may respond differently to environmental triggers [145].

One of the age-specific differences observed was a higher prevalence of atopic conditions. Atopic predisposition is known to evolve as children progress from early childhood into adolescence [146]. Consistent with this, I found a higher prevalence of food allergies and eczema in the younger children changing to a higher prevalence of allergic rhinitis in the older children, which parallels findings from the Global Asthma Network Phase 1 study covering 16 countries across the world [147].

One of the striking characteristics was the lack of BMI recordings, this missing data did appear to be an asthma-related 'characteristic' as it was significantly, independently, associated with children's exacerbation risk. The level of missingness differs considerably from adults where BMI is only missing in around 10%, as opposed to 40% in children [72]. However, it should be recognised in adults, a single height recording is sufficient, and weight tends to change slowly therefore such studies can use a longer range, for example 5 years, for which to accept a BMI as representing the patient at the time of the study dates. In children, such measurements must be frequently recorded due to their constantly changing status. Weight recording is not a routine activity in primary care and has been shown to be recorded for only around one third of patients, repeated on average every two years [148]. Routine recording in EHR of BMI is higher in high-risk groups, such as obese patients and those with comorbid conditions. Childhood asthma should fit in that category; this is discussed more in the section below (7.2.3).

A critical, modifiable, and well-recognised risk factor for asthma is active and passive exposure to cigarette smoke. The proportion of children with active and passive smoking in this study is likely to be a considerable underrepresentation of the true values as studies of UK primary care records have consistently shown underreporting [149-151]. This problem is not limited to the UK, in a longitudinal study of Finnish adults with asthma in primary care, there was also

significant lack of reporting and documentation of simple smoking variables [152]. Some studies suggest that younger people with asthma are more likely to smoke so inventive solutions to prevent this and quit are needed [153]. Documentation of smoking in children was added as a QOF asthma indicator in 2020, this study precedes this change to financial incentives and would be of value to assess its impact in future studies. However, the increasing uptake of e-cigarettes in children may override this issue as their use appears to be associated with asthma and wheezing [154, 155].

Inhaler use appeared to be suboptimal in my cohort, particularly in the older children who had relatively fewer ICS prescriptions than the younger children, and more reliever prescriptions. This pattern of age-based disparities in asthma medication prescriptions aligns with findings from other real-world studies, which show that younger children are more likely to receive preventer medications, while older children may receive less consistent asthma management [156], potentially due to greater healthcare providers' focus on early asthma control or greater parental engagement in younger children. Older children, particularly adolescents, are often perceived to self-manage their asthma with little adult support, which may result in lower ICS use and inconsistent medication adherence [107]. In this study I could only assess the prescription rates, not adherence. Yet studies have reported around only 30-50% adherence in children to asthma inhalers and although use of e-health and FeNO testing may aid adherence, these are not currently available in routine primary care [157, 158]. Factors reducing adherence in children and families include lower severity of their asthma and reduced education about their asthma [159, 160].

### 7.2.3 Exacerbation rates and risk factors, by age (*chapter 4; objective 2*)

Alongside the above-mentioned age-specific differences in children's characteristics, I also found a stronger association between younger age and higher exacerbation risk, an association that has been reported in previous studies. A large comprehensive systematic review conducted in 2017, including 68 observational studies, found younger age to be a significant independent risk factor [21]. The review categorised the risk factors by their level of risk based on the strength of association, ranging from 'no risk' to 'greatly' increased risk, through 'slightly' and 'moderately' increased. However, the review found age to only slightly

increase the risk of exacerbations, in contrast to my study. This difference in the strength of association may be because in the studies included in the systematic review, children's age was considered within a broad range, 5 to 12 years, without applying the more granular age categorisation I have applied.

Although the large systematic review mainly included studies from the United States, the authors found other similar exacerbation risk factors to my UK study, such as previous exacerbations, presence of respiratory symptoms, atopy and socioeconomic deprivation; these risk factors have also been repeatedly shown in more recent studies [161-163]. Surprisingly the review did not find gender to be a risk factor, unlike my study and many previous studies [19, 164]. As the studies included in the review did not breakdown the effect of gender within the school-age bracket this could have led to a dilution of the effect estimate, as the increased risk associated with males in younger children would have been essentially cancelled out by the decreased risk of males in older children (as shown in my study), resulting in an overall null effect.

Interestingly the systematic review found obesity to also only slightly increase the risk of exacerbations, whereas in my UK study it was found to be a strong risk factor, especially in adolescents. Again, the finer breakdown of age in my study allowed for a more comprehensive look, as obesity becomes a stronger risk factor with increasing school-age. Other studies have previously reported a strong association between BMI and asthma exacerbations in children [165]. More recently, children with persistently high BMI trajectories from birth have been shown to also have lower lung function growth [166]. This evidence coupled with the lack of BMI recordings observed in our nationally representative cohort, demonstrates the need to integrate weight management into routine asthma care, considering dietary modifications and potentially therapeutic interventions as necessary. Weight is a modifiable risk factor for asthma and all-round general childhood health and longevity, we should be highlighting the importance of this social determinant of health to children and their carers at an early age. Financial incentives successfully increase the recordings of BMI in primary care and could be advocated for here [148].

Behavioural factors may also play a role in the increased risk of exacerbations in younger children. Inhalers in younger children are often administered with the help of their caregivers

who may have concerns over the potential side effects of steroids, including suppression of growth or dependence on the inhaler [107]. Such factors tend to be worsened by lower health literacy. Studies have not assessed if adherence differs within primary school-age groups, instead focussing more on differences between infants, primary school age and adolescents.

Lastly, exacerbations may occur more frequently in younger children due to their increased risk of viral infections as compared to older children [107]. This observed effect could occur from a higher viral exposure or from differences in the host response due to a more immature respiratory immunity. Currently, primary care data is not linked to respiratory virology test data, but this may be possible in the future as demonstrated by the linkage to specific covid-19 virology data [167].

#### 7.2.4 Prevalence and disparities in the implementation of the good clinical care activities (*chapter 5; objective 3*)

Nearly half of the children did not receive an annual asthma review, inhaler technique check or asthma management plan. Only 8% received all three in one consultation. There was poor recording of the uptake of influenza vaccine, but this is likely due to the receipt of vaccinations occurring outside the GP practice (e.g. schools, local pharmacies) with no update in the children's medical records. The low prevalence of asthma reviews and management plans is similar to that found in adults in the UK [29]. The proportion in both children and adults likely reflects the threshold required for financial incentives in the QOF system, as discussed in more detail in Chapter 5. There is limited data available on the prevalence of implementation of good clinical practice activities outside of the UK. However, studies from the UK, United States and Canada suggest asthma guidelines are frequently not adhered to [30-33]. There are several reasons postulated for the lack of implementation, including insufficient resources, unawareness of their potential benefit and lack of understanding [31, 32].

I also postulated that that some children were at greater risk of not receiving these activities than others. Younger age, residing in more socioeconomically deprived areas and obesity were all found to be factors associated with not receiving a good clinical practice activity, yet worryingly these are also significant independent risk factors for future exacerbations. Previous studies both inside the UK and the US, have also shown differences in asthma

management depending solely on where people reside, in relation to region or local healthcare infrastructure [33, 34]. Furthermore, children with no recorded BMI, were at the greatest risk of also not receiving a good clinical practice activity, again implying general reduced healthcare engagement or lack of service provision. Although interestingly, lack of recording of BMI was not associated with socioeconomic status, or any other discernible parameters I measured in this cohort. As may be expected and reassuring, the factors associated with receiving a good clinical practice activity, included reporting of respiratory symptoms and higher number of ICS and SABA prescriptions.

#### 7.2.4 Effectiveness of good clinical practice activities in preventing exacerbations (chapter 6; objective 4)

Although good clinical practice activities are supported by clinical guidelines, there has been limited evidence of their effectiveness from real-world clinical settings. Here I have shown that overall, these clinical practices are effective in children. Whilst there was strong evidence for effectiveness when used together in a single clinic visit, and for standalone asthma management plans, there was no association between reduction in asthma exacerbations and standalone inhaler technique checks.

A Cochrane review of 29 RCTs assessing interventions to improve inhaler technique found these interventions to be insufficient in terms of improving clinical outcomes [36]. Therefore, although checking a child's technique is critical, how healthcare professionals can intervene best to improve any suboptimal technique is unclear. These trials were difficult to do, particularly in terms of blinding, so were at risk of bias. Furthermore, the trials including children were smaller and far fewer in number. However, the agreement between the trial data and real-world data, provides reasonable evidence that standalone inhaler technique checks do not improve asthma outcomes and must instead be part of a comprehensive management and education package.

Although both standalone asthma management plans and asthma reviews appeared to be associated with a small reduction in exacerbations, it was only when provided together, there was a significant, approximate, 30% reduction in exacerbations found. This real-world evidence is therefore in keeping with the findings from clinical trials. A large systematic meta-

review including 27 systematic reviews (244 RCTs) and an additional 13 update RCTs concluded that supported self-management successfully reduces asthma exacerbations, as well as quality of life and school absenteeism [39]. Notably, self-management was most effective when the asthma management plan was provided alongside patient education and regular review by a healthcare professional; found to be true for both adults and children. Trials often do not replicate what happens in day-to-day clinical practice or real-life behaviour as many asthma patients are not eligible for trials (including children), many asthma patients do not want to partake in trials, and trial conditions are optimised [52]. Therefore, the agreement between this population-level real-life clinical practice data and the RCTs, substantiates current guideline recommendations.

In summary, as discussed in the introduction, the integration of structured asthma reviews, inhaler technique checks, and personalised asthma management plans is grounded in three primary mechanisms: patient behaviour, clinician practice, and system-level integration. My findings show that while standalone inhaler technique checks showed limited benefit, patient engagement and effective management were improved when multiple good clinical practice activities were combined. The 30% reduction in exacerbations highlights the synergy of combining elements that address both self-management and clinician-led interventions. This aligns with the existing mechanisms, where patient behaviour is transformed through regular reviews and ongoing education, and clinician practice is optimised when assessments and interventions are consistently applied. Moreover, integration into routine care processes, supported by system-level frameworks like the QOF, enhances adherence to guidelines and ensures the delivery of asthma care. These findings provide further evidence for the effectiveness of combining asthma management components, supporting the translation of guideline recommendations into real-world practice.

### 7.3 Summary of the strengths of this work

One of the main strengths of this research lies in the use of the Clinical Practice Research Datalink (CPRD), which with data from over 20% of the UK population, has been shown to be broadly nationally representative [64]. The long follow-up period in CPRD Aurum, with a median of 9 years for current patients, enabled me to investigate long-term asthma outcomes and management patterns. This study is one of the first and largest nationwide evaluations of

key asthma clinical practices in children, providing a large, unselected cohort that reflects real clinical practice across diverse settings in the UK. The ability to link primary care data with secondary care datasets enabled me to have more comprehensive understanding of asthma exacerbations.

The use of different study designs, including a traditional cohort and self-controlled case series, as well different analysis approaches, including logistic regression, Cox proportional hazards and inverse propensity-score treatment weighting, each offered different advantages in overcoming and revealing the biases inherent to observational studies.

By using routinely recorded data, this study avoided issues like recall and selection bias, which are often challenges in prospective cohort studies or trials.

## 7.4 Limitations and areas for future work

Many of the limitations to this thesis are those that are inherent to the use of observational data. One of the primary limitations specific to this study is the potential for misclassification of asthma diagnosis. While efforts were made to mitigate this by requiring two asthma codes for inclusion, asthma diagnosis in children in primary care settings can be challenging. The absence of objective diagnostic testing in the data, such as spirometry or peak flow measurements, may reduce the accuracy of the diagnosis. Future studies could aim to include datasets that incorporate objective diagnostic criteria for asthma, improving diagnostic precision. However, these would need to be prospective cohorts which are expensive to conduct and time-consuming, therefore not well suited for assessing routine clinical activities.

Another limitation is the reliance on coded variables in medical records. While the strength of coded data lies in its systematic capture of large amounts of information, including many codes under a broad umbrella can obscure clinical nuances and lead to potential misclassification. Missing data was a significant issue for certain key variables, such as BMI, smoking status, and passive smoking exposure. Missing or unrecorded data could lead to residual confounding. Factors like exposure to environmental triggers (e.g., smoking or pollution) may not have been fully captured, or not capture at all. To address the issue with missing BMI I took two approaches, multiple imputation and treating the missing values as a

strata within the categorisation of BMI. Social desirability bias can also influence the reporting of smoking or other sensitive behaviours, as discussed above, or even BMI in obese children. An area of future interest would be to assess the impact of the introduction of QOF on smoking recording. Future studies could also benefit from linking to more complete environmental data, such as pollution data, indoor and outdoor, and lifestyle data such as children's activity levels at home and school.

Furthermore, QOF and other drivers of health provision and data collection likely influenced the dataset and the findings reported. The financial incentives associated with QOF, including exception reporting, may have contributed to lower recorded rates of certain activities—such as inhaler technique checks—relative to the approximately 70% completion rate commonly reported. Exception reporting permits practices to exclude certain patients from performance targets, potentially underestimating the proportion of children receiving these checks.

The absence of free-text data from GP records is another limitation. Information on milder asthma exacerbations, management of symptoms without oral corticosteroids, or unscheduled care that did not result in a hospital visit was therefore omitted.

Additionally, medication adherence was unknown, including whether prescribed medications were dispensed and/or adhered to, which could influence asthma control and outcomes. Including pharmacy dispensing records and exploring patient adherence in future research could help to better evaluate the effectiveness of prescribed asthma treatments. Currently such information is not available at a national level, and there is no linkage of local pharmacy data available to CPRD.

Similarly, the quality of the good clinical practice activities could not be assessed from the coded data alone, as some interventions may have been suboptimal. For example, an inhaler technique check might have been rushed or incomplete. Exploring qualitative aspects of clinical practice through surveys or direct observation would be a valuable complement to the data used here.

Moreover, as the data are observational, they inherently limit our ability to infer causality and fully elucidate the how the good clinical practice activities enable reduction in exacerbations. Therefore, while associations are evident, it is challenging to determine if the improvements

in outcomes are directly attributable to the interventions or are influenced by unmeasured confounding factors.

The exclusion of asthma control measures beyond exacerbations represents another limitation. Key indicators such as asthma control scores, school absenteeism and quality of life, were not available in this dataset. Expanding future research to include such outcomes would provide a more comprehensive view of asthma management in children, particularly in understanding how good clinical practice activities affect day-to-day asthma control and overall wellbeing.

There was potential for selection bias in this study, as children receiving all three good clinical practice activities might have been treated by primary healthcare professionals with a particular interest in respiratory. But since nearly half of the children in the study received good clinical practice activities, it is unlikely that this bias was prevalent or explains the findings. However, investigating the role of specialist respiratory care would be interesting to understand the importance of specialist support in primary care on asthma outcomes and good clinical practice activities uptake, particularly in high-risk groups.

I would have liked to investigate the impact of remote consultations but due to the study's calendar years, there were very few consultations documented as occurring remotely. Since the covid-19 began, telemedicine in primary care has been a rapidly growing area in asthma care. The covid-19 pandemic highlighted its potential and virtual asthma care may improve asthma outcomes in some children, however, there are also several concerns about its use [168]. CPRD could be used to investigate some of the multiple potential benefits and disadvantages of telemedicine in routine asthma care in modern times. The use of digital health tools, like mobile apps for asthma monitoring, shows promise in improving adherence to asthma action plans and regular check-ins, especially among adolescents [169]. Future research could examine how digital tools, including reminders for good clinical practice activities, might increase care consistency, especially among adolescents with low good clinical practice activity uptake.

Finally, the lack of access to asthma control questionnaire results is a notable limitation, as it restricts our ability to assess the impact of interventions on day-to-day asthma control beyond exacerbation rates.

## 7.5 Implications and Actionable Recommendations

Drawing on the extensive analyses and discussions presented throughout this thesis, several key implications emerge that inform recommendations for different stakeholders:

### **For Healthcare Professionals:**

Clinicians should adopt an integrated, bundle approach to asthma management that combines regular asthma reviews, personalised management plans, and inhaler technique checks with ongoing patient education. This comprehensive strategy reinforces medication adherence and self-management, and it facilitates early detection and timely intervention when asthma control wanes. Embracing telemedicine and digital health tools - such as remote monitoring and mobile app-based reminders - can further improve follow-up and engagement, especially among adolescents who may benefit from more flexible care options [39].

### **For Patients:**

Patients and their caregivers must be encouraged to actively participate in their asthma care by attending scheduled reviews and understanding the full spectrum of recommended clinical practices. By recognising the importance of proper inhaler technique and adherence to management plans, patients can better control their condition and reduce the risk of exacerbations. Empowering patients to communicate any difficulties they experience with their treatment or to seek clarification on their care plans is essential for optimising outcomes.

### **For Organisations:**

Healthcare organisations should invest in systems and infrastructures that support the delivery of comprehensive asthma care. This includes integrating digital health solutions—such as mobile apps for asthma monitoring, automated reminders for appointments, and platforms that facilitate secure telemedicine consultations—to enhance consistency and continuity of care. Organisations are also encouraged to prioritise continuous staff training on best practices for asthma management and to refine data collection processes, ensuring that key clinical activities are accurately recorded and utilised to inform ongoing quality improvement.

### **For Policy Makers:**

Policy makers play a critical role in creating an environment that supports high-quality, integrated asthma care. Policies should incentivise the use of bundled intervention strategies and promote the adoption of standardised, accurate coding practices in electronic healthcare records. Revising frameworks such as the Quality and Outcomes Framework (QOF) to address issues like exception reporting - which may underlie lower recorded rates of essential checks - and enhancing incentives for comprehensive care can drive improvements in asthma

management. Furthermore, policies that expand access to objective diagnostic tools and digital health innovations will help ensure that the benefits of integrated care are realised across all patient populations.

## 7.6 Final conclusions

To my knowledge, this is the first and largest cohort of UK children with school-age asthma to be considered not as a homogenous population but broken down within three age-groups. Within that framework I determined the characteristics of the children and their risk of exacerbations as well as the risk factors. Many of these have not previously been delineated and could be accounted for in clinical practice and policy guidance, such as routine measurement of BMI, education around weight management and recording of cigarette and smoke exposure as part of routine asthma care for children. Furthermore, this work provides strong evidence to suggest considering the age of the children at the time of their diagnosis in planning their care.

I believe this is also the first and largest cohort to address the prevalence and effectiveness of annual asthma review, asthma management plans and inhaler technique checks in a real-life UK primary care, clinical setting. This work has shown the importance of these activities, particularly when implemented together in a comprehensive asthma consultation.

This study is also an exemplar of how real-world data from primary care can inform us on the gaps in national asthma management and the effectiveness of clinical activities. The policy implications of which are considerable and could contribute towards improving our national guidelines.

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## Appendices

### Appendix 1: Asthma medical and Read codes

| Medical code | Read code | Description                                                |
|--------------|-----------|------------------------------------------------------------|
| 5867         | 173A.00   | Exercise induced asthma                                    |
| 22752        | 173c.00   | Occupational asthma                                        |
| 73522        | 173d.00   | Work aggravated asthma                                     |
| 41017        | 1780      | Aspirin induced asthma                                     |
| 102341       | 1781      | Asthma trigger - pollen                                    |
| 103955       | 1782      | Asthma trigger - tobacco smoke                             |
| 102952       | 1783      | Asthma trigger - warm air                                  |
| 103952       | 1784      | Asthma trigger - emotion                                   |
| 103945       | 1785      | Asthma trigger - damp                                      |
| 103321       | 1786      | Asthma trigger - animals                                   |
| 102301       | 1787      | Asthma trigger - seasonal                                  |
| 103813       | 1788      | Asthma trigger - cold air                                  |
| 102449       | 1789      | Asthma trigger - respiratory infection                     |
| 103944       | 178A.00   | Asthma trigger - airborne dust                             |
| 102871       | 178B.00   | Asthma trigger - exercise                                  |
| 11370        | 102..00   | Asthma confirmed                                           |
| 93736        | 388t.00   | Royal College of Physicians asthma assessment              |
| 103631       | 388t000   | Royal College Physician asthma assessment 3 question score |
| 98185        | 38DL.00   | Asthma control test                                        |
| 100397       | 38DT.00   | Asthma control questionnaire                               |
| 102209       | 38DV.00   | Mini asthma quality of life questionnaire                  |
| 105674       | 661M100   | Asthma self-management plan agreed                         |
| 105420       | 661N100   | Asthma self-management plan review                         |
| 81           | 663..11   | Asthma monitoring                                          |
| 7416         | 663N.00   | Asthma disturbing sleep                                    |
| 30815        | 663N000   | Asthma causing night waking                                |

|        |         |                                                           |
|--------|---------|-----------------------------------------------------------|
| 38146  | 663N100 | Asthma disturbs sleep weekly                              |
| 13175  | 663N200 | Asthma disturbs sleep frequently                          |
| 38143  | 663O000 | Asthma never disturbs sleep                               |
| 7191   | 663P.00 | Asthma limiting activities                                |
| 102713 | 663P000 | Asthma limits activities 1 to 2 times per month           |
| 102888 | 663P100 | Asthma limits activities 1 to 2 times per week            |
| 103998 | 663P200 | Asthma limits activities most days                        |
| 7378   | 663U.00 | Asthma management plan given                              |
| 13064  | 663V.00 | Asthma severity                                           |
| 3458   | 663V000 | Occasional asthma                                         |
| 3018   | 663V100 | Mild asthma                                               |
| 13065  | 663V200 | Moderate asthma                                           |
| 3366   | 663V300 | Severe asthma                                             |
| 24479  | 663d.00 | Emergency asthma admission since last appointment         |
| 25181  | 663e.00 | Asthma restricts exercise                                 |
| 26861  | #####   | Asthma sometimes restricts exercise                       |
| 26506  | #####   | Asthma severely restricts exercise                        |
| 26504  | 663f.00 | Asthma never restricts exercise                           |
| 10487  | 663j.00 | Asthma - currently active                                 |
| 47337  | 663m.00 | Asthma accident and emergency attendance since last visit |
| 19520  | 663n.00 | Asthma treatment compliance satisfactory                  |
| 19519  | 663p.00 | Asthma treatment compliance unsatisfactory                |
| 42824  | 663q.00 | Asthma daytime symptoms                                   |
| 39570  | 663r.00 | Asthma causes night symptoms 1 to 2 times per month       |
| 26501  | 663s.00 | Asthma never causes daytime symptoms                      |
| 31225  | 663t.00 | Asthma causes daytime symptoms 1 to 2 times per month     |
| 24884  | 663u.00 | Asthma causes daytime symptoms 1 to 2 times per week      |
| 26503  | 663v.00 | Asthma causes daytime symptoms most days                  |
| 38144  | 663w.00 | Asthma limits walking up hills or stairs                  |
| 38145  | 663x.00 | Asthma limits walking on the flat                         |

|        |         |                                                              |
|--------|---------|--------------------------------------------------------------|
| 9018   | 663y.00 | Number of asthma exacerbations in past year                  |
| 9552   | 66Y5.00 | Change in asthma management plan                             |
| 9663   | 66Y9.00 | Step up change in asthma management plan                     |
| 18223  | 66YA.00 | Step down change in asthma management plan                   |
| 41020  | 66YC.00 | Absent from work or school due to asthma                     |
| 10043  | 66YJ.00 | Asthma annual review                                         |
| 13176  | 66YK.00 | Asthma follow-up                                             |
| 31167  | 66YP.00 | Asthma night-time symptoms                                   |
| 19167  | 66YQ.00 | Asthma monitoring by nurse                                   |
| 30458  | 66YR.00 | Asthma monitoring by doctor                                  |
| 102170 | 66Yp.00 | Asthma review using Roy Colleg of Physicians three questions |
| 102400 | 66Yq.00 | Asthma causes night time symptoms 1 to 2 times per week      |
| 102395 | 66Yr.00 | Asthma causes symptoms most nights                           |
| 103612 | 66Ys.00 | Asthma never causes night symptoms                           |
| 107167 | 66Yu.00 | Number days absent from school due to asthma in past 6 month |
| 100107 | 679J000 | Health education - asthma self management                    |
| 100740 | 679J100 | Health education - structured asthma discussion              |
| 103318 | 679J200 | Health education - structured patient focused asthma discuss |
| 24506  | 8791    | Further asthma - drug prevent.                               |
| 16785  | 8794    | Asthma control step 1                                        |
| 16667  | 8795    | Asthma control step 2                                        |
| 18224  | 8796    | Asthma control step 3                                        |
| 20886  | 8797    | Asthma control step 4                                        |
| 20860  | 8798    | Asthma control step 5                                        |
| 10274  | 8B3j.00 | Asthma medication review                                     |
| 99793  | 8CMA000 | Patient has a written asthma personal action plan            |
| 25791  | 8CR0.00 | Asthma clinical management plan                              |
| 7058   | 8H2P.00 | Emergency admission, asthma                                  |
| 100509 | 9NNX.00 | Under care of asthma specialist nurse                        |
| 46529  | 9OJ1.00 | Attends asthma monitoring                                    |

|        |         |                                               |
|--------|---------|-----------------------------------------------|
| 19539  | 9OJA.00 | Asthma monitoring check done                  |
| 8355   | 9OJA.11 | Asthma monitored                              |
| 5798   | H312000 | Chronic asthmatic bronchitis                  |
| 78     | H33..00 | Asthma                                        |
| 1555   | H33..11 | Bronchial asthma                              |
| 7146   | H330.00 | Extrinsic (atopic) asthma                     |
| 2290   | H330.11 | Allergic asthma                               |
| 15248  | H330.13 | Hay fever with asthma                         |
| 7731   | H330.14 | Pollen asthma                                 |
| 14777  | H330000 | Extrinsic asthma without status asthmaticus   |
| 5627   | H330011 | Hay fever with asthma                         |
| 27926  | H330100 | Extrinsic asthma with status asthmaticus      |
| 6707   | H330111 | Extrinsic asthma with asthma attack           |
| 45782  | H330z00 | Extrinsic asthma NOS                          |
| 5267   | H331.00 | Intrinsic asthma                              |
| 3665   | H331.11 | Late onset asthma                             |
| 29325  | H331000 | Intrinsic asthma without status asthmaticus   |
| 58196  | H331100 | Intrinsic asthma with status asthmaticus      |
| 18323  | H331111 | Intrinsic asthma with asthma attack           |
| 45073  | H331z00 | Intrinsic asthma NOS                          |
| 185    | H333.00 | Acute exacerbation of asthma                  |
| 40823  | H334.00 | Brittle asthma                                |
| 106805 | H335.00 | Chronic asthma with fixed airflow obstruction |
| 4442   | H33z.00 | Asthma unspecified                            |
| 4892   | H33z000 | Status asthmaticus NOS                        |
| 233    | H33z011 | Severe asthma attack                          |
| 232    | H33z100 | Asthma attack                                 |
| 8335   | H33z111 | Asthma attack NOS                             |
| 12987  | H33z200 | Late-onset asthma                             |
| 16070  | H33zz00 | Asthma NOS                                    |

|       |         |                               |
|-------|---------|-------------------------------|
| 4606  | H33zz11 | Exercise induced asthma       |
| 21232 | H33zz12 | Allergic asthma NEC           |
| 93353 | H35y600 | Sequoiosis (red-cedar asthma) |
| 39478 | H35y700 | Wood asthma                   |
| 47684 | H47y000 | Detergent asthma              |

## Appendix 2: Good clinical practice activity medical codes

|                         | Medical code     | Description                                               |
|-------------------------|------------------|-----------------------------------------------------------|
| Asthma review           | 1488421017       | Asthma review                                             |
|                         | 1753401000006117 | Asthma review                                             |
|                         | 7518271000006114 | Asthma review                                             |
| Inhaler technique check | 264515013        | Demonstration of inhaler technique                        |
|                         | 264516014        | Inhaler technique observed                                |
|                         | 264534013        | Inhaler technique - good                                  |
|                         | 264535014        | Inhaler technique - poor                                  |
|                         | 1484902013       | Inhaler technique - moderate                              |
|                         | 3518260015       | Inhaler technique demonstrated by patient                 |
|                         | 855741000006114  | Inhaler technique                                         |
|                         | 1658981000000111 | Provision of written information on inhaler technique     |
|                         | 2264951000000115 | Review of inhaler technique using inhaler checking device |
|                         | 8295311000006117 | Check of inhaler technique not appropriate                |
|                         | 500000           | Asthma self-management plan review                        |
| Asthma management plan  | 5000000          | Asthma management                                         |
|                         | 30000            | Change in asthma management plan                          |
|                         | 200000           | Step up change in asthma management plan                  |
|                         | 90000            | Step down change in asthma management plan                |
|                         | 100000           | Asthma clinical management plan                           |
|                         | 7000             | Does not have asthma management plan                      |

|  |         |                                                                      |
|--|---------|----------------------------------------------------------------------|
|  | 60000   | Health education - asthma self management                            |
|  | 40000   | No change in asthma management plan                                  |
|  | 2000000 | Asthma self-management plan agreed                                   |
|  | 20      | Education about asthma self management                               |
|  | 60      | Registration for access to online asthma self-management application |

### Appendix 3: Product codes for influenza vaccine

| Product codes     | Vaccine                                                                                                                                   |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 762141000033114   | Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes                                       |
| 770341000033117   | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes                                          |
| 1043841000033120  | Pasteur Merieux Inactivated Influenza Vaccine 0.5 ml                                                                                      |
| 2189441000033120  | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)                         |
| 5093141000033120  | Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes                       |
| 5415841000033120  | Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes                        |
| 6494541000033120  | Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose                                                                      |
| 9702041000033120  | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)                             |
| 12364041000033100 | Quadrivalent influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)            |
| 12599041000033100 | Influenza Tetra MYL vaccine suspension for injection 0.5ml pre-filled syringes (Viatris UK Healthcare Ltd)                                |
| 12605941000033100 | Influenza MYL vaccine suspension for injection 0.5ml pre-filled syringes (Viatris UK Healthcare Ltd)                                      |
| 13011941000033100 | Trivalent influenza vaccine (split virion, inactivated) High Dose suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)     |
| 13133041000033100 | Adjuvanted trivalent influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd) |

|                   |                                                                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 13913741000033100 | Cell-based quadrivalent influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd) |
| 13913841000033100 | Adjuvanted quadrivalent influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd) |
| 3954341000033110  | Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes                                |
| 3347241000033120  | Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes                                            |
| 147441000033115   | Begrivac vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)                                  |
| 588341000033111   | Fluvirin vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)                                  |
| 596641000033118   | Fluarix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)                                                  |
| 759741000033113   | Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes (Viatris UK Healthcare Ltd)                                     |
| 2078941000033120  | Infanrix-Hib vaccine injection pack (GlaxoSmithKline UK Ltd)                                                                                 |
| 2641741000033120  | Agrippal vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd)                                                         |
| 2739241000033120  | Hiberix vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)                                           |
| 2890941000033110  | Mastaflu vaccine suspension for injection 0.5ml pre-filled syringes (Masta Ltd)                                                              |
| 3179041000033110  | Pediacel vaccine suspension for injection 0.5ml vials (sanofi pasteur MSD Ltd)                                                               |
| 3188641000033120  | Invivac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)                                          |
| 3331741000033120  | Enzira vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)                                                               |
| 3855441000033110  | Infanrix-IPV + Hib vaccine powder and suspension for suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)             |
| 3939141000033110  | Menitorix vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)                                         |
| 3952441000033110  | Imuvac vaccine suspension for injection 0.5ml pre-filled syringes (Viatris UK Healthcare Ltd)                                                |
| 3954241000033110  | Viroflu vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)                                                       |

|                   |                                                                                                                |
|-------------------|----------------------------------------------------------------------------------------------------------------|
| 5093241000033110  | Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd) |
| 5208541000033110  | Pandemrix vaccine emulsion and suspension for emulsion for injection (GlaxoSmithKline UK Ltd)                  |
| 5415741000033110  | Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)  |
| 6452541000033120  | Inflexal V vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)                      |
| 6453341000033120  | Preflucel vaccine suspension for injection 0.5ml pre-filled syringes (Baxter Healthcare Ltd)                   |
| 6494641000033110  | Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)                                           |
| 8123441000033120  | Optaflu vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd)                            |
| 8534741000033120  | Influvac Desu vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)      |
| 8563041000033110  | Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)              |
| 9306941000033120  | Fluenz Tetra vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)                                     |
| 10647441000033100 | FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)                             |
| 12593041000033100 | Fluad vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd)                              |
| 12598941000033100 | Influvac sub-unit Tetra vaccine suspension for injection 0.5ml pre-filled syringes (Viatris UK Healthcare Ltd) |
| 12884141000033100 | Flucelvax Tetra vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd)                    |
| 13718641000033100 | Fluad Tetra vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus UK Ltd)                        |

#### Appendix 4: Atopy medical codes

| Medical codes | Description  |
|---------------|--------------|
| 9.0566E+14    | [RFC] Eczema |

|            |                                                        |
|------------|--------------------------------------------------------|
| 9.3954E+14 | [RFC] Eczema                                           |
| 456418010  | [V]Personal history of aspirin allergy                 |
| 9.8049E+14 | [X]Exacerbation of eczema                              |
| 301824017  | [X]Other allergic rhinitis                             |
| 301823011  | [X]Other seasonal allergic rhinitis                    |
| 112396014  | Acute atopic conjunctivitis                            |
| 4.7712E+14 | Allergic (intrinsic) eczema                            |
| 1483199016 | Allergic asthma                                        |
| 350152014  | Allergic asthma NEC                                    |
| 357566010  | Allergic contact dermatitis                            |
| 308581011  | Allergic contact dermatitis due to plants, except food |
| 2.239E+14  | Allergic dermatitis - eyelid                           |
| 1.6948E+15 | Allergic emergency drugs Band 1                        |
| 106800011  | Allergic eosinophilia                                  |
| 2622113011 | Allergic reaction                                      |
| 102311013  | Allergic rhinitis                                      |
| 396097015  | Allergic rhinitis due to other allergens               |
| 481104016  | Allergic rhinitis due to pollens                       |
| 396098013  | Allergic rhinitis due to unspecified allergen          |
| 301268012  | Allergic rhinitis NOS                                  |
| 4.777E+14  | Allergic rhinosinusitis                                |
| 63796016   | Allergic urticaria                                     |
| 1.7133E+15 | Allergy - specialty                                    |
| 256624011  | Allergy skin test positive                             |
| 256641013  | Allergy test positive                                  |
| 1495072016 | Allergy to animal                                      |
| 1.8998E+15 | Allergy to banana                                      |
| 2.3664E+15 | Allergy to banana                                      |
| 2577418017 | Allergy to grass pollen                                |
| 7.6961E+15 | Allergy to hazelnut                                    |

|            |                                           |
|------------|-------------------------------------------|
| 2.006E+15  | Allergy to kiwi fruit                     |
| 1.7572E+15 | Allergy to mushrooms                      |
| 3306233018 | Allergy to pineapple                      |
| 442106016  | Allergy to pollen                         |
| 2578548019 | Allergy to pork                           |
| 2.0196E+15 | Allergy to rice                           |
| 2.2326E+15 | Allergy to soya                           |
| 1.7796E+15 | Allergy to strawberries                   |
| 152309013  | Allergy to strawberries                   |
| 2578554018 | Allergy to tomato                         |
| 1.9688E+15 | Allergy to tomato                         |
| 2577421015 | Allergy to tree pollen                    |
| 1.8084E+15 | Anticipatory OTC allergy eye drops given  |
| 1.8084E+15 | Anticipatory OTC allergy medication given |
| 308485016  | Atopic dermatitis and related conditions  |
| 308497015  | Atopic dermatitis NOS                     |
| 4.9734E+14 | Atopic dermatitis/eczema                  |
| 8.8916E+14 | Atopic eczema/dermatitis                  |
| 8.8919E+14 | Atopic eczema/dermatitis NOS              |
| 1.0623E+15 | Beconase Hayfever                         |
| 348103016  | Cat allergy                               |
| 8.8925E+14 | Chronic Eczema                            |
| 9.048E+14  | Clinical immunology and allergy referral  |
| 1488511010 | Clinical immunology/allergy               |
| 26953014   | Cow's milk allergy                        |
| 348104010  | Dander (animal) allergy                   |
| 8.8917E+14 | Dermatitis/eczemas                        |
| 8.8915E+14 | Dermatitis/eczemas NOS                    |
| 5.9834E+14 | Dietary advice for food allergy           |
| 6.3612E+14 | Dietary education for food allergy        |

|            |                                    |
|------------|------------------------------------|
| 6.345E+14  | Dog allergy                        |
| 2.911E+12  | Drugs Used For Allergic Disorders  |
| 3.0811E+13 | Drugs Used In Allergic Emergencies |
| 399917015  | Eczema NOS                         |
| 512310013  | Eczema of external ear             |
| 1.0089E+15 | Eczema/Dermatitis                  |
| 1.5771E+15 | Eczema/Dermatitis                  |
| 6.3649E+14 | Eczematous eyelid dermatitis       |
| 6.3714E+14 | Egg allergy                        |
| 2.175E+14  | Egg free diet - allergy            |
| 324777010  | Egg protein allergy                |
| 6.6035E+14 | Extrinsic (atopic) asthma          |
| 348106012  | Feather allergy                    |
| 1.131E+15  | Fish allergy                       |
| 2534292019 | Food allergy                       |
| 9.8252E+14 | Food allergy                       |
| 216657014  | H/O: cat allergy                   |
| 251845019  | H/O: drug allergy NOS              |
| 251847010  | H/O: food allergy                  |
| 251711015  | H/O: hay fever                     |
| 251846018  | H/O: non-drug allergy              |
| 481105015  | Hay fever                          |
| 9.3336E+14 | Hay fever                          |
| 348109017  | Hay fever - other allergen         |
| 8.1734E+14 | Hay fever - pollens                |
| 348110010  | Hay fever - unspecified allergen   |
| 350153016  | Hay fever with asthma              |
| 8.1736E+14 | Hay fever with asthma              |
| 348107015  | House dust allergy                 |
| 348108013  | House dust mite allergy            |

|            |                                                            |
|------------|------------------------------------------------------------|
| 1.9548E+15 | Medical allergy (secondary group)                          |
| 2.1749E+14 | Milk free diet - allergy                                   |
| 1.7399E+15 | Mushroom allergy                                           |
| 2.8045E+14 | Non-drug allergy                                           |
| 1235714019 | Nut allergy                                                |
| 2.0115E+15 | OH respiratory questionnaire: history of hay fever         |
| 5.6137E+14 | Oral allergy syndrome                                      |
| 1.5916E+15 | Oral allergy syndrome                                      |
| 2.3676E+14 | Peanut allergy                                             |
| 1.9631E+15 | Reason for referral: Chronic Allergy/Immunological Problem |
| 448999010  | Referral to clinical allergy service                       |
| 1.1371E+15 | Referral to eczema clinic                                  |
| 1235716017 | Seafood allergy                                            |
| 492457012  | Seasonal allergic rhinitis                                 |
| 84231014   | Seborrhoeic eczema                                         |
| 448351017  | Seen by clinical allergy - service                         |
| 442109011  | Shellfish allergy                                          |
| 2.1684E+15 | Strawberry allergy                                         |
| 6.3251E+14 | Wheat allergy                                              |

#### ***Appendix 5: Smoking medical codes***

| Medical codes | Description                           |
|---------------|---------------------------------------|
| 216212011     | Smoking reduced                       |
| 338608011     | Smoking cessation advice              |
| 342443012     | Smokes drugs                          |
| 342444018     | Smokes drugs in cigarette form        |
| 342445017     | Smokes drugs through a pipe           |
| 1484932017    | Smoking cessation milestones          |
| 1484934016    | Smoking status at 4 weeks             |
| 1484935015    | Smoking status between 4 and 52 weeks |

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| 1484936019      | Smoking status at 52 weeks                                |
| 1488873010      | Smoking free weeks                                        |
| 1773560017      | Smoking cessation programme start date                    |
| 2669652019      | Smoking started                                           |
| 137711000006111 | Smoker (Read codes)                                       |
| 137811000006119 | Smoking Status                                            |
| 303501000000115 | Smoking cessation advice provided by community pharmacist |
| 482771000000118 | Smoking cessation drug therapy                            |
| 492511000000117 | Smoking cessation therapy                                 |
| 604961000006114 | Current Smoker NOS                                        |
| 649851000006112 | Ex- Rolled Tobacco Smoker                                 |
| 649861000006114 | Ex-Cigarette Smoker                                       |
| 852121000006114 | Smoking cessation-maintain abstinence                     |
| 852131000006112 | Smoking cessation-practice nurse support                  |
| 856371000006111 | Smoking clinic                                            |
| 903041000006110 | EX-Smoker NOS                                             |
| 904011000006114 | Smoking cessation declaration signed by patient           |
| 904071000006117 | Smoking cessation 4 week follow up                        |
| 904081000006119 | Smoking cessation 52 week follow up                       |
| 904141000006112 | Smoking cessation 4 week F/U not completed                |
| 904151000006114 | Smoking cessation 4 week F/U completed                    |
| 904161000006111 | Smoking cessation 52 week F/U completed                   |
| 904171000006116 | Smoking cessation 52 week F/U not completed               |
| 904181000006118 | Smoking cessation counselling                             |
| 904191000006115 | Smoking cessation motivation score                        |
| 904201000006117 | Smoking cessation confidence score                        |
| 904211000006119 | Smoking cessation service patient satisfaction score      |
| 904221000006110 | Smoking cessation bupropion therapy                       |
| 904231000006113 | Smoking cessation counselling by telephone                |
| 904241000006115 | Smoking cessation counselling in person                   |

|                  |                                                                  |
|------------------|------------------------------------------------------------------|
| 909391000006117  | [RFC] Smoking cessation                                          |
| 961581000006114  | Smokes/uses tobacco products                                     |
| 128130017        | Smoker                                                           |
| 78013015         | Smokers' cough                                                   |
| 1009271000006118 | Non Smoker - Nos                                                 |
| 1176421000000118 | Smoking cessation advice declined                                |
| 1538681000006118 | Smoke                                                            |
| 1591651000006110 | Smoking cessation referral declined                              |
| 1708051000000119 | Smoking status at 12 weeks                                       |
| 1626121000006116 | Smoking cessation drug therapy - varenicline                     |
| 1746211000006111 | Smoking status at 12 weeks                                       |
| 1777011000006118 | Reason for referral: Smoking Cessation                           |
| 1819411000006114 | Smoking increased                                                |
| 1823811000006115 | Smoking cessation 12 week follow up                              |
| 1825071000006116 | Smoking cessation 12 week F/U not completed                      |
| 1825081000006118 | Smoking cessation 12 week F/U completed                          |
| 1833971000006116 | Stop Smoking satisfaction questionnaire given                    |
| 1873511000006118 | Care contact service: Smoking/substance cessation/interven prog. |
| 2141561000000115 | Smoking cessation drug therapy declined                          |
| 2670126018       | Smoking restarted                                                |
| 1979491000006115 | Smoking cessation follow-up                                      |
| 489931000000114  | Smoking cessation therapy NOS                                    |
| 736241000000116  | Smoking cessation - enhanced services administration             |
| 1704491000006115 | Smoking cessatn monitor template complet - enhanc serv admin     |
| 1741641000006117 | Smoking cessation ESA monitoring template completed              |
| 1175011000000112 | Smoking cessation programme declined                             |
| 137721000006115  | Smoker - amount smoked                                           |
| 137791000006118  | Smoking restarted                                                |
| 2203381000000113 | Smoking cessation 12 week follow-up                              |
| 137761000006114  | Smoking Age Ceased                                               |

|                 |                                               |
|-----------------|-----------------------------------------------|
| 14866014        | Non-smoker                                    |
| 250368013       | Keeps trying to stop smoking                  |
| 250372012       | Trying to give up smoking                     |
| 250373019       | Stopped smoking                               |
| 250374013       | Current non-smoker                            |
| 250385010       | Date ceased smoking                           |
| 136515019       | Pipe smoker                                   |
| 265092010       | Pregnancy smoking advice                      |
| 285793015       | Stop smoking monitor default                  |
| 285805010       | Stop smoking monitoring delete                |
| 99639019        | Cigar smoker                                  |
| 342574011       | Total time smoked                             |
| 108938018       | Cigarette smoker                              |
| 397732011       | Never smoked tobacco                          |
| 418914010       | Ex-cigarette smoker                           |
| 459722017       | Referral to stop-smoking clinic               |
| 503483019       | Current smoker                                |
| 1484933010      | Negotiated date for cessation of smoking      |
| 1488576014      | Thinking about stopping smoking               |
| 1488577017      | Ready to stop smoking                         |
| 1488578010      | Not interested in stopping smoking            |
| 1489355012      | Referral to smoking cessation advisor         |
| 1780273014      | Seen by smoking cessation advisor             |
| 1780360012      | Reason for restarting smoking                 |
| 2982426011      | Provision of smoking cessation leaflet        |
| 62881000000117  | DNA - Did not attend smoking cessation clinic |
| 852111000006118 | Gradual smoking reduction                     |
| 852991000006114 | Ex-cigar smoker                               |
| 853001000006110 | Ex-smoker NOS                                 |
| 854021000006115 | Cigarette smoker                              |

|                  |                                                                             |
|------------------|-----------------------------------------------------------------------------|
| 854051000006112  | Ex-pipe smoker                                                              |
| 854071000006119  | Current smoker                                                              |
| 854111000006110  | Past smoker                                                                 |
| 854151000006111  | Date stopped smoking                                                        |
| 854951000006113  | Grade A non-smoker                                                          |
| 854961000006110  | Grade B light smoker (1-10/day)                                             |
| 854981000006117  | Grade C moderate smoker (11-20/day)                                         |
| 855001000006114  | Grade D heavy smoker (>20 Day)                                              |
| 903981000006117  | Not interested in stopping smoking                                          |
| 904001000006111  | Ready to stop smoking                                                       |
| 904021000006118  | Previous smoking quit attempts                                              |
| 904031000006115  | Thinking about stopping smoking                                             |
| 923201000006112  | Pregnancy smoking advice                                                    |
| 923611000006113  | Health ed. - smoking                                                        |
| 1059701000000119 | Ex roll-up cigarette smoker                                                 |
| 1123541000000118 | Stop smoking face to face follow-up                                         |
| 1125741000000111 | Brief intervention for smoking cessation                                    |
| 1151791000000117 | Recently stopped smoking                                                    |
| 1152111000000118 | Current smoker annual review                                                |
| 1154431000000112 | Non-smoker annual review                                                    |
| 1154471000000114 | Ex-smoker annual review                                                     |
| 1563081000000115 | Practice based smoking cessation programme start date                       |
| 1592611000000110 | Failed attempt to stop smoking                                              |
| 1694421000006112 | Stop smoking monitoring admin.                                              |
| 1709641000000115 | Referral for smoking cessation service offered                              |
| 1716141000000117 | Lost to smoking cessation follow-up                                         |
| 1750931000000118 | Stop smoking service opportunity signposted                                 |
| 1751721000000113 | Stop smoking invitation short message service text message                  |
| 1755201000006117 | Consent given for follow-up evaluation after smoking cessation intervention |

|                  |                                                                                |
|------------------|--------------------------------------------------------------------------------|
| 1755231000006113 | Declined consent for follow-up evaluation after smoking cessation intervention |
| 1758971000006113 | Stop smoking monitoring invitation SMS text message sent                       |
| 1758981000006111 | Stop smoking monitoring invitation first SMS text message sent                 |
| 1758991000006114 | Stop smoking monitoring invitation second SMS text message sent                |
| 1759001000006114 | Stop smoking monitoring invitation third SMS text message sent                 |
| 1771191000006119 | Attends smoking cessation clinic not at practice                               |
| 1778181000006110 | Group session: Stop smoking education programme                                |
| 1809131000006111 | Total time smoked                                                              |
| 1888831000006110 | Primary carer current smoker                                                   |
| 1653781000000119 | Declined consent for smoking cessation data sharing                            |
| 1662911000000114 | Consent given for follow-up by smoking cessation team                          |
| 1662951000000113 | Declined consent for follow-up by smoking cessation team                       |
| 2251871000000112 | Referral to smoking cessation service declined                                 |
| 2251911000000114 | Referral to smoking cessation service                                          |
| 2462391000000119 | Varenicline smoking cessation therapy declined                                 |
| 2462431000000110 | Varenicline smoking cessation therapy offered                                  |
| 2717211000000112 | Signposting to smoking cessation service                                       |
| 250363016        | Ex-trivial smoker (<1/day)                                                     |
| 250364010        | Ex-light smoker (1-9/day)                                                      |
| 250365011        | Ex-moderate smoker (10-19/day)                                                 |
| 250366012        | Ex-heavy smoker (20-39/day)                                                    |
| 250367015        | Ex-very heavy smoker (40+/day)                                                 |
| 250371017        | Ex-smoker - amount unknown                                                     |
| 16261000000110   | Stop smoking monitor admin.NOS                                                 |
| 21681000000118   | Anti-smoking monitoring admin.                                                 |
| 21691000000116   | Stop smoking monitoring admin.                                                 |
| 25281000000119   | Stop smoking clinic admin.                                                     |
| 67621000006112   | Very heavy smoker - 40+cigs/d                                                  |
| 88471000006112   | Trivial smoker - < 1 cig/day                                                   |

|                  |                                                             |
|------------------|-------------------------------------------------------------|
| 482871000000111  | Other specified smoking cessation therapy                   |
| 498831000006118  | Attends stop smoking monitor.                               |
| 649821000006115  | Ex cigar smoker                                             |
| 649831000006117  | Ex pipe smoker                                              |
| 649841000006110  | Ex smoker                                                   |
| 700121000006118  | Moderate smoker - 10-19 cigs/d                              |
| 743331000006116  | Light smoker - 1-9 cigs/day                                 |
| 818061000006111  | Health ed. - smoking                                        |
| 819331000006110  | Heavy smoker - 20-39 cigs/day                               |
| 1123751000000113 | Non-smoker annual review - enhanced services administration |
| 1123951000000110 | Ex-smoker annual review - enhanced services administration  |
| 1704551000006110 | Referred for COPD structured smoking assessment             |
| 1714541000006110 | Current smoker annual review - enhanced services admin      |
| 1715591000006117 | Referral to NHS stop smoking service                        |
| 1785671000006116 | Stop smoking invitation first SMS text message              |
| 1785681000006118 | Stop smoking invitation second SMS text message             |
| 1785691000006115 | Stop smoking invitation third SMS text message              |
| 128311000006112  | Stop smoking monitor 1st lettr                              |
| 128321000006116  | Stop smoking monitor 2nd lettr                              |
| 128331000006118  | Stop smoking monitor 3rd lettr                              |
| 128361000006110  | Stop smoking monitor phone inv                              |
| 128371000006115  | Stop smoking monitor verb.inv.                              |
| 128381000006117  | Stop smoking monitor.chk done                               |
| 936011000006114  | Lifestyle advice regarding smoking                          |
| 397733018        | Occasional smoker                                           |
| 285792013        | Refuses stop smoking monitor                                |
| 1651711000000113 | Consent given for smoking cessation data sharing            |
| 250375014        | Rolls own cigarettes                                        |
| 852981000006111  | Rolls own cigarettes                                        |
| 904041000006113  | Waking time to first cigarette                              |

|                 |                                                  |
|-----------------|--------------------------------------------------|
| 904091000006116 | Date of last cigarette                           |
| 2474719011      | Minutes from waking to first tobacco consumption |
| 298701000000114 | [V]Personal history of tobacco abuse             |

#### **Appendix 6: Passive smoking codes**

| Medcodeid  | Terms                                                            |
|------------|------------------------------------------------------------------|
| 1.8897E+15 | child 27-30 mth exam.- smoking cessation support provided        |
| 1.8897E+15 | child 27-30 mth exam.- signpost to smoking cessation             |
| 1.8996E+15 | mother's smoking status at time of baby's birth - ex-smoker      |
| 1.8996E+15 | mother's smoking status at time of baby's birth - never smoked   |
| 1.9119E+15 | carer's partner current smoker                                   |
| 1.8897E+15 | child 27-30 mth exam. - refused smoking cessation service        |
| 1.812E+15  | health education - parental smoking                              |
| 251157013  | mother smokes                                                    |
| 251158015  | both parents smoke                                               |
| 251159011  | passive smoking risk                                             |
| 1.9796E+15 | socio-economic classification code (stop smoking): home carer    |
| 1.8897E+15 | child 27-30 mth exam. - discuss with smoking cessation service   |
| 1.8995E+15 | mother's smoking status at time of baby's birth                  |
| 1.8996E+15 | mother's smoking status at time of baby's birth - passive smoker |
| 411033014  | smoker in the family                                             |
| 72373013   | passive smoker                                                   |
| 406164016  | family smoking history                                           |
| 1.8996E+15 | mother's smoking status at time of baby's birth - smoker         |
| 1.8888E+15 | primary carer current smoker                                     |
| 1.8897E+15 | child 27-30 mth exam. - requ. assist. from smoking cessation     |
| 251156016  | father smokes                                                    |

#### **Appendix 7: Breathlessness medical codes**

| Medical codes | Description                    |
|---------------|--------------------------------|
| 252385016     | Breathless - moderate exertion |

|                  |                                                           |
|------------------|-----------------------------------------------------------|
| 252386015        | Breathless - mild exertion                                |
| 252387012        | Breathless - at rest                                      |
| 252412011        | Breathlessness NOS                                        |
| 397888010        | Breathlessness                                            |
| 451467013        | [D]Breathlessness                                         |
| 1484904014       | Breathless - strenuous exertion                           |
| 525691000006114  | Breathlessness lying flat                                 |
| 525741000006111  | Breathlessness symptom                                    |
| 1857671000006115 | Subjective breathlessness score at start of exercise test |
| 1861181000006114 | Breathlessness causing anxiety                            |
| 2287071000000115 | Anxiety about breathlessness                              |
| 2287881000000112 | Breathlessness causing difficulty eating                  |
| 3488351000006112 | Breathlessness on exertion                                |
| 5307671000006113 | Breathlessness rating                                     |
| 5497741000006119 | Breathless                                                |
| 5837641000006114 | Increasing breathlessness                                 |
| 7563281000006118 | Difficulty eating due to breathlessness                   |
| 253889014        | O/E - dyspnoea                                            |
| 317395018        | [D]Dyspnoea                                               |
| 371012016        | Nocturnal dyspnoea                                        |
| 498862013        | Dyspnoea on exertion                                      |
| 140461000006116  | Dyspnoea                                                  |
| 633381000006111  | Dyspnoea - symptom                                        |
| 982351000006118  | Dyspnoea                                                  |
| 1807841000006119 | O/E - dyspnoea at rest                                    |
| 1807851000006117 | O/E - dyspnoea on exertion                                |
| 3488371000006119 | Dyspnoea on effort                                        |
| 3488381000006116 | Exertional dyspnoea                                       |
| 3676941000006119 | Dyspnoea, class 2                                         |
| 4545421000006118 | Dyspnoea at rest                                          |

|                  |                                             |
|------------------|---------------------------------------------|
| 252419019        | Breath symptom                              |
| 252421012        | Breath symptom NOS                          |
| 253929011        | O/E - shallow breathing                     |
| 317392015        | [D]Shortness of breath                      |
| 317994012        | Abnormal breathing                          |
| 344917018        | Difficulty breathing                        |
| 397890011        | Shortness of breath                         |
| 1232138017       | Short of breath on exertion                 |
| 1484903015       | Short of breath dressing/undressing         |
| 2159189012       | Unable to complete a sentence in one breath |
| 961761000006112  | Abnormal breathing patterns                 |
| 2379631000000117 | Able to complete sentence in one breath     |
| 3488411000006118 | SOBOE - Shortness of breath on exertion     |
| 4545441000006113 | SOBAR - Shortness of breath at rest         |
| 5004081000006113 | DIB - Difficulty in breathing               |
| 5258891000006111 | Short of breath at night                    |
| 5258901000006110 | Laboured breathing                          |
| 5497761000006115 | SOB - Shortness of breath                   |
| 5738271000006118 | Unable to breathe                           |
| 5741241000006119 | Unable to take deep breaths                 |
| 6458181000006118 | Shallow breathing                           |
| 6462341000006118 | Breathing problem                           |

#### Appendix 8: Wheeze medical codes

| Medical codes | Description                |
|---------------|----------------------------|
| 317433010     | Chest tightness            |
| 252406018     | Nocturnal cough / wheeze   |
| 253894014     | O/E - expiratory wheeze    |
| 264514012     | Increasing exercise wheeze |
| 454009015     | Wheeze absent              |

|                   |                                                                  |
|-------------------|------------------------------------------------------------------|
| 473141000000114   | Viral wheeze                                                     |
| 494261000000111   | Viral induced wheeze                                             |
| 1667621000000114  | [D]Mild wheeze                                                   |
| 1667631000000111  | [D]Moderate wheeze                                               |
| 1667641000000119  | [D]Severe wheeze                                                 |
| 1667651000000116  | [D]Very severe wheeze                                            |
| 1706101000000118  | On examination - inspiratory wheeze                              |
| 1834141000006113  | Constant wheeze                                                  |
| 1904881000006110  | Number of days absent from school due to wheeze in past 6 months |
| 2655541000006110  | Expiratory wheeze                                                |
| 2892871000006111  | Wheeze - rhonchi                                                 |
| 3410141000006112  | Wheeze                                                           |
| 5897201000006117  | Expiratory polyphonic wheeze                                     |
| 7586621000006111  | O/E - inspiratory wheeze                                         |
| 8232711000006115  | Mild wheeze                                                      |
| 8232731000006114  | Moderate wheeze                                                  |
| 8232751000006119  | Severe wheeze                                                    |
| 8232771000006112  | Very severe wheeze                                               |
| 8437071000006113  | Wheeze clinical management plan                                  |
| 13651301000006113 | Bronchitis co-occurrent with wheeze                              |
| 13651461000006115 | Chronic bronchitis co-occurrent with wheeze                      |
| 13651601000006119 | Bronchitis co-occurrent with acute wheeze                        |
| 13651611000006116 | Acute bronchitis co-occurrent with wheeze                        |

#### Appendix 9: Cough medical code

| Medcodeid | Term         |
|-----------|--------------|
| 82824016  | Cough        |
| 252359015 | Chesty cough |
| 407081018 | C/O - cough  |

|                  |                                    |
|------------------|------------------------------------|
| 20419011         | Dry cough                          |
| 317403015        | [D]Cough                           |
| 252352012        | Productive cough -green sputum     |
| 252357018        | Night cough present                |
| 252406018        | Nocturnal cough / wheeze           |
| 423230012        | Persistent cough                   |
| 252353019        | Productive cough-yellow sputum     |
| 252351017        | Productive cough -clear sputum     |
| 397882011        | Productive cough                   |
| 252358011        | Night cough absent                 |
| 252366019        | Cough symptom NOS                  |
| 113213012        | Chronic cough                      |
| 46589015         | Whooping cough                     |
| 598431000006113  | Coughing up phlegm                 |
| 252363010        | Morning cough                      |
| 30371011         | Barking cough                      |
| 216653013        | Cough with fever                   |
| 252360013        | Bronchial cough                    |
| 1970531000006111 | COPD assessment test score - cough |
| 252364016        | Evening cough                      |
| 317404014        | Cough syncope                      |
| 479311018        | Cough on exercise                  |
| 303321000000115  | Reflux cough                       |
| 1780331000006117 | Daytime cough                      |
| 78013015         | Smokers' cough                     |
| 5533011000006112 | Complaining of cough               |
| 2168391000000116 | [D]Episodic dry cough              |
| 253356015        | Cough aggravates symptom           |
| 286452015        | Whooping cough NOS                 |
| 317408012        | [D]Cough with haemorrhage          |

|                   |                                                                             |
|-------------------|-----------------------------------------------------------------------------|
| 442503015         | Difficulty in coughing up sputum                                            |
| 459738011         | Unexplained cough                                                           |
| 264414014         | Notification of whooping cough                                              |
| 13768761000006115 | Chesty cough                                                                |
| 5754161000006114  | Croupy cough                                                                |
| 8260311000006113  | Episodic dry cough                                                          |
| 3516981000006112  | Nocturnal cough                                                             |
| 318642011         | Cough fracture                                                              |
| 384668019         | Cough swab                                                                  |
| 961781000006119   | Cough                                                                       |
| 1231963019        | Pneumonia with whooping cough                                               |
| 1936661000006118  | Coughing incontinence of urine                                              |
| 3587071000006111  | Coughing up blood                                                           |
| 7305041000006116  | Postviral cough                                                             |
| 907541000006113   | [RFC] Whooping cough                                                        |
| 1786081000006116  | Benign cough headache                                                       |
| 1709331000006110  | Cough on exercise                                                           |
| 961791000006116   | Unable to cough/expectorate independently                                   |
| 5468241000006113  | Coughing                                                                    |
| 1709261000006111  | Cough swab                                                                  |
| 3524231000006119  | Spasmodic cough                                                             |
| 5243651000006110  | Painful cough                                                               |
| 5891001000006117  | Does not cough up sputum                                                    |
| 1012841000006117  | Adverse reaction to Expectorant, Demulcent, And Compound Cough Preparations |
| 5887221000006111  | Allergic cough                                                              |
| 6782071000006115  | Cough variant asthma                                                        |
| 4943451000006119  | Able to cough up sputum                                                     |
| 5097221000006114  | Cough - urge incontinence of urine                                          |
| 5259531000006115  | Cough when swallowing                                                       |

|                   |                                                            |
|-------------------|------------------------------------------------------------|
| 4316191000006113  | Coughed sputum specimen                                    |
| 5890991000006118  | Does cough up sputum                                       |
| 11823221000006114 | Non-productive cough                                       |
| 465171000006119   | Cough suppressant adverse reaction                         |
| 5890901000006113  | Effective cough                                            |
| 5741441000006118  | Able to cough                                              |
| 5741451000006116  | Does cough                                                 |
| 4943441000006116  | Unable to cough up sputum                                  |
| 3520051000006112  | Increasing frequency of cough                              |
| 5583481000006118  | Coughing ineffective                                       |
| 3057121000006116  | Cough reflex                                               |
| 3193611000006114  | Fit of coughing                                            |
| 5259521000006118  | Character of cough                                         |
| 13768751000006117 | Bronchial cough                                            |
| 1763631000006115  | Cough with physiotherapy                                   |
| 1819551000006111  | History of productive cough                                |
| 2724991000000113  | Suspected whooping cough                                   |
| 2828791000006112  | Brassy cough                                               |
| 3193591000006115  | Paroxysmal cough                                           |
| 4060421000006116  | Cough headache syndrome                                    |
| 5259541000006113  | Coughs when swallowing                                     |
| 5741361000006113  | Ability to cough                                           |
| 5890971000006119  | Ability to cough up sputum                                 |
| 6781071000006112  | Non-productive cough                                       |
| 13046071000006115 | Recently performed mobilisation with intent to cause cough |