Emergency care re-attendance for acute childhood asthma in a low-resource setting: The Childhood Asthma Re-attendance Assessment (CARA) Study

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy

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Declaration

I, Cristina Ardura Garcia, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

My Role

I undertook the literature review for the thesis, as well as the systematic review and meta-analysis of the risk factors for emergency care re-attendance for acute asthma. I was supported for the systematic review search by a Cochrane Information Specialist (Vittoria Lutje), and by two other University of Liverpool PhD students for the data extraction (Seher Zaidi and Marie Stolbrink), while I conducted the meta-analysis.

I designed the study protocols for the prospective cohort study, given my previous experience working in the setting, with the guidance of my supervisors John Blakey and Philip Cooper. The questionnaires used were based on those previously employed in a pilot case-control study I conducted in this setting, which is a modified version of the International Study of Allergies and Asthma in Childhood (ISAAC), together with other validated questionnaires. I produced all the standard operating procedures, other than the specific laboratory procedures, which were written by Phil Cooper's laboratory team. I oversaw the set-up of the study office in Esmeraldas, as well as the recruitment and training of the study nurse, laboratory technician and study assistant (respiratory therapist). The laboratory technician was further trained in specific laboratory techniques by Carlos Sandoval at Phil Cooper's laboratory in Quinindé, Esmeraldas, Ecuador. I organised informative sessions at the participating hospitals and health centres for the health care workers to cooperate informing

possible participants. I recruited the children for the study, undertook the questionnaires, lung function and FeNO measurements tests, and follow-up of the participants, together with the study assistant (Diana Farah), nurse (Paola Hurtado) and laboratory technician (Erick Arias). Erick Arias and Phil Cooper's laboratory team carried out the laboratory analysis of blood, stool and nasal wash samples. Paola Hurtado and Erick Arias were responsible for the data entry, while I performed data cleaning and management. I conducted the statistical analysis, with the guidance and strict supervision of Laura Bonnett (post-doctoral research statistician at the University of Liverpool).

I designed the study protocol and interview guides for the qualitative study, with input from Natalia Romero, an experienced Ecuadorian qualitative researcher from the International University of Ecuador (UIDE). I carried out the recruitment of study participants and conducted the in-depth interviews and focus group discussions together with Natalia Romero. I designed the coding framework and analysed the qualitative data under the supervision of Natalia Romero.

I wrote the whole thesis chapters, with corrections and input from John Blakey, Philip Cooper, Natalia Romero and Laura Bonnett.

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Publications related to work presented in this thesis

Journal papers

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Ardura-Garcia, C., Stolbrink M., Zaidi S., Cooper, PJ. and Blakey, J. 2018 Identifying predictors of risk of re-attendance to emergency care and hospital readmission due to asthma attacks in children: a Systematic Review and Meta-Analysis. *Pediatric Pulmonology* (Submitted, mayor corrections).

Ardura-Garcia C, Garner P, Cooper PJ. , 2018. Is childhood wheeze and asthma in Latin America associated with poor hygiene and infection? A systematic review. *BMJ Open Respiratory Research,* 5:e000249. doi:10.1136/bmjresp-2017-000249

Papers in preparation or submitted for publication

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Conference papers

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Ardura-Garcia, C., Cooper, P.J. and Garner, P., 2015. Exposure to poor hygiene and early life infections and the risk of wheeze or asthma in Latin American children: a systematic review. *World Allergy Organization Journal*, *8*(1), p.A110.

Abstract

Background

Asthma is a public health problem in Latin America, where asthmatic children are mainly treated at emergency rooms during acute attacks. These attacks result in loss of lung function and quality of life for the asthmatic child and family, risk of death and high direct and indirect economic costs. In order to improve paediatric asthma management in Esmeraldas, Ecuador, we aimed to identify predictors of recurrent asthma attacks requiring emergency care and to explore the caregivers' (CGs) and health care workers' (HCWs) perceptions of barriers and facilitators to asthma health and home care access.

Methods

First, a systematic review and meta-analysis of published studies analysing predictors for emergency department (ED) re-attendance or hospital readmission for acute asthma in children was performed. Second, a prospective cohort study of children treated for an asthma attack at an emergency room in Esmeraldas, Ecuador, was undertaken to define the characteristics of these children, determine the rate of ED re-attendance for acute asthma and identify the predictors for this to occur. Third, a qualitative study to explore acute asthma significance and perceived barriers and facilitators for health and home care access from the asthmatic children's CGs' and HCWs' perspective was performed.

Results

In both the meta-analysis and prospective cohort study, children of a younger age and a history of severe asthma attacks during the previous year were at a greater risk of ED re-attendance for acute asthma. Forty six percent of the children

recruited during the prospective cohort suffered a subsequent asthma attack requiring emergency care in the following 6 months. Other identified predictors of ED re-attendance for acute asthma were: existing asthma diagnosis (AOR: 2.17, 95% CI: 1.19-3.94; AHR: 1.66, 95% CI: 1.15-2.39); food triggers (AOR: 1.99, 95% CI: 1.11-3.55); existing eczema diagnosis (AOR: 4.22, 95% CI 1.02-17.54); and urban residence as protective (AHR: 0.69, 95% CI: 0.50-0.95).

Twelve HCWs and 20 CGs participated in the in-depth interviews and focus group discussions, expressing a differing significance of asthma attacks. This difference was also observed between experienced and inexperienced HCWs. Multiple barriers and several facilitators were identified by HCWs and CGs that affect health and home care access for asthmatic children. When shown the predictors of ED-reattendance for acute asthma combined in a risk-assessment tool, both HCWs and CGs reported finding the tool easy to use and understand, as well as a useful aid in the decision-making process concerning asthma treatment and follow-up.

Conclusion

A combination of several question-based predictors may result in an effective and simple risk-assessment tool to be used at the ED to identify asthmatic children at a higher risk of recurrent severe asthma attacks. Increasing CGs' and HCWs' asthma knowledge as well as HCWs' communication skills, to establish a patient-centred approach with a shared decision-making process could mean a difference in the quality of the asthma care in this setting. The use of the described recurrent risk assessment tool could prove useful in this process, as reported by the participants in this study.

List of abbreviations

ABPM: allergic bronchopulmonary mycosis
ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
Af: Afro-Ecuadorian
AHR: adjusted hazard ratio
AIRLA: Asthma Insights and Reality in Latin America
ALSPAC: Avon Longitudinal Study of Parents and Children
AMR: asthma medication ratio
AOR: adjusted odds ratio
API: asthma predictive index
ATS: American Thoracic Society
AUC: area under curve
BD: bronchodilator
BDP: beclomethasone dipropionate
BHR: bronchial hyperresponsiveness
BMI: body mass index
CAC: children's' asthma care
C-ACT: Childhood Asthma Control Test
CCL24/26: CC chemokine ligand 24/26
CF: cystic fibrosis
CG: caregiver
CI: confidence interval
CIOMS: Council for International Organizations of Medical Sciences
COPD: chronic obstructive pulmonary disease
CXCL: CXC chemokine ligand
d: days
DALY: disability adjusted life-year
dx: diagnosis
DUOX: dual oxidase
E: experienced doctors
ED: emergency department
EDTA: ethylenediaminetetraacetic acid
EPO: eosinophil peroxidase

EPR-3: Expert Panel Report 3

ER: emergency room

ERS: European Respiratory Society

ETS: exposure to tobacco smoke

FeNO: fraction of exhaled nitric oxide

FEPIS: Fundación Ecuatoriana para Educación en Salud

FEV_1: forced expiratory volume in the first second

FGD: focus group discussion

FU: follow-up

FVC: forced vital capacity

GCASR: Greater Cincinnati Asthma Rik Study

GCP: good clinical practice

GD: general doctor

GEMA: Guía Española de Manejo de Asma (Spanish Asthma Management Guide)

GINA: Global Initiative for Asthma

GLE: generalized liner equations

GM-GSF: granulocyte-macrophage colony-stimulating factor

GNI: gross national income

GP: general practitioner

HC: health centre

HCW: health care worker

HDTC: Hospital Delfina Torres de Concha (or DTCH)

HLA: human leukocyte antigens

HMPC: home management plan care

HMPV: human metapneumovirus

HR: hazard ratio

ICS: inhaled corticosteroids

ICU: intensive care unit

IESS: Instituto Ecuatoriano de Seguro Social (Social Security Ecuadorian Institute)

IFNc: interferon-c

IgE: immunoglobulin class E

IL: interleukin

IM: intramuscular

INEC: instituto nacional de estadística (Ecuadorian National Statistics Institute)

iNOS: inducible nitric oxide synthase

IP: in-depth semi-structured interview to a paediatrician

IQR: interquartile range

IR: in-depth semi-structured interview to a medical resident

IRR: incidence rate ratio

ISAAC: International Study of Asthma and Allergy in Childhood

ISI: in-depth semi-structured interviews

IT: in-depth semi-structured interview to a respiratory therapist

IV: intravenous

LABA: long-acting beta2-agonist;

LSTM: Liverpool School of Tropical Medicine

LTFU: lost to follow-up

LTRAs: leukotriene receptor antagonists

m: months

MAD: mucosal atomization device

MARS-A: medication adherence report scale for asthma

MHA: multiple hospital admission

MUC5AC: mucin 5AC

NA: not addressed

N/A: not applicable

NAKQ: Newcastle Asthma Knowledge Questionnaire

ND: not determined

NHLBI: National Heart, Lung, and Blood Institute

NK: natural killer

NO: nitric oxide

N-O: Newcastle Ottawa Score

NS: non statistically significant

NSAIDSs: nonsteroidal anti-inflammatory drugs

OCS: oral corticosteroids

OR: odds ratio

OX40/L: CD134 ligand

PAQLQ: pediatric asthma quality of life questionnaire

PBS: phosphate buffered saline

PCR: polymerase chain reaction

PEF: peak expiratory flow

PEFR: peak expiratory flow rate

PFTs: pulmonary function tests

PGD2: prostaglandin D2

PI: Principal Investigator

PIAMA: Prevention and Incidence of Asthma and Mite Allergy

PIV: parainfluenza virus

PMNs: polymorphonucleocytes

ProAR: Programme for control of asthma and Allergic Rhinitis in Bahia (Brazil)

PUCE: Pontificia Universidad Católica del Ecuador

QoL: quality of life

RCT: randomised-controlled trial

ROC: receiver operating characteristic

RR: response rate

RSV: respiratory syncytial virus

RT: respiratory therapist

SABA: short-acting beta2-agonist.

SARP: American Severe Asthma Research Program

SD: standard deviation

SDM: shared decision making

SE: standard error

SES: socioeconomic status

SHA: single hospital admission

SLIT: sublingual immunotherapy

SPT: skin prick test

START: inhaled Steroid Treatment As Regular Therapy in early asthma

Tc1: cytotoxic T-cell type 1

TGFb: transforming growth factor-b

Th1: T-helper cell type 1

Th2: T-helper cell type 2

TNFα: tumor necrosis factor α

TSLP: thymic stromal lymphopoietin

U-BIOPRED: Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

UIDE: Universidad Internacional de Ecuador

UK: United Kingdom

US: United States

USA: United States of America

USD: United States Dollar

WAP: written asthma action plan

WHO: World Health Organization

Y: young, inexperienced doctors

y: years

YLD: years lived with to disability

YLL: years of life lost to premature death

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1. Introduction

1.1 Background

Over 330 million people are affected by asthma worldwide, according to the latest Global Asthma Report. Asthma is the most common chronic disease in children, and up to 14% of the world's children have experienced asthma symptoms in the last year[1]. Although asthma prevalence may have reached a plateau in developed countries with high rates, such as the UK or New Zealand, global asthma prevalence is still rising, mainly due to a more recent increase in developing countries[2]. This is the case of some Latin American countries, such as Brazil or Costa Rica, where current asthma rates are now as high as in traditionally high prevalence countries[2].

Traditionally asthma severity has been classified according to daily symptom control, and questionnaires have been developed and validated to assess this, such as the Asthma Control Test[3], which has been also adapted for children (C-ACT)[4]. Consequently, daily symptoms are the focus of treatment guidelines, and physicians have used asthma control questionnaires to make treatment adjustments. However, current guidelines[5,6] have included the concept of 'future risk' to define asthma severity and control, referring to the risk of adverse events such as acute exacerbations and loss of lung function. Children with well-controlled asthma are still at risk of developing severe, life-threatening, acute asthma attacks[7].

An asthmatic exacerbation is an acute or subacute worsening of respiratory symptoms and lung function. It can be either mild or severe, the latter defined in the last American Thoracic Society (ATS) and European Respiratory Society (ERS) 2009 statement, as an event that requires systemic corticosteroids (for at

least 3 days) and emergency department attendance or hospital admission[8]. Asthma exacerbations are still common[9] and are associated with high healthcare costs [10] as well as missed school and workdays. These acute events are especially relevant among children in whom they are extremely common, often following a viral respiratory tract infection[11,12]. Asthma acute attacks are also a cause of great anxiety in patients[13] due to the potential severe complications, risk of death and long-term effects such as loss of lung function[14].

Asthma attacks are generally preventable, either by avoiding previously identified triggers (acute respiratory infections, aeroallergen exposure, etc.) or by appropriate preventive treatment. Although exacerbations may occur despite the use of inhaled corticosteroids[15], these may still reduce the number of overall exacerbations by 40% when compared to other anti-inflammatory treatments such as leukotriene receptor antagonist[7], as well as attenuate the decline in lung function associated with acute exacerbations[16]. It is therefore important to be able to identify patients at risk of further attacks and hospital admission to provide additional education and support or adjustments to treatment. Strategies to reduce such risks among underprivileged populations through the provision of inhaled corticosteroids through the public health system have been done with considerable success in research programmes such as Pro-AR in Salvador, Brazil[17].

Even though uncontrolled symptoms are a risk factor for asthma exacerbations[18], the adequate management of daily symptoms does not guarantee an absence of acute attacks[19]. Therefore, asthma control questionnaires based on daily symptoms, such as those previously mentioned, have limited utility for the prediction of individual risk of exacerbations[20]; for example, a study including more than 7000 patients found current control was not associated with the risk

of a future asthma attack after controlling for potential confounders in a multivariable model[21]. In addition, health care workers may not rely on subjective evaluations of asthma control, as airflow obstruction perception varies between patients[22]. A tool to enable clinicians to identify asthmatic children at a greater risk of suffering repeated acute exacerbations would be extremely useful to optimise treatment strategies and address modifiable risk factors. This is especially relevant when treating patients with discordant manifestations of asthma, such as few daily symptoms but evidence of active eosinophilic inflammation in the airways and therefore a high risk of exacerbations, and vice versa[23]. All in all, individualised therapies reduce the patient's risk of adverse reactions from asthma medications they may not even need. This fact is even more important in resource poor settings, where access to specialised health care and treatment is limited[24].

1.2 Starting points

Asthma has been described as a public health problem in Latin America[25], not only due to its high prevalence, but also to the significant associated morbidity and mortality. There is an important under-diagnosis of asthma because of the limited availability of clinical expertise and lung function measurements outside private health care in the main urban centres. As for asthma treatment, essential drugs are not usually available or affordable, and long-term medications are rarely prescribed[26,27]. These factors are aggravated by a low rate of compliance with medication. Finally, adequate follow-up of diagnosed asthma is uncommon[28]. As a result, asthmatic patients are treated mainly in emergency health services during their acute attacks, with a poor control of daily symptoms and exacerbations. The lack of appropriate asthma management causes an

increase of indirect (e.g. loss of hours from work and school) and direct (e.g. use of emergency services and quick-relief medications) costs[24].

There is scarce data regarding asthma prevalence in Ecuador. In the 2004 GINA burden report, 16% of the Ecuadorian population had self-reported current asthma symptoms[29], while 0.8% prevalence of recent wheezing amongst children aged 8-12 years old was found in a rural setting in the ISAAC phase II study[30]. As described in other Latin American countries[31,32], asthma cases in Ecuador may be concentrated in growing and overpopulated cities such as the city of Esmeraldas, while rural populations may have a much lower prevalence[33].

Esmeraldas is the capital city of the province of Esmeraldas, one of the poorest provinces in Ecuador situated on the northern coast. There is an important lack of adequate asthma management and control in Ecuador, as reflected in a pilot study we carried out in Esmeraldas city: only 20% of 60 cases recruited from the emergency department with an acute asthma attack had visited a doctor during the last year for a regular review of their asthma, whilst 86% had attended the emergency department at least once in this same period[34]. None of these children were receiving long-term inhaled corticosteroids, even though 53% had 4 or more acute exacerbations in the previous year[34].

1.3. Hypothesis, aims and objectives

1.3.1. Hypothesis

We hypothesised that a risk assessment tool could be designed that encompassed those parameters shown to be associated with future risk of emergency care re-attendance due to an asthma attack in a low resource setting. Such a tool should be simple to administer and should be of direct benefit to patients and clinicians, guiding shared decision-making about subsequent lifestyle and therapeutic

choices. It could also be useful as a standardised measure of future risk for asthma control in children living in other low and middle-income countries in the near future.

1.3.2. Aims

The overall aims of this thesis were to investigate the factors associated with emergency care re-attendance for acute asthma exacerbations in children in the city of Esmeraldas (Ecuador), to combine these factors into a risk score that provided an individual-level assessment of the likelihood of future emergency attendances with acute asthma, as well as to explore the meanings of acute asthma, the barriers and facilitators for asthma health care access and the behaviours and beliefs towards the use of such a risk score, from the caregivers and health care workers perspective.

1.3.3. Objectives

The specific objectives of the study are:

- To describe and critically appraise study designs and methods that have been used to analyse factors associated with subsequent asthma exacerbations that require emergency care amongst children.

- To identify factors related to a future risk of re-attendance to emergency care due to asthma exacerbations, and to quantify their influence.

- To describe the characteristics of children attending emergency care with bronchodilator-responsive wheeze in Esmeraldas, Ecuador.

- To estimate the proportion of children attending emergency care with bronchodilator-responsive wheeze who recur with a subsequent severe asthma exacerbation requiring emergency care in the following 6 months in Esmeraldas, Ecuador.

- To determine the factors associated with emergency care re-attendance for later asthmatic exacerbations in children, in Esmeraldas, Ecuador.

- To use this cohort of children to design an instrument to provide an assessment of the risk of future asthma exacerbations requiring emergency care re-attendance in Esmeraldas, Ecuador, and thus assist with decision-making regarding lifestyle modifications, medication use, and tertiary referral.

- To explore the meanings of acute asthma attacks and their recurrence, in children from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador.

- To describe the barriers that limit health care access and home care and facilitators, in children with recurrent asthma exacerbations, from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador.

- To describe behaviours and beliefs towards the use of a recurrent asthma attack risk assessment tool in asthmatic children with recurrent asthma attacks, from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador.

1.4. Outline of thesis

Chapter 1 holds the project's starting points, aims and objectives. In Chapter 2, an extensive review of the literature concerning asthma and its management, acute asthma attacks, and Ecuadorian health system, is introduced. Chapter 3 includes a Systematic Review and Meta-analysis of predictors of emergency care re-attendance for acute asthma.

Chapter 4 describes a prospective cohort study analysing predictors for emergency care re-attendance for acute asthma in Esmeraldas, Ecuador. Chapter

5 refers to a qualitative study of acute asthma significance, barriers and facilitators for health care access for asthmatic children and opinions regarding the use of a recurrent asthma attack risk assessment tool, from the health care workers' and caregivers' perspective.

In Chapter 6, the potential implementation and intervention strategies and main conclusions are discussed.

2. Literature review

2.1. Definition of asthma

The term asthma derives from the Greek word for 'panting' (ἄσθμα), originally used by Hippocrates to describe a specific respiratory problem in 450 B.C[35].

Asthma is a chronic inflammatory disease of the airways characterised by the presence of respiratory symptoms, reversible airflow obstruction and airway hyperresponsiveness[6,36]. The respiratory symptoms include cough, wheeze, shortness of breath and chest tightness[37]. These symptoms, together with the characteristic expiratory airflow limitation, are highly variable in intensity and time, depending on the exposure to certain environmental factors (such as viral respiratory infections, allergens, irritants and cold temperatures) or exercise[37]. An important characteristic of asthma is the partial or total reversibility of the airflow obstruction either spontaneously or in response to treatment[6]. The interaction between the main features of asthma (symptoms, airway obstruction, hyperresponsiveness and inflammation) may determine the severity and clinical manifestations, as well as the response to treatment[6]. Common to all forms of asthma are episodes of acute worsening of respiratory symptoms and lung function that are normally referred to as acute asthma exacerbations or asthma attacks.

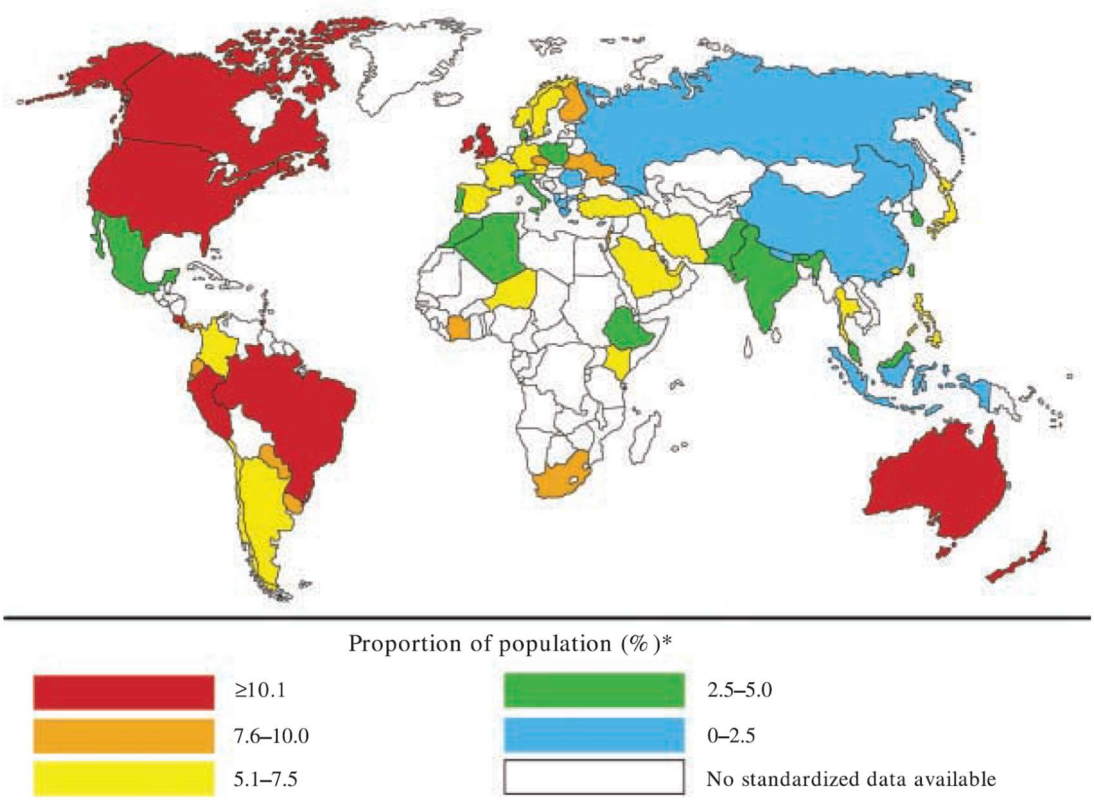
2.2. Global burden of asthma

2.2.1. Prevalence

According to the 2014 Global Burden of Disease study, undertaken in 2008-2010, an estimated 334 million people have asthma[1] and 14% of the world's children suffer asthma symptoms[38]. Even though there is a high variability in asthma prevalence between different regions[37] (1-18%,) it is no longer considered a disease of high-income countries.

There has been a growing interest in defining asthma prevalence over recent decades, with multiple studies conducted worldwide. However, definitions used to assess asthma prevalence varied greatly between studies, precluding adequate comparisons[39]. To overcome these limitations, the International Study of Asthma and Allergy in Childhood (ISAAC) was undertaken. The study comprised standardised definitions and methodology and was carried out in 155 centres in 56 countries in 1992-6 (Phase I), including a total of 463 801 children 13-14 years old and 257 800 children 6-7 years old[40]. This worldwide study was followed by a Phase III completed 5-10 years later (2000-2003) in 106 centres in 56 countries with 304 679 13-14-year-old children, and in 66 centres in 37 countries with 193 404 6-7-year-old children[2]. The main definitions used were: current wheeze ("wheezing in the last 12 months''), lifetime asthma ("ever had asthma") and severe asthma (≥4 attacks of wheezing in the previous 12 months")[39]. To date, these have been the most extensive international surveys performed to assess asthma symptom prevalence in childhood.

Figure 2.1: World map of prevalence of clinical asthma (2004)



Source: Masoli et al, Allergy, 2004[29].

Key findings from the ISAAC Phase I, revealed a high asthma prevalence in Anglophone countries (United Kingdom, Australia, New Zealand and US) and Western Europe, as expected[40]. More surprising were the high asthma symptoms rates found in certain Latin American countries, such as, Peru, Costa Rica and Brazil[40]. Prevalence of asthma symptoms was much lower in Africa, Eastern Europe and Asia, except for more industrialised countries like Japan and Singapore. Phase III enabled a time-trend analysis of asthma prevalence, revealing a slight worldwide increase (from 13.2% to 13.7%)[2] . Highly relevant were the different regional patterns found, with a slight decrease in the regions with the previous highest rates, like Oceania, and an increase in some of the low prevalence regions. Exceptions to these were countries such as Albania and India, which remained low throughout the two phases of the study, and certain Latin

American countries with a relatively high prevalence in Phase I and an important increase in Phase III (Costa Rica, Panama, Mexico, Argentina and Chile)[2]. We may therefore conclude that the global burden of asthma in children is still rising while differences between regions are lessening.

The use of current wheeze as a proxy for asthma has been widely validated[41] and has a sensitivity of 0.58-0.88 and specificity of 0.64-0.95 for doctor's diagnosis of asthma in children[35]. Nevertheless, it may represent certain limitations related to differences in understating or translation of the term 'wheeze' as was reflected in the discrepancies found between the written and the video questionnaire results in the ISAAC study, with lower positive responses in the latter[2]. However, this may not affect global and regional patterns, especially as there was a good correlation between 'current wheeze' and 'severe asthma'[2,38]. On the other hand, given the diverse access to health care in different countries, 'current wheeze' may be a more consistent definition to use compared to physician-diagnosed asthma.

As wheezing may be present in other respiratory diseases and self-reported current mild wheezing may not be diagnostic of clinical asthma, Masoli et al[29] used an arbitrary figure to estimate 'clinical asthma' prevalence in children of 50% of the prevalence of 'current wheeze'. This figure appears to be the best current estimate and seems to correlate well with certain findings, e.g., the prevalence of a positive response to the video sequence of wheezing was around 50% of 'current wheeze' in the written ISAAC questionnaire[29]. All in all, 'current wheeze' has been globally accepted as the most accurate term to use in epidemiological studies analysing asthma prevalence.

The location of the participating centres in epidemiological studies is also something to bear in mind, given the higher asthma prevalence in urban versus

rural settings. Countries with only one centre may not be representative of the national prevalence[29]. Another limitation associated with multi-national studies is the difference in expertise in developing large population surveys between centres and collaborators[2].

Over-diagnosis of asthma is an issue that should be adequately addressed, now that access to health care and diagnosis is increasing worldwide. A recent study from Canada revealed that one third of adults with physician-diagnosed asthma were misdiagnosed and could be weaned from their asthma medications[42]. Similarly, studies from primary care have shown that around one third of adults with an asthma diagnosis do not present evidence of airflow obstruction or bronchial hyperresponsiveness[43,44]. This should also be considered when evaluating asthma prevalence worldwide.

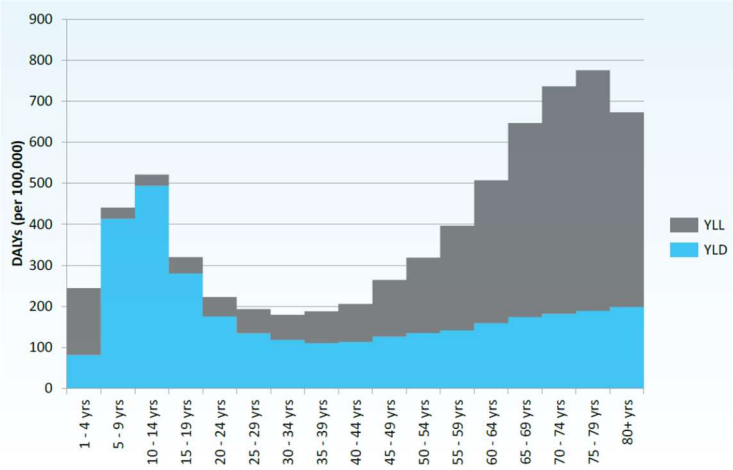
Updated large international population surveys are needed to assess the current prevalence of asthma both regionally and worldwide, as the data previously described is already more than 10 years old. The Global Asthma Network is planning to undertake these studies, which will hopefully contribute to a better understanding of the evolution of this important disease.

2.2.2. Morbidity and mortality

An estimated 489 000 deaths worldwide were caused by asthma in 2013 (8 age-standardised deaths per 100.000), 0.89% of all-cause global deaths[45].

Asthma is not only a cause of mortality, but of morbidity, and a standard way to measure the loss of quality of life together with mortality due to a disease is the 'disability adjusted life-year (DALY). This measure is the sum of the years lived with disability (YLD) and the years of life lost to premature death (YLL), and one DALY is equivalent to the loss of one year of healthy life.

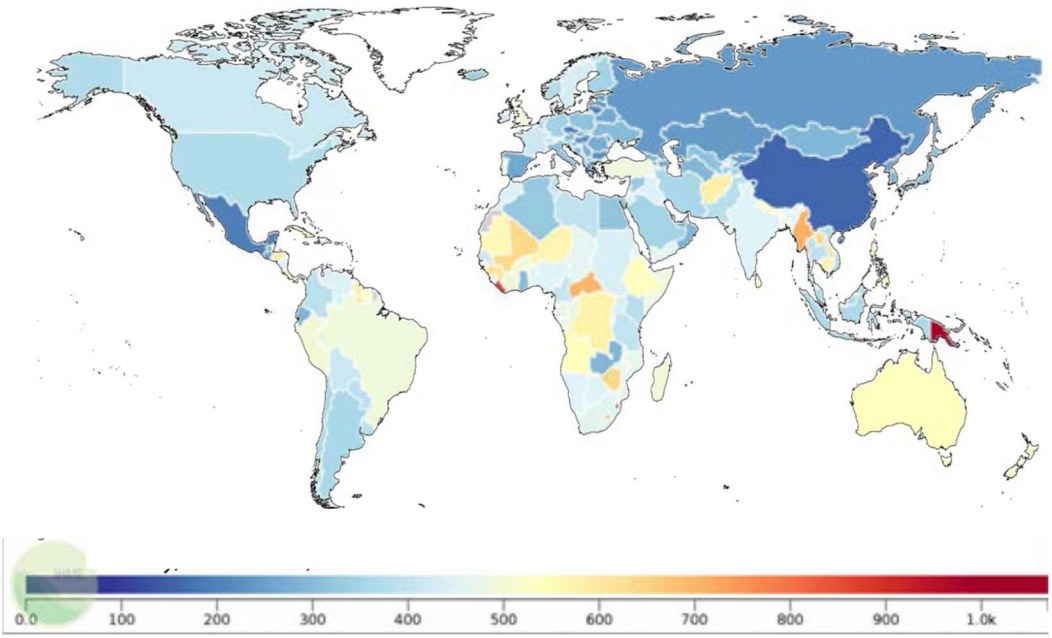
Figure 2.2: Components of disability adjusted life years (DALYs): years lived with disability (YLD) and years of life lost (YLL) per 100,000 population attributed to asthma by age group. Global population, 2010.



Source: Global Asthma Network, Global Asthma Report, 2014[1].

The number of DALYs lost due to asthma worldwide has been estimated to be currently about 22 million per year (326.4 age-standardised DALYs per 100.000)[45]. This represents a 1% of the total DALYs for all causes and is similar to that caused by meningitis, protein-energy malnutrition or hypertensive heart disease[45]. However, children are one of the most affected age groups: asthma represents 1.79% of total DALY's for all causes in the 5-14 years old group[45] (Figure 2.2). As represented on Figure 2.2, disability is the most important component of asthma burden in children and young adults. It is estimated that asthma is the 14th most important disorder accounting for years lived with disability, and this affects children and adolescents (5-19-year-old) above all age groups[1]. This burden of disease due to asthma is, nevertheless, unequally distributed, with a greater burden in high prevalence regions such as Australia, as well some low and middle-income regions with a lower prevalence (Figure 2.3).

Figure 2.3. Disability adjusted life years (DALYs) per 100,000 population attributed to asthma by country, both sexes, 2010.



Source: Global Asthma Network, Global Asthma Report, 2014[1].

It is important to highlight that around 75-90% of asthma morbidity and mortality appears easily preventable with an adequate management that includes medical treatment and lifestyle modifications[7]. However, physicians treating asthmatic patients are identifying rather poorly who is at risk of asthma morbidity and mortality[46] and basic recorded features do not seem to assist in the identification of mortality risk due to asthma[47].

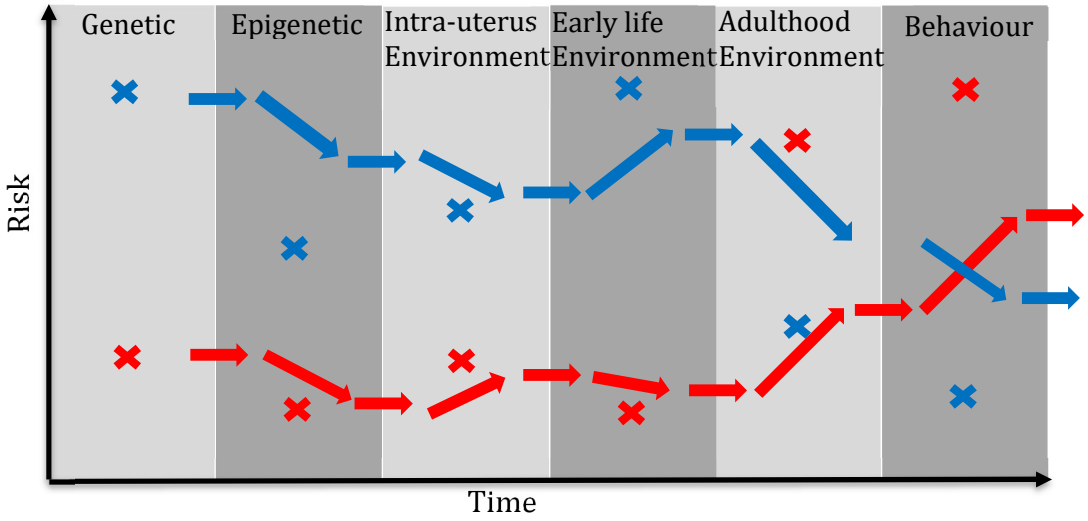
2.3. Risk factors

During the last three decades, asthma prevalence has increased worldwide[48], currently affecting over 300 million people[29]. Asthma is a highly complex disease, as a result of an intricate gene-environment interaction. An extensive number of risk factors for the development of asthma have been analysed over the last 30 years, in the search for primary interventions to reduce the burden of asthma. However, these associations are not always straightforward when studying

asthma, showing contradictory results[49]. This might be in part due to the different asthma phenotypes and its complex natural history, which complicates the study of individual risk factors[50].

Asthma risk factors may be divided into different groups, according to the moment in life they may play a role (intra-uterus, early life, childhood or adulthood) as well as to their characteristics. As shown in Figure 2.4 they may include genetic, epigenetic, environmental and behavioural factors. The risk of developing asthma may vary over time depending on the different risk factors they are exposed to.

Figure 2.4: Schematic illustrating risk of developing symptomatic asthma trajectories for two individuals



The crosses indicate the risk for each influence, and the arrows indicate the individual's total risk. One individual is shown in red, the other in blue.
Source: Modified from Blakey et al, Clinical & Experimental Allergy, 2014[51]

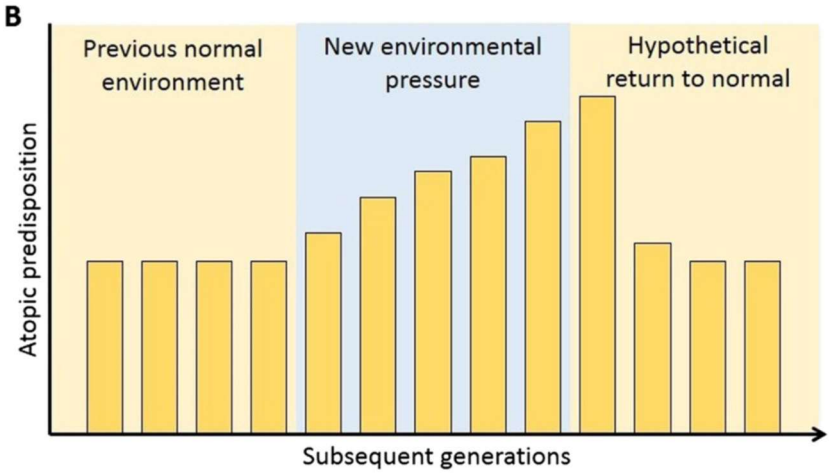
2.3.1. Genetics and epigenetics

There exists a clear genetic predisposition (family history of asthma) for asthma risk, though the specific genetic transmission is still not well understood. Asthma genetics is highly complex, and for the moment, more than 100 genes have been described as possible contributors to asthma manifestations[52-54]. These genes are

involved in different aspects of the disease, such as primary disease conferring risk, severity and treatment response[55].

Epigenetics encompasses all the mechanisms that affect or regulate gene expression. The term was first introduced in the 1950's by C.H. Wadding to describe the mechanisms involved in cell differentiation from pluripotent stem cells[56]. Epigenetics regulates inflammation in asthma and specific mechanisms have been described, such as DNA methylation and histone modifications at the Th2 locus control region, which may be responsible for the Th1/Th2 imbalance[57]. These epigenetic mechanisms may be induced by environmental exposures and it may alter the epigenome enabling its transmission through generations, what is known as transgenerational inheritance of epigenetic traits[57]. For example, tobacco smoke and airway pollution have been shown to cause DNA methylation[58,59]. This would explain how a persistent change in an environmental exposure increases the baseline risk of asthma exponentially, as it induces transmittable epigenetic changes inducing an amplification of the phenotypes at each generation[57] (Figure 2.5). Epigenetics is therefore the bridge between genetic and environmental risk factors for asthma.

Figure 2.5: Epigenetic transgenerational inheritance model



Source: Begin et al, Allergy, Asthma & Clinical Immunology, 2014[57]

2.3.2. Environmental

Hygiene hypothesis

Until the 1990's this increased asthma rate was mainly seen in industrialised countries, and it was explained by what is known as the 'hygiene hypothesis'. According to this hypothesis a diminished exposure to certain microorganisms during the early years of life, may increase the risk of developing allergic diseases[60]. It was first described in 1989 when Strachan et al.[61] demonstrated a reduced rate of hay fever amongst families with a higher number of siblings, and it has been used for many years to explain the lower rates of asthma in rural populations and farming environments[62].

The immunological mechanisms underlying the hygiene hypothesis are still under debate. The original concept pictured a skewed T cell differentiation towards a T helper 2 (Th2) pro-allergic response because of a diminished T helper 1 (Th1) stimulus, caused by certain bacteria and viruses[63]. However, this did not explain the increase in prevalence of other chronic inflammatory Th1-mediated diseases such as Type 1 diabetes or multiple sclerosis, or the protective effect of helminth infestation, associated to a Th2-type response[63]. Advances in immunology have identified certain immunoregulatory cells such as regulatory T cells (Treg) and regulatory cytokines such as IL-10 and TGF-B, which may exert negative feedback over Th1 and Th2 cells. A defect in this feedback circuit could induce either a Th1- or Th2-mediated inflammatory chronic disorder[64]. Therefore, another possible explanation for the hygiene hypothesis is that certain environmental organisms, such as those present in the gut microbiota, nasal colonizers or intestinal helminths, are responsible for driving Treg cells and consequently, a reduced or altered exposure to these microorganisms may lead to chronic inflammatory diseases[64]. In addition, inflammation caused by other

diseases such as obesity or metabolic syndrome, may drive changes in the microbiome, worsening the severity of asthma symptoms.

Even though the hygiene hypothesis may not be the only explanation for increasing asthma prevalence, it is reasonable to blame changes in environmental exposures for the increase in asthma prevalence occurred over such a short period of time, as well as an improved diagnosis and greater access to health care. Several studies have demonstrated a reduced risk of atopy and allergic diseases associated to farming environments[65], helminth infestations[66]and having older siblings[67] In a similar way, endotoxin exposure was found to increase the risk for wheeze in younger children but act as a protective factor for asthma in older children in a recent meta-analysis of observational studies from developed countries[68].

Recent findings by Stein et al.[69] have shown that the high endotoxin levels found in Amish house dust may partly explain the low prevalence of asthma and allergic sensitization among this population. Airways hyperreactivity was significantly inhibited in mice after instillation of dust extracts from Amish homes. The same did not happen when using dust extracts from Hutterite homes, an agricultural population very similar to the Amish population, except that they use industrialized farming practices with limited contact with farm animals and that they present high rates of asthma and allergic sensitization, comparable to the rest of the US population. This study showed that the protective effect of the Amish environment required the activation of innate immune signalling and suggested that asthma susceptibility may be increased as a consequence of a weak innate immune stimulation[69]. This study is highly relevant to better understand the main role of the innate immune system in the development of asthma.

Intra-utero and peri-natal exposures

Peri-natal factors such as pre-term birth or low birth weight[70] and being born by caesarean section[71] have been associated with an increased asthma risk. Together with this, there is now increasing evidence that in-utero exposure to certain environmental exposures such as tobacco smoke, antibiotics[72], paracetamol[73] or maternal stress[74] may also increase the risk of asthma in offspring.

Early-life exposures

Multiple environmental factors in early life have been associated with asthma risk: exposure to tobacco[75] and biomass smoke[76], health inequalities due to low socioeconomic status leading to poorer health and higher stress[77], early-life respiratory viral infections (especially Respiratory Syncytial Virus (RSV) and rhinovirus)[78], body-mass index[79,80], sedentary lifestyle[80], diet (salt, trans fatty acids and fast-foods)[81,82], exposure to dampness and mould[83], rhinitis and sinusitis[84,85]. Urbanisation has been linked to an increased risk of asthma, especially in developing countries[86,87], though it is probably due to the combined effect of various factors such as lifestyle, diet, socio-economic and housing changes. This may as well be the case of the association of asthma with certain ethnic groups[88].

Other factors are still under debate, such as allergen exposure in early life[89] or the protective effect on asthma risk of a diet rich in fruits and vegetables[81,82]. There are also contradictory findings concerning the effect of breastfeeding on the later development of asthma[90].

Some of these environmental factors may alter the child's microbiome, such as the use of antibiotics, caesarean section or living in an urban environment with no animal exposure. There is a growing interest in the study of how the

microbiome (both in the gastrointestinal and respiratory tract) may affect the development of the immune system, and therefore the risk of developing certain inflammatory diseases like asthma[91]. There are now studies that have associated dysbiosis in the bacterial microbiota of the gut, respiratory tract and skin with the development of allergic diseases[91]. For example, Arrieta et al.[92] showed that microbiota and bacterial metabolic products during early life could alter the risk of childhood asthma. The next question to be answered is how to alter the microbiome both to prevent the development of asthma in high-risk populations and to treat asthmatic patients.

Adulthood exposures

Some adults may develop new-onset asthma when exposed to asthmagens at their place of work while others suffer exacerbations of their illness[93]. These are both defined as occupational asthma. Asthmagens are agents that are causally related to the development of asthma, and may include organic dusts that may sensitize the airways (such as wood, flour or animal dander), or chemicals that irritate the respiratory tract (such as cyanates or glutaraldehyde)[94]. A recent study from Australia (Australian Workplace Exposure Study-Asthma) estimated that 47% of men and 40% of women are exposed to at least one asthmagen at their workplace[95]. Occupational asthma may account for around 16-17% of adult-onset asthma[96] and it is highly relevant, given its possibility of prevention.

2.3.3. Behavioural

Diverse behavioural and mental health problems such as anxiety, depression and personality disorders, have been associated with asthma risk. Studies from Brazil have shown an association between the presence of behavioural problems in children or community violence and occurrence of asthma symptoms in children[97,98].

However, this not only includes the patient's own behaviour, but also his or her family's behaviour, especially the mother's. Maternal mental disorders have been associated with wheezing (both atopic and non-atopic)[99,100]. According to a recent study[101] there is not a critical exposure period for maternal mental disorders or distress, but it is rather the cumulative exposure that determines the increased risk of asthma in the offspring.

Some other risk factors that we have already mentioned, such as smoking, exposure to pets or cold dry air in skiers, could also be interpreted as behavioural aspects that may influence the development and/or severity of the disease.

2.3.4. Atopy

Atopy has been described as one of the most important risk factors associated with asthma. However, the proportion of asthma cases attributable to atopy varies greatly between regions, increasing with economic development[30].

The more widely used classification of asthma into atopic and non-atopic asthma (see below) may reflect different underlying mechanisms and therefore different associated environmental exposures[50]. This fact highlights the importance of analysing the risk factors for each asthma phenotype separately, for example, atopic and non-atopic asthma. However, until now, most studies have used a combination of different comparison groups making it difficult to define which are the risk factor for atopy, and which for asthma (both atopic and non-atopic)[RW.ERROR - Unable to find reference:239], and have not analysed risk factors for atopic and non-atopic asthma in the same population, using appropriate control groups.

In European and North American studies, atopic asthma has been associated with family history of asthma, male gender, a higher body mass index (BMI), and presence of eczema or rhinitis, while a higher endotoxin load in the house, having

pets at home, and higher mean poverty income ratio have been described as protective[102-109]. On the other hand, non-atopic asthma in developed countries has been associated with male gender, family history of asthma, dampness at home, smoking in parents, breastfeeding less than 3 months, a higher endotoxin load at home, a higher BMI, early life infections, recurrent chest infections in infancy and a dirty school, with contradictory results regarding parental educational level[102-109]. Overall, underlying mechanisms and risk factors for both atopic and non-atopic asthma are not well understood, resulting in a lack of any preventive strategy to reduce asthma burden prevalence.

2.3.5. Other

There are some other factors that are difficult to classify into either genetics or exposures. This is the case of the metabolic or hormonal environment, such as the influence of sex on asthma risk. This effect is age-dependant, as it is the male sex that increases asthma risk until adolescence, after which it is the female sex that increases the risk[110]. The reason for this variation over time has not yet been clarified.

2.4. Asthma phenotypes and endotypes

Asthma is a complex and heterogeneous[111-113] disease and encompasses a wide spectrum of disease characteristics[111,114,115]. Given its heterogeneity, scientists have tried to classify asthma into different subgroups with similar characteristics to study the disease and search for specific and more efficient treatments. However, this has proven to be challenging and there is still no international consensus on the classification of asthma. Multiple studies have been now published in an attempt to classify asthma into phenotypes (according to

observable characteristics) and endotypes (according to specific underlying biologic mechanisms).

2.4.1. Asthma phenotypes

Phenotypes are identified by a set of outward manifestations of the disease, including clinical, physiologic and immunological features[55], which may be studied using cluster analysis approaches. These characteristics correspond to certain underlying genetics and each phenotype may also be associated with a different underlying pathogenetic process. The importance of defining asthma phenotypes lies in their different response to asthma treatments and the search for phenotype-specific treatments.

Diverse cluster analyses of asthmatic patients have identified different sets of asthma phenotypes[116-118]. The most commonly used characteristics that have been used include: age, sex, age of onset, atopy, lung function, airflow obstruction reversibility, and obesity. The last GINA report, describes one possible phenotype classification[37]:

a. Allergic asthma: Also referred to as 'atopic asthma'. It is the best-known form of asthma, with an early onset during childhood and an association with a personal or family history of allergic diseases (food or drug allergies, eczema and allergic rhinitis). Eosinophils are responsible for the airway inflammation in these patients, they have a greater risk of exacerbations and they respond well to corticosteroid treatment.

b. Non-allergic asthma: Or non-atopic asthma. These patients have no history of allergic diseases and may not respond well to corticosteroid treatment. Both neutrophils and eosinophils may predominate in induced sputum.

c. Late-onset asthma: This phenotype is more common among women, and is characterised for appearing during adult life.

d. Asthma with fixed airflow limitation: Different asthma phenotypes can evolve into this phenotype due to airway wall remodelling causing a fixed airflow obstruction.

e. Asthma with obesity: Obese asthmatic patients may present a poor response to corticosteroid treatment, with notable daily symptoms that may limit their everyday life. Scarce eosinophilic inflammation is also characteristic of this asthma phenotype.

Nevertheless, there are many other possible classifications, according to different characteristics, as shown on Table 2.1.

Table 2.1: Example of different asthma phenotypes according to various characteristics

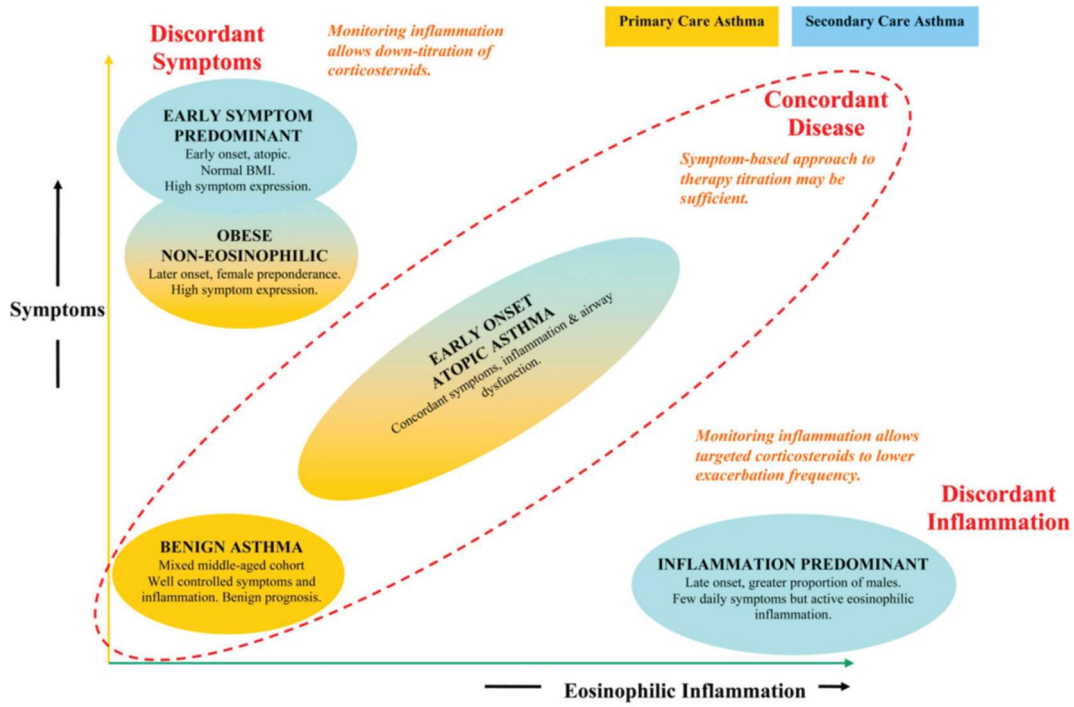
	Example phenotypes
Age of onset	Childhood *vs* adult
Clinical	Episodic *vs* persistent
Pathophysiological	Partially reversible airflow obstruction
Comorbidities	Rhinosinusitis
Genetic	β2 receptor polymorphisms
Environmental risks	Occupational asthma
Inflammatory	Eosinophilic *vs* non-eosinophilic
Immunological	Atopic *vs* non-atopic
Biomarkers	Fractional exhaled nitric oxide
Endotypes	Aspirin sensitivity
Response to therapy	Steroid resistance
Severity	Amount of treatment needed to achieve control
Mortality risk	History of life threatening attack

Source: Beasley et al, Lancet, 2015[50].

Cluster analysis of asthma phenotypes allows for more objective analysis of asthma subgroups with consistent patterns of disease. It uses mathematical algorithms to group asthmatic patients into clusters based on the similarity between them according to multiple pre-specified variables. As an example,

Haldar et al.[23] performed a cluster analysis using two different asthma populations (primary and secondary care asthma) and based on multiple socio-demographic, inflammation markers, lung function, treatment and behavioural factors. As a result, they obtained 5 distinct asthma phenotypes illustrated in Figure 2.6. They then classified these phenotypes into concordant (symptom and inflammation expression agree) and discordant, showing that patients in secondary care, with refractory asthma are more prone to discordant manifestations of asthma, and would therefore benefit from inflammation monitoring for treatment adjustments[23]. This is an example of how asthma phenotyping may be used to improve clinical management.

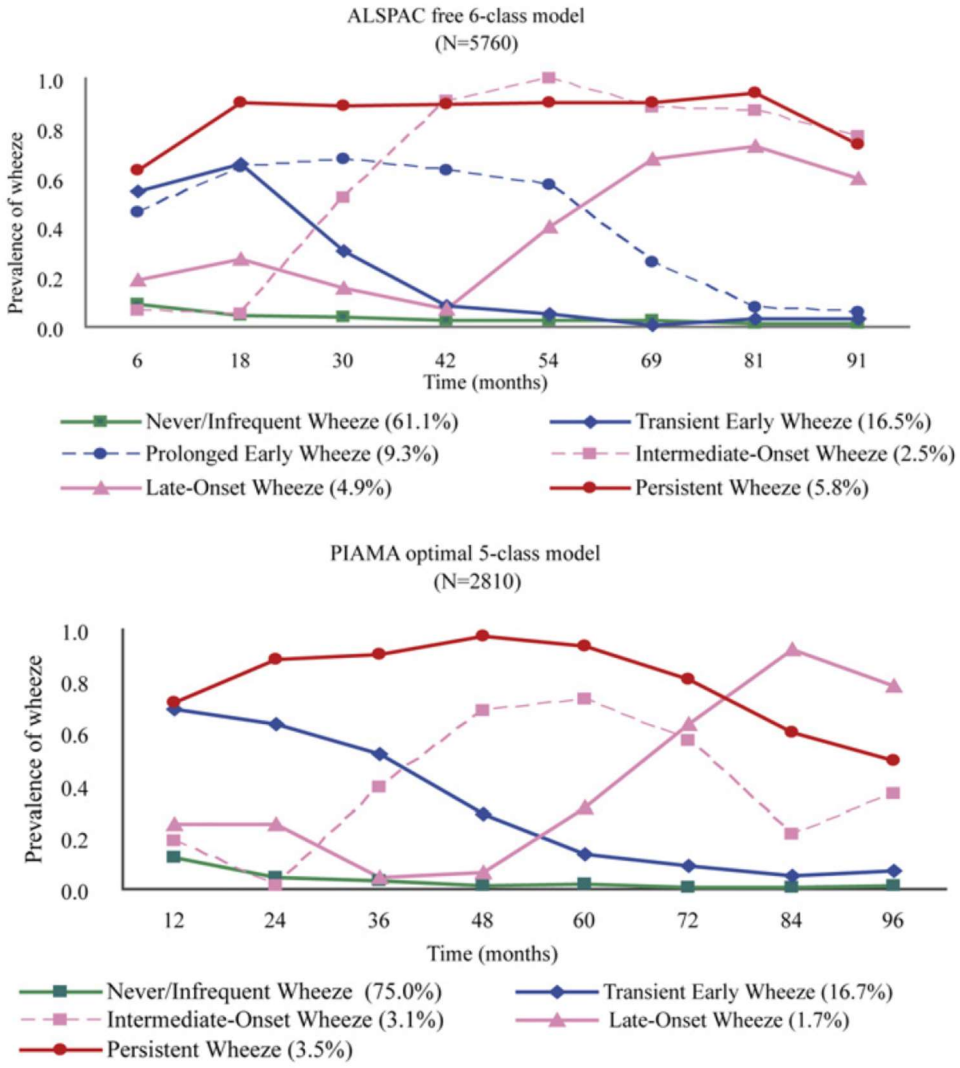
Figure 2.6: Clinical phenotypes of asthma.



A summary of phenotypes identified using cluster analysis in primary- and secondary-care asthma populations. The clusters are plotted according to their relative expression of symptoms and inflammation because these are the two clinically pertinent and modifiable dimensions of the disease. The plot highlights greater discordance to be a feature of secondary-care asthma. Although reasons for this dissociation are unclear, the use of measures of airway inflammation in these subgroups is clinically informative. BMI = body mass index.
Source: Haldar et al, Am J Respir Crit Care Med, 2008[23].

Similar techniques have been used in paediatric populations to assess childhood asthma and wheeze phenotypes. Two separate birth cohorts, the Avon Longitudinal Study of Parents and Children (ALSPAC)[119], and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA)[120] were used to study wheeze phenotypes in children, obtaining comparable subgroups: never/infrequent, transient early, prolonged early (only in ALSPAC), intermediate-onset, late-onset and persistent wheeze (Figure 2.7)[121].

Figure 2.7: Estimated prevalence of wheeze at each time point from birth to age 8 years for each wheezing phenotype in ALSPAC free 6-class model (N= 5760) and PIAMA optimal 5-class model (N = 2810).



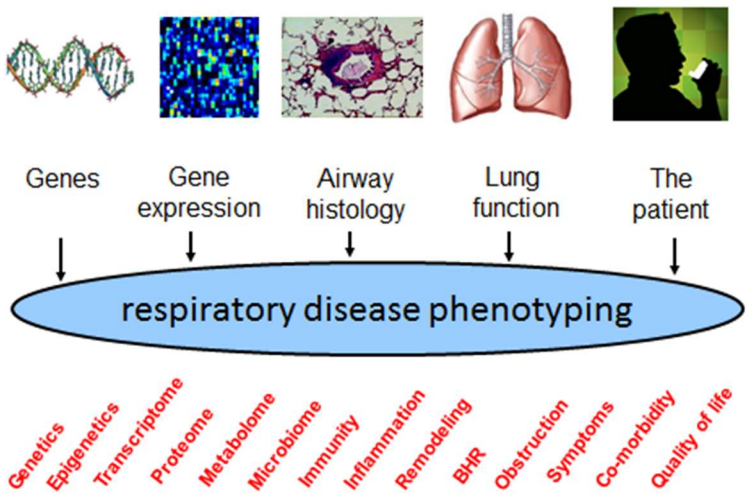
Source: Savenije et al, J Allergy Clin Immunol, 2011[121]

Savenije et al.[121] fitted the results of the PIAMA cohort to the ALSPAC 6-class wheezing phenotypes, obtaining similar proportions. Even though these are wheeze and not asthma phenotypes, the persistent, late-onset and intermediate-onset wheeze phenotypes were strongly associated with doctor-diagnosed asthma at age 8 years in the PIAMA cohort, all of which are non-transient phenotypes[121].

However, cluster analysis should be taken with caution, as it is a mathematical discovery tool and does not confirm the truth of the phenotypes identified. It is the person undertaking the analysis who selects the variables included in the model, and therefore they offer relatively little new insight beyond what we already observe, and they may be radically modified by adding in other variables. As they are defined by the things we have already measured, they always sound plausible even though they may not be true.

Since 2010 a new research project called 'Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes' (U-BIOPRED) has brought together scientists from academia, biopharma industry, patients or care organisations, small companies and multinational industry across Europe. One of their aims was to identify different phenotypes of severe asthma by collecting various samples and information from the 893 adults and children with mild-moderate or severe asthma that participated, and use advanced mathematics to produce what they defined as a 'handprint' of severe asthma[122-124]. These phenotype handprints are more molecular-based than clinical feature-based, enabling classifications of patients by the underlying cause of their asthma. For this, they collected blood, sputum, exhaled breath, throat swabs and urine samples and performed 'omics' studies at different levels (genomics, transcriptomics, proteomics and metabolomics) (Figure 2.8). These were then combined with clinical data and lung function parameters from the patients[122,123].

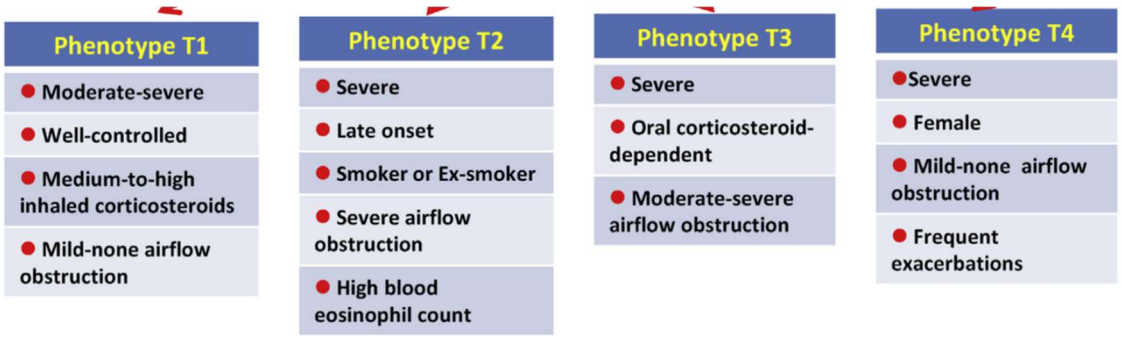
Figure 2.8: Different types of information collected from the trial participants (black text) used to identify the subtypes of severe asthma in the U-BIOPRED project.



Source: UBIOPRED webpage[124] *http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/news-and-events/news/u-biopred-on-course-to-create-a-handprint-of-severe-asthma*

The classification of patients with severe asthma into these different phenotype handprints should facilitate the selection of the specific treatment for each patient, evolving into a personalized medicine that may increase efficacy and reduce side effects of asthma drugs. So far, the 4 adult severe asthma phenotypes they have identified coincide with those described by the American Severe Asthma Research Program (SARP) consortia, and are associated with different pathobiological pathways[123] (Figure 2.9).

Figure 2.9: Adult severe asthma phenotypes identified by the U-BIOPRED consortium

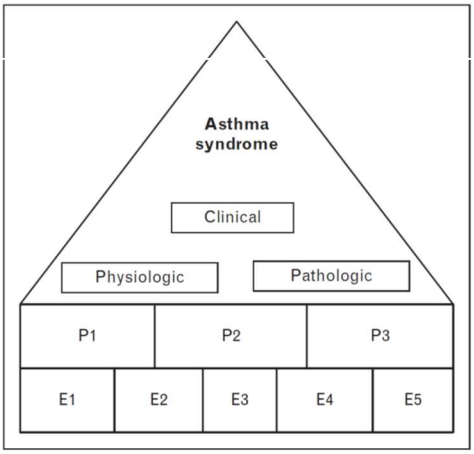


Source: Lefaudeux et al, J Allergy Clin Immunol 2017[123].

2.4.2. Asthma endotypes

Endotypes provide some insight into the underlying biological mechanisms. These mechanisms may be common for different phenotypes (that is, there can be more than one phenotype sharing a common endotype), as there may also be more than one endotype for the same phenotype, as represented in Figure 2.10[55].

Figure 2.10 Schematic representation of the asthma syndrome and its phenotypes and endotypes.



P: Phenotype; E: Endotype
Source: Skloot et al, Curr Opin Pulm Med, 2015[55].

The most common endotypes proposed by different experts are shown in Table 2.2 and are based on 7 characteristics: genetics, physiology, clinical characteristics, biomarkers, histopathology and epidemiology, as well as response to treatment[125].

Table 2.2: Selected endotypes and their characteristics

Proposed endotype	Clinical findings	Biomarkers	Histopathology	Epidemiology	Proposed mechanism/genetics
Aspirin-sensitive asthma	Nasal polyposis, severe rhinosinusitis, more severe asthma	Eosinophils, urinary leukotrienes	Often eosinophilic	Adult onset, poor prognosis, 2–5% prevalence	Eicosanoids-related; leukotriene-related gene polymorphisms
ABPM	Severe, mucus production	Blood eosinophils, high IgE, high FeNO	Bronchiectasis, eosinophils, PMNs	Adult onset, long duration, poor prognosis	Colonization of airways; HLA and rare CF variants
Allergic asthma	Allergic rhinitis, allergen-associated symptoms	Positive skin prick tests, high IgE, FeNO	Eosinophils, subbasement membrane thickening	Childhood onset, history of eczema	Th2 dominant; Th2 pathway single nucleotide polymorphisms
Severe late-onset hypereosinophilic asthma	Severe exacerbations, late-onset disease	Blood and sputum eosinophils	Tissue eosinophilia	20% of severe asthmatics	Nonatopic, genetics unknown

ABPM: allergic bronchopulmonary mycosis: CF: cystic fibrosis; FeNO: Fractional exhaled nitric oxide; HLA: Human leukocyte antigens; PMNs: polymorphonucleocytes.
Source: Skloot et al, Curr Opin Pulm Med, 2015[55].

2.4.3. Treatable traits

Given the complexity of asthma and to enable the development of personalised and precision medicine for asthmatic patients, a different management strategy has been proposed. This strategy moves away from the "diagnostic labels", to concentrate on 'treatable traits' of a particular patient[126]. These treatable traits include aspects of the patient's phenotype, endotype and comorbidities, and they are non-mutually exclusive. A list of possible treatable traits based on current knowledge, and how each of them should be treated and managed, was collected in a paper by Agusti et al[126]. Examples of these treatable traits are: airflow limitation, eosinophilic airway inflammation, airway bacterial colonisation, obesity, gastro-oesophageal reflux, rhino-sinusitis, psychiatric disorders, smoking, exposure to sensitising agents or pollution, adherence to treatment, or poor inhalation technique. Each of these traits should be addressed separately with a specific and adequate treatment.

Recently, Pavord et al.[127] have called for a more pragmatic approach, proposing to use the term 'asthma' as a descriptive label for a collection of symptoms, such as we do with the term 'arthritis'. It is just the beginning of the diagnostic process, that should be followed by the questions: What asthma does this patient have? How should I treat it?[127]. This way, we should focus on traits that are treatable by dissecting a patient's airway disease into its component parts and offering an individualised and precise approach[127].

2.5. Diagnosis

Asthma diagnosis is based on three main pillars: detailed medical history, physical examination and lung function testing. These three elements are necessary for an adequate asthma diagnosis, given that some other pulmonary

diseases may mimic its symptoms and examination (chronic pulmonary disease, cystic fibrosis, bronchiectasis, vocal cord dysfunction, etc.), and therefore an accurate history and physical examination may not be sufficient to obtain an accurate asthma diagnosis[128]. The aim is to ascertain the presence of episodic symptoms of airflow obstruction that is at least partially reversible, and to exclude alternative diagnoses[6].

2.5.1. Personal history

Risk factors for asthma including personal and family history of allergic diseases (atopic dermatitis, allergic rhinitis, food allergies, etc.), increase the probability of asthma diagnosis[37].

A comprehensive history is necessary to search for the presence of intermittent respiratory symptoms such as cough, shortness of breath, chest tightness and/or wheezing. They are usually present more than one at a time, though children may present isolated coughing which is accompanied by wheezing and difficulty breathing only during acute exacerbations. These symptoms may present spontaneously or triggered by exercise, allergens, cold air, laughter, airborne irritants or respiratory viral infections. They characteristically vary in intensity and over time, and particularly worsen at night[6,37].

On the other hand, there are several clinical features which are not suggestive of asthma such as chest pain, difficulty breathing together with dizziness or paresthesias, and/or chronic production of sputum.

2.5.2. Physical examination

The most frequent abnormal finding in asthmatic patients during physical examination is the expiratory wheezing on auscultation or a prolonged phase of forced exhalation[6,37]. However, this is often not present between attacks, and

therefore physical examination may be perfectly normal. During asthma exacerbations, physical signs of difficulty breathing may appear (nasal flaring, intercostal retractions, etc.) together with wheezing (both inspiratory and expiratory if severe), though this latter may be absent in severe exacerbations (silent chest) because of severely reduced airflow. Apparent wheezing may also appear in other conditions, such as respiratory infections, inhaled foreign body, tracheomalacia, upper airway dysfunction or chronic obstructive pulmonary disease (COPD).

Other physical findings during examination in asthma are hyper expansion of the thorax and chest deformity (especially in children). There may also be other accompanying allergic conditions, like atopic dermatitis or allergic rhinitis (increased nasal secretion, mucosal swelling and nasal polyps)[6].

2.5.3. Lung function testing

Medical history and physical examination are not sufficient to exclude alternative diagnoses and assess lung impairment severity. Perception of airflow obstruction is dependent on the patient's subjectivity, and therefore highly variable. There are several studies showing that an important proportion of patients are under or over-classified according to symptoms, when compared to the results of pulmonary function tests[129,130]. Therefore, every child over the age of 5 should have spirometry measures both before and after short acting bronchodilator, to assess the presence of airflow obstruction, its severity, reversibility and variation[6,37]. The most important spirometry measures used are the Forced Vital Capacity, or FVC, which is the maximal volume of air forcibly exhaled from the point of maximal inhalation, and the Forced Expiratory Volume in the first second, or FEV_1, which is the volume of air exhaled during the first second of this manoeuvre[6].

Spirometry is also recommended over peak expiratory flow (PEF) measurements, given the variability in the latter depending on the brand of the peak flow meter[131]. Thus, PEF measurements would be confined to monitoring purposes rather than initial diagnosis[6]. Nevertheless, spirometry should be undertaken following international guidelines recommendations with adequately maintained and calibrated equipment[131,132] and by trained professionals[131]. The patients should also perform the test at its maximal effort to avoid diagnostic errors. In addition, appropriate standard values should be used according to the populations' characteristics (ethnicity, age, location, etc.). Both FEV_1 and FVC may be expressed as a proportion of the predicted values for the patient's age and size.

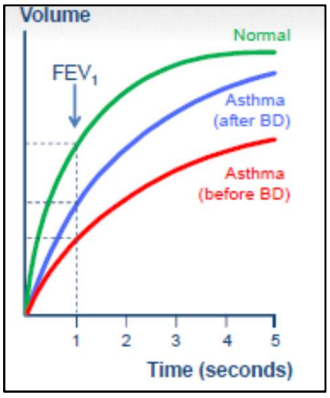


Figure 2.11: Theoretical spirometric tracings in asthmatic patients

Source: GINA 2017 Slide Teaching Set[133]

Asthma is characterized by airflow obstruction which translates into a reduced FEV_1 and FEV_1/FVC ratio. FEV_1 values may show an excessive variability (improvement or deterioration) in asthma, either during the day or between days, or even between seasons. They will also show reversibility, which is a rapid improvement after the use of a rapid acting bronchodilator, such as a β2- agonist (salbutamol). This improvement or deterioration of FEV_1 should be of at least >12% or >200ml from baseline in adults to be considered diagnostic[131]. These variations in FEV_1 values may be evidenced either by administration of a bronchodilator or controller treatment (a trial of inhaled corticosteroids (ICS) for example), after exercise or bronchial provocation test (with methacholine, for

example), or by repeated measurements over time. The specific GINA criteria for the different procedures are summarised in Table 2.3.

Table 2.3: Diagnostic criteria for asthma in adults, adolescents, and children 6-11 years

DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
Documented excessive variability in lung function* (one or more of the tests below) **AND** documented airflow limitation*	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. At least once during diagnostic process when FEV_1 is low, confirm that FEV_1/FVC is reduced (normally >0.75–0.80 in adults, >0.90 in children)
Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	*Adults*: increase in FEV_1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 of >12% predicted
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%** *Children*: average daily diurnal PEF variability >13%**
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults*: increase in FEV_1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	*Adults*: fall in FEV_1 of >10% and >200 mL from baseline *Children*: fall in FEV_1 of >12% predicted, or PEF >15%
Positive bronchial challenge test (usually only performed in adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	*Adults*: variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections *Children*: variation in FEV_1 of >12% in FEV_1 or >15% in PEF† between visits (may include respiratory infections)

BD: bronchodilator (short-acting SABA or rapid-acting LABA); FEV1: forced expiratory volume in 1 second; LABA: long-acting beta2-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta2-agonist.
*These tests can be repeated during symptoms or in the early morning. **Daily diurnal PEF variability is calculated from twice daily PEF as ([day's highest minus day's lowest] / mean of day's highest and lowest), and averaged over one week. †For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections. If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced, and diagnostic testing arranged within the next few weeks, but other conditions that can mimic asthma should be considered, and the diagnosis of asthma confirmed as soon as possible.

Source: GINA 2017[37]

The FVC and the response to bronchodilators may decrease with time in certain patients, because of a reduced lung function in chronic asthma[6]. On the other hand, variability may also decrease with treatment, as inflammation diminishes, and lung function improves[37]. Therefore, it is recommended to assess lung function at the initial diagnosis, before starting treatment. The extent of reversibility depends on the eosinophilic inflammation[134], and therefore patients with greater response to short-acting β-agonists (SABA) are also at a higher risk of reduced lung function and fixed airflow obstruction in the long term[135] . Finally, response to SABA may be reduced during viral respiratory infections or when using SABA during the previous hours.

2.5.4. Additional tests

On some occasions, further tests are necessary to rule out other respiratory diseases which may mimic asthma. As explained, the asthmatic symptoms may be present in other conditions, and some asthmatic patients may be asymptomatic during physical examination. Similarly, there may be no airflow obstruction or reversibility present. These are the different additional tests we may undertake to confirm the asthma diagnosis:

Chest X-ray

To exclude other diagnoses such as malformations, chronic infections (tuberculosis), or foreign body. Other imaging investigations may be necessary.

Allergy testing

As described, not all asthma is atopic, however the diagnosis of atopy may facilitate the diagnosis of atopic asthma. There are two methods to diagnose atopy: skin prick test (SPT) and the measurement of allergen specific

immunoglobulin E (sIgE). Skin prick test has a high sensitivity when performed by an experienced professional, it is simple, quick and cheap. However, sIgE measurement may be have a higher sensitivity, though require a specialised laboratory, take a longer time to obtain the results, and is more expensive[37]. It is important to confirm the positive findings of the SPT and sIgE with the patient's history, as not all diagnosed atopy is symptomatic.

Inflammation biomarkers

Blood, nasal and sputum eosinophilia: These may be studied to assess the patient's inflammatory profile (eosinophilic vs neutrophilic) which may affect treatment response to certain drugs such as ICS.

Fraction of Exhaled Nitric Oxide (FENO): FENO measurements correlate with eosinophilic inflammation of the airways, thus may be increased in atopic asthma, as well as eosinophilic bronchitis and allergic rhinitis[37]. Several studies have shown that high FENO values are associated with a positive response to inhaled corticosteroids[136]. The 2017 GINA guidelines[37] do not currently recommended FeNO measurements for either diagnosis or control of asthmatic patients. However, the NICE 2015 guidelines[128] do recommend offering a FeNO test in adults when considering an asthma diagnosis and to children (5-16 years old) in case of an uncertain asthma diagnosis due to a normal spirometry or obstructive spirometry with negative bronchodilator reversibility.

2.5.5. Asthma diagnosis in children

Children under 5 years old (and some under 8) may not be able to perform an adequate spirometry manoeuvre, thus diagnosis should be based on medical history and physical examination, together with additional tests results (see above) or even a therapeutic trial[6]. Diagnosis may be therefore challenging in this

age group, resulting in under-diagnosis of asthma in early childhood. One of the reasons for this, is the variations in the natural history of asthma in the early stages[137], resulting in even more phenotypes of asthma in preschool children.

Table 2.4: Classic Asthma Phenotypes in children with wheeze from the Tucson study, based on their natural history in the long term.

Transient Early Wheeze
- Start before 1 year old, disappear around 3 years old. - Negative sIgE and SPT, no atopic features or family history. - Decreased lung function at birth, normal at 16 years of age. - Negative bronchial hyperresponsiveness or PEF variability at age of 11. - Risk factors: maternal smoking during pregnancy, male, prematurity, having older siblings and/or attending childcare.
Persistent Wheeze
- Generally appear before the age of 1 and persist at the age of 6. - No gender differences. - Negative sIgE and SPT, no atopic features or family history. - Normal lung function at birth and decreased at age of 6 and 11. - Bronchial hyperresponsiveness that decreased with age. - Normally disappears during adolescence.
Late-onset Wheeze
- First episode after the age of 1 and is predominant among males. - Positive sIgE and/or SPT, with atopic features and/or family history. - Normal lung function at birth, decreased at age of 6, followed by an onward stabilization below average. - Bronchial hyperresponsiveness present. - Normally persists during adolescence.

Source: Stein et al, Paediatr Respir Rev., 2004[69]

The first description of childhood wheeze phenotypes emerged from the Tucson study[69] (Table 2.4) and even though there have been other prospective studies (birth cohorts)[138,139] and complex statistical analysis of various study populations[140], there is still no clinically-useful asthma phenotype classification available for children.

As seen, this classification is based on parental reporting of 'wheeze', which is rather unreliable and unspecific[137]. Parents understand the term wheeze differently[141] and often fail to recognise it[142].

Another added difficulty is the lack of evidence-based consensus on standard definitions, diagnosis and management[137] In order to facilitate asthma diagnosis in pre-school children and predict the future risk of asthma in late childhood and adulthood, various tools have been developed though only few have been validated. The most widely used is the Asthma Predictive Index (API) (Table 2.5), developed from the Tucson cohort[143] and which was later modified[144].

Table 2.5: Original and Modified Asthma Predictive Index for children 0-3 years of age

Original Asthma Predictive Index	Modified Asthma Predictive Index
A history of ≥3 wheezing episodes during the first 3 years of life	A history of ≥4 wheezing episodes in the past year with ≥1 physician's diagnosis.
In addition, the child must meet ≥1 of the major criteria or ≥2 of the minor criteria:	
Major Criteria	
• Parental history of asthma • Doctor-diagnosed atopic dermatitis	• Parental history of asthma • Doctor-diagnosed atopic dermatitis • Allergic sensitization to ≥1 aeroallergen
Minor Criteria	
• Doctor-diagnosed allergic rhinitis • Blood eosinophils ≥4%	• Allergic sensitization to milk, egg, or peanut • Wheezing unrelated to colds • Blood eosinophils ≥4%

Source: Castro-Rodriguez et al, Am.J.Respir.Crit.Care Med., 2000[143] and Bacharier et al, J Allergy Clin Immunol. 2012[144].

2.5.6. Classification

There exist multiple different classifications and definitions of asthma severity according to each country or organisation, and they are continuously changing over the years. We will now introduce some of the most widely used classifications.

Initial asthma severity classification

Asthmatic patients may be classified at initial diagnosis, before starting baseline treatment, according to the frequency and severity of their symptoms. There have been different classifications used by diverse organisations.

Below is the NHLBI classification which includes 2 main components: impairment and risk. The impairment component consists of all the respiratory symptoms present during the day or night, as well as the use of relievers (salbutamol) and the lung function.

Table 2.6: Asthma Severity in Treatment Naïve Patients

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function		Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations									
	→ FEV_1* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	→ FEV_1/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	Generally, more frequent and intense events indicate greater severity.		≥2/year	Generally, more frequent and intense events indicate greater severity.				
		Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.*											

Source: National Asthma Education and Prevention Program, 2007[6]

Given that asthma severity assessed by daily asthma symptoms does not exactly correlate with future risk of serious adverse outcomes[46,47], they added a new component to the initial asthma severity classification. This is the risk component, which recollects the future risk of suffering acute severe asthma exacerbation.

The 2017 GINA guidelines[37] do not include a classification of asthma severity for treatment naïve patients, as the initial symptoms do not predict the response to treatment and therefore it is not useful from a practical and clinical point of view. However, some other international (such as the NHLBI[6]) and national guidelines (Spanish[145], Brazilian) still include this initial classification of asthmatic patients (Table 2.6). Even though learned institutions do not agree on severity

classification of asthma, it is now more widely accepted to define asthma severity based on the treatment required to gain adequate control.

Table 2.7: Initial classification of asthma severity in children

	Intermittent Occasional	Intermittent Frequent	Persistent Moderate	Persistent Severe
Episodes	-Few hours/days duration - <1 every 10-12 weeks - Max 4-5 per year	- <1 every 5-6 weeks - Max 6-8 per year	< 1 every 4-5 weeks	Frequent
Symptoms between episodes	Asymptomatic Good tolerance to exercise	Asymptomatic	Mild	Frequent
Wheezing	-	With intensive efforts	With moderate efforts	With minimum efforts
Night-time symptoms	-	-	≤2 nights per week	>2 nights per week
SABA use	-	-	≤3 days per week	3 days per week
Lung function - FEV1 - PEF variability	 >80% <20%	 >80% <20%	 <70% - <80% >20% -<30%	 <70% >30%

FEV1: Forced Expiratory Volume 1st second; PEF: Peak Expiratory Flow; SABA: Short Acting β-Agonists

Source: GEMA, 2015[145].

On the other hand, there are several national guidelines which differentiate the adult from the children's initial classification. This is the case of the Spanish guideline[145] -Guía Española para el Manejo del Asma (GEMA, Spanish Guide for Asthma Management)- and the Ecuadorian 'Consensus'[146]. Both guidelines use the above classification for adults, though they acknowledge the existence of 2 types of intermittent asthma in children: occasional and frequent, according to the frequency of the episodes, though both are symptom-free in-between the acute episodes and have normal lung function[145] (Table 2.7). The justification for this difference, is the frequent episodic presentation of asthmatic symptoms with scarce impairment between acute episodes in children, compared to adults. Likewise, this classification does not present a 'Mild Persistent Asthma' group, as

persistent asthma in children should at least be considered as moderate[147]. According to this line of thought, the number of acute worsening of respiratory symptoms in children is highly relevant, regardless the presence or absence of daily impairment.

Asthma control

Asthma control may be classified as controlled, partly controlled or uncontrolled according to the 2017 GINA guidelines[37] based on the current clinical characteristics of the patient. However, the assessment of future risk is also considered, including the risk of side effects from medication, of loss of lung function, of instability, together with the risk of suffering future exacerbations.

Table 2.8: Levels of asthma control

A. Assessment of current clinical control (preferably 4 weeks)			
Characteristics	**Controlled (All of the following)**	**Partly Controlled (Any measure presented)**	**Uncontrolled**
Daytime symptoms	None (≤2/week)	>2/week	Three of more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awaking	None	Any	
Need for reliever/ rescue inhaler	None (≤2/week)	>2/week	
Lung function (PEF or FEV_1) ‡	Normal	<80% predicted or personal best (if known)	
B. Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)			
Features that are associated with increased risk of adverse events in the future include: Poor clinical control, frequent exacerbations in the past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications.			

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
† By definition, an exacerbation in any week makes that an uncontrolled asthma week
‡ Without administration of bronchodilator
Lung function is not a reliable test for children 5 years and younger.

Source: GINA 2017[37]

Other national and international guidelines use slightly modified classifications of the level of asthma control, including up to 4 groups: complete, good, partial and bad. The items of the impairment section, however, are the same, as those of the future risk component, though the latter is also quantified (using the number of acute exacerbations in the previous year and none vs. variable medication adverse effects).

The main way to evaluate the level of control of asthma is through regular medical visits during follow-up. During these visits the health care worker should evaluate the presence of symptoms, measure the lung function (spirometry) and enquire about possible exacerbations and emergency care visits. In addition, the impact on the patient's everyday life and activity should also be explored, as well as side effects of the medications and adherence to baseline treatment. Different tests have been validated which may facilitate and standardise the measurement of asthma control. The most used are the Asthma Control Test (ACT)[3] and the Asthma Control Questionnaire (ACQ)[148]. The ACT has been specially validated to be used at the clinic during the routine visits, with defined cut points: a score equal to or above 20 is consistent with a well-controlled asthma, a score between 16 and 19 with a partially or not well-controlled asthma and equal to or below 15 with an uncontrolled asthma[136,149]. Similarly, an ACQ score equal to or below 0.75 is a well-controlled asthma, and a score of 1.5 or above is an uncontrolled asthma[150]. However, studies carried out in different settings, such as Spain, have shown different cut points[151]. Nevertheless, the overall reliability of both tests to detect uncontrolled asthma is poor[152], so they should not be used in isolation to assess asthma control. As commented before, poor control of daily asthma symptoms does not necessarily increase a person's risk of suffering severe acute asthma attacks.

Severe asthma definition

Given the lack of consensus of severe asthma definition, whether it should be based on symptom severity or the type or dose of medication needed to control those symptoms, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) organised a Task Force in 2013[153] addressing this problem. The definition for severe asthma they finally agreed upon is:

"Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming ''uncontrolled'' or which remains ''uncontrolled" despite this therapy.

- Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, Asthma Control Test (ACT) <20 (or ''not well controlled'' by National Asthma Education and Prevention Programme or GINA guidelines)

2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year.

3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year.

4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).

- Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)."[153]

As shown, this definition of severe asthma combines both the level of control of the disease and the medication needed to achieve it. It also includes those patients with uncontrolled asthma due to incomplete treatment of comorbidities[153]. Most of the guidelines and medical professionals have accepted this ATS/ERS definition, reaching an international consensus. However, this statement is based on experts' opinion and the cut-off values they used could be altered. There is still a strong debate around the definition of severe asthma, given the lack of supportive evidence for a severe asthma distinct phenotype and the heterogeneity of the disease[154]. On the other hand, those patients with uncontrolled asthma due to inadequate or inappropriate treatment or poor adherence should be considered as suffering 'difficult to treat asthma'[37].

2.6. Asthma treatment

The main aim of asthmatic treatment is to achieve and maintain control of the disease as soon as possible, together with preventing acute exacerbations and chronic airflow obstruction, and reduce mortality[145]. Adequate treatment should control daily symptoms, prevent exacerbations and loss of lung function, as well as cause the least damage possible. To attain this, a global and individualized long-term strategy is necessary based on an optimal pharmacological therapy and supervision, environmental control measures and education on asthma[155].

2.6.1. Pharmacological treatment

Medication should be adjusted according to the level of control, using the most effective, safe, affordable and acceptable for the patient[145]. Pharmacological treatment of asthma is not static, as it should be modified to adjust to the changing circumstances of the condition. As explained above (Classification section) both the current control of daily symptoms and the future risk domains

should be taken into consideration when deciding upon asthma medication, given the different response they may show to treatment[19,156].

To enable this continuous adjustment, asthma treatment is now modified following a stepwise approach. Before explaining the different steps, I will introduce a brief description of the different medications available.

Reliever medications

They are also called rescue medications and include the drugs that are used to treat acute bronchoconstriction rapidly. The main two are:

- Inhaled short acting β-agonists (SABA): The most commonly used are salbutamol (or albuterol) and terbutaline, which may be used in inhalation, nebulized or oral. They are the first line treatment for acute asthma, as they are the most effective to rapidly reverse the airway obstruction. Their effect starts just 3-5 minutes after inhalation and lasts for around 3-4 hours. They may cause tachycardia, muscle tremor, hypokalaemia, increased lactic acid, headache and hypoglycaemia as side effects.

- Inhaled anticholinergic: Ipratropium bromide is used in combination with a SABA to treat moderate or severe acute asthma exacerbations, especially in children, given its synergistic effect. It may be used as an inhaler or nebulized. It should only be used alone as a reliever drug, in case of allergy or intolerance to SABA[37]. It may cause certain side effects such as blurry vision, dry mouth, urinary retention and bronchospasms.

Controller medications

They are also called maintenance or long-term baseline treatment. They should be used daily during long-term periods and include:

- Inhaled (ICS) or systemic corticosteroids: They are the most effective maintenance therapy for asthma, either for controlling daily symptoms or to decrease the risk of future exacerbations[157-159]. There are different types of ICS such as: beclomethasone, budesonide, ciclesonide, fluticasone and mometasone. ICS may cause coughing, dysphonia, oropharyngeal candidiasis, growth retardation in children and increase the risk of fractures[160-164]. They are the first step treatment for persistent asthma, as an inhaler, though they are sometimes prescribed orally to treat severe persistent asthma or to gain control rapidly (for example, during an acute exacerbation).

Systemic corticosteroids may produce much more serious side effects, especially if used over long periods. These include: diabetes, hypertension, skin atrophy, osteoporosis, cataracts, muscle weakness, moon face, peptic ulcer, immunosuppression, aseptic necrosis of the femoral head and mood swings. Additionally, when suspended abruptly, they may induce an acute adrenal failure or unmask an underlying condition such as the Churg-Strauss Syndrome.

- Leukotriene Receptor Antagonists (LTRAs): Montelukast and zafirlukast are an alternative to ICS[165] for persistent asthma, though in the long-term, ICS have been shown to be superior to LTRAs[165,166], as patients who are well controlled with low-dose ICS, do not obtain the same degree of control when using montelukast[167]. They are therefore indicated as an alternative to ICS in patients who do not wish to use or do not tolerate well ICS, who have difficulties with the inhaling technique or who present with concomitant allergic rhinitis[168]. On the other hand, they are mostly used as complementary therapy associated with ICS in patients who do not achieve good control of symptoms on ICS alone. When compared to the combination of ICS and long-acting β-agonists (LABA), patients using LTRAs as add-on therapy to ICS have a higher median adherence

to therapy[169], an advantage of oral treatments. LTRAs may produce weakness, epigastralgia, diarrhoea, dizziness, headache and mouth pain.

- Long-acting β-agonists (LABA): Formoterol and salmeterol are used together with ICS as maintenance therapy, and they should not be used in monotherapy for asthma. There exist specific combinations of ICS and LABA (inhalers). Formoterol is a LABA, but with a rapid effect (3-5 minutes) so it may be used in combination with ICS during an acute exacerbation. Their effects last for around 12 hours, and salmeterol starts to show an effect after 20-45 minutes. Their side effects include cardiovascular stimulation, muscular tremor, hypokalaemia and tachyphylaxis.

- Tiotropium: It is a long-acting inhaled anticholinergic which may be added to other maintenance treatment (ICS and LABA) in patients with moderate or severe persistent asthma who do not achieve an adequate control. It has shown to be efficacious in reducing the number of asthma attacks and improving asthma control in school-age children with moderate-to severe asthma, as well as being well tolerated[170].

- Monoclonal antibodies

→Anti-IgE, Omalizumab: It is used subcutaneously and as for tiotropium is indicated for patients with moderate or severe persistent asthma who do not achieve an adequate control with ICS. Side effects that have been described with omalizumab include pain and bruising at the injection site, anaphylaxis and malignant neoplasms, though the relationship with the medication in latter case is unclear[6].

→Anti-IL5, mepolizumab: Anti-IL5: Various new treatments are now becoming available, such as mepolizumab that has been just recently included in the 2017 GINA guidelines, to be used in the last step of

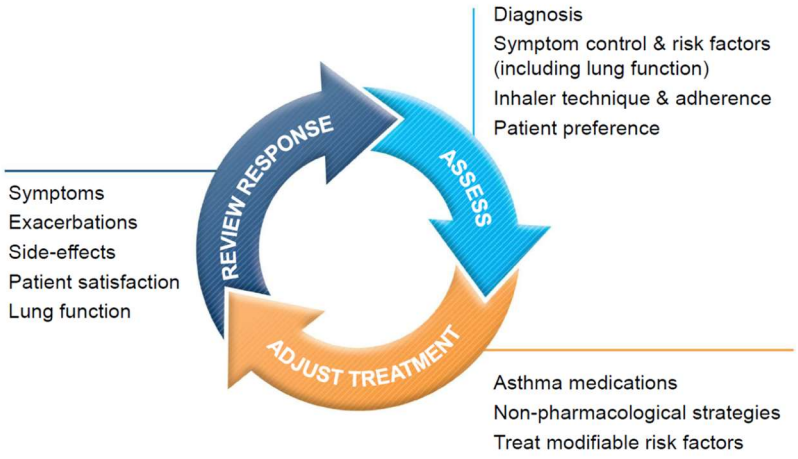
treatment (see Figure 2.13) as an add-on therapy for patients older than 12 years old, with severe eosinophilic asthma[37]. Other examples are reslizumab (approved by the U.S. Food and Drug Administration in March 2016 and by the European Medicines Agency in June 2016) and benralizumab (approved by the US FDA in November 2017)[171].

- Theophylline: It is a weaker bronchodilator, when compared to LABA, though it also has a modest anti-inflammatory effect at low doses. It is available in sustained-release formulae to be taken once or twice a day, with an overall weak efficacy in asthma[172-174]. It may be used as an add-on therapy for patients who do not achieve an adequate control with ICS and LABA. However, it has common side effects, such as nausea and vomiting, arrhythmias, convulsions and even death at high doses[175].

- Azithromycin: Low dose azithromycin during several months may play a role as an add-on therapy for patients with severe non-eosinophilic asthma and frequent exacerbations[176,177]. However, it is not currently recommended in international asthma guidelines[37,128].

Stepwise treatment

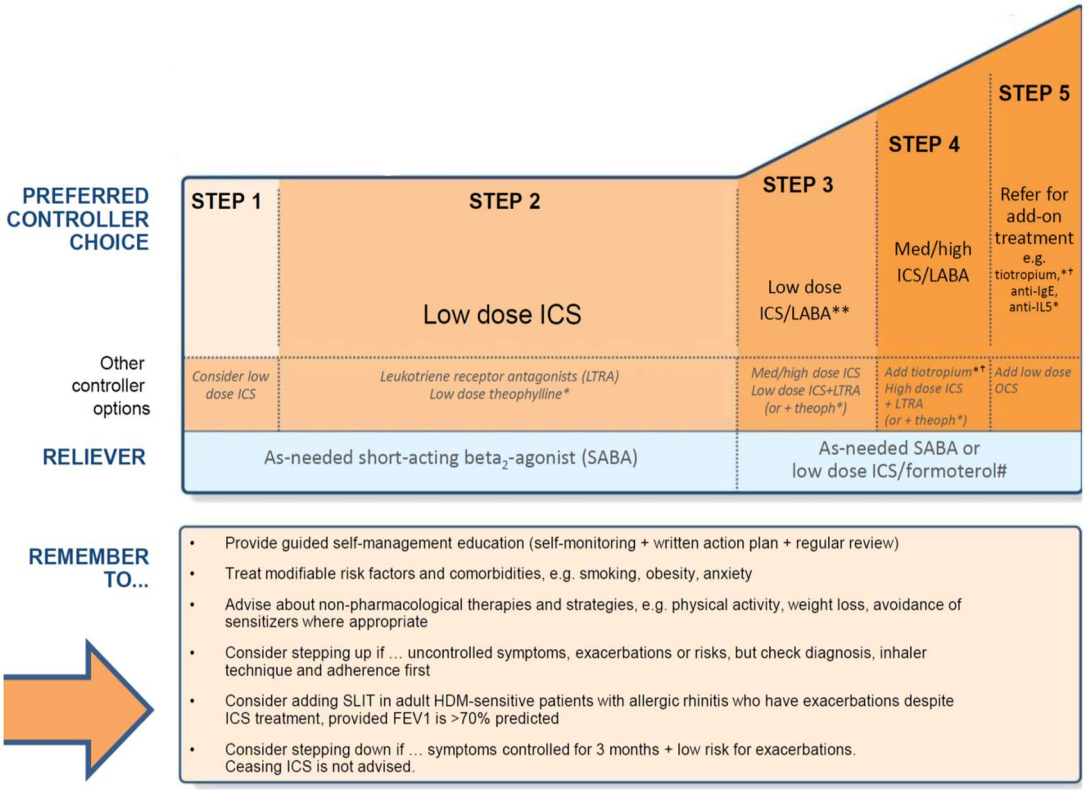
Figure 2.12: The control-based asthma management cycle



Source: GINA 2017 Teaching Slides[133]

The strategy used for the stepwise treatment, is to increase or decrease the number and doses of controller drugs used to treat asthma, in relation to the patient's degree of control. This may be done using the GINA classification in controlled, partly controlled or uncontrolled asthma (see above, Table 2.8). According to the 2017 GINA guidelines, asthma management should be a continuous process following the steps: assess, adjust (both pharmacological and non-pharmacological treatment) and review the response[37] (Figure 2.12).

Figure 2.13: Stepwise approach to control symptoms and minimise risk



*ICS: inhaled corticosteroids; LABA: long acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. *: Not for <12 years; ** For 6-11 years, the preferred Step 3 is medium dose ICS; #: Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy. ŧ: Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; not indicated for <12 years.*

Source: GINA 2017 Teaching Slides [133]

The different drugs recommended by GINA[37] at each step are described in Figure 2.13. The first step is the use of SABA as needed, with no maintenance therapy.

This should be only used for patients with infrequent symptoms (<2 times per month), of short duration and with no risk factors for exacerbations[37].

Steps 2 to 5 include maintenance therapy together with SABA as a rescue medication. Step 2 begins with low dose ICS as preferred therapy. In the next steps, other drugs are added to the ICS and/or the dose of the ICS is increased. The other drugs added are LABA, LTRAs, tiotropium, theophylline, omalizumab and mepolizumab. The last step includes the use of low dose oral corticosteroids[37]. Before upgrading patients to the next step, it is always necessary to assess adherence and correct inhaler technique. Similarly, it is recommended to refer the patient for specialist investigation before moving on to Step 5. At this stage, it may be advisable to use sputum-guided treatment.

Combinations of ICS and fast-acting LABA exist as maintenance and reliever therapy (MART) in a single inhaler that may be used for both daily maintenance therapy and the relief of symptoms as required.

During follow-up visits, patients who have been well controlled and have stable lung function during ≥3 months, should be considered to try to step down their treatment[37]. This should always be done under close supervision and engaging the patient in the process by providing understandable information and self-monitoring guidance. The 2017 GINA guidelines[37] include specific options on how to step down depending on the current medication and dose.

Table 2.9: Instructions for stepping down treatment once asthma is well controlled

General principles of stepping down asthma treatment
• Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. If the patient has risk factors for exacerbations or fixed airflow limitation, do not step down without close supervision. • Choose an appropriate time (no respiratory infection, patient not travelling, not pregnant). • Approach each step as a therapeutic trial. Engage the patient in the process;

document their asthma status (symptom control, lung function and risk factors; provide clear instructions; provide written asthma action plan and ensure patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit.

- Stepping down ICS doses by 25-50% at 3 month intervals is feasible and safe for most patients.

Current step	Current medication and dose	Options for stepping down
Step 5	High dose ICS/LABA plus oral corticosteroids (OCS)	• Continue high dose ICS/LABA and reduce OCS dose • Use sputum-guided approach to reducing OCS • Alternate-day OCS treatment • Replace OCS with high dose ICS
	High dose ICS/LABA plus other add-on agents	• Refer for expert advice
Step 4	Moderate to high dose ICS/LABA maintenance treatment	• Continue combination ICS/LABA with 50% reduction in ICS component, by using available formulations • Discontinuing LABA may lead to deterioration
	Medium dose ICS/formoterol* as maintenance and reliever	• Reduce maintenance ICS/formoterol* to low dose, and continue as- needed low dose ICS/formoterol* reliever
	High dose ICS plus second controller	• Reduce ICS dose by 50% and continue second controller
Step 3	Low dose ICS/LABA maintenance	• Reduce ICS/LABA to once daily • Discontinuing LABA may lead to deterioration
	Low dose ICS/formoterol* as maintenance and reliever	• Reduce maintenance ICS/formoterol* dose to once daily and continue as-needed low dose ICS/formoterol* reliever
	Moderate- or high-dose ICS	• Reduce ICS dose by 50%
Step 2	Low dose ICS	• Once-daily dosing (budesonide, ciclesonide, mometasone) • Adding LTRA may allow ICS dose to be stepped down • Insufficient evidence to support step-down to as-needed ICS with SABA
	Low dose ICS or LTRA	• Consider stopping controller treatment only if there have been no symptoms for 6–12 months, and patient has no risk factors. • Provide a written asthma action plan, and monitor closely. Complete cessation of ICS in adults is not advised as the risk of exacerbations is increased

BDP: beclometasone dipropionate; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids.
**ICS/formoterol maintenance and reliever treatment can be prescribed with low dose budesonide/formoterol or BDP/formoterol.* *Source: GINA 2017*[37]

2.6.2. Other treatments

Environmental exposure control

Smoking and exposure to tobacco smoke (ETS) worsens asthmatic symptoms and the response to treatment with ICS, even in mild asthmatics[178] and may produce a rapid lung function decrease[179], making it necessary to step-up the treatment needed[180]. Additionally, longitudinal studies have associated tobacco smoke with the development of asthma in adults, adolescents[181] and infants[182], and ETS may also worsen respiratory symptoms in asthmatic children. It is therefore one of the most important environmental exposures which should be addressed during asthma follow-up visits, informing about the most effective smoking cessation interventions[183].

Certain asthmatic patients may develop acute exacerbations when treated with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (NSAIDs), especially those with concomitant nasal polyps. These reactions may be severe or even fatal[184], therefore early diagnosis in these patients by medical history or oral provocation is essential[185,186]. These patients should avoid taking these drugs.

In the case of proven allergies, certain specific measures should be taken into consideration. The most effective are those which imply a marked reduction in the level of exposure to the specific allergen, such as occurs in occupational asthma, animal dander allergy (by removing the animal) and cockroach (by eliminating the cockroaches from the house)[187-191]. However, individual isolated measures, like the use of acaricides or mattress covers, have not proven to be as effective, even in decreasing the allergen exposure level[192-194]. On the other hand, the application of a combination of specific interventions has been shown to significantly reduce the level of allergen exposure and therefore the clinical efficacy[195-197]. Two different meta-analysis concluded that the efficacy of isolated

environmental mite control measures is limited in patients with rhinitis[187], and null in asthmatic patients[194], though a more recent systematic review analysing a combination of these measure showed more promising results[198].

Allergen immunotherapy

Subcutaneous allergen immunotherapy is an efficient treatment for well-controlled allergic asthma in the 2-4th step of treatment, as long as IgE mediated sensitization has been shown to common aeroallergens and is clinically relevant, well characterized and standardized extracts are used[199,200], and complex mixtures are not applied[201]. It should not be prescribed to patients with severe or uncontrolled asthma, as it is ineffective and implies a high risk of severe adverse reactions which could be fatal[202,203]. Given this risk, the efficacy of other safer and more convenient alternatives have been studied, such as sublingual immunotherapy. Two systematic reviews concluded that sublingual immunotherapy may significantly reduce clinical bronchial manifestations in children and adolescents with allergic asthma[204,205], as well as in adults[206]. Most clinical trials which demonstrated the efficacy of this method used well characterized extracts and at higher doses than those usually prescribed for subcutaneous immunotherapy. Sublingual immunotherapy is well tolerated, and no fatal reactions have been described[206].

To my knowledge, there have been no comparative cost-effectiveness studies of immunotherapy vs. conventional pharmacotherapy, and they may well not be any, given the complexity of the study design. Nevertheless, immunotherapy has some additional advantages over pharmacotherapy, such as the maintained clinical improvement up to several years after stopping treatment[207,208] or the ability to halt the progression of rhinoconjunctivitis to asthma[208]. Finally, immunotherapy has been shown to be a cost-effective treatment for patients with

coexistent rhinoconjunctivitis and asthma, when compared to exclusive pharmacological treatment[209,210].

Flu and Pneumococcal Vaccination

Vaccination against seasonal flu[211,212] and *Streptococcus pneumoniae*[213] have not been shown to prevent asthma exacerbations. However, given the high risk of complications in patients with chronic diseases[214,215], vaccination against seasonal flu should be considered in patients with moderate to severe asthma, both adults and children.

Other methods

Weight loss in overweight and obese adults with asthma has shown to improve asthma control and decrease daily symptoms, even though they may not reduce eosinophilic airway inflammation[216]. There are scarce data on overweight or obese children[216].

Pulmonary rehabilitation improves exercise capacity and disease specific and generic questionnaire scores in the long term in asthmatic adults[217].

2.6.3. Education

Educating asthmatic patients and their families is an important part of the management of these patients, as it reduces the risk of suffering acute exacerbations, it increases quality of life and decreases health care costs[218,219]. It is therefore an indispensable part of a comprehensive asthma care[37,220-222]. The main objective is to provide the patient with the necessary knowledge and skills to improve his/her self-management and adherence to treatment. This may improve asthma control and the patient's self-sufficiency.

Knowledge and skills

From a practical point of view, education in asthma should consider both the knowledge transmission and the acquisition of necessary skills[223]. The patient's needs, previous knowledge, beliefs, age, asthma severity and the degree of involvement necessary for an adequate self-management should all be considered when considering the information given[145]. Educational interventions should include: self-management (by symptoms and PEF monitoring), written asthma action plans, and regular review of the level of asthma control and treatment by the health care worker[224]. Interventions that do not include an asthma action plan are less effective[224,225], and those which only include information actions have been shown to be ineffective[222,224,225].

As for the development of skills, the asthmatic patient should receive inhaler technique training for the specific device he/she may be using[226-231]; should be taught how to recognize and manage an exacerbation promptly; and how to avoid triggers[232].

Asthma action plan:

The written asthma action plan (WAP) is a set of written instructions individualized for each patient, according to the severity and level of control of their asthma and the treatment prescribed. The main objective of this action plan is early recognition of an acute worsening of their asthma and a quick initiation of actions to enable a rapid remission. The level of control may be assessed by the frequency and severity of symptoms or the measurement of daily PEF, depending on patient and doctor preferences[233-235]. A meta-analysis of randomized controlled trials to assess the efficacy of symptom-based vs peak-flow-based WAPs in the paediatric population, concluded that those using symptom-based WAPs had lower risk of exacerbations requiring acute care visits[236]. Therefore,

symptom-based WAPs should be preferably used when treating asthmatic children, over peak-flow based WAPs.

The action plan should comprehend two main parts: the usual patient's treatment during the stable phase of asthma and the actions that should be followed in case a worsening occurs[237-239]. It should be revised during each medical visit, as well as during ED visits or hospital admissions.

In adults, providing asthmatic patients WAPs can reduce hospital admissions, acute care visits, missed days of work and night awakenings by one third[225]. This, together with its simplicity and low cost, is the reason why WAPs are now universally recommended for all asthmatic patients as part of their regular management.

Treatment adherence:

The patient's adherence to the medication prescribed is a critical factor to attain and maintain an adequate level of control of the disease. It is estimated that treatment adherence in asthma is below 50%[240,241]. Poor adherence has been associated with morbidity and mortality, as well as a greater use of health care services[242,243].

There are three main types of non-adherent patients: the erratic (forgets to take the medications), the intentional (does not want to take the medication), and the involuntary (who is unaware of the disease or its treatment)[244,245].

It is vital to assess the patient's adherence to treatment, using additional methods than only clinical history which tends to overestimate adherence. These may include the use of the pharmacies' electronic records of the medication withdrawn or standardized questionnaires completed by the patient[37], such as the Medication Adherence Report Scale for Asthma (MARS-A)[246].

The educational programme should always consider assessing the adherence to treatment and promote appropriate corrective measure in case of poor adherence, adapted to the type of non-adherent patient.

2.7 Latin American perspective of asthma

2.7.1. Introduction

Latin America extends from Argentina to Mexico, comprising 20 different countries with highly varied geographical and climatic contexts. Its 600 million inhabitants are also a mixture of Amerindian, African or European descendants and their primary languages are Spanish and Portuguese. Poverty and inequality are, however, present throughout the region where approximately 25% of the population live in poverty (less than 2 USD per day)[247-249].

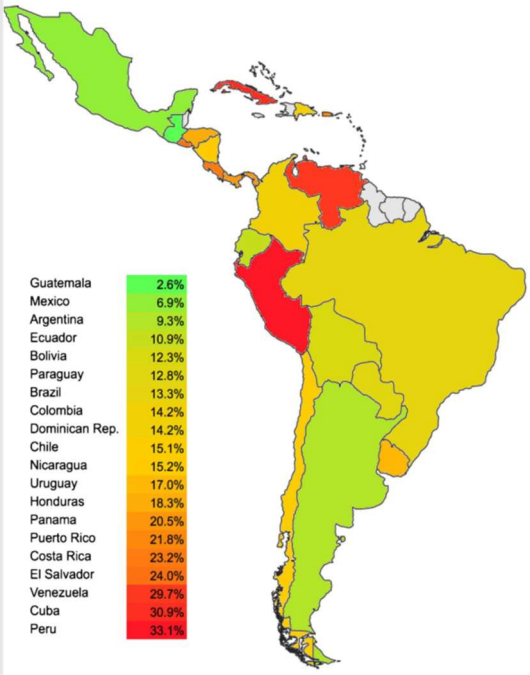
2.7.2. Asthma prevalence

Table 2.10 Current wheeze and asthma in children ages 13–14 years and asthma mortality in Latin American countries

Country	Population (millions)	Asthma diagnosis, ever (%)	Asthma mortality*
Argentina	41 505 209	9.3	14.7
Bolivia	10 489 027	12.3	
Brazil	202 332 357	13.3	
Chile	17 198 908	15.1	23.5
Colombia	47 258 555	14.2	19.6
Costa Rica	4 667 048	23.2	18.0
Cuba	11 112 443	30.9	
Dominican Republic†	9 982 315	14.2	
Ecuador	15 609 215	10.9	
El Salvador	6 371 795	24.0	
Guatemala	15 439 192	2.6	33.0
Haiti	10 333 866		
Honduras	8 566 536	18.3	
Mexico	114 407 027	6.9	27.1
Nicaragua	6 002 266	15.2	41.8
Panama	3 633 434	20.5	
Paraguay	6 824 642	12.8	
Peru	30 475 572	33.1	25.8
Puerto Rico‡	3 628 043	21.8	33.0
Uruguay	3 310 730	17.0	
Venezuela	30 704 465	29.7	
Total population/ *mean*	599 852 642	*18.0*	*26.3*

*Per 100 000 deaths.
†Prevalence of adult asthma.
‡Possession of the USA.

Figure 2.14 Prevalence of childhood asthma in Latin America. Prevalence in the Dominican Republic is based on adult asthma.



Source: Forno et al., Thorax 2015[250].

Some Latin American countries were among those with the highest asthma rates worldwide, as was the case of Costa Rica (25.5%), Peru (22.8%) or Brazil (21.3%) for current wheeze in 13-14-year olds, and again Costa Rica (34.8%), Brazil (22.9%) or Panama (23.1%) for 6-7-year olds in the ISAAC III studies[2]. Even though the majority of the participating centres had >15% prevalence of current asthma symptoms and lifetime asthma, there were great variations both between and within countries. Current wheeze ranged between 8.7% in Mexico and 30.8% in El Salvador, and lifetime asthma diagnosis ranged between 6.9% in Mexico and 33.1% in Peru[250]. Similarly, lifetime asthma diagnosis in Brazil varied from 7.3% in Nova Iguaçu to 21.2% in Porto Alegre. These variations appeared regardless of their cultural or ethnic background and the level of socioeconomic development[250].

Table 2.11 Prevalence of recent wheeze (within the previous 12 months) among school children participating in the ISAAC studies in Latin America

	ISAAC Phase I (13–14 year olds)		ISAAC Phase II (8–12 year olds)		ISAAC Phase III (13–14 year olds)	
Country (centres)	*N*	Wheeze (12 months) (%)	*N*	Wheeze (12 months) (%)	*N*	Wheeze (12 months) (%)
Argentina						
Buenos Aires	2996	9.9	–	–	–	–
Cordoba	–	–	–	–	3445	13.6 (+0.48)
Rosario	3008	11.8	–	–	–	–
Brazil						
Curitiba	3008	18.4	–	–	3628	18.9 (+0.09)
Porto Alegre	3198	24.7	–	–	3008	18.2 (−0.72)
Recife	3086	19.7	–	–	2865	19.1 (−0.07)
Salvador	3119	27.1	–	–	3022	24.6 (−0.33)
Sao Paulo	3008	23.3	–	–	3161	18.7 (−0.65)
Uruguaiana	–	–	1971	25.6	–	–
Chile						
Central Santiago						
Punta Arenas	3482	6.8	–	–	3044	13.6 (+0.83)
South Santiago	3231	11.1	–	–	3026	17.0 (+0.98)
Valdivia	3231	11.5	–	–	3105	16.0 (+0.63)
Costa Rica						
Costa Rica	3200	23.7	–	–	2436	27.3 (+0.46)
Ecuador						
Pichincha	–	–	894	0.8	–	–
Mexico						
Cuernavaca	3102	6.6	–	–	1431	11.6 (+0.63)
Panama						
David	2885	17.6	–	–	3183	22.9 (+0.88)
Paraguay						
Asuncion	2996	19.4	–	–	3000	20.9 (+0.31)
Peru						
Lima	3158	26.0	–	–	3022	19.6 (−1.06)
Uruguay						
Montevideo	3072	19.0	–	–	3177	17.9 (−0.13)
Overall	52 549	16.9			44 550	18.8 (+0.32)

Phase III study shows change in prevalence per year between Phase I and III studies (brackets).

Source: Cooper et al, Allergy, 2009[25]

When considering the regional variations on asthma symptoms prevalence in Latin America, no differences were observed between coastal and inland centres, as well as between tropical and non-tropical centres[251]. There seemed to be an inverse correlation between altitude and lifetime asthma and current wheeze, though the correlation disappeared once the 8 centres situated at an altitude >2000m were excluded from the model[251]. When studying socioeconomic status indicators, such as gross national income (GNI) or percentage of population living under the poverty line, no correlation was found with asthma symptoms[251]. Finally, when considering the latitude of the participating centre, only current wheeze showed an association (greater prevalence in Southern latitude centres)[251], while there were no differences in lifetime asthma.

Over the years following ISAAC Phase III, other countries from Latin America undertook population-based cross-sectional studies using similar methodology and questionnaires to investigate asthma prevalence in 6-7 and 13-14-year olds. Table 2.12 includes the results of some of these published studies. As with the ISAAC studies, the prevalence of asthma symptoms was highly heterogeneous between countries and studies.

Table 2.12: Latin American studies of asthma symptoms prevalence undertaken after ISAAC study.

Study	Location	Year	Size	Age	Asthma Symptom	Prevalence
Cooper 2003[33]	Ecuador (Esmer. & Pichincha)	1998 - 2001	4443	5-18 y	Current wheeze Lifetime asthma dx	2.1% 10.3%
De Farias 2010[252]	Brazil (Amazon)	2007	1072	6-7 y	Current wheeze Lifetime asthma dx	21.4% 5.8%
			999	13-14 y	Current wheeze Lifetime asthma dx	12.4% 6.1%
Del Rio-Navarro 2006[253]	Mexico (Mexico city)	2002 - 2003	3211	6-7 y	Current wheeze Lifetime asthma dx > 4 attacks last 12m	6.8% 4.5% 0.8%
			3899	13-14 y	Current wheeze Lifetime asthma dx > 4 attacks last 12m	9.9% 8.0% 2.5%
Dennis 2012[254]	Colombia (6 large cities)	2009 -10	5878	5-17 years	Current wheeze Lifetime asthma dx	30.5% 8.6%
Garcia 2008[255]	Colombia (Bogotá)	2002	3256	6-7 y	Current wheeze Lifetime asthma dx	10.4% 5.6%
			3829	13-14 y	Current wheeze Lifetime asthma dx	8.6% 9.7%
Kausel 2013[256]	Chile (Los Ríos)	2002 + 2009	3105	13-14 y	Current wheeze Asthma ever	16.0% (urban) 15.8% (urban)
			159	13-14 y	Current wheeze Asthma ever	16% (s-urban) 28%(s-urban)
			100	13-14 y	Current wheeze Asthma ever	6% (rural) 20% (rural)
Moncayo 2010[257]	Ecuador (Esmeraldas)	2005 -7	3858	6-16 years	Current wheeze	10.5%
Penny 2001[258]	Peru (Lima)	1997	808	8-10 years	Current wheeze Lifetime asthma dx	9.5% 20.7%
Robinson[#] 2011[86]	Peru (Lima and Tumbes)	2009 - 2010	725	13-15 y	Current wheeze Lifetime asthma dx	10.1% (urban) 13.0% (urban)
			716	13-15 y	Current wheeze Lifetime asthma dx	2.8% (rural) 2.2% (rural)
Rodrigues Valle 2014[259]	Brazil (Rio d Janeiro)		3216	6-7 y	Current wheeze Lifetime asthma dx Severe asthma[*]	20.9% 7.3% 8.8%
Roncada 2016[260]	Brazil (Porto Alegre)		2500	8-16 years	Current wheeze Asthma[**]	28.6% 20.4%
Schei 2004[31]	Guatemala (W. Highlands)	1998	1058 homes	4-6 years	Current wheeze Lifetime asthma dx	3.3% 2.6%
Soto 2014[261]	Bolivia (Oropeza)	2011	2340	9-15 years	Current wheeze (WQ) Current wheeze (Video)	16.4% urban 21.7% rural 7.3% urban 3.9% rural

*: ≥4 wheezing episodes, >1 night disturbance or speech limitations due to wheezing; **: Answered Yes to all 4 questions: asthma symptoms last 12 months, rescue treatment last 12 months, physician asthma diagnosis ever in life, asthma symptoms ever in life; #: Cross-sectional household survey, not ISAAC methodology.

The reasons why urbanisation may increase asthma prevalence are still being studied, though some contributing factors have been proposed, such as changes in diet and lifestyle, exposure to higher levels of environmental irritants (indoor and outdoor air pollution, household allergens and tobacco smoke), decreased parasitic infections and increased viral infections in early life, greater antibiotic use and vaccine coverage, increased stress and smaller families[262-268]. To better understand the effect of urbanisation on asthma prevalence, Rodriguez et al[87] undertook an ecological study in 59 communities in transition from rural/traditional to urban/modern way of life, in Esmeraldas, Ecuador. They found a current wheeze prevalence ranging from 0 to 31.4% with an overall 10.1%, in 7-15-year-old children[87] (same population as Moncayo et al[257] in Table 2.12). The global summary urbanisation index was associated with current wheeze, and the variables indicating a higher socioeconomic status and a more urban lifestyle were shown to be more relevant compared to those related to urban infrastructure[87].

One other interesting finding that emerged from the ISAAC studies when comparing asthma rates in Phase I and III, was that the prevalence in Latin America is rising in contrast with the stabilization experienced in other high prevalent countries such as the UK or New Zealand[2]. Current wheeze increased in Latin America an overall 0.32% per year in 13-14-year olds and 0.07% in 6-7-year olds; severe asthma (>4 attacks per year) increased 0.02% and 0.09% per year respectively; and lifetime asthma 0.25% and – 0.15% per year, respectively[2]. However, the results from the video questionnaire in 13-14-year olds, were slightly different, with an overall 0.04% decrease in current wheeze prevalence in Latin America[2]. As discussed previously, the discrepancies between findings obtained through the video and the written questionnaire were one of the limitations of the ISAAC studies. Of note was the increase described in Costa Rica

with already a high asthma prevalence in Phase I, as well as other low and intermediate prevalence countries (Argentina, Panama, Mexico, Chile and Paraguay), raising the concern that asthma rates in Latin America may continue to rise over the coming years (Table 2.11). On the other hand, the apparent decline in a high asthma rate country (Peru) may also indicate the possibility that asthma rates in high prevalent countries in Latin America may be reaching a plateau as described in the UK or Australia[2].

2.7.3. Asthma control

The high rates of asthma symptoms in some Latin American countries are only one of the reasons that explain the significant burden of asthma in this region. One other factor is high morbidity consequent to inadequate management of the disease[25]. To study the quality of asthma control and treatment in Latin America through the patient's experience, Neffen et al.[24] undertook the Asthma Insights and Reality in Latin America (AIRLA) in 2003 in 11 countries. Children and adults with asthma diagnosis were identified by systematic household surveys in urban areas in each country. As seen in Table 2.13, they assessed the proportion of asthmatic children and adults that met the GINA criteria for adequate control. Nearly 70% of 808 children had used emergency care during the previous 12 months (twice as much as reported in a similar study in Europe[269]), 57% reported asthma symptoms in the past month, 68% referred daily activities limitation due to asthma and only 2.4% fulfilled all GINA criteria for optimal asthma control[24]. On the other hand, there was a poor recognition of asthma severity, and even though 21% of the participants (children and adults) had severe asthma according to the GINA guidelines, only 6% of them perceived their disease as severe. Similarly, 44.7% of those with severe persistent asthma described their asthma as well or completely controlled[24].

Table 2.13 The Global Initiative for Asthma (GINA) recommendations and results of the Asthma Insights and Reality in Latin America (AIRLA) survey in 11 Latin American countries in 2003

GINA definition for control of asthma	AIRLA findings	Adults %	Children %
Minimal (ideally no) chronic symptoms, including nocturnal symptoms	Asthma symptoms:		
	• During day (past 4 weeks)	56	57
	• Night wakening (past 4 weeks)	54	47
	• Exercise-induced asthma (past 12 months)	41	37
Minimal exacerbation	Sleep disruption at least once per week	39	34
No emergency visit for asthma	Use of emergency care in past 12 months: hospitalization, emergency service visit and unscheduled emergency visits	52	69
Minimal need for short-acting β_2-agonists	Current use of quick-relief bronchodilators[a]	55	61
No limitation on activities, including exercise	Asthma restricts:		
	• Sports and recreation	55	42
	• Normal physical activity	46	33
	• Choice of jobs or careers (adults)	30	–
	• Social activities	31	24
	• Sleeping	48	43
	• Lifestyle	39	33
	• Household chores	46	21
	• Any of the above	79	68
Normal or near-normal lung function (PEF[b] variability <20%)	Never had a lung-function test	49	62

[a] Includes short-acting β_2-agonists (inhaled and oral) and anticholinergics.
[b] PEF = peak expiratory flow.

Source: Neffen et al., Rev Panam Salud Publica, 2005[24].

A new survey was undertaken in 2011 in Argentina, Brazil, Mexico, Puerto Rico and Venezuela: The Latin America Asthma Insight and Management (LA AIM)[270]. The aim of this survey was to explore the realities of living with asthma, to identify the disconnect between expectations in asthma management and the patient experience, and to identify unmet needs in asthma management[270]. They identified 2168 patients with asthma aged older than 12, of which only 7% had well-controlled asthma, 57% partially controlled asthma and 36% uncontrolled asthma[271], as defined by GINA criteria[37]. For those aged between 12-17 years old asthma control was better, with a distribution of 23%, 16% and 15%, respectively[271]. The proportion of well-controlled asthma ranged from 3% in Venezuela to 9.3% in Brazil[271]. Patients with uncontrolled asthma had a higher

medication (relievers, oral corticosteroids and preventers) and health care (emergency room visits and hospitalizations) use[271], than patients with well-controlled asthma.

Several other smaller studies have described a similar picture in diverse Latin American countries. In Peru, of those children reporting current wheeze, 28.6% and 45.5% (urban and rural residency, respectively) reported an emergency department (ED) visit during the previous year[86]. Similarly, in a population survey in the 6 largest cities of Colombia, 38% of 6507 asthmatic adults and children had visited the ED or had been hospitalized during the previous year[272]. We obtained comparable results from a case-control study in Esmeraldas, Ecuador, with 86% of the children treated for a bronchodilator responsive wheeze at the ED reporting having been treated for a similar episode during the previous year[34]. Even though the population, setting and outcome of these studies differed, the findings were very similar, suggesting that asthma control in Latin America is very poor, resulting in an excessive use of emergency care and hospitalisations for acute exacerbations[273].

In Salvador, Brazil, Antunes et al.[274] studied the hospitalization rates for asthma over the period 1998-2009. Although asthma accounted for 18% of all respiratory diseases hospitalizations, they also experienced the largest decline in this period (88%), with a mean annual drop of 1.2 per 10 000 inhabitants, and this drop was greater between 2003-2006[274]. There are scarce data on hospitalization trends for asthma in Latin America, and even though this study is highly relevant, it is important to acknowledge some of its limitations, such as the use of secondary data (Hospital Information System and Brazilian Institute of Geography and Statistics) which may lead to under-reporting and lack representation of private hospitals or the possibility of incorrect or altered diagnosis (to maximise repayment for hospitalisation).

2.7.4. Asthma mortality

Asthma mortality in Latin America is higher than that reported in other regions[29,275]. Neffen et al.[275] studied asthma mortality rates in 11 Latin American countries in the 1980s, showing a high asthma mortality rate in most of them. The lowest rates were found in Colombia (1.35 per 100 000) and Paraguay (0.8 per 100 000) and the highest in Uruguay and Mexico (5.36 per 100 000)[275].

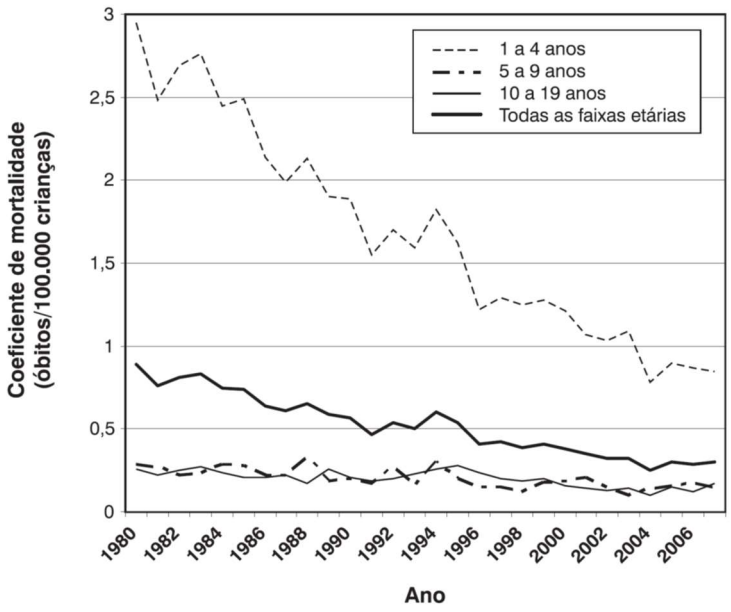
Since then, several studies from Brazil revealed a rising trend of asthma mortality, up to a peak of 1.5 deaths per 1000 during the 1990s[276], followed by a decline after the mid 1990s[277,278]. The same was described in Puerto Rico, with a mean asthma mortality rate of 4.77 per 100 000 and a decrease after 1999 (3.01 per 100 000)[279]. These asthma mortality rates were 1.77 to 4 times greater than that in the US. A study from Uruguay, presented a progressive decline in asthma mortality rates over the period 1984-1998 (mean 5.10 per 100 000) with a more pronounced decrease in 1995-98[280]. This decreasing trend was inversely correlated with sales of inhaled corticosteroids[280]. An analogous inverse correlation between inhaled corticosteroid sales and asthma mortality trends was also described in Argentina, where crude asthma mortality rates decreased from 3.38 (per 100 000) between 1980 to 89 to 2.58 in the following decade[281]. Still, this decline was also positively correlated with the decrease in theophylline sales[281].

Even though asthma mortality rates varied greatly between countries, it is clear that they are declining throughout the region. Nevertheless, when analysing asthma mortality trends in different regions of Brazil, De Souza-Machado et al.[282] showed that this decline was mainly seen in the most affluent regions, while it had increased in the less affluent regions, highlighting the effects of inequality on health. One of the reasons for this, as explained below, is that asthma, a complex

chronic disease, is mostly being managed as if it were an acute illness rather than a chronic disease.

There is scarce data on asthma mortality in children in Latin America. A study undertaken in Brazil, showed that there were 9051 deaths due to asthma in patients under 19 years old, and that 69% of these occurred before the age of 5[283]. As described in adult studies, mortality rate also decreased during the study period, from 0.89 per 100 000 children in 1980 to 0.30 in 2007[283] (Figure 2.15). This decline was more accentuated in the 1-4 year old group[283], as seen in Figure 2.15. However, Lotufo et al.[278] showed that, even though there was a decreased in asthma mortality rate in Brazil between 2001- 2010 in the 15-24 and 24-34 year-old groups, this decrease was not observed among the 5-14 year olds.

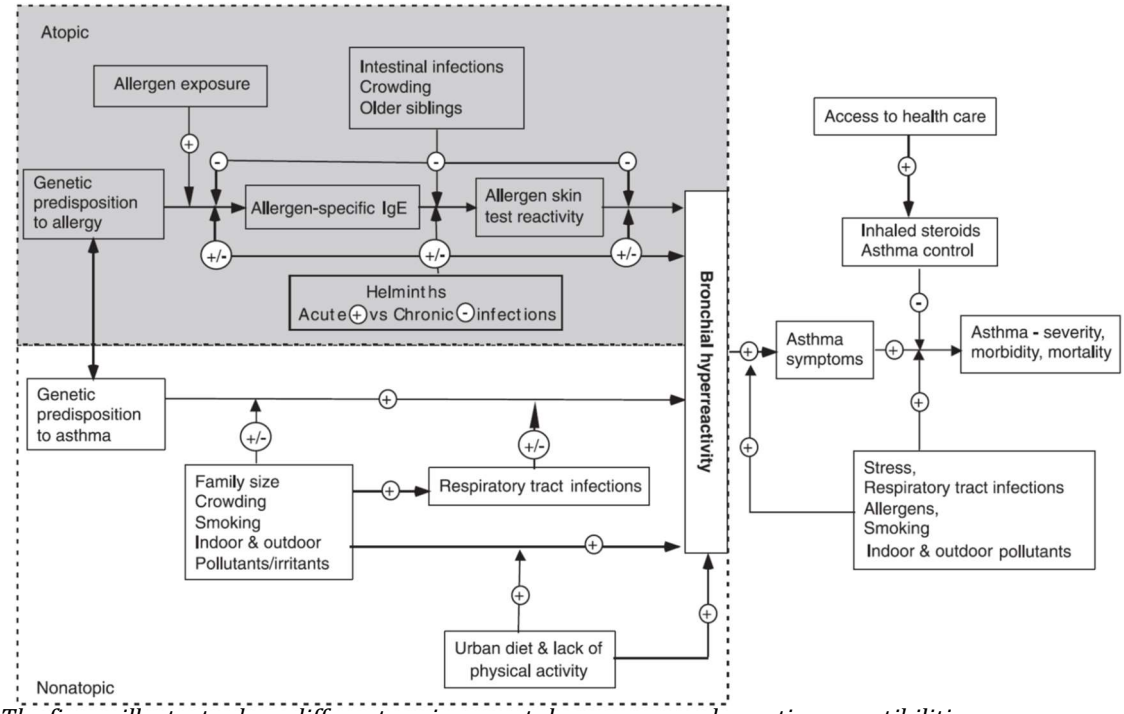
Figure 2.15: Asthma mortality in children under 19 years old in Brazil, 1980-2007



Source: Prietsch et al., J Pediatr, 2012[283].

*2.*7.5. Asthma risk factors

Figure 2.16: Conceptual framework for environmental and host factors affecting the development of atopic and nonatopic asthma in Latin America.



The figure illustrates how different environmental exposures and genetic susceptibilities may lead to the development of bronchial hyper-reactivity and asthma symptoms that are associated with or not associated with atopy. The effects of intestinal infections (such as helminths), crowding, and older siblings may modify the development of asthma through effects on the development of allergic inflammation, while other distinct (environmental irritants and respiratory tract infections) or similar (crowding) exposures may affect the development of asthma through distinct biological mechanisms and genetic factors. Many social and environmental factors may be involved in determining asthma severity. Risk (+) and protective (-) effects are shown. Arrows pointing at arrows represent interactions. Urban residence would be expected to increase both atopic and nonatopic asthma through effects on important environmental exposures (e.g. decreasing helminth infection prevalence, increasing exposure to pollutants, urban diet and physical inactivity, increased allergen exposure, etc.).
Source: Cooper et al., Allergy, 2009[25]*.*

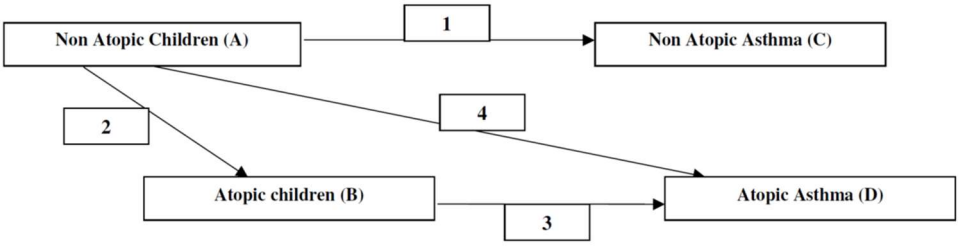
The observation of asthma rates being higher in large Latin American cities where overcrowding, dirt and infections are frequent, has led researchers to study whether risk factors for asthma in Latin America are different to those in Europe or North America, and do not conform to the 'Hygiene Hypothesis' described in the first section of this chapter. One of the reasons for these observed discrepancies may be due to the predominance of non-atopic asthma as discussed above, with alternative physiological pathway sand causal

mechanisms, and therefore different risk factors (Figure 2.16)[25]. In this sense, urban lifestyle and environments characterized by overcrowding, intestinal and respiratory infections, indoor and outdoor pollution, smoking, among many factors and frequently observed in Latin American cities, may be more conducive to the development of a non-atopic rather than atopic asthma phenotype.

However, when reviewing the associations between poor hygiene and infections and asthma risk, current evidence is not sufficient to allow us to derive a conclusion as to whether poor hygiene exposures and early life infections affect the risk of developing childhood asthma in Latin America[284]. This was the conclusion of a systematic review we undertook, where we found that selective reporting of statistically significant results was common to many studies (except for the 6 cohort studies included in the review), exposure variables measured varied greatly between studies, and most of studies showed no associations with asthma or wheeze. The exception was early life acute respiratory infections, which showed reasonably consistent positive associations with wheeze/asthma across studies[284]. Nevertheless, as mentioned above, most of the studies did not stratify their results by atopic and non-atopic asthma hampering an analysis of the specific risk factors for each phenotype. Barreto et al.[285] highlighted the importance of selecting appropriate comparison groups for asthma studies to avoid bias (Figure 2.17). In this sense, they investigated separately risk factors for asthma among atopic and non-atopic children, concluding that factors related to poverty, dirt and contact with other young children (day care attendance) were associated with a higher risk of non-atopic wheeze alone[285]. Overall, large prospective cohort studies with standardised outcomes are needed in Latin America to clarify the role of poor hygiene exposures and early life infections on the development of childhood wheeze or asthma. Such studies should help guide

policy makers on decisions of potential strategies to reduce the high asthma burden in Latin America.

Figure 2.17: Conceptual framework for development of asthma/wheezing, with and without atopy, and choice of appropriate comparison groups.



What is being investigated	What are the comparison groups	Number in diagram
Risk factors for asthma/wheezing in non atopic children	Non atopic asthma/wheezing (C) and non atopic non asthma/wheezing (A)	1
Risk factors for asthma/wheezing in atopic children	Atopic asthma/wheezing (D) vs. atopic non asthma/wheezing (B)	3
Risk factors for atopy	Atopic children (B+D) vs. non atopic children (A+C)	2
Risk factors for atopic asthma/ wheezing in non atopic children *	Atopic asthma/wheezing (D) vs. non atopic non asthma/wheezing (A)	4

*of public health interest only as it turns the process of developing atopy and the process of subsequently developing asthma/wheezing into a black box .

Source: Barreto et al., Respiratory Research, 2010[285].

Other than poor hygiene and infections, risk factors that have been associated with asthma in Latin America include overweight, psychosocial factors and diet. Being obese and overweight are now major public health problems in Latin America[286], and have been associated with non-atopic asthma[287]. A study from Salvador, Brazil, reported that wheezing and asthma were more common among overweight children (4-12 years old) (prevalence ratio: 1.34; 95%CI 1.07-1.67)[288].

When studying intrafamilial violence, Barreto et al.[289] (2015) found that maltreatment non-violent discipline (adjusted OR: 1.95; 95% CI: 1.19-3.20) and non-violent discipline (adjusted OR: 1.95; 95% CI: 1.17-3.25) were associated with non-atopic asthma but not with atopic asthma in Brazil. For the most severe form of intrafamilial violence (maltreatment violent discipline), this association

disappeared after adjustment for confounders[289]. On the other hand, minor maternal psychiatric or mental disorders were associated with both atopic and non-atopic asthma in 4-12-year-old children[99,100]. Similarly, behavioural problems in children and community violence were also shown to be associated with asthma risk in Brazil[97,98]. Contextual violence (both from the community and family) as well as minor psychological or behavioural disorders may be frequently found in poor and highly stressed neighbourhoods that tend to grow at the peripheries of Latin American cities.

As for the role of diet, a Mediterranean diet has been described to reduce asthma risk in Mexico and Peru[290-292]. In addition, fish consumption was found to have a protective effect against asthma in Brazil[293]. Fish fried in palm oil (a frequent way of consuming fish in Latin America) is rich in selenium, zinc and vitamin A, all of which may protect against asthma given their antioxidant effects[294]. Gomes de Luna et al.[295] also showed that consumption of biscuits and fried snacks ≥3 times per week, was associated with asthma in adolescents in Brazil, while fruits ≥3 times per week were found to be protective. All these factors have been associated previously with asthma outside Latin America as already discussed[81,82].

Other highly relevant risk factors, such as atopy and urbanisation have already been discussed in the previous sections.

2.7.6. Asthma phenotypes in Latin America

As presented previously in this thesis, asthma may be classified into very different phenotypes according to several characteristics (time of onset, associated symptoms or comorbidities, complementary tests results, etc.). We are now going to focus on the most widely used phenotype classification of atopic and non-atopic asthma. According to several studies, non-topic asthma is the

predominant presentation in Latin America. This was the case in Penny et al.[258] study in a low-income urban area in Peru, were there was no association between atopy (measured by Skin Prick Test, or SPT) and recent asthma, and only 28.6% of children with recent asthma and 24.3% with lifetime asthma were atopic. In another low-income urban population in Chile, the proportion of atopy (measured by SPT) among children with and without current wheeze was similar (44.2% vs 42.3%, respectively)[296]. Likewise, only 21% of the 9-13 year-old-children with current wheeze in the small town of Uruguaiana (Brazil) were atopic (measured by SPT)[297]. Furthermore, 26.2% of Cuban schoolchildren with current wheeze were SPT positive and 38.2% were specific IgE positive[298]. Finally, the Phase II ISAAC study, revealed that only 11% of asthma was attributable to atopy in Latin American participating centres[30]. None of the previously mentioned studies reported the population attributable fractions (PAFs) of asthma due to atopy.

However, there are also contradictory findings. In Peru, 77% of urban asthmatic children were atopic and 55.9% of the rural, when using SPT as a measure of atopy[86]. A study from urban Colombia found a 60% atopy among asthmatics and 40% among non-asthmatics using allergen specific IgE[254]. In Esmeraldas, Ecuador, 68% of the children treated at the ED for bronchodilator-responsive wheeze were atopic when measured by SPT and 82% when measured by allergen specific IgE[34]. These discrepancies may be due to the prevalence of atopy among the general population in each location, the method used to diagnose atopy (SPT vs allergen specific IgE), as well as the severity of the disease. The differences in the degree of urbanisation and climate may also explain some of the variation observed, though for both low and high proportions of atopy among the asthmatics, there were studies carried out in similar Latin American urban settings. The study by Ardura-Garcia et al[34] in Esmeraldas, Ecuador, included

children recruited at the ED for acute asthma, a sample of asthmatic children with a higher severity profile than those obtained from school or home-based surveys when enquiring about current wheeze. All in all, even in the populations where asthma is predominantly non-atopic, atopy is still one of the most important risk factors for those with persistent or severe asthma[299].

Urban or rural residency may also play a role in the differences observed in the proportions of atopy among Latin American asthmatics. Endara et al.[300] analysed the fraction of wheeze attributable to atopy in urban vs rural residency, obtaining similar results both using SPT (23.5% vs 10.1%, respectively) or allergen specific IgE for house dust mite (26.5% vs 10.5%, respectively). Atopy was therefore more strongly associated with current wheeze in urban than rural populations (adjOR: 5.19; 95% CI: 3.37-8.00 vs. adjOR: 1.81; 95% CI: 1.09-2.99)[300].

2.7.7. Asthma management and costs

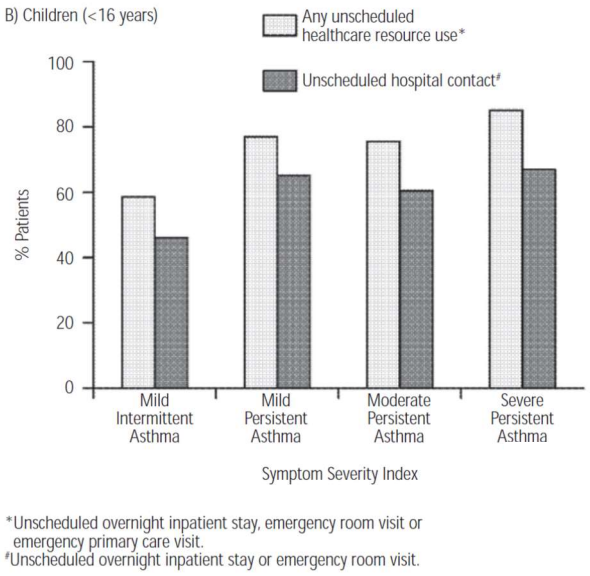
Asthma is inadequately managed in many Latin American centres. Many factors may be responsible for this situation (Table 2.14) and the result is that in numerous Latin American countries, asthma is managed as an acute disease[301].

Table 2.14: Barriers to reduce asthma morbidity and mortality in Latin America

Feature
High asthma prevalence
Lack of specialist doctors
Poor asthma diagnosis and management
Basic asthma drugs not available or affordable
Limited availability of lung function tests
Lack of regular follow-up of asthmatic patients
Insufficient use and poor accessibility to long-term medications for asthma control
Low adherence to long-term medications for asthma control

Data from the AIRLA study[24] revealed that only 38% of the children included in the study had ever had a lung function test, and 49% had a written asthma action plan. In addition, just 6% of the children and adults interviewed were using inhaled corticosteroids, with no increasing trend with increasing severity[24]. In addition, 57.1% of the participants had required an unscheduled health care attendance and 45.1% had visited the ED department for acute asthma during the previous year[10]. These proportions were even higher among children[10] (Figure 2.18). Similarly, we found that only 20% of the children treated at the ED for acute asthma in Esmeraldas, Ecuador were being followed-up regularly for their asthma, none had received inhaled corticosteroids, and 86% had had a previous ED visit for acute asthma during the preceding year[34]. This lack of long-term follow-up and baseline medication is likely playing a vital role in the poor asthma control in Latin America, and it is an issue that affects patients, families and health care providers.

Figure 2.18: Unscheduled health care resource use in children under 16 years old.



Source: Neffen et al., J Investig Allergol Clin Immunol, 2010[10].

The AIRLA study also evaluated the costs associated with the use of unscheduled health care resources in Latin America. According to this study from 10 Latin American countries, 74.6% of annual costs for childhood asthma-related health care was due to unscheduled health care use, ranging from 45.6% in Ecuador to 90.4% in Venezuela[10]. Together with these direct health costs, there are other indirect costs which should also be considered, such as those related to the school and work days lost due to acute asthma exacerbations. This clearly reflects the importance of poor asthma control on the economic burden to families and health systems produced by this disease.

Asthma is an important economic burden for the patients and their families. Stirbulov et al.[302] estimated that the annual direct costs per patient with severe asthma incurred by families varied between USD 764 and USD 929 in Brazil. Another analysis of the economic impact of severe asthma in low-income families in Salvador, Brazil revealed that up to 47% of family members had lost their job due to asthma, and that the costs derived from asthma management consumed 29% of family income[303]. It is easily understandable that low-income families will abandon long-term treatments such as inhaled corticosteroids if forced to choose between basic necessities.

However, there are examples of public health intervention programmes in Latin America for severe asthmatic patients that have proven to be cost-effective in reducing direct and indirect costs for families and public health systems, as well as improving asthmatic patients' and their families' quality of life. This is the case of The Programme for control of asthma and Allergic Rhinitis in Bahia (Brazil) (ProAR), a state-funded project aimed at acquiring control of severe asthma by providing free medication and care for severe asthmatics of low income in the city of Salvador[304]. ProAR reduced the hospital admissions rate for asthma in the city of Salvador by 74% (with an inverse correlation with inhaled corticosteroid

prescriptions), improved the asthma control scores by 50% and the quality of life by 74%[304]. This decreased consequently the costs to the public health system by 387 USD per patient/year and the families by 789 USD per patient/year, thus increasing annual income of families by 18%[304]. The ascertainment of the feasibility and cost-effectiveness of such public health asthma programmes is of extreme importance to design similar interventions in other Latin American countries, supported by the Ministries of Health.

2.8. Ecuador

2.8.1. Geographical Location

Ecuador is situated in South America, surrounded by Peru and Colombia and the Pacific Ocean. It comprises 4 very differentiated areas: coast, Andean, Amazonian and Galapagos Islands. Each has a different climate, culture and population characteristics.

Figure 2.19: Political Map of Ecuador *(Source: Perry-Castañeda Library Map Collection. University of Texas Libraries. 2011*[305]*. http://www.lib.utexas.edu/maps/americas/txu-pclmaps-oclc-785902207-ecuador_pol-2011.jpg)*

2.8.2. Population

In 2010[306], the total population in Ecuador was 14.5 million inhabitants. The distribution according to self-determined ethnicity was as follows: 72% mestizo, 7% Afro-Ecuadorian, 7% indigenous, 6% white and 8% other. The median age was 28.4 years.

2.8.3. Poverty

The proportion of people living under poverty line has decreased from 36.7% in 2008 to 22.9% in 2016 (less than 84.68 USD/month), with 8.7% living under extreme poverty (less than 47.72 USD/month) in 2016[307]. The GINI index, a standard economic measure of income inequality, (0 represents perfect equality and 1 represents total inequality) was 0.466 in Ecuador for the year 2016[307].

2.8.4. Employment

As for the employment rate, 68.9% of the population of working age (11.7 million) were economically active, of which 95.6% were employed (including self-employed) in March 2017[308]. The national unemployment rate in 2017 was 4.4% (5.5% for men and 3.6% for women)[308]. However, only 47.3% of the considered 'employed', have an adequate or full employment, the rest are considered underemployed (20.9%), not fully employed (20.5%) or in an unpaid employment (5.4%)[308]. There is also a very high proportion of informal employment (45.6% in 2017), that is, employed in small unregistered businesses[308]. The mean monthly income for the employed population was 325 USD in 2017 (355 USD for men and 277 USD for women)[308].

2.8.5. Access to clean water and sanitation

Around 70% of Ecuadorians have access to a source of safe water (piped, water well, spring or bottled water), 79% of those living in an urban setting and 51% of those in a rural setting[309]. Up to 86% of people have access to basic sanitation (sewerage, septic tank or latrine) for the household exclusive use, in Ecuador (89% urban, 80% rural)[309]. Finally, 86% of Ecuadorians have access to a hand-washing station (water and soap) inside the household (90% urban, 75% rural)[309].

2.8.6. Health system

Organizational levels

The health system in Ecuador is organised at three different levels.

a. First level:

- Health sub-centre*:* Operational unit that performs basic health promotion, prevention and rehabilitation activities, including emergency delivery care for normal labour and dental care. On certain occasions, it promotes basic environmental sanitation and communal activities. It is formed by a basic team of: doctor, dentist, nurse and auxiliary nurse. It is normally situated in the parish centre.

- Health Centre: Operational unit that offers integrated, comprehensive health promotion, prevention and rehabilitation activities and dental care. It offers auxiliary diagnosis services such as clinical laboratory and imaging studies (optional) and promotes environmental sanitation and communal activities. Some centres have observation beds for normal delivery and rehydration, and

others fulfil health control functions. It is normally situated in the province capital and main town of the municipality.

Health centres are now divided into three categories: A, B and C.

→ A: For a population of 2000 – 10 000 inhabitants.

→ B: For a population of 10 000 – 50 000 inhabitants. It offers auxiliary diagnosis services such as clinical laboratory, basic imaging studies, optional audiometry and pharmacy. Attends referrals and counter-referrals.

→ C: It offers also basic specialties (gynaecology and paediatrics), dental care, psychology, nursing, short stay delivery and emergency care, as well as auxiliary diagnosis services such as clinical laboratory, basic imaging studies, optional audiometry and pharmacy. Attends referrals and counter-referrals. The emergency department of these health centres operates 24 hours a day.

- Basic hospital: Offers outpatient care, emergency care and short stay hospitalization in: general medicines, gynaecology and obstetrics, paediatrics and emergency surgery. It is part of the first level services for patients' referral and counter-referral system and is normally situated in the main town of the municipality.

b. Second level:

- General hospital: Offers outpatient and inpatient care for the main four medical specialties as well as other subspecialties. It resolves the referrals received from less complex units and counter-refers them if necessary. It undertakes training and research. It corresponds to the second level of sanitary

services and is normally situated in the province capital and of the municipalities with a larger population.

c. Third level:

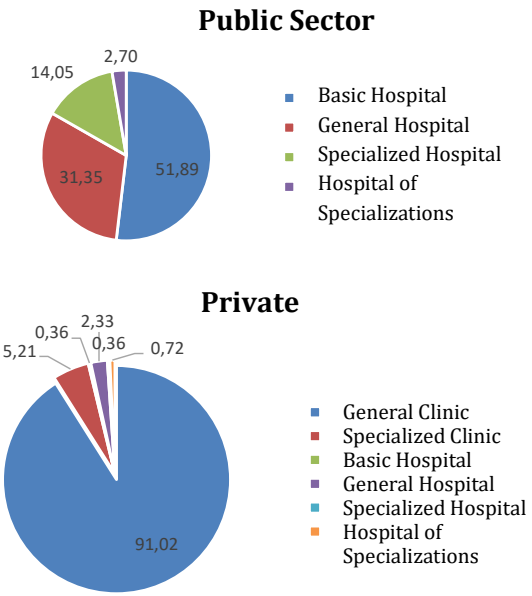
- Specialised hospital: Operational unit that offers specialised outpatient care, reference and inpatient care for a specific specialty or subspecialty, or that serves a specific age group. It serves both local and national population through the referral and counter-referral system and it may act as an acute or chronic care unit. It corresponds to the third level of sanitary services; it undertakes training and research and is normally situated in cities considered highly developed and with the greatest population density.

Distribution

Of the 742 establishments with hospitalization in Ecuador in 2014, 25% belonged to the public system, most of them being basic hospitals (52%)[310]. The vast majority of the private sector establishments were general clinics (91%).

Figure 2.20: Number of Health Establishments with Hospitalization, divided by sector and establishment class. Ecuador, Year 2014.

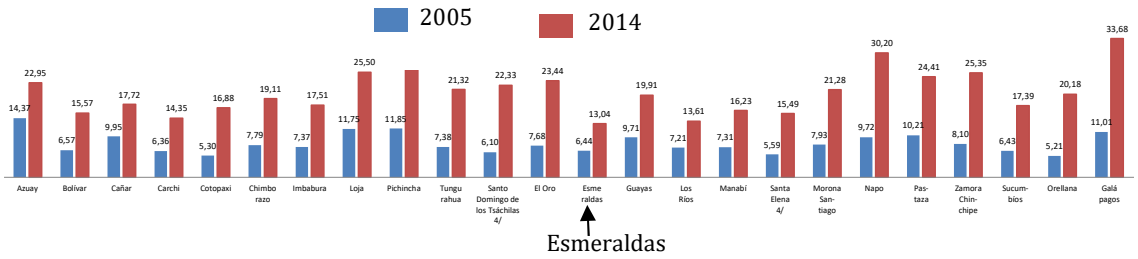
Sector and Class	Number	%
Total	742	100.00
Public Sector	185	24.93
Private Sector	557	75.07
Public Sector	185	100.00
Basic Hospital	96	51.89
General Hospital	58	31.35
Specialized Hospital	26	14.05
Hospital of Specializations	5	2.70
Private Sector	557	100.00
General Clinic	507	91.02
Specialized Clinic	29	5.21
Basic Hospital	2	0.36
General Hospital	13	2.33
Specialized Hospital	2	0.36
Hospital of Specializations	4	0.72



Source: INEC 2014[310]

The distribution of health care professionals throughout the country was unequal in the year 2014[310], as reflected in Figure 2.21. The highest ratio of doctors per 10 000 inhabitants was found in the provinces of Galapagos (33.68) and Napo (30.20), and the lowest in Los Ríos (13.61) and Esmeraldas (13.04)[310].

Figure 2.21: Ratio of doctors per 10 000 inhabitants in Ecuador years 2005 and 2014, divided by provinces.



Source: INEC 2014[310]

Health care access

Health care access in Ecuador is universal, that is, everyone has the right to have access to health care (management and treatment). However, health care is managed and offered by different institutions.

The Ministry of Health manages the public hospitals and health centres, which are available to every person who is not regularly employed (no national insurance or social security contribution) and his/her family.

Parallel to this, there are hospitals that belong to the Ecuadorian Social Security Institute (Instituto Ecuatoriano del Seguro Social, IESS), which are used by all those who are regularly employed or who pay social security/national insurance voluntarily. Together with this, the Police, the Armed Forces and the Navy, have their own hospitals for their employees.

Patients treated at any of these hospitals or health centres mentioned above do not pay any contribution for the consultations, diagnostic procedures or treatment received. The medication available at the public hospitals are those

included in the List of Essential Medicines of Ecuador, based on the WHO recommendations[311].

Private health centres and hospitals are also available to any person who wishes to pay for the services and treatment provided.

2.8.7. Asthma in Ecuador

Asthma prevalence and mortality

There are scarce data regarding asthma prevalence in Ecuador. In the last GINA burden report, 16% of the Ecuadorian population had self-reported current asthma symptoms[29], while 0.8% prevalence of recent wheezing amongst children aged 8-12 years old was found in a rural setting in the ISAAC phase II study[30]. A studies undertaken in rural schools, from the provinces of Pichincha (mountainous area) and Esmeraldas (coastal area), found a prevalence of current wheeze of 2.1% and of lifetime asthma of 10.3%[33] (Table 2.12). On the other hand, children attending rural schools in Afro-Ecuadorian communities in Esmeraldas alone, had a 10.5% prevalence of current wheeze[257].As described in other Latin American countries [31,32], asthma cases in Ecuador may be concentrated in growing and overpopulated cities such as the city of Esmeraldas, while rural populations may have a much lower prevalence[33].

To our knowledge there is no published data on asthma mortality from Ecuador. According to the WHO, in 2012, 4% of total deaths in Ecuador (81 000) were attributable to chronic respiratory conditions.

Asthma management

Asthmatic patients (both adults and children) may be treated at the public hospitals or the IESS hospitals, depending or whether they (or the child's parents) pay social security quotas or not. Second level hospitals may be found in

every province capital, and these may or may not have a respiratory specialist, depending on the demand and the hospital's health priorities. Third level hospitals are only found in the largest cities of Ecuador (Quito and Guayaquil), where there are both adult and paediatric pulmonologists and allergologists available. Therefore, asthmatic patients are mainly treated by general doctors or paediatricians (either at a hospital or primary care). In cases when asthma is not easily managed, then they are referred to specialist in Quito or Guayaquil. Patients may also be treated at private hospitals or with private specialists who visit province capitals once or twice a month.

As for asthma medicines, acute bronchodilators (salbutamol and ipratropium bromide), systemic corticosteroids (oral prednisone, intramuscular or intravenous dexamethasone or hydrocortisone) and inhaled corticosteroids (budesonide) are part of the list of basic medicines from the Ministry of Health[312] and should therefore be available for free at the public hospitals. The IESS hospitals have their own list of available medicines (also for free for the IESS patients) and cover the same asthma medications. Even though these drugs should be available for free, this is not always the case, for different reasons. First, each hospital decides which medications to order from the basic medicines list, based on doctor's demands. In the province of Esmeraldas, for example, inhaled corticosteroids (ICS) were not available at the public hospital, as they had not been demanded by the treating doctors. Second, the bureaucratic procedure to order medicines may delay the arrival of certain drugs. This was also the case with the ICS during the study period. I was invited to be part of the Pharmaceutical Committee at the public hospital of Esmeraldas during the study period, in order to ask for the inclusion of ICS in the hospital's pharmacy. This was approved, but as budesonide (the ICS described in the list of basic medicines) was out of stock in the country, the procedure to order another ICS

(fluticasone), which was not in the list, was very slow and time consuming. As a result, ICS were still not available at the public hospital by the end of the study period). Third, on occasions specific medications run out of stock at the hospital's pharmacy due to an unexpected overuse or to an inadequate stock control or inaccurate estimate.

The public health system in Ecuador has a list of basic medicines that should be available for free at the public hospitals. This list includes acute bronchodilators (salbutamol and ipratropium bromide), systemic corticosteroids (oral prednisone, intramuscular or intravenous dexamethasone or hydrocortisone) and inhaled corticosteroids (budesonide)[312]. However, at the moment there were no inhaled corticosteroids available at the health centres, nor at the public hospital (HDTC), only at the social security hospital (IESS hospital), and there were no combined ICS with long acting beta-agonists or leukotriene receptor antagonists (LTRA) (montelukast) available for free.

Oral salbutamol (both tablets and syrup) were freely available and widely used at the initiation of the study. However, they were no longer included in the 2014 list of basic medicines[312] and were therefore no longer available at public and IESS hospitals in Ecuador. This led to a shift in the prescription of salbutamol during the study period, from oral to inhaled. Nevertheless, oral salbutamol is still available at pharmacies all over the country and is easily bought over-the-counter.

2.8.8. Risk factors for acute asthma in the city of Esmeraldas, Ecuador: a case-control study

In October-December 2012 we undertook a case-control study in the city of Esmeraldas, Ecuador[34]. We aimed to collect some pilot data on the characteristics

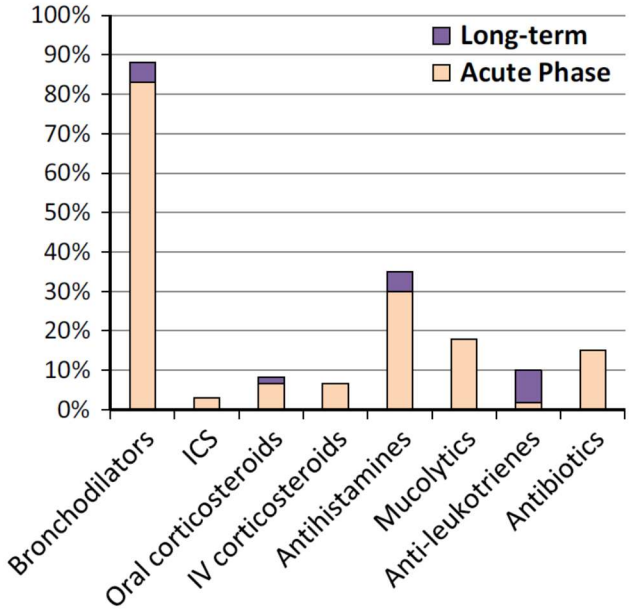
of 5-15 year old children treated at the city's public hospital for an acute episode of bronchodilator-responsive wheeze with difficulty breathing. These were defined as cases, while controls were age- and sex-matched children attending the emergency department for a reason other than asthma.

The children's parents completed a filed-tested questionnaire based on the ISAAC questionnaire. We collected blood (haematocrit, total white cell and differential count, ant total and specific IgE), stool (intestinal parasites detection) and nasopharyngeal swabs (PCR for respiratory viral infections). Lung function (pre and post-bronchodilator spirometry) and inflammation (fraction of exhaled nitric oxide (FeNO)) were also measured.

We recruited 60 cases and 119 controls. The most relevant findings were that 82% of children with an acute asthma attack had a positive allergen specific IgE for any aeroallergen (vs 43% of controls), all of them being positive to house dust mite. The population fraction of asthma attributable to mit IgE was 64%. History of bronchiolitis in early childhood, atopy (any positive sIgE), and higher parental education level were all independent risk factors for acute asthma when compared with non-asthmatic controls. Thirty-six percent of the 59 cases and 8% of the 103 controls with a nasopharyngeal swab sample were positive for rhino virus infection.

As for asthma management, 77% of the 60 cases had been previously diagnosed with asthma by a doctor, 20% had had a regular asthma control appointment during the previous year, and 86% had suffered an acute asthma exacerbation requiring emergency care during this same period. Only 5 children had been taking long-term controller treatment during the previous year, being montelukast (none had taken ICS). On the other hand, 91% had used oral bronchodilators (salbutamol) during asthma exacerbations (Figure 2.22).

Figure 2.22: Treatment received during the previous 12 months by children with acute bronchospasm.



ICS, inhaled corticosteroids; IV, intravenous. *Source: Ardura-Garcia et al, Pediatric Allergy and Immunology, 2015*[34].

To conclude, this study showed that children treated for acute asthma symptoms at an ED in coastal Ecuador were mainly atopic, underdiagnosed and inadequately managed.

2.9 Acute asthma attacks

2.9.1. General definition

An acute asthma attack or acute exacerbation, is an acute or subacute worsening of respiratory symptoms and lung function. They are identified as episodes outside the patient's usual status and daily variations, that require an increase in treatment (mainly anti-inflammatory treatment, as they do not improve on increased bronchodilators alone) and an unscheduled health-care visit. These

events may vary in severity, as well as in speed of onset (from minutes to 2 weeks) and time to resolution (5 days to 2 weeks)[47,313]. Several different terms are also used throughout the literature, for example, 'asthma attack' is usually used to refer to severe asthma exacerbations[8].

Asthma exacerbations are very common[9]. These acute events are especially relevant among children in whom they are extremely frequent, often following a viral respiratory tract infection[11,12].

2.9.2. Severity

Severe asthma exacerbation

The American Thoracic Society (ATS) and European Respiratory Society (ERS) published a joint statement in 2009 on asthma control and exacerbations, where they included the following definitions for severe exacerbations[8]:

"Events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.

The definition of a severe asthma exacerbation for clinical trials should include at least one of the following:

- Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.

- A hospitalization or ER visit because of asthma, requiring systemic corticosteroids."[8]

Moderate asthma exacerbation

This same document also included a definition for moderate exacerbations:

"Events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation.

A moderate asthma exacerbation is an event that, when recognized, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe.

The definition of a moderate asthma exacerbation should include one or more of the following: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, may be classified as moderate exacerbations.

The magnitude of change in these outcomes will differ depending on the population studied and each individual patient's baseline variation."[8]

Mild asthma exacerbations:

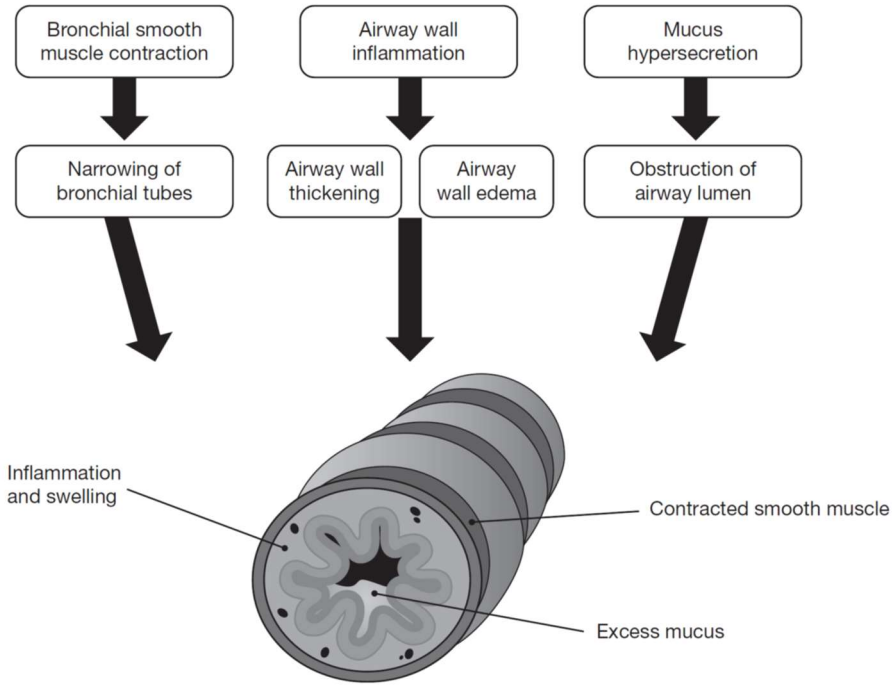
According to the referred ATS/ERS joint statement, there is no clear definition of what a mild asthma exacerbation is, as it is extremely difficult to differentiate from a person's daily asthma symptoms variation, that is, a transient and short-lasting loss of asthma control.

2.9.3. Pathophysiology

The decreased expiratory airflow evidenced during an asthma attack is caused by mucus hypersecretion, airway wall inflammation and bronchial smooth muscle contraction (Figure 2.23). This produces luminal obstruction and airwall oedema, that narrow the luminal space available for adequate airflow[314,315].

These series of events occur as a response to a trigger (see below), though the specific immunologic mechanism underlying this process varies between patients, depending on their asthma phenotype and endotype, as described previously[315].

Figure 2.23: Mechanisms of asthma exacerbations



Source: Graham et al, Curr Med Res Opin, 2015[315]*.*

When analysing peak expiratory flow (PEF) variability, Reddel et al.[316] observed a linear decrease during the duration of the asthma attack (few days) followed by a similar linear improvement. However, PEF variability during these same days was quite low, comparable to that found during stable asthma periods (7.7% vs 5.4%). This contrasted with the great PEF variability observed during poor asthma control periods in these same patients (21%)[316]. Additionally, bronchodilator response was barely inexistent during asthma attacks (1% mean differences improvement of pre vs post-bronchodilator PEF) compared to the mean 28% increase in PEF after bronchodilator use during poor asthma control

periods[316]. These findings suggest a different physiological phenomenon underlying loss of asthma control and asthma attacks[317].

2.9.4. Triggers

A wide range of factors have been described to trigger acute asthma attacks. These include allergens (both indoor and outdoor), smoking, air pollutants (indoor and outdoor), occupational exposures, foods and drinks (additives), exercise, drugs (e.g. non-steroidal anti-inflammatory drugs), viral and bacterial infections, hormones (menstruation and pregnancy) and emotional stress[314].

An asthmatic person may be affected by one or more of these triggers, and associations between them have been also described. This is the case of allergen sensitization and viral respiratory infections. Around 80% of adult and childhood asthma exacerbations may be secondary to viral respiratory infections, with human rhinovirus being the most common virus associated with asthma attacks[318-320]. However, several studies have shown how allergen-sensitized children and adults are more prone to suffering an asthma attack during a viral respiratory infection, especially if caused by human rhinovirus[320,321]. This association is stronger as the allergen-specific IgE titre increases[321]. Similarly, an exposure to high-levels of allergens (such as mite) may increase the risk of asthma attacks[322].

2.9.5. Short and long-term consequences of asthma attacks

The relevance of acute asthma attacks, is not only due to their high frequency, but to the serious short and long-term consequences they may cause.

Clinical consequences

a. Hospitalization and mortality: Severe asthma attacks may lead to hospitalization and even death if not treated promptly and adequately[314]. For example, half a million people were hospitalized for an acute asthma exacerbation in 2004[323] and 3651 died in 2014, in the US[324].

b. Loss of lung function: A decline in lung function may appear secondary to airway remodelling caused by the activation of diverse inflammatory pathways during acute asthma exacerbations, leading to airway narrowing[314]. As part of the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study, a randomized controlled study analysing the effect of early intervention with low-dose inhaled budesonide on severe asthma-related events, which included 7165 patients between 5-66 years old, an association between severe asthma exacerbations and a more rapid decline in lung function was found[16]. In a separate retrospective cohort study of 93 non-smoking asthmatics with moderate-to-severe disease, those who had suffered a severe exacerbation in the previous year had accelerated loss of lung function, with a 30.2ml greater annual decline in FEV1 compared to those who did not experience any exacerbations[325]. This association was independent of airflow obstruction at baseline[325], an important finding that suggests asthmatics with chronic airflow obstruction (reduced FEV_1) have a greater risk of asthma exacerbations, and that this reduced FEV_1 may be caused by specific types of lung inflammation or other factors such as smoking, which would act as effect modifiers by increasing the risk of asthma exacerbations and reducing lung function at the same time[314].

Strunk et al.[14] analysed how children with mild to moderate persistent asthma have a decreased lung growth when compared to healthy children, despite treatment with budesonide or nedocromil. However, to our knowledge there is

still a lack of data concerning the study of the effect of asthma attacks on lung growth and lung function on the long-term, in children.

c. Stress and anxiety: Active asthma (asthma attacks or asthma-like breathing problems in the previous 12 months) was associated with panic disorder and/or panic attacks in a cohort study of 591 young adults[326]. Multiple other studies have shown an increased rate of anxiety and depression in asthmatic patients[327,328]. Additionally, extreme anxiety regarding asthma symptoms may negatively affect the patient's response to an asthma attack[329].

d. Quality of life: Suffering an exacerbation in the previous year reduces quality of life measures[330]. This may be caused by the stress and anxiety mentioned above, as well as by the clinical symptoms and economic burden that asthmatic patients suffer because of acute exacerbations.

Economic consequences

Asthma attacks may incur in both direct (inpatient care, emergency visits, physician visits, nursing services, diagnostic tests and education) and indirect costs (school and work days lost, traveling and waiting time). Even though there is some discrepancy between studies, some publications have shown that indirect costs associated to asthma may be as high or even higher than direct costs[331].

a. Health care costs: According to Rodrigo, Rodrigo and Hall[332], developed countries spend about 1-2% of total health-care expenditure on asthma. A total of $6 billion are spent on asthma each year in the US[333]. Acute asthma exacerbations account for a large proportion of health care costs associated to asthma, due to unscheduled outpatient appointments, emergency care visits or hospitalizations. In the US, patients that have been admitted to emergency care or hospitalization for an acute asthma exacerbation account for more than 80% of total direct costs

for asthma, even if they represent only 20% of the total asthmatic population[332]. Similarly, 73.2% of annual health care asthma-related costs was due to unscheduled health care in a study including 10 Latin American countries, though in this case, 57.1% of the patients required unscheduled health care resource use[10]. These unscheduled health care visit costs may take away resources from other clinical priorities, such as chronic asthma management.

b. Missed school and work days: Data from the US revealed that adult asthma patients spent 1.4 times more days off work annually than non-asthmatic adults and they are also more likely to have activity or work limitations[334]. School and work performance may also be adversely affected by asthma attacks, even if these are not severe enough for them to stop their daily activities[335].

2.9.6. Prevention of acute asthma attacks

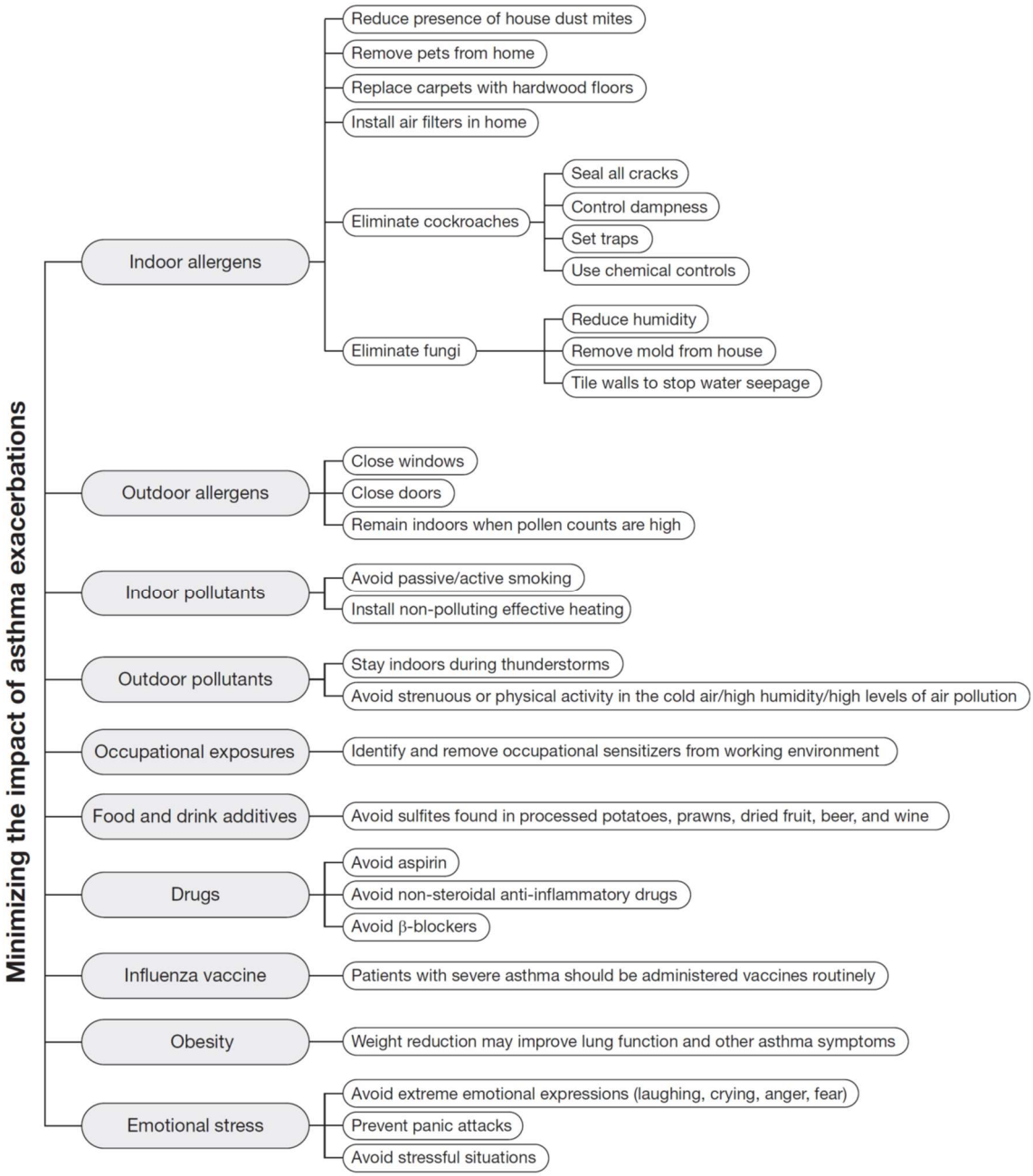
Asthma attacks are generally preventable, either by avoiding previously identified triggers (acute respiratory infections, aeroallergen exposure, etc.) or by appropriate preventive treatment.

Triggers and environmental factors avoidance

Removing triggers and environmental risk factors completely is not always feasible unless severe restrictions are imposed on patients. However, minimizing the exposure should be attempted when possible[315]. Figure 2.24 includes some examples of who to minimize asthma exacerbation risk by avoiding environmental factors and triggers.

Through asthma education, patients should be given advice on how to stop smoking and lose weight when indicated[37,336]. An initial correct diagnosis of asthma and associated co-morbidities (allergic rhinitis and gastroesophageal reflux) is also essential to attain adequate control[37,336].

Figure 2.24: Strategies to reduce exposure to environmental triggers.



Source: Graham et al, Curr Med Res Opin, 2015[315]*.*

Preventive treatment

Although exacerbations may occur despite the use of inhaled corticosteroids (ICS) [15], they have been shown to be the single most effective treatment for reducing asthma exacerbations in adults when taken regularly[337]. ICS reduce the number of overall exacerbations by 40% when compared to other anti-

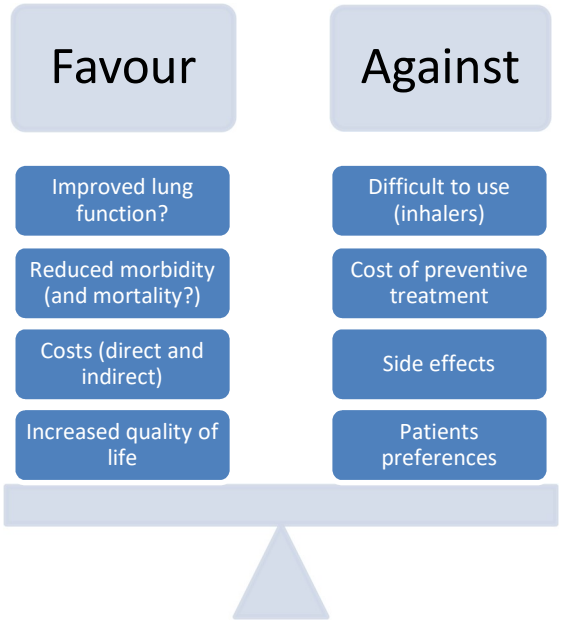
inflammatory treatments such as leukotriene receptor antagonist[7], or by 55% when compared to placebo or short-acting beta2 agonists[337], as well as attenuate the decline in lung function associated with acute exacerbations[16].

Certain add-on medications may decrease the risk of exacerbation even further than ICS alone. Long-acting beta2 agonist (LABA) reduced the rate of exacerbations by 26% when added to ICS, compared to ICS monotherapy[337]. Montelukast (a leukotriene receptor antagonist) can reduce the risk of asthma exacerbations in around one third of the patients when combined to fluticasone (ICS), compared to the combination of fluticasone and salmeterol (LABA)[338]. In addition, omalizumab (humanized monoclonal antibody to IgE) may also reduce asthma exacerbations by 26% when combined with high-dose ICS and LABA, compared to high-dose ICS and LABA alone, in patients with severe allergic asthma, reduced lung function and clinically significant exacerbations[339]. A Cochrane meta-analysis concluded that omalizumab may reduce asthma exacerbations by 45% and hospitalizations by 84%, as an adjunct to ICS in patients with moderate to severe asthma[340]. Omalizumab, however is a very expensive medication that needs to be administered subcutaneously and is only effective in allergic asthma patients.

Nevertheless, when considering the use of a certain medication, side-effects, cost and patient preferences should be all considered to assess the benefit-harm balance. Inhaled corticosteroids have demonstrable systemic effects, especially affecting the hypothalamo-pituitary-adrenal axis. They produce a reduced growth velocity and slight reduction in final adult height (a 1cm decrement)[160] and have been associated with decreased bone mineral density and increased risk of fratures[161], cataracts[162], oropharyngeal candidiasis[163], skin thinning and bruising[164], and a higher risk of pneumonia[341]. These side effects are related to dose and type of ICS (higher risk with fluticasone)[342]. Montelukast has also been

associated with headaches, pharyngitis, abdominal pain, dyspepsia, cough, arthralgia, pulmonary eosinophilia, hypersensitivity reactions, gastrointestinal disturbances, respiratory infections, seizures, raised liver enzymes and neuropsychiatric adverse effects[343-345]. On the other hand, it is important to bear in mind patient's preferences. For instance, an asthmatic patient may prefer suffering an acute asthma attack a year (even if it means going to the ED) than taking daily medication for years. This would inevitably lead to a lack of adherence to preventive medication. Finally, the cost of baseline treatment (used daily) should also be considered, for an effective use of the resources: Is it cost-effective to treat every asthmatic child that suffered an acute asthma attack with a preventive medication? Which of these children should then be treated? All these questions need to be answered before deciding upon initiating an asthmatic child on preventive treatment (Figure 2.25).

Figure 2.25: The balance of benefits and harms that need to be considered before initiating an asthmatic child on preventive treatment.



Education and self-management

There are several other important factors that may affect asthma exacerbation risk and that may be attained through adequate patient information and self-management. Improving inhaler technique and increasing medication adherence are early steps to be taken when asthma control is not optimal[37]. As mentioned previously, providing the patient with a written asthma action plan that he/she may follow to modify their treatment accordingly when suffering an acute worsening of the respiratory symptoms may reduce hospital admissions for acute asthma by 40% and emergency care attendances by 20%[225].

On the other hand, increasing the community's awareness of asthma may reduce asthma mortality as it reduces the risk of patients ignoring their symptoms or not being prepared for them[346]. This is the case of the Stop Asthma Deaths campaign by Asthma UK[346].

2.10. Communicating risk

The relationship between health care providers and patients has been changing over the years in high income countries, shifting from a paternalistic position where the doctor makes all the decisions concerning the patient's health and treatment, to one where the patient is included in the process of discussing and selecting the most appropriate treatment. This later is commonly referred to as a shared decision making (SDM) process in which the patient plays an important and active role, expressing his preferences and opinion after being informed of the evidence available by the health care provider [347]. Evidence-informed patient choice "involves providing people with research-based information about the effectiveness of health care options and promoting their involvement in decisions about their treatment"[348].

For patients to be able to make informed choices, evidence needs to be presented in a way which is easy for them to understand. This should include risk communication, which is the base of the uncertainty that is present in everyday general practice[349]. Different tools have been developed to help patients consider the best choice for them by presenting the information in a structured fashion and using lay language. These tools, or 'decision aids' have been shown to improve patient's understanding and increase their participation, decrease the proportion of hesitant patients, as well as decrease the disagreement and increase the concord between patient and provider[350]. However, decision-aids are not commonly used in clinical practice, particularly in lower income settings.

A study consisting of focus group discussions to address the use of an informative webpage for patients with chronic back pain, showed that patients acknowledged the accessibility of the easy to understand, research-based information, though they did not rely entirely on the source of the information[351]. The credibility depended more on the previous patients' beliefs or attitudes towards research than on the presentation of the information, especially if they considered this information could be biased if derived from the government or a pharmaceutical company[351]. Finally, they expressed a difficulty in applying the research-based information to them, particularly when addressing medical uncertainty, as they found that a population-level statistic was not relevant for them at an individual level[351]. This study reflects the problems encountered when transferring medical evidence to patients, specifically risk and uncertainty in chronic diseases with multiple treatment alternatives, where one choice does not preclude the rest. Even though this setting may seem very different to that affecting asthmatic children in Ecuador, patients' beliefs and attitudes towards research in relation to chronic diseases could show similarities across the globe. In a setting where patients and caregivers are offered less information regarding there disease and

where patients may have a lower health literacy, it may prove even more difficult to transfer medical evidence to patients.

Several studies have explored risk communication for conditions with a high level of concordance between the patient and the provider, such as cancer or genetic conditions [352]. However, there is a relative lack of evidence regarding health behaviours including those involving long-term daily medication to prevent future risks[353]. The RISAP study, aimed to investigate the effect of shared decision making and risk communication tools in a long-term condition such as hypercholesterolemia and future cardiovascular risk[353]. The general practitioners participating in this study, identified two types of medical uncertainty: the epistemological uncertainty (related to the evidence-based medicine) and the situational uncertainty (related to the patient-provider relationship)[353]. They described optimal risk communication tools as those with simple access and handling, easy to understand and obvious colouring, as well as with straight forward explanations of the risk and available options[353].

Asthma is an example of a chronic disease requiring long-term treatments to prevent future risks. There is scarce evidence around risk communication in asthma, and even less concerning provider-caregiver-child communication, given asthma is more prevalent in the paediatric population. Children present a greater challenge, as medical interaction is normally dominated by the provider and the caregiver, and therefore they seldom speak during visits[354]. They have difficulties communicating and reporting their symptoms and questions, even more the greater the asthma severity is[355,356]. Even when provided specific educational interventions to improve communication skills, they still need prompting to disclose symptoms to the provider[357]. This may hamper the patient-provider communication and the shared decision-making process. For example, Gilette et al.[358] described that providers rarely discussed asthma drug risk with children.

Another adversity faced when communicating risk to asthmatic children in our specific setting, is the disparities that have been found in asthma outcomes and care concerning minority populations. The differences in socioeconomic status, educational level, environmental exposures and access to care, only partially explain the greater asthma morbidity observed in certain minority groups, such as African-Americans in the United States[359]. Therefore, another important factor to consider may be the disparate quality of care these minorities receive[359]. The reasons behind this disparity in the quality of care are numerous, including a poor patient-provider communication[359]. Bicksey et al.[360] found in a study of 12 families, that white parents of asthmatic children were more conscious of asthma triggers in their home environment compared to African American parents, while there were no differences by education or income level. Additionally, African-American parents admitted not having received any information concerning asthma triggers by their providers, while white parents had received such information[360]. Thus, health care disparities in the doctor-patient communication are not only due to the differences in health literacy or beliefs on the patient's side, language barriers and lack of self-efficacy, but also to the stereotyping and expectations of health outcomes from the doctor's side, an inadvertent racial bias in decision making and deficient appreciation of ethnic and cultural disease experience[359]. Consequently, minority asthmatic patients receive less information from their providers.

A cross-sectional survey to caregivers of asthmatic children in Mexico[361] revealed how they frequently change of health care providers (5 or more doctors seen in 72% of the children included in the study), due mainly to a lack of improvement, high costs and long delays. This frequent relay of health care provider may well be a consequence as well as a cause of a deficient patient-provider relationship.

More than half of the families surveyed were little or not satisfied with the care their asthmatic children were receiving[361].

There is no published data of communicating asthma risk to children in Ecuador, though many of the raised points could be easily applied. However, in Ecuador, doctor-patient communication has not yet evolved into a shared decision making relationship, but rather it is the doctor who tells the patient what to do and information offered is scarce. The disparities that have been described in asthma care in minority populations may well be experienced in Ecuador as a whole, and even more in areas of lower income and with a predominance of ethnic minorities (Afro-Ecuadorian or Indigenous).

All in all, it is vital to explore the best way to inform asthmatic children and their carers of their future risk of suffering acute asthma exacerbations, as only through this knowledge will they understand the importance of having an adequate follow-up and adhering to baseline long-term treatment when indicated. To the best of our knowledge there is no published study analysing the communication of future risk of acute asthma exacerbations to children, nor in a setting with low health-care literacy. Together with this, it is also crucial to understand the barriers to health care access and treatment, as the final aim of an adequate asthma management is to minimise future risk in every patient, either through lifestyle modifications, appropriate self-management of exacerbations or long-term medications if needed. Mixed-methods, that is, combining quantitative with qualitative data is the only way we may obtain a complete picture of a highly complex aim, such as an improving the management of asthmatic children with frequent acute asthma attacks, reducing their future risk (both of asthma attacks and side-effects of medications), and decreasing asthma health-care costs.

2.11 Qualitative data on acute asthma attacks significance and barriers and facilitators to health care access

2.11.1. Asthma acute attacks significance

Initiatives to improve asthma control highlight the need for: qualitative data to better understand and address asthma; the creation of associations between patients and providers (such as asthma clubs); improving their participation through the recognition of perceived barriers and facilitators; increasing their self-efficacy asthma care skills[362]. Understanding how asthma is perceived by caregivers and health care workers, how they deal with asthma and its recurrence, and exploring their needs and expectations is a challenge for health researchers both in high and low-income countries.

In general terms, for Latin-American populations residing in the United States, paediatric asthma is perceived as a burden, not only for the child, but for the caregivers and family. Latino caregivers of asthmatic children in Connecticut, US, reported being concerned about asthma, especially about asthma attacks, which they perceived as inevitable[363]. They felt powerless and were afraid of not being well prepared in case their child suffered an acute asthma attack, because of their lack of knowledge [363]. They discussed feeling vulnerable, deflated and confused, mainly because of limited English which made them struggle with communication and understanding[363].

Chen et al.[364] described how persistent asthma in children caused a negative impact on the health and daily life of caregivers in Taiwan, as it brought along feelings of chaos and instability, such as worry, fear, frustration, helplessness and physical distress. Likewise, Mansour et al.[365] undertook a qualitative study in Cincinnati, US, with low-income caregivers of asthmatic children who voiced

concerns about the constraints that their child's asthma made on them, and how their quality of life was affected.

A study from Detroit, US, described how caregivers often forget about their own health and chronic diseases[366], and in order to fight these stressors, caregivers of asthmatic children need to develop different coping strategies such as meditation, prayer, time management or self-awareness of emotional reactions[366].

Caregivers perceive asthma as unpredictable and causing fear[365,366]. Even though some caregivers talked about being afraid of the next exacerbation and felt overwhelmed, others experienced denial, anger and rejection, or even resignation[364,367].

Together with these, caregivers discussed how the burden of the child's asthma care also caused a disorientation of daily activities and economic constraints. This could also lead to family disagreements or mistrust on certain family members who take care of their asthmatic children[364,366,368]. On the other hand, social support is also discussed as something important that relieves caregivers from the burden of taking care of their child's asthma, though the degree of social support they may count on is highly variable[365,366].

There is scarce data on caregivers' perception of their children's asthma from Latin America, though these may not vary significantly from other settings. A Mexican cross-sectional study including 300 caregivers of asthmatic children (different degree of severity) reported that 77% of the caregivers agreed that their child's asthma affected their family life in a variety of ways (emotional, functional, social and labour wise)[369]. Similarly, a Colombian analysed family functionality (capacity to confront stressful situations and perform basic tasks such as communication or problem-solving) among caregivers of asthmatic

children aged 7-12 years[370]. Family dysfunctionality was more frequently observed among families of children with uncontrolled asthma when compared to those with controlled asthma[370].

As was the case in non-Latin American qualitative studies previously described, Colombian caregivers of asthmatic children perceive asthma attacks as potentially fatal episodes that could mean the death of their child[371]. They also reported how asthma affects the quality of life of their children, by limiting their daily activities[371]. Similarly, In Peru, mothers of children hospitalized for asthma described feeling confused, uncertain, nervous, desperate, angry and scared at the possibility of their child dying[372]. These mothers reported feeling guilty, as they are responsible for taking care of the child[372]. During these moments of uncertainty, mothers relied on their faith in God and that gave them strength to bear such a stressful event[372]. Finally, as described above, caregivers of asthmatic children in Brazil also highlighted the importance of social support (family, friends) to share the burden of the care[373]. Taking care of asthmatic children may cause social isolation and lack of self-care for the caregivers, given the excessive time they need to dedicate to their sick child[373].

There are also some published papers of the children's perception of asthma and experiences. Several Brazilian qualitative studies undertaken with children with asthma, showed how asthmatic children are also worried about missing school days and decreased opportunity to learn, due to their asthma attacks, even more than their parents are[374,375]. As described previously, missed school days and work-days for caregivers are an important consequence of asthma attacks. Other effects on their daily life that children mentioned in these studies were daily activity and play restrictions, and conflicting interactions with other children[374,375]. The level of activity limitations depended on the asthma severity, from living a normal life between asthma attacks, to having their daily activities

and routines greatly affected most of the time[375]. These limitations and make them feel sad, and isolated. The fear of transmitting asthma to their peers and of showing their limitations in front of others increased even further this isolation[375]. They also reported night-time symptoms as those more trouble or worrisome for them[375].

Several qualitative studies have been undertaken among asthmatic adolescents, though mainly in non Latin-American countries[376]. Adolescents, as did children, described having activity limitations, feeling different from their peers, the importance of social support (family, teachers, friends, etc.) for an adequate self-management and the difficulties faced to access/use treatment during school time[376]. Social stigma for use of inhalers in public is a concern associated to asthma that has also been reported by adolescents[377].

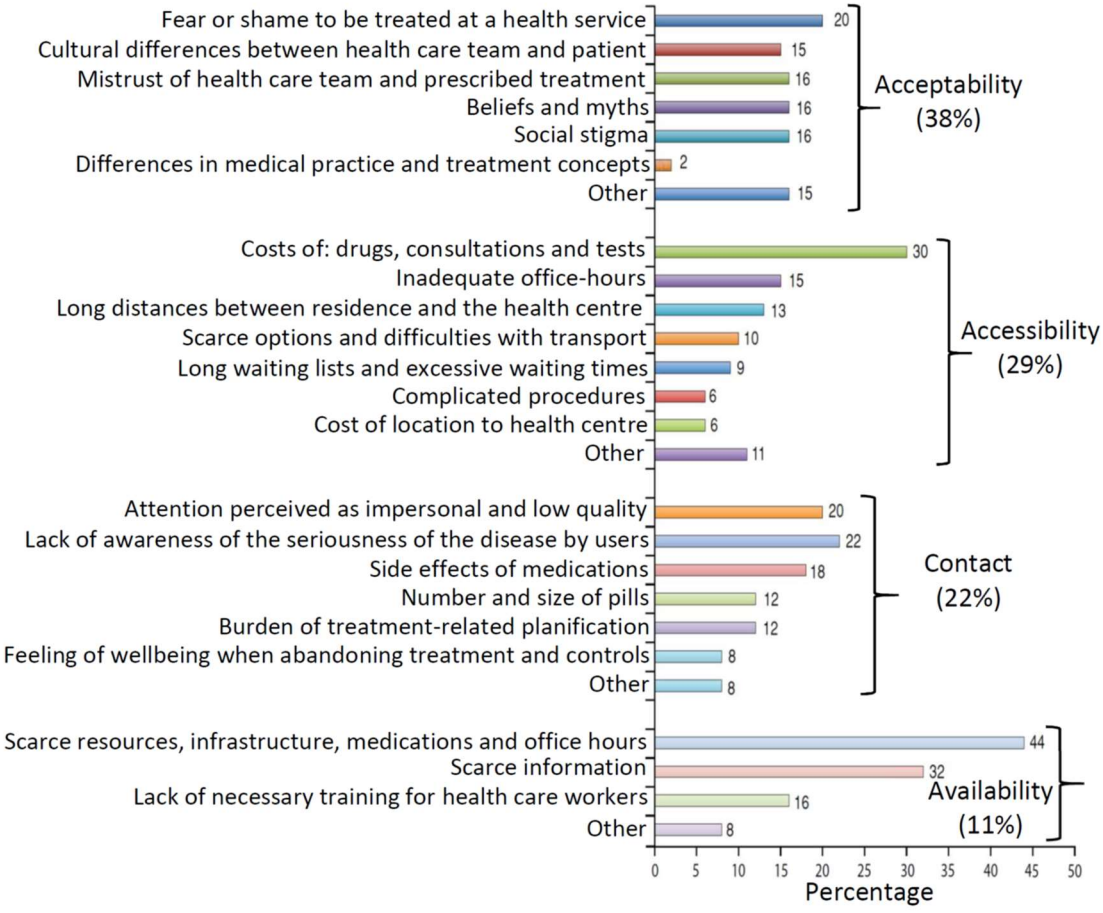
These qualitative studies explored the caregivers' or asthmatic children's understanding of the disease process of paediatric asthma, though they did not specifically study the significance of children's acute asthma attacks for them. There is even less published information on the significance of paediatric acute asthma from the health care workers point of view.

2.11.2. Barriers for Health and Home Care Access

Multiple qualitative studies have described the perceived barriers to health care access for different diseases. Hirmas et al[378] published a qualitative systematic review of barriers and facilitators to health care access, including 19 studies undertaken in people who had contacted health care systems (mainly) and health care workers, between 2000-2010. The 230 barriers found were classified according to Tanahashi's model[379] into 4 categories: acceptability (87), accessibility (67), contact (51) and availability (25)[378] (Figure 2.26). This classification proved to be very useful, as there was great heterogeneity in the

barriers identified and the classification systems used. Figure 2.26 shows the main barriers identified, organised into subcategories with the percentage number for each subcategories and category. Only 4 of the included studies identified barriers perceived by health care workers, which corresponded mainly to availability and contact categories[378]. Even though this systematic review included studies analysing barriers to general health care access, they could well be applied to asthma health care. These studies were carried out mainly in the US and Canada, though it included also 5 studies from Latin American countries, and one from Zambia.

Figure 2.26: Barriers to health care access



The percentages illustrated by the bars and the numbers along them represent the proportion of the number of barriers identified for that subcategory (e.g. social stigma) in relation to the number of barriers in that category (e.g. acceptability). The percentage in brackets along each category represents the proportion of the number of barriers identified in that category in relation to the total number of barriers.

Source: Modified from Hirmas et al., Rev Panam Salud Publica, 2013[378].

Acceptability

For the acceptability domain, that includes social, cultural, or religious factors, beliefs, cultural norms and values that may influence the health services perception and its use, German caregivers of asthmatic children expressed mistrust in generic prescribed asthma drugs[367]. Similarly, caregivers of children discharged from the emergency department (ED) following an acute asthma attack in the US, reported feeling concerned about the health care worker's judgement[380].

Health beliefs led caregivers to modify the asthma management prescribed in the US[365], as they prefer non-medical alternatives to drugs[368]. They also mistrusted the physician's interests (more worried about costs than the patient)[365] or feared hospitals[366]. Another acceptability barrier, described by caregivers, is a cultural difference with health care workers in that they do not treat their asthmatic child in the 'holistic' manner, they preferred[365,367].

Belief in natural or ancestral remedies, or alternative medicines, is frequently described in Latin American populations. Caregivers of asthmatic children from Colombia described having used natural remedies to treat their child's asthma[381]. They follow their family's advice to choose the adequate natural remedy[381]. Some caregivers reported preferring natural remedies[371], a belief that may be influenced by the cosmovision of the indigenous peoples and their traditional knowledge of natural resources. However, they are frequently taken as a complement of traditional medicines[381].

In addition, caregivers from Peru and Colombia reported several myths concerning inhaled drugs for asthma, such as that they damage the heart and lungs, cause dependency and behavioural problems, affect growth, the nervous

and osteomuscular system, cause overweight and obesity, affect the child's intellectual abilities and cause asthma[371,382].

Accessibility

Accessibility barriers include physical and geographic location of the health service in relation to the population served, as well as administrative requirements. Cost of drugs and the inconvenience of their use (inhalers), waiting times and waiting lists, difficulties obtaining time off-work, as well as transportation issues have also been mentioned by caregivers of asthmatic children as accessibility barriers to asthma health care[365-368,383]. These barriers were also reported in Latin-American studies[361,372].

On the other hand, the cost of making lifestyle adjustments such as replacing a carpet or buying an air conditioner were also barriers for an adequate asthma care at home[365]. These adjustments, or similar ones adapted to the different climates would be even more inaccessible for deprived families, especially when living in low-resource settings.

In a qualitative study of focus group discussions with general practitioners, the cost of the drugs and the patient's access to drugs and medical care was also reported as a barrier to adherence to medication[384].

Contact

Characteristics and quality of the health care service and treatment continuity, including doctor-patient relationship are classified as contact barriers. One of the contact barriers to asthma health care that is frequently described in qualitative studies with caregivers is the mistrust in medications, due to either their side-effects, or the fear of developing dependency, addiction or tolerance[364,365,367,368,383]. These beliefs have also been mentioned in the

acceptability section, and it affects not only inhaled corticosteroids, but salbutamol inhalers too[371,382].

In a qualitative study that included both adult asthmatic patients and caregivers of asthmatic children, participants reported not taking their medication as they believed their disease was not serious and that they should only be taken in response to symptoms[368]. Colombian caregivers also reported interrupting their child's asthma inhalers once the symptoms had improved[371].

Dissatisfaction with communication with health care workers is also commonly brought up. Caregivers feel misunderstood, ignored and helpless and report that health care workers act in a judgemental or discriminating manner and distrust caregivers, and that there is no real shared decision-making process nor patient-centred approach[365-368]. Language barrier is an important component of a deficient patient-physician communication, as was described by some caregivers[363,368] who also reported the use of medical terminology which they could not fully understand[380]. General low quality or inadequate care and burden of care for the caregiver associated with the management of the asthmatic child, were also reported[364,367].

Availability

Lack of available health care services and programmes for the population served are defined as availability barriers. Some availability barriers such as scarce office hours and protected time with the health care provider, or limited health care resources were also reported by caregivers[361,367,368,380]. Likewise, general practitioners (GPs) in the UK also stated that they needed more time to spend with the patient, but that they were often time-pressured[384]. Additionally, they reported a lack of access to spirometry to offer a correct diagnosis[384]. There is a

lack of comparable studies undertaken in health care providers in Latin America with which to compare these findings.

Caregivers in different studies discussed the lack of information that they received from health care workers on asthma medications, home care and recommended physical activity, leading to a lack of knowledge concerning their child's asthma management[365,367,368,380]. They also reported discordant or contradictory indications from different health care workers [367,368,371,380].

Besides, GPs in the UK also thought that they needed a continuing medical education, though they lacked time and access to it [384]. The cost and time needed to provide patient education on asthma was again reported as a barrier by GPs[384].

The written asthma action plan, which is recommended to be offered to every asthmatic patient in asthma management guidelines, was not valued by either patients or health care workers, who reported several barriers to its implementation such as lack of time to provide and explain, not being available, not having storage space for them, the need to update them regularly and the existence of different formats [385].

2.11.3. Facilitators for health and home care access

The qualitative systematic review also identified 35 facilitators to health care access, though they did not follow the same classification[378]. Some of these were: social support, value assigned to health care to reduce risks and complications, adaptation of health care services to the patient's needs and management programmes, patient-physician communication and quality of their relationship, diagnosis acceptance, available reminder systems for treatment adherence, and trust in medication prescribed[378]. Some of the previously mentioned qualitative

studies also described facilitators reported by caregivers, which we will classify into the same 4 categories.

Acceptability

Colombian caregivers of asthmatic children also appreciated and believed in traditional medicine, even if taking natural remedies as a complement[371].

Accessibility

As for the accessibility category, caregivers reported that the existence of a public health system or drug plan that enabled them buy cheaper or free medicines, was a facilitator for adherence to long-term treatment[368]. The existence of new, more efficient drugs was also discussed by caregivers as a facilitator to increase adherence to their child's asthma medication[368]. Finally, caregivers expressed feeling reassured when they had access to health care professionals and prescription renewal[368].

A Brazilian qualitative study evaluated the effect of a specific asthma programme (National Plan for Asthma Control) from the caregivers' perspective[386]. This programme included, among other measure, access to free drugs to treat mild and moderate asthma. Caregivers expressed relieve at receiving free treatment for their asthmatic child, as they did not count with the necessary money to pay for it always[386]. They reported how their children's asthma had improved after being enrolled in the programme and how they were now less worried[386].

Contact

In the contact category, some caregivers reported using the asthma medication prescribed for their children (both acute medications and preventive long-term treatment), understanding asthma as a chronic condition, finding asthma medications easy to use, perceiving their child's asthma as well-managed and

feeling satisfied with the medication which they perceived had beneficial effects[367,368].

They discussed how being proactive (to obtain information on asthma management) and establishing routines for taking the medication helped adhere to long-term baseline treatment[368]. Likewise, some caregivers were fond of Peak Expiratory Flow (PEF) measurements and used them for own estimation and reassurance[367]. They also reported finding rehabilitation positive and helpful[367].

Another contact facilitator caregivers brought up was having a good relationship with the health care worker, trusting him/her, being followed-up by the same professional in a structured way and receiving a patient-centred approach in which the caregiver and health care worker agreed together on the management plan and treatment[367,368]. Trusting the health care worker is also part of the acceptability category, for which we found no other published facilitators.

Mothers of children admitted to hospital for acute asthma in Peru, reported having a good relationship with the healthcare workers, for whom they felt grateful[372]. They highlighted the nurses' role, who did not only take care of the medical aspect of the treatment, but also treated affectively[372].

Availability

As for the availability category, caregivers in different studies expressed the desire to improve their asthma knowledge and receive further asthma education[363,380], though they differed on the preferred way to receive this information: video[363], verbal teaching and communication[380] or oral information direct from the treating doctor[367].

Sufficient explanation about asthma and its management, good inter-professional communication and adapting the information provided to the patient, improved

reported adherence to the health care worker's indications[368]. Some caregivers reported feeling comfortable with their asthma knowledge and how they manage their child's asthma and his/her medications[365,368]. They also discussed how they found the written asthma action plans useful, motivational, and reassuring as well as helpful to mitigate the language barrier[363,365,368]. Likewise, they reported how self-management could be useful in anticipation of triggers[368].

Social support and agreement between the asthmatic child caregivers was seen as an availability facilitator to health and home asthma care access by caregivers[366,368]. Some caregivers reported that the availability of a written asthma action plan could act as a motivational instrument for other family members to use[363]. Others discussed how receiving a clear and precise diagnosis, together with a formal assessment of their child's asthma severity could also act as an availability facilitator[368].

Other

Another facilitator caregivers brought up, which is difficult to classify in any of the 4 categories, was the use of coping strategies to reduce the stress produced by taking care of their asthmatic child[366]. These coping strategies included prayer, laughter, meditation, time management, social support and conscious self-awareness of emotional reactions[366]. Religious faith was mentioned in some Latin American studies, as a mechanism that enabled them to cope with stressful situations[371,386].

Possible facilitators or opportunities described by general practitioners were: improving patient education and self-management, including the use of written asthma action plans; establishing continuing medical education , especially for the use of new drugs, managing severe asthma, diagnosis, use of spirometry and stages and complications of treatment; prioritising patient's access to asthma

medications and medical care; reviewing patients regularly; offering the patient an accurate diagnosis; increasing the available time per patient; improving care at the community level by increasing public awareness[384].

3. Predictors of risk of re-attendance to emergency care and hospital readmission due to asthma attacks in children: a systematic review and meta-analysis.

3.1. Introduction

Asthma attacks are common [9] and are associated with high healthcare costs [10] as well as missed school and workdays. They cause anxiety [13] and carry a risk of death and long-term effects such as loss of lung function[11,14]. These acute events are especially relevant for children among whom there is the greatest potential for reduction in disability. Attacks often follow a viral respiratory tract infection[11,12] but secondary care attendance is generally preventable. Attacks may occur despite the use of inhaled corticosteroids [7,15], though it is neither affordable nor safe to provide all children with more aggressive treatment, particularly in low-middle income countries. It is therefore important to be able to identify patients at greatest risk of further attacks and hospital admission to better prioritize limited resources and provide additional education and support or adjustments to treatment where most needed.

Currently, it is not possible to predict which children amongst those treated for an acute asthma attack, are at a greater risk of suffering repeated attacks. The development of a tool to enable clinicians to identify such children could be useful to optimise treatment strategies and address modifiable risk factors. This is especially relevant when treating patients with discordant manifestations of asthma such as few daily symptoms but evidence of active eosinophilic inflammation in the airways and therefore a high risk of exacerbations, and vice

versa[23], and when healthcare resources are stretched. Individualising therapy has the potential to reduce the patient's risk of adverse outcomes from their disease and from medications.

Several factors have been associated with a higher risk of attack amongst asthmatic children[387] such as past attacks and low FEV1. However, findings from large database or cohort studies do not necessarily reflect the population seen in the emergency department (ED) or hospital ward. They therefore may not be informative for the common clinical scenario of reviewing a child in the ED or ward and deciding who needs changes in treatment or specialist referral.

3.2 Study objectives

3.2.1. Research question

What are the risk factors for repeated asthma exacerbations that require emergency care re-attendance or hospital readmission among children?

3.2.2. Objectives

1. To describe and critically appraise study designs and methods that have been used to analyse factors associated with subsequent asthma exacerbations that require emergency care amongst children.

2. To identify factors related to a future risk of re-attendance to emergency care due to asthma exacerbations.

3. To quantify the influence of factors associated with a future risk of re-attendance to an emergency room due to asthma exacerbations.

3.3. Methods

3.3.1. Data sources and search strategy

We conducted systematic searches of bibliographic databases as described in the Annex A. All databases were searched with no date or language of publication restriction. Searches were carried out by a Cochrane Information Specialist up to 9th January 2017. Duplicate references were removed using reference management software (EndNote X7). The reference list of each selected publication was hand-searched for relevant studies.

3.3.2 Study selection

Studies with the following criteria were included: (1) prospective observational design (cohort and case-cohort) analysing factors related to asthma clinical history, previous treatment, lung function, biomarkers or readily measured environmental exposures; or controlled trials that involve a lifestyle or social (not educational or pharmaceutical) interventions; (2) asthmatic children aged between 5 to 15 years old recruited from the ED or ward, treated for an acute asthma exacerbation, included as participants; (3) emergency re-attendance or hospital readmission due to an asthma attack listed as outcomes.

The list of abstract and titles was reviewed to exclude publications that were clearly not contributory on this basis and duplicate titles. Full text articles of selected papers were obtained via University library and inter-library loan and reviewed for eligibility, excluding those not fulfilling inclusion criteria.

3.3.3. Data extraction

Data were extracted by three independent authors using a standard data extraction form. Possible disagreements were resolved by discussion. RevMan 5

and Endnote X7 software were used to assist in the collection and management of data from abstracts and papers.

3.3.4. Quality and risk of bias assessment

Studies' accuracy and risk of bias was assessed using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions. Observational studies' quality was also assessed using the Newcastle-Ottawa Quality Assessment Scale[388], with a score of 7 or more defined as of high methodological quality.

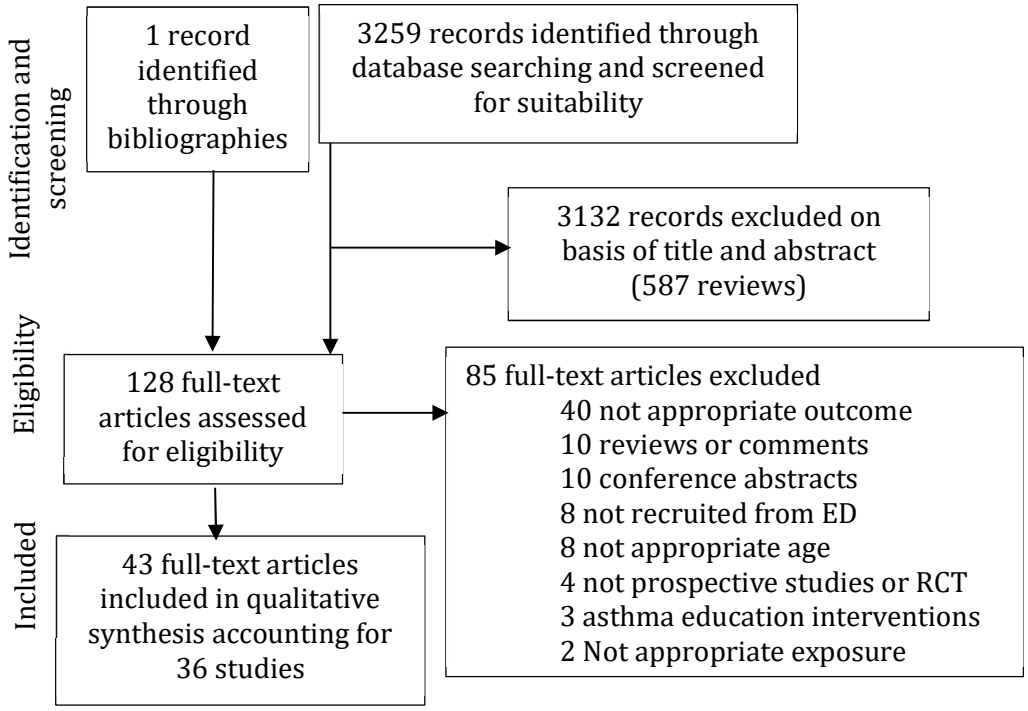
3.3.5. Analysis

Data from comparable studies were combined in quantitative analyses. We pooled data using a random effect model in RevMan5, creating pooled estimates of effects for Hazard and Odds Ratios separately. Reports that presented the results using mean values, with no other data, were not included in the meta-analyses. We used the generic inverse variance as the analysis method for some of the pooled estimate of effects, as some studies only reported Odds or Hazard Ratios. We assessed the degree of statistical variation in study outcomes using the I^2 statistic[389].

3.4. Results

A total of 3259 records were identified and screened for eligibility with one additional paper obtained through reference list screening (Figure 3.1). Forty-three papers fulfilled our inclusion criteria after full-text screening, accounting for 36 studies.

Figure 3.1: Flow diagram of included and excluded studies



3.4.1. Studies' characteristics and definitions (Table 3.1)

Design, participants and setting:

Twenty-three studies were retrospective analyses of health-care databases. There were 5 prospective cohorts, 3 randomised-controlled trials (RCT), and 4 with other prospective designs. Most studies were carried out in North America (21 in USA and 3 in Canada). Participants were recruited among inpatients admitted for acute asthma in most of the studies (27).

Outcome

The study outcome was ED re-attendance in 4 reports, ED or hospital readmission in 6, hospital readmission alone in 21 studies and a further 5 studies analysed data for both outcomes separately.

Table 3.1: Studies' Characteristics

Study Design	Study	Location	Sample selection and setting	Age (years)	Sample size	Years	Recruit-ment	Outcomes measured
RCT	**Gorelick 2006**[390]	US (Milwauke)	Simple random allocation. Hospital based. Intervention: improve linkage of patients back to primary care. FU: 6 months. LTFU: 22%	2-18	352	2003-2004	ED	ED within 6 months
	Kercsmar 2006[391]	US (Ohio)	Stratified random permuted block scheme. Hospital, primary care and other community sources. Intervention: home remediation of moisture sources. FU: 12 m. LTFU: 10% intervention, 24% control	2-17	62	ND	≥2 ED or hosp. admis. last year	ED or hospital admission
	Madge 1997[392]	UK (Glasgow)	Simple random allocation. Hospital based. Intervention: educational and training programme. FU: 2-14 months. LTFU: 0%	2-14	201	1994-1995	Inpatient	ED and hospital admission
Cohort	**Bloomberg 2003**[393]	US (St Louis)	Review of hospital database All eligible. Hospital-based study. FU: up to 1 year. LTFU: 0%	0-20	8761	1999	Inpatient	Single vs multiple admissions
	Brittan 2017[394]	US (Colorado)	Review of health database. All eligible. Hospital-based. FU: 15-90 days LTFU: 0%	2-18	9288	2009-2011	Inpatient	Hospital admission
	Camargo 2007[395]	US (Florida)	Medicaid claims review. All eligible. Hospital-based. Follow-up: 12 months	0-8	10 976	1999-2001	ED/Inpatient	ED or hospital admission
	Chabra 1998[396]	US (California)	Hospital discharge data review. All eligible. Non-federal acute care hospitals. Only Medicaid patients.	1-12	4947	1994	Inpatient	Single vs multiple hospital admission
	Chen E. 2003[397]	US (St Louis)	Prospective. All eligible. Hospital-based study. FU: 1 year. LTFU: 0%	4-18	115	1999	Inpatient	Hospital admission
	Chen Y. 2003[398]	Canada (Ottawa)	Review of national hospital discharge data All eligible. Hospital-based study. FU: 1m – 3 years. LTFU: 0%	0-20	60 641/ 86 863*	1994-1997	Inpatient	Hospital admission
	Cincinnati I [399-402]	US (Cincinnati)	Prospective. All eligible. Hospital-based study. FU 12-14 months. LTFU: 0%	1-16	601	2008-2009	Inpatient	ED or hospital admission
	GCARS[403-407]	US (Cincinnati)	Prospective. All eligible. Hospital-based study. FU 12 months. LTFU: 0%	1-16	774	2010-2011	Inpatient	Hospital admission
	Giarola 2014[408]	Australia (Darwin)	Review of electronic hospital database. All eligible. Hospital-based study. FU 12 months. LTFU: 0%	≤ 15	200	2005 + 2010	Inpatient	Hospital admission
	Gurkan 2000 [409]	Turkey	Review of hospital admissions. All eligible. Hospital-based study. FU: 13-48 months. LTFU: 0%	3-15	140	1995-1997	Inpatient	Hospital admission
	Kenyon 2014[410]	US	Review of health database. All eligible. Hospital-based study. FU: 12 months. LTFU: 0%	≥ 2	36 601	2008-2010	Inpatient	Hospital admission
	Kenyon 2015[411]	US	Review of health database. All eligible. Hospital-based study. FU: 3 months. LTFU: 0%	2-18	31 658	2006-2007	Inpatient	Hospital admission
	Kocevar 2005[412]	Norway	Review of national inpatient database. All eligible. Hospital-based study. FU: up to 2 years. LTFU: 0%	0-14	2961	1998-1999	Inpatient	Hospital admission
	Lasmar 2006[413]	Brazil (Belo Horizonte)	Review of hospital admissions. All eligible. Hospital-based study. FU: Maximum 24 months. LTFU: 0%	<15	202	1994-1995	Inpatient	Hospital admission
	Li 2012[414]	Canada (Ontario)	Multiple linked health administrative datasets review. All eligible. Hospital based. Follow-up: 12 months. LTFU: 0%	2-17	29391	2006-2009	ED	ED and hospital admission

	Liu 2009[415]	US (Rhode Island)	Review of hospital admissions. All eligible. Hospital-based study. FU: 5 years. LTFU: 0%	0-18	2913	2001-2005	Inpatient	Hospital admission
	Minkovitz 1999[416]	US ()	Review of hospital admissions. All eligible. Hospital-based study. FU: 12 months. LTFU: 0%	0-14	119	1994-1995	Inpatient	Hospital admission
	Mitchell 1994[417]	New Zealand (Auckland)	Review of hospital admissions. All eligible. Hospital-based study. FU: Maximum 33 months. LTFU: 0%	0-14	1034	1986-1987	Inpatient	Hospital admission
	Morse 2011[418]	US	Multicentre review of databases. Simple random. Hospital based. Follow-up: 3 months-3 years. RR: 60% of all freestanding children's hospitals.	2-17	37267	2008-2010	Inpatient	ED attendance at 30 and 90 days
	Rodriguez-Martinez 2014[419]	Colombia	Prospective. Convenience sample. Hospital-based study. FU: 12 months. LTFU: 0%	1-18	101	?	Inpatient	Hospital admission
	Rasmussen 2002[420]	New Zealand	Prospective. All eligible. Included only those admitted to hospital for asthma. Hospital-based study. FU: 26 years. LTFU: 18 died (from total cohort)	0	62 (766 wheeze)	Born 1972-3	Birth cohort	Single vs multiple hospital admission
	Rushw. 1995[421]	Australia (New South Wales)	Review of Inpatient Statistics Collection. All eligible. Hospital-based study. FU: Maximum 6 months. LTFU: 0%	1-14 (1-44)	(15682)	1989-1990	Inpatient	Hospital admission
	Smiley 2016[422]	US	Review of Department of Defence Military Health System database. All eligible. Hospital based. FU: 12 months LTFU: 0% (15% incomplete data)	2-17	10460	2010-2013	ED	ED
	Sporik 1993[423]	UK	Prospective. All eligible. Hospital based. FU: 6 months. LTFU: 11%	1-15	82	1988-1989	Inpatient	Hospital admission within 6 months
	Taylor 1999[424]	Canada (Nova Scotia)	Review of ED billing and admission databases. All eligible. Hospital based. FU: 6 months. LTFU: 0%	<18	16994	1997	ED	ED and hospital admission
	Tolomeo 2009[425]	US (New England)	Review of medical records. Convenience sample. Hospital based. FU: 12 months. LTFU: 0%	2-15	298	2006	Inpatient	ED and hospital admission
	Wallace 2004[426]	US (New Jersey)	Review of hospital admissions. All eligible. Hospital-based study. FU: 180 days. LTFU: 9 % (incomplete data)	1-14	21 016	1994-2000	Inpatient	Hospital admission
	Wu 2016[427]	US	Retrospective cohort study of participants in RCT. Hospital-based. All eligible. FU: 12 months. LTFU: 0%	1-17	108	?	ED	ED and hospital admission
	Zipkin 2016[428]	US (Los Angeles)	Retrospective cohort study. Hospital-based. All eligible. FU: 12 months. LTFU: 0%	2-17	1176	2006-2013	Inpatient	ED or hospital admission
Other	**Bergert 2014**[429]	Hawaii	Before and after quality improvement study. Hospital-based intervention. No sample selection. LTFU: 0%	2-18	763	2006-2012	ED	ED or hospital admission
	Davis 2011[430]	US (California)	Matched cohort with non-randomly applied intervention. Intervention for all eligible. Controls: Matched by age and past hospital care utilization. Hospital-based. FU: 1 year LTFU: 0%	1-18	1396	2005-2007	Inpatient	ED
	Fassl 2012[431]	US (Salt Lake City)	Before and after quality improvement study. Hospital-based intervention. No sample selection. LTFU: 0%	2-17	1865	2005-2011	Inpatient	ED or hospital admis. within 6 m
	Vicendese 2015[432]	Australia (Melbourne)	Case-control, nested in cohort study. Cases at least 2 admissions, controls only 1 admission. Non-random. Hospital based.	2-17	44 (22 cases)	2009-2011	Inpatient	Hospital admission

Abbreviations: GCASR: Greater Cincinnati Asthma Risk Study; ND: Not determined; LTFU: lost to follow-up; RR: response rate; ED: emergency department; dx: diagnosis; y: years; m: months; US: United States.

Predictors

The risk factors or predictors studied varied amongst studies, including: socio-demographic characteristics such as age, gender, sex and socioeconomic status (SES, including household/neighbourhood income, private vs. public insurance and working rank); and asthma characteristics (severity, treatment, previous admissions).

3.4.2. Risk of bias

The number of reports with low, unclear or high risk of bias was 22, 7 and 7 respectively. Those with an unclear risk of bias lacked information on relevant aspects of the methods, mainly sample selection, or did not state clearly the number or factors studied to assess reporting bias. The details of the risk of bias assessments are shown in Table 3.2.

Table 3.2: Statistical Methods and Risk of Bias

Study Design	Study	Analysis Method	Adjust-ment*	Multiple testing	Risk of Bias	Source risk of bias	N-O Score
RCT	Gorelick 2006[390]	Analysis per risk factor	NA	Few	Low	-	
	Kercsmar 2006[433]	Analysis per risk factor	NA	Few	High	Performance and detection (blinding)	
	Madge 1997[434]	Cox regression	NA	Few	Unclear	Performance and detection	
Cohort	Bloomberg 2003[393]	Cox regression	Adequate	NA	Low	-	
	Brittan 2017[394]	Log regression	Unclear	NA	Low	-	7
	Camargo 2007[435]	Cox and log regression	Partial	NA	Unclear	Reporting	7
	Chabra 1998[436]	Log regression	Adequate	NA	Low	-	7
	Chen E. 2003[397]	Log regression	Adequate	Statistical correction	Unclear	Response	7-8
	Chen Y. 2003[398]	Cox regression	Partial	Few	Low	-	7-8
	Cincinnati I cohort[399-402]	Log and Cox regression	Adequate	NA/Few	Low	-	8-9
	GCARS[403-407]	Log and Cox regression	Adequate	NA/Few	Low	-	9
	Giarola 2014[408]	Analysis per risk factor	NA	Few	Low	-	7
	Gurkan[409]	Log regression	Unclear	NA	Unclear	Reporting	6
	Kenyon 2014[411]	Log regression	Adequate	NA	Low	-	8
	Kenyon 2015[410]	Log and Cox regression	Unclear	Few	Low	-	7
	Kocevar[412]	Cox regression	Adequate	Few	Low	-	7
	Lasmar 2006[413]	Log regression + survival	Adequate	NA	High	Selection	8-9
	Li 2012[414]	Cox regression	Adequate	NA	Unclear	Selection	9
	Liu 2009[415]	Cox regression	Adequate	NA	Low	-	9
	Minkovitz 1999[416]	Analysis per risk factor	NA	NA	High	Reporting	7
	Mitchel 1994[417]	Cox regression	Adequate	NA	High	Reporting	9
	Morse 2011[437]	GLE	Adequate	Statistical correction	Low	-	7
	Rasmusssen 2002[438]	Log regression	NA	NA	Unclear	Reporting and follow-up	7
	Rod-Mart 2014[419]	Poisson regression	Adequate	NA	High	Selection	7
	Rusworth 1995[421]	Log regression	Partial	NA	Low	Reporting	7
	Smiley[422]	Cox regression	Adequate	Few	Low	-	9
	Sporik 1993[439]	Analysis per risk factor	NA	Few	Low	-	7
	Taylor 1999[424]	Analysis per risk factor	NA	Few	Low	-	7
	Tolomeo 2009[440]	Log regression	Adequate	NA	High	Selection and reporting	8
	Wallace[426]	None	NA	NA	Low	-	6-7
	Wu 2016[427]	Multivar. Poisson regression	Partial	Few	Low	-	7
	Zipkin[428]	Log regression	Adequate	NA	Low	-	8
Other	Bergert 2014[429]	Analysis per risk factor	NA	Few analysis	Low	-	6-7
	Davis 2011[441]	Cox regression	Adequate	NA	High + unclear	Selection (high), follow-up and response	7
	Fassl[442]	Log regression	Adequate	NA	Low	-	9
	Vicendese 2015[432]	Log regression	Adequate	NA	Unclear	Selection	7

**: Adjustment for: age, sex, ethnicity and sociodemographic status. GCARS: Greater Cincinnati Asthma Rik Study; NA: Not addressed, N-O: Newcastle Ottawa Score; GLE: Generalized Liner Equations*

3.4.3. Predictors

Factors related to the person:

Age: The effect of age on the future risk of ED or hospital readmission was examined in 16 studies (Table 3.3). There was a marked variation in the age group classification and statistical methods used for the comparisons, precluding a meta-analysis of this factor. As shown, in general, studies were consistent in reporting that younger children had a higher risk of ED or hospital readmission.

Table 3.3: Association between age and risk of ED or hospital readmissions

Study Design	Study	Exposure		Outcome	Association	Measure	C.I. 95%	P value
Cohort	Brittan 2017[394]	**2-4 years**		**Hospital readmission**	**N (%)**	**92 (35.3)**		**0.05**
				No hosp readmission	**N (%)**	**3519 (39)**		
		5-11 years		**Hospital readmission**	**N (%)**	**119 (45.6)**		
				No hosp readmission	**N (%)**	**4306 (48)**		
		12-18 years		**Hospital readmission**	**N (%)**	**48 (18.5)**		
				No hosp readmission	**N (%)**	**1204 (13)**		
	Camar 2007[435]	**Older age**		**ED/Hosp readmission**	**HR**	**0.98**	**0.95-0.99**	**0.032**
	Chabra 1998[436]	6-12 years vs 1-6y		Multiple hosp admissions	OR	0.91	0.75-1.09	
	Chen Y 2003[398]	**Males (vs 15-19 years)**	**<1**	Hospital readmission	HR	**2.36**	**2.15-2,59**	
			1-4			**1.54**	**1.41-1.61**	
			5-9			1.08	0.98-1.19	
			10-14			1.05	0.95-1.17	
		Females (vs 15-19 years)	**<1**			**1.54**	**1.42-1.66**	
			1-4			**1.15**	**1.08-1.22**	
			5-9			**0.87**	**0.80-0.93**	
			10-14			**1.15**	**1.06-1.24**	
	Cincinn. I[401]	Age (years, continuous)		Hospital readmission	AHR	0.99		NS
	Gurk 2000[409]	**Age ≤5 years (vs 5-15 y)**		**Multiple hosp admis**	**OR**	**5.12**	**2.02-12.95**	**0.02**
	Kenyon 2014[411]	**Age (vs. 2-4 years)**	5-11 y	Hospital readm 30d	**AOR**	1.0	0.9-1.2	
				Hospital readm 1 y		1.0	0.9-1.0	
			12-18 y	**Hospital readm 30d**		**2.0**	**1-7-2.5**	
				Hospital readm 1 y		**1.1**	**1.1-1.2**	
	Kenyon 2015[410]	**2-4 years**		**H. readmis***	**N (%)**	**681 (44)**		**0.001**
				No hosp readmiss*	**N (%)**	**12410 (41)**		
		5-11 years		**H. readmis***	**N (%)**	**613 (39)**		
				No hosp readmiss*	**N (%)**	**13116 (44)**		
		12-18 years		**H. readmis***	**N (%)**	**273 (17)**		
				No hosp readmiss*	**N (%)**	**4565 (15)**		

	Li 2012[414]	**Age (vs. 2-5 years)**		**6-9 y**	**ED re-visits**	**HR**	**0.83**	**0.78-0.89**	
				10-13 y			**0.76**	**0.71-0.82**	
				14-17 y			**0.80**	**0.74-0.87**	
		Age (vs. 2-5 years)		**6-9 y**	**Hospital admission**	**HR**	**0.56**	**0.46-0.67**	
				10-13 y			**0.51**	**0.41-0.65**	
				14-17 y			**0.42**	**0.32-0.57**	
	Liu 2009[415]	**Age (vs 0-4 y)**		5-10 y	Hospital readmission	HR	0.58	0.64-2.03	
				11-18 y			**0.57**	**0.40-0.81**	
	Mitch. 1994[417]	**Age <5 y (vs. 5-14 y)**			**Hospital readmission**	**AOR**	**1.71**	**1.41-2.08**	
	Rod-Ma 2014[419]	Age (continuous)			Hospital readmission	IRR	1.08	0.39-3.03	0.87
	Smiley 2016[422]	**Age (vs 12-17)**		**2-4 y**	**ED re-visit**	**AHR**	**1.69**	**1.48-1.93**	**< 0.001**
				5-11 y			**1.24**	**1.10-1.39**	
	Wallace 2004[426]	Female (vs 10-14 y)	W	1-4 y	Hospital readmission within 180 days of index admission	RR	1.1		
				5-9 y			0.8		
			B	1-4 y			0.6		
				5-9 y			0.7		
			H	1-4 y			0.8		
				5-9 y			1.0		
		Male (vs 10-14 y)	W	1-4 y			0.9		
				5-9 y			0.7		
			B	1-4 y			0.8		
				5-9 y			0.8		
			H	1-4 y			1.0		
				5-9 y			1.0		
	Zipkin 2016[428]	**Age (vs 13-17 years)**		**2-5 years**	**Hospital readmission**	AOR	**0.45**	**0.25-0.80**	**0.007**
					ED re-utilization		**2.23**	**1.32-3.79**	**0.003**
				6-12 years	**Hospital readmission**		**0.41**	**0.22-0.75**	**0.004**
					ED re-utilization		1.29	0.75-2.21	0.36
Other	Vicendese 2016[432]	2-6 years			≥2 Hospital admissions	N (%)	17 (77)		0.73
					1 hospital admission	N (%)	16 (73)		
		7-14 years			≥2 Hospital admissions	N (%)	5 (23)		0.73
					1 hospital admission	N (%)	6 (27)		

**: in 15-90 days time. Abbreviations: ED: Emergency Department; HR: Hazard Ratio; AHR: Adjusted Hazard Ratio, OR: Odds Ratio; AOR: Adjusted Odds Ratio; IRR: Incidence Rate Ratio; SD: Standard Deviation; NS: Non statistically significant; W: White ethnicity; B: Black ethnicity; H: Hispanic ethnicity.*

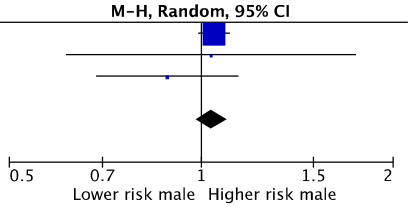
Sex: Six reports analysed sex as a risk factor for ED and 17 for hospital readmission, though some of them stratified its effect by age. There was a decreased odds of hospital readmission among boys compared to girls (OR 0.91, 95%CI: 0.86-0.97) in the pooled analysis of data from 17 studies (Figure 3.2C), but no difference in the pooled analysis of other 2 studies reporting hazard ratios (Figure 3.2D). There was no difference in ED re-attendance by sex in the studies reporting either odds or hazard ratios (Figure 3.2A and 3.2B).

Figure 3.2: Forest plots for the association of sex with emergency department re-attendance and hospital readmission for acute asthma in children using a random effects model.

A: Odds Ratio ED Re-attendance

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Random, 95% CI
Li 2012	4160	18574	2336	10817	94.2%	1.05 [0.99, 1.11]
Tolomeo 2009	60	197	30	101	1.1%	1.04 [0.61, 1.75]
Zipkin 2016	220	750	136	426	4.7%	0.89 [0.68, 1.14]
Total (95% CI)		**19521**		**11344**	**100.0%**	**1.04 [0.98, 1.10]**
Total events	4440		2502			

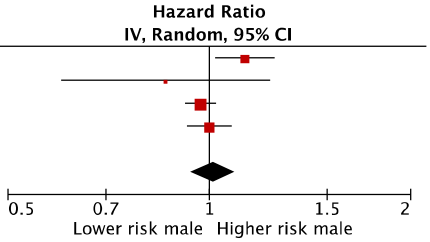
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.57$, df = 2 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 1.36 (P = 0.17)



B: Hazard Ratios ED Re-attendance

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Camargo 2007	0.1222	0.0523	25.4%	1.13 [1.02, 1.25]
Davis 2011	-0.1508	0.1837	4.0%	0.86 [0.60, 1.23]
Li 2012	-0.0305	0.027	38.6%	0.97 [0.92, 1.02]
Smiley 2016	0	0.0393	31.9%	1.00 [0.93, 1.08]
Total (95% CI)			**100.0%**	**1.01 [0.94, 1.09]**

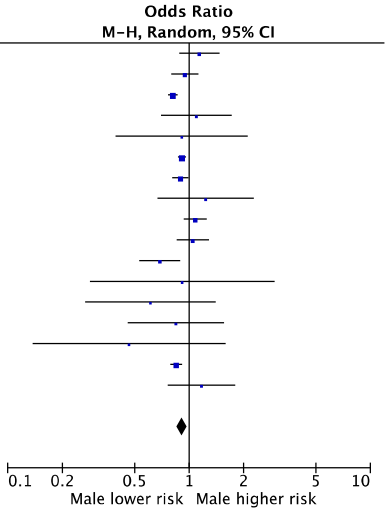
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.41$, df = 3 (P = 0.06); $I^2 = 60\%$
Test for overall effect: Z = 0.34 (P = 0.73)



C: Odds Ratios Hospital Readmission

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Random, 95% CI
Brittan 2017	167	5715	92	3573	4.5%	1.14 [0.88, 1.47]
Chabra 1998	387	3147	232	1800	7.7%	0.95 [0.80, 1.13]
Chen Y 2003	2859	15776	2352	10990	16.1%	0.81 [0.76, 0.86]
GCARS (Howrylak 2014)	69	404	34	215	1.8%	1.10 [0.70, 1.72]
Gurkan 2000	19	91	11	49	0.5%	0.91 [0.39, 2.11]
Kenyon 2014	4509	27008	3094	17195	16.9%	0.91 [0.87, 0.96]
Kenyon 2015	916	19303	651	12355	12.6%	0.90 [0.81, 0.99]
Lasmar 2006	91	136	41	66	1.0%	1.23 [0.67, 2.27]
Li 2012	519	18558	282	10883	9.3%	1.08 [0.93, 1.25]
Liu 2009	274	1743	177	1170	6.2%	1.05 [0.85, 1.29]
Mitchell 1994	188	619	161	415	4.4%	0.69 [0.53, 0.89]
Rasmussen 2002	11	41	6	21	0.3%	0.92 [0.28, 2.96]
Rodriguz-Martinez 2014	19	61	17	40	0.6%	0.61 [0.27, 1.40]
Tolomeo 2009	34	197	20	101	1.0%	0.84 [0.46, 1.56]
Vicendese 2015	11	26	11	18	0.3%	0.47 [0.14, 1.59]
Wallace 2004	1970	14418	1319	8389	14.9%	0.85 [0.79, 0.91]
Zipkin 2016	69	750	34	426	1.9%	1.17 [0.76, 1.79]
Total (95% CI)		**107993**		**67706**	**100.0%**	**0.91 [0.86, 0.97]**
Total events	12112		8534			

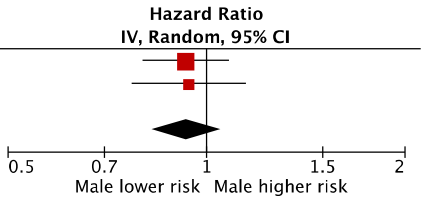
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 33.21$, df = 16 (P = 0.007); $I^2 = 52\%$
Test for overall effect: Z = 2.88 (P = 0.004)



D: Hazard Ratios Hospital Readmission

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Li 2012	-0.0726	0.0768	63.7%	0.93 [0.80, 1.08]
Liu 2009	-0.0619	0.1018	36.3%	0.94 [0.77, 1.15]
Total (95% CI)			**100.0%**	**0.93 [0.83, 1.05]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = 1.12 (P = 0.26)

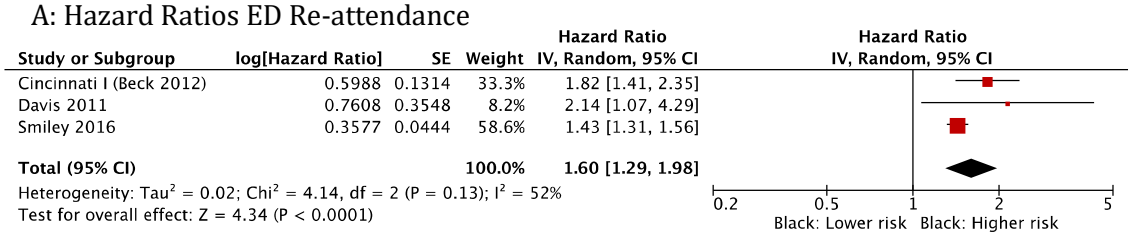


Ethnicity: The effect of ethnicity on ED or hospital readmission was included in 18 reports, using different classifications. The most frequent was the comparison between black or African-American and white or other origins, and the risk of readmission for asthma. The results of 7 of these comparisons were pooled together

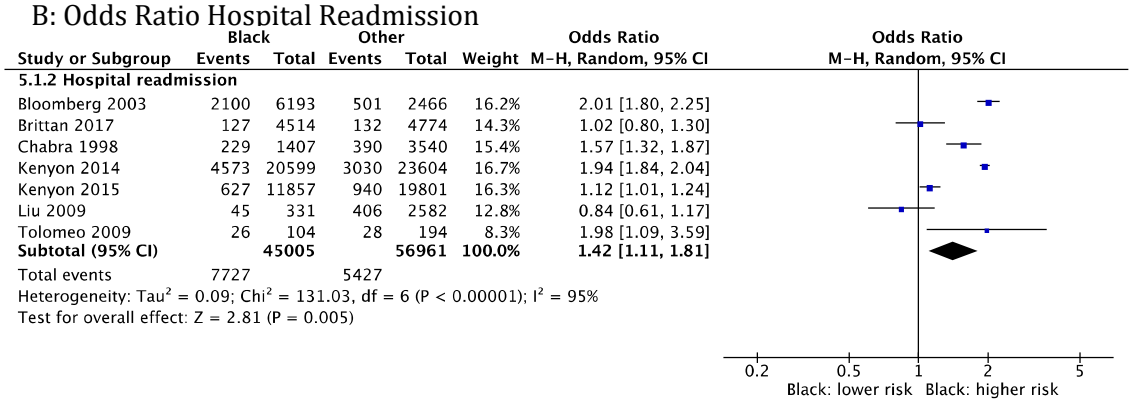
obtaining a positive association between black ethnicity and the odds of hospital readmission for acute asthma (OR: 1.42, 95% CI: 1.11-1.81) (Figure 3.3B). This model had a considerable heterogeneity (I^2= 95%), mainly due to the Liu 2009 study. Four other studies reporting Hazard Ratios for hospital readmission showed no association between black ethnicity and hospital readmission (Figure 3.3C). There was also an increased risk of ED re-attendance among African-American compared to white children (HR: 1.60, 95% CI: 1.29-1.98) in the pooled analysis of 3 studies reporting Hazard Ratios (Figure 3.3A). One paper studying hospital readmission was excluded from the meta-analysis as results were stratified by age and sex [426].

Figure 3.3: Forest plots for the associations of ethnicity (black vs other) with emergency department re-attendance and hospital readmission for acute asthma in children using a random effects model.

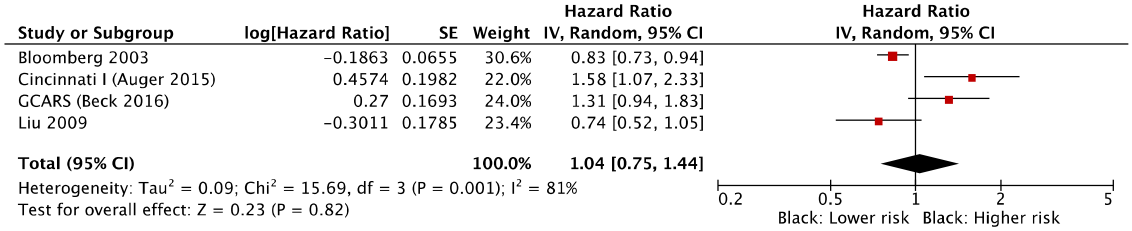
A: Hazard Ratios ED Re-attendance



B: Odds Ratio Hospital Readmission



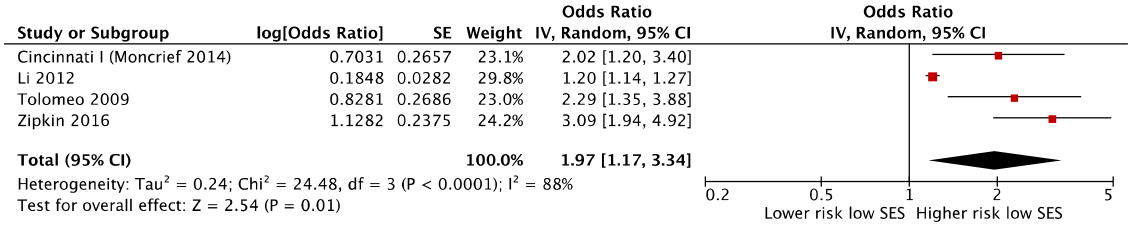
C: Hazard Ratios Hospital Readmission



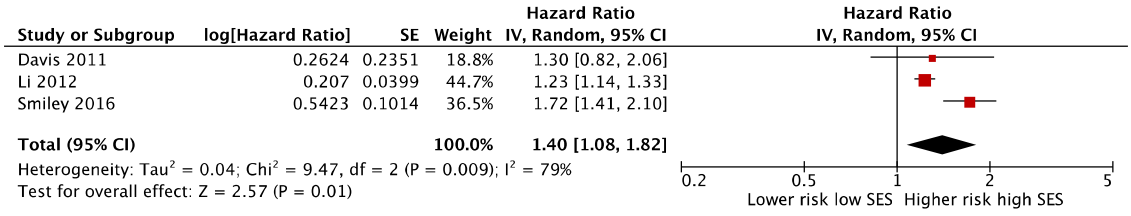
Socioeconomic status (SES): 21 reports examined SES as a predictor for ED or hospital readmission for asthma. The specific predictor used differed, with public insurance (vs. private or other) or low household income being the most frequent markers adopted for low SES. A meta-analysis of data from 4 studies showed increased odds of ED re-attendance for acute asthma in children of low SES (OR: 1.23; 1.17-1.30) (Figure 3.4A), consistent with the pooled analysis of 3 other studies reporting HR (HR: 1.40, 95% CI: 1.08-1.82) (Figure 3.4B). Another 9 studies reporting odds ratios and 5 studies reporting Hazard ratios were used to analyse the effect of low SES on hospital readmission for acute asthma, producing a pooled OR: 1.25 (95% CI: 1.07-1.47) (Figure 3.4C) and a pooled HR: 1.20 (95% CI: 1.07-1.35) (Figure 3.4D).

Figure 3.4: Forest plots for the associations of socioeconomic status (SES) with emergency department re-attendance and hospital readmission for acute asthma in children using a random effects model.

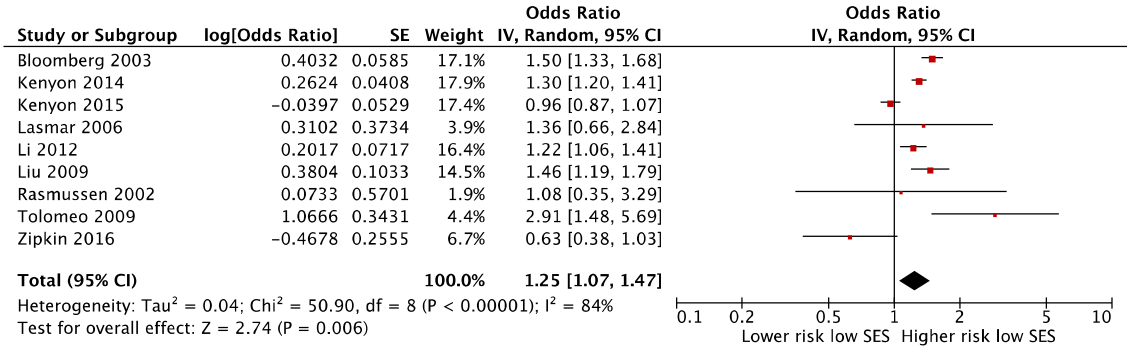
A: Odds Ratios ED Re-attendance



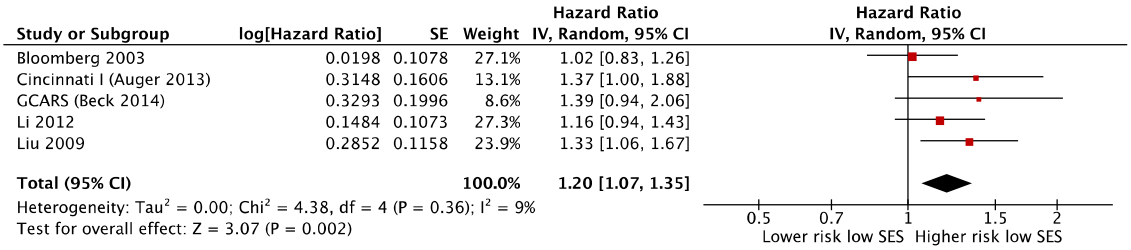
B: Hazard Ratios ED Re-attendance



C: Odds Ratios Hospital Readmission

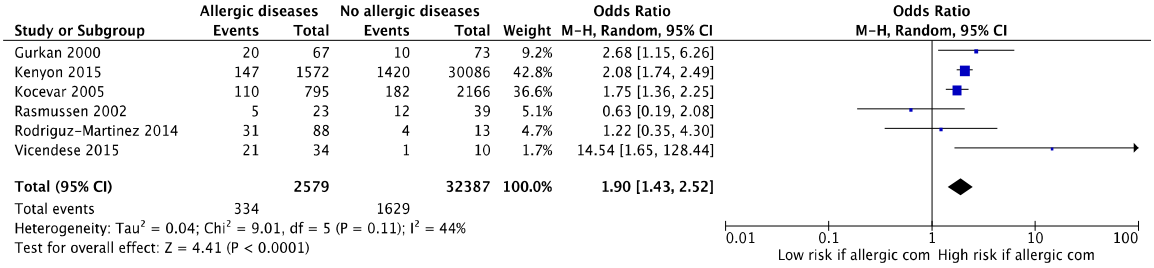


D: Hazard Ratios Hospital Readmission



Comorbidities: Seven reports analysed the risk of hospital readmission among children with other concomitant allergic diseases, including allergic conjunctivitis, allergic rhinitis or eczema. The pooled OR of six of these studies showed an increased risk of hospital readmission for asthma for children with concomitant allergic diseases (OR: 1.90, 95% CI: 1.43-2.52) (Figure 3.5). The heterogeneity of the model was moderate (I^2= 44%).

Figure 3.5: Forest plot for the associations of concomitant allergic diseases (allergic rhinitis /rhinoconjunctivitis or eczema) with hospital readmission for acute asthma in children using a random effects model (odds ratios).



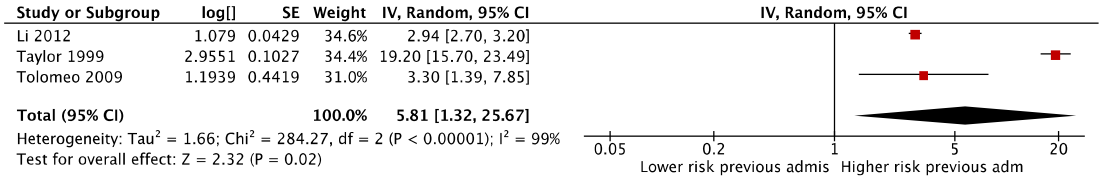
Factors related to asthma characteristics:

Previous ED or hospital admission: Eight reports included data on the risk of ED or hospital readmission according to a history of previous hospital or ED admissions, either in the previous 12-24 months (the most common) or ever in life. The 3 reports studying ED re-attendance odds ratios (OR: 5.81, 95% CI: 1.32-25.67) and the 2 reports studying hazard ratios (HR: 1.88, 95% CI: 1.58-2.24), showed an increased risk among children with a history of previous ED or hospital admissions for acute asthma (Figure 3.6A and 3.6B). The same occurred with the 8 studies reporting odds ratio and the 3 studies reporting hazard ratios for hospital readmission (Figures 3.6C and 3.6D). The

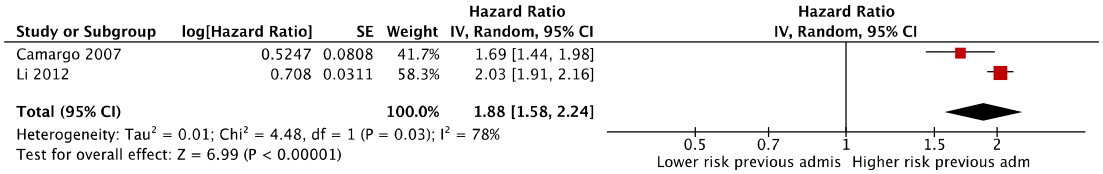
substantial heterogeneity of the odds ratio models (I^2= 95 and 99%) were due mainly to the Taylor 1999 [424] study, though when removed from the model the association was still significant (results not shown).

Figure 3.6: Forest plots for the associations of previous ED or hospital admissions for acute asthma with emergency department re-attendance and hospital readmission for acute asthma in children using a random effects model.

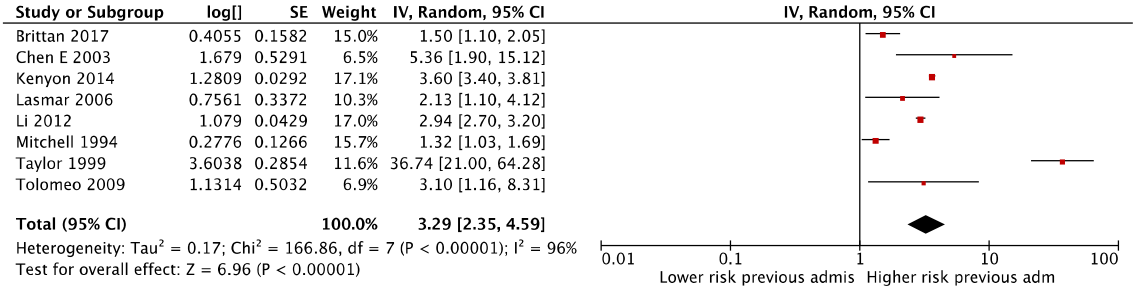
A: Odds Ratios ED Re-attendance



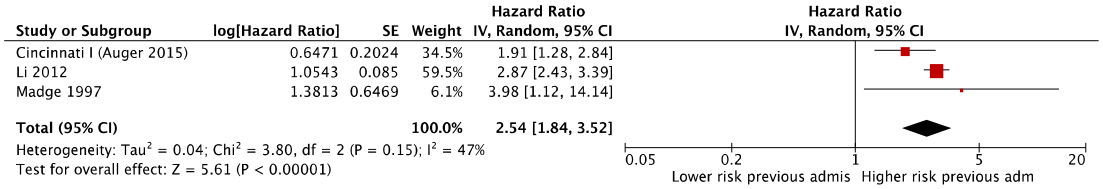
B: Hazard Ratios ED Re-attendance



C: Odds Ratios Hospital Readmission



D: Hazard Ratios Hospital Readmission



Asthma severity and controller treatment: Ten studies assessed the association between asthma severity, control or controller treatment received with the risk of ED or hospital readmission (Table 3.4). The type of predictor and definition of severity varied greatly between studies, precluding a meta-analysis. The findings related to severity as defined by treatment were inconsistent, though past events were associated with increased future risk.

Table 3.4: Association between asthma severity, control and baseline treatment and risk of ED or hospital readmissions

Study Design	Study	Exposure		Outcome	Association	Measure	C.I. 95%	P value
Cohort	Camargo 2007[435]	Pre-index OCS use		ED/Hosp readmission	HR	1.10	1.07-1.14	<0.001
		Pre-index SABA use				1.04	1.02-1.05	
	Cincinnati cohort	Severity (ICS use in the past)		Hospital readmission	AHR**	1.49	1.03-2.15	
		Severity (ICS use in the past)[401]		Hospital readmission	AHR	0.81		NS
	GCARS[403-407]	Severity (vs mild intermit.)	Severe persistent	Hospital readmission	HR	1.83	1.07-3.14	
			Moderate persistent	Hospital readmission	HR	1.70	1.18-2.46	
			Mild persistent	Hospital readmission	HR	1.12	0.80-1.56	
		Use of controllers	Yes	Hosp readmis	N(%)	57 (23)		<0.001
				No hosp readm	N(%)	192 (77)		
			No	Hosp readmis	N(%)	45 (12)		
				No hosp readm	N(%)	324 (88)		
	Gurkan 2000[409]	Using ICS		Multiple hospital admis	OR	0.37	0.16-0.86	0.03
	Kenyon 2015[410]	≥1 controller fill		Hosp readmission	N(%)	1013 (65)		<0.001
				No hosp readm	N(%)	14488 (48)		
		Persistent asthma		Hospital readmission	N(%)	1093 (70)		<0.001
				No hospital readmission	N(%)	15070 (50)		
	Lasmar 2006[413]	Moderate persistent vs. mild intermittent		Single vs multiple hosp admissions	AOR	6.23	2.82-13.76	<0.001
		No. attacks >4/month			OR	2.19	1.03-4.71	0.03
	Minkovitz 1999[416]	ICS as usual medication		SHA	N(%)	4 (5)		0.03
				MHA		6 (17)		
		Prescribed routine asthma medications		SHA	N(%)	65 (77)		0.07
				MHA		32 (91)		
	Rasmussen 2002[438]	FEV_1 % predicted at 9 y		SHA	Mean ±SD	94 ± 13		0.04
				MHA		86 ± 11		
		FVC % predicted at 9 y		SHA		99 ± 10		0.93
				MHA		99 ± 12		
		FEV_1/VC at age 9 y (%)		SHA		84 ± 6		0.03
				MHA		78 ± 7		
		AHR at age 9 y		SHA	N(%)	51		0.03
				MHA		82		
	Smiley 2016[422]	Controller medic. (vs LTRA)	None	ED re-visit	AHR	0.90	0.73-1.10	
			ICS			1.10	0.94-1.28	
			ICS/LABA			1.20	1.02-1.41	
			ICS+LTRA			1.19	0.94-1.49	
			ICS/LABA +LTRA			1.43	1.16-1.75	
		AMR ≥0.5 vs <0.5		ED re-visit	AHR	0.68	0.58-0.81	
	Zipkin 2016[428]	Discharged with ICS		Hospital readmission	OR	0.67	0.44-1.02	
				Ed utilization	OR	0.92	0.70-1.20	

*Asthma control scale: 0-2 (higher score=worse control); #: Parents perceiving asthma as more severe.
**: Adjusted for: age, ethnicity, insurance, maternal education and income;
OCS: Oral corticosteroids; SABA: short-acting β-adrenergic agonist; ICS: inhaled corticosteroids; ED: Emergency Department; PEFR: Peak Expiratory Flow Rate; FEV_1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; AHR: Airway hyperresponsiveness; HR: Hazard Ratio; AHR: Adjusted Hazard Ratio; SHA: Single Hospital Admission; MHA: Multiple hospital admission; OR: Odds Ratio; AOR: Adjusted Odds Ratio; SD: Standard Deviation; AMR: Asthma Medication Ratio

Factors related to potential follow-up

Asthma follow-up: Ten papers examined aspects of follow-up after the index ED or hospital admission (Table 3.5).

Table 3.5: Association between asthma follow-up and management after index admission or ED visit for asthma and risk of ED or hospital readmissions

Study Design	Study	Exposure		Outcome	Association	Measure	C.I. 95%	P value
RCT	Gorelick 2006[390]	Usual Care		ED re-visit (self-reported)	%	38.4		0.90
		Intensive primary care linkage			%	39.2		
		Case management programme			%	35.8		
Cohort	Brittan 2017[394]	Post-discharge outpatient visit		Hospital readmission (15-90 d)	OR	1.00		NS
	Cincinnati cohort[402]	Med. home access vs. adequate	Almost always adequate	Hospital readmission	AHR	1.11	0.77-1.60	
			Sometime/ often/never adequate	Hospital readmission	AHR	1.56	1.06-2.32	
	Li 2012[414]	Follow-up visits (vs no)		ED re-visit	AHR	0.98	0.93-1.03	
				Hospital readm		1.06	0.92-1.23	
		Number FU visits (vs 0)	1	ED re-visit	AHR	0.99	0.94-1.05	
				Hospital readm		1.05	0.89-1.23	
			2	ED re-visit	AHR	0.91	0.82-1.01	
				Hospital readm		1.12	0.94-1.56	
			≥3	ED re-visit	AHR	1.07	0.91-1.26	
				Hospital readm		0.78	0.48-1.29	
		Type of physician for FU (vs none)	General	ED re-visit	AHR	0.98	0.93-1.04	
				Hospital readm		1.05	0.91-1.22	
			Specialist	ED re-visit	AHR	1.01	0.83-1.23	
				Hospital readm		1.41	0.88-2.26	
			General + special.	ED re-visit	AHR	0.93	0.71-1.21	
				Hospital readm		0.86	0.38-1.93	
	Minkovitz 1999[416]	Post-discharge visit	Paediatrician	Single hosp adm	N(%)	77 (92)		0.28
				Mult hosp. admission		34 (97)		
			Allergy	Single hosp adm	N(%)	10 (12)		0.40
				Mult hosp. admission		6 (18)		
			Pulmonary	Single hosp adm	N(%)	10 (12)		0.002
				Mult hosp. admission		13 (37)		
	Morse 2011[437]	CAC-3 compliance (5% improvement)		ED re-visit 30d	OR	0.97	0.90-1.04	0.36
				ED re-visit 90d		0.96	0.77-1.18	0.68
				Hospital readmi 30d		0.99	0.96-1.02	0.53
				Hospital readmi 90d		1.01	0-90-1.12	0.90
				Multip hosp. admission		82		
	Smiley 2016[422]	Follow-up appointment (vs no)		ED re-visit	AHR	0.86	0.76-0.93	0.002
	Zipkin 2016[428]	HMPC compliance (partial/full vs none)		Hospital readmission	OR	0.63	0.41.0.95	0.028
				Ed re-utilization	OR	0.73	0.56-0.96	0.022

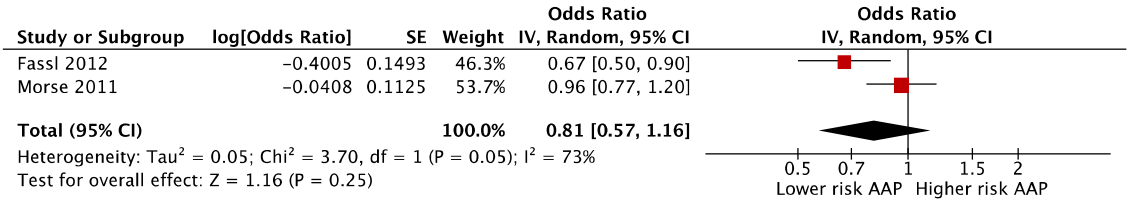
Other	Bergert 2014[429]	Post-CAC Implementation vs Pre-CAC	ED re-visit	0-30d	OR	N/A	N/A	
				31-90 d		1.60	0.44-5.81	
				91-180 d		0.57	0.20-1.67	
			Hosp readm.	0-30 d		0.29	0.05-1.73	
				31-90 d		0.87	0.21-3.50	
				91-180 d		0.29	0.11-0.78	
	Fassl 2012[442]	Post-CAC Implementation vs Pre-CAC	Hospital readmission		AOR	0.67	0.50-0.91	0.01

Abbreviations: RCT: Randomized Clinical Trial; HR: Hazard Ratio; AHR: Adjusted Hazard Ratio, OR: Odds Ratio; AOR: Adjusted Odds Ratio; ED: Emergency Department; FU: follow-up; CAC: Children's' Asthma Care; HMPC: Home Management Plan Care (part of the CAC); N/A: not applicable; d: days.

Three studies explored the effect of the Children's Asthma Care (CAC) measures set implementation, which comprises providing reliever medication and systemic corticosteroids for children admitted to hospital for asthma, and discharging them with a home management plan. They showed no effect on ED re-attendance after the initial admission for asthma and two of them demonstrated a reduced risk of hospital re-admission after the implementation of the CAC measures. One further study showed a decreased risk of both hospital readmission and ED re-utilization for acute asthma after Home Management Plan Care implementation (part of CAC)[428].

Five studies analysed the effect of different follow-up visit characteristics and ED or hospital readmission for asthma with disparate outcomes. Three reports studied the effect of receiving an asthma action plan at discharge on the risk of ED or hospital readmission. Two of them were combined (Figure 3.7) showing no association.

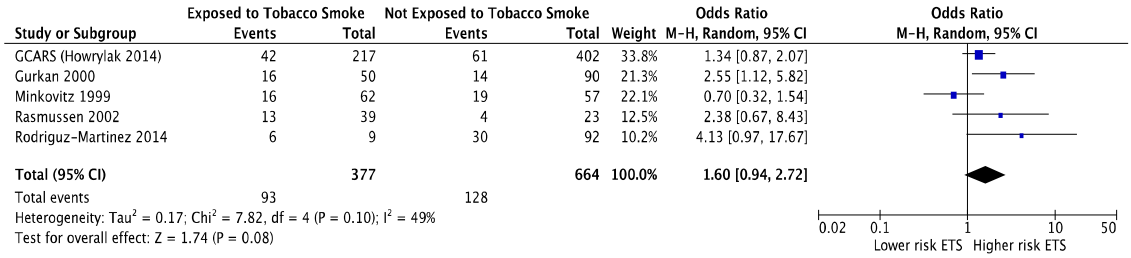
Figure 3.7: Forest plots for the associations of being offered an asthma action plan at discharge with emergency department re-attendance or hospital readmission for acute asthma in children using a random effects model (odds ratios).



Other factors:

Exposure to tobacco smoke (ETS): Five studies included data on ETS, producing a pooled odds ratio of 1.60 (95% CI: 0.94-2.72) for hospital readmission for acute asthma for those exposed to tobacco smoke (Figure 3.8). One other paper [401] measuring Hazard ratio, showed no association between ETS and hospital readmission risk for asthma (AHR: 0.83, 95% CI: not published, p value: not significant).

Figure 3.8: Forest plots for the associations of second-hand tobacco smoke exposure (ETS) with hospital readmission for acute asthma in children using a random effects model (odds ratios).



Other factors included: family history of asthma or allergic diseases, parental level of education, personal history (previous immunizations, early life feeding methods), caregiver's situation (psychological stress, beliefs, knowledge, marital status or concerns), asthma triggers, exposure to allergens or pollution and home characteristics, adherence to asthma treatment, characteristics of index asthma admission, and home remediation interventions of water infiltration. The outcomes and specific exposures used were highly heterogeneous between studies meaning no robust consensus conclusions could be drawn.

3.5. Discussion

Asthma is a very common reason for emergency attendance. Clinicians are therefore often faced with decisions on whether to increase treatment and who to refer for a specialist opinion. This systematic review and meta-analysis has identified a history of previous ED or hospital admissions to be the major risk factor for emergency care and hospital readmissions for acute asthma in children. Further, our results indicate that children of African-American ethnicity (compared to white or other ethnicity), low socioeconomic status (as measured by having public insurance or low family income), with concomitant allergic diseases (allergic rhinitis/rhinoconjunctivitis or eczema) and being younger than 5 years of age, are at a greater risk of subsequent emergency care visits or hospital readmissions for acute asthma.

This systematic review answers a relevant question with public health implications for future asthma management that has been developed in accordance with best practice and using an extensive search with no time or language publication restrictions to ensure the inclusion of potentially suitable studies. The data collected had a moderate to low strength of evidence. Risk of bias was assessed and presented for each included study separately. We were also able to undertake a quantitative analysis of the most relevant predictors, increasing the relevance of our findings.

Most of observational studies included were retrospective cohorts using hospital or insurance databases with a large number of patients (more than 10 000 participants in 6 studies). However, unclear and high risk of bias were common because of inadequate sampling and reporting of only significant results in more than 50% of the observational studies. The RCT's included in the review had some important risk of biases which precluded increasing the strength of evidence of the review.

Despite a wide literature search with no language restriction, all selected papers were published in English and the clear majority were developed in Anglophone countries, mainly in the US. This likely reflects the fact that asthma has been an important public health problem in these countries for a long period[29] but limits the generalizability of the findings to other relevant regions such as Latin America were asthma has emerged as an important public health issue[2]. Decisions on who should be the focus of treatment are crucial in such settings where resources are likely to be very limited. Another important factor is the inclusion of children younger than 2 years old in several studies, an age at which it is difficult to ascertain an asthma diagnosis[443]. The outcomes used in the studies are also a possible source of bias, as there is no consensus on when a child should be admitted to the ED or hospital for acute asthma. However, this is the current definition used by the ATS for a severe asthma attack[8].

Children younger than 5 years old were at a higher risk of ED or hospital readmission for acute asthma when compared to different age groups in more than half of the studies that explored age as a predictor of future risk. Preschool children suffer a larger number of acute asthma attacks driven mostly by respiratory viruses[320,444]. It is also difficult to diagnose asthma in this age group [443], potentially leading to inadequate management. Lintzenich et al.[445] showed that children 1-6 years old hospitalized for asthma were less likely to receive ICS baseline treatment and asthma education than older children.

Children from families with lower SES had a higher risk of ED or hospital readmission[446]. Lower SES has previously been shown to be associated with more frequent ED visits and hospital admissions for other diseases[447]. It may reflect poorer long-term management due to inadequate access to primary and specialist care, and that caregivers may be less able to adequately manage a long-term condition thus relying more on ED attendance. Flores et al.[448] showed that among ethnic minority

children with asthma in urban settings, poorer children were less likely to have an asthma specialist than wealthier children.

Children of African-American origin living in Anglophone countries were at higher risk of re-attendance for asthma. It is likely there is some residual effect of SES as not all reports provided an adjusted odds ratio that could be used in the analysis. This confounding was shown by Beck et al.[404] who reported that up to 80% of the readmission disparity between African-American and white asthmatic children could be explained by other associated factors, such as access to care or disease management. Nevertheless, non-white ethnicity has also been described as a predictor of hospitalisation or ED visits in adults with severe or difficult-to-treat asthma[449]. On the other hand, when selecting child's characteristics which best predict future ED or hospital use for acute asthma, black ethnicity should be considered, irrespective of whether it is a confounder or causal factor.

Allergic rhinitis and asthma often coexist and have been described to be two symptoms of the same disease[450]. This may explain why children with co-existing allergic diseases (allergic rhinitis/rhinoconjunctivitis and eczema) had a greater risk of hospital readmission for asthma. Treatment for allergic rhinitis, such as nasal corticosteroids and antihistamines has been, associated with a decreased risk of emergency care use for acute asthma attacks[451].

Asthmatic children with a history of a previous ED or hospital admission for acute asthma had between 2 to 5.8 times more risk of ED re-attendance and 2.5 to 3 times more risk of a hospital readmission. This was therefore the clearest factor related to asthma that was associated with future risk. Similarly, other studies have identified several variables related to previous healthcare utilization for acute asthma that are associated with future risk of severe asthma attacks[452,453].

3.6. Conclusion and key findings

Table 3.6: Identified risk factors for subsequent severe asthma attacks requiring emergency care re-attendance or hospital readmission.

Identified Risk Factors for Subsequent Severe Asthma Attacks	
Requiring Emergency Care re-attendance*	**Requiring Hospital Readmission***
- Younger age (no summary measure) - African-American ethnicity (HR) - Low socioeconomic status (OR, HR) - Previous ED or hospital admission for asthma (OR, HR)	- Younger age (no summary measure) - African-American ethnicity (OR) - Low socioeconomic status (OR, HR) - Previous ED or hospital admission for asthma (OR, HR) - Female sex (OR) - Concomitant allergic diseases (OR)

OR: Odds ratio; HR: Hazard ratio.

*: In parenthesis are the summary measures that showed an association

In conclusion, we have identified individual-level and factors related to asthma severity that are associated with a greater risk of future asthma attacks requiring emergency care or hospital readmission. This description of the current evidence base and its limitations could help inform future prospective studies that robustly assess the magnitude and interaction of such risk factors. In future, being able to identify children at risk of future asthma attacks requiring emergency care will guide specific interventions such as educational sessions, management of comorbidities, and personalised treatment adjustments. This approach has the potential to reduce the chance of long-term complications such as loss of lung function, psychological morbidity, and death.

4. Predictors for emergency care re-attendance for acute asthma in Ecuadorian children: a prospective cohort study

4.1 Introduction

Severe asthma attacks requiring emergency care, hospital admission or systemic corticosteroids[8] are a common source of preventable morbidity in children. As discussed in Chapter 2, asthma attacks are associated with loss of lung function[14,16], anxiety in patients and their families[326], as well as elevated healthcare and family costs[10], and missed school and workdays. Asthma attacks remain common despite international guidelines and a range of effective treatments[9]. They are a major problem in Latin America, given the high prevalence of asthma[2], the relative lack of available or affordable essential drugs[26,27] and the inadequate capacity to provide long-term asthma management[28]. As a result, children with asthma are treated mainly in emergency health service settings, and have a poor control of their disease[24,34].

Many asthma attacks are preventable, either by avoiding previously identified triggers or by appropriate preventive treatment. For example, use of long-term inhaled corticosteroids (ICS) reduces the number of asthma attacks in children by approximately 40%[7] and can attenuate the decline in lung function associated with acute exacerbations[16]. However, asthma medicines can be associated with significant side-effects and costs as shown in Chapter 2. It is not appropriate or feasible to offer treatment and specialist follow-up care for every person with asthma, especially in overburdened health care systems. Thus, it is important to be able to identify patients at risk of further attacks and hospital admission to target resources such as additional education and support or augmentation of treatment. Given the absence of asthma

clinics and specialist follow-up in many Latin American cities, the emergency department is a key opportunity to identify children at the highest risk of recurrent attacks.

Previous emergency department (ED) attendance for asthma exacerbations[414,435,440,454], younger age[414,422,435], black ethnicity[399,422] and low socioeconomic status[400,422,428] have been associated with a higher risk of subsequent asthma exacerbations requiring emergency care in children. However, such studies have been almost exclusively conducted in North America, and have not considered the potential additional information provided by biomarkers commonly available in higher income countries.

4.2 Objectives

This Chapter presents the findings from a prospective cohort study to analyse clinical factors and biomarkers associated with recurrent severe asthma attacks in children presenting with bronchodilator-responsive wheeze to a regional emergency department in Esmeraldas, Ecuador.

The objectives of the study were to:

- Describe the characteristics of children attending emergency care with bronchodilator-responsive wheeze.

- Estimate the proportion of children attending emergency care with bronchodilator-responsive wheeze who recur with a subsequent severe asthma exacerbation requiring emergency care in the following 6 months.

- Determine the factors associated with emergency care re-attendance for later asthmatic exacerbations among Ecuadorian children.

- Use this cohort of children to design an instrument to provide an assessment of the risk of future asthma exacerbations requiring emergency care re-attendance, and thus assist with decision-making regarding lifestyle modifications, medication use, and tertiary referral.

4.3. Methods

4.3.1. Study setting

The research project took place in the city of Esmeraldas, the provincial capital of the north-eastern province of Esmeraldas, one of the poorest regions in Ecuador. Esmeraldas province has a population of 534.000 inhabitants, with 44% considered Afro-Ecuadorians and 45% mestizos[306]. The province is divided into 7 cantons, as represented in Figure 4.1.

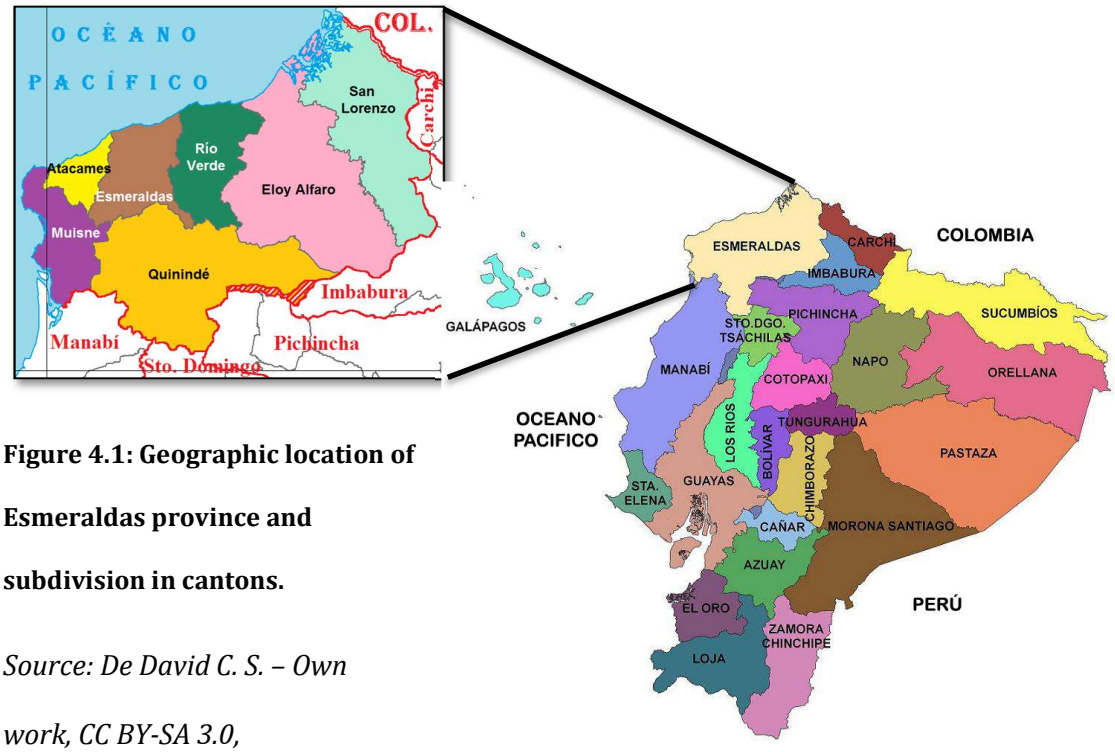


Figure 4.1: Geographic location of Esmeraldas province and subdivision in cantons.

Source: De David C. S. – Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=16949148[455]

In the province of Esmeraldas, there were a total of 26 hospitals, 11 public and 15 private, in 2014[310]. Of the public institutions, 8 belonged to the Ministry of Public Health (1 of them situated in the city) and 1 to the Social Security Institute (IESS), situated in the city of Esmeraldas. There were a further 158 health units without hospitalizations facilities in the province in 2014, of which 152 were public[310]. Of the total 864 294 consultations documented during 2014 in Esmeraldas province, 7.5% were for children 5-9 year old and 6% for 10-14 years old. As reported in the Chapter 2, Esmeraldas province had the lowest ratio of doctors per 10 000 inhabitants in 2014 (13.04). In addition, the distribution of health care workers throughout the province is highly heterogeneous, with nearly 70% of doctors present in the urban areas[310].

The city of Esmeraldas is situated in the Esmeraldas 'canton' and has a population of over 150 000 inhabitants, of which nearly 50 000 are under 15 years old and 55% are considered Afro-Ecuadorians. The urban population comprises mainly communities in the district of Esmeraldas city, which is the provincial capital and home to the country's largest refinery, a thermoelectric power plant and a wood-processing plant.

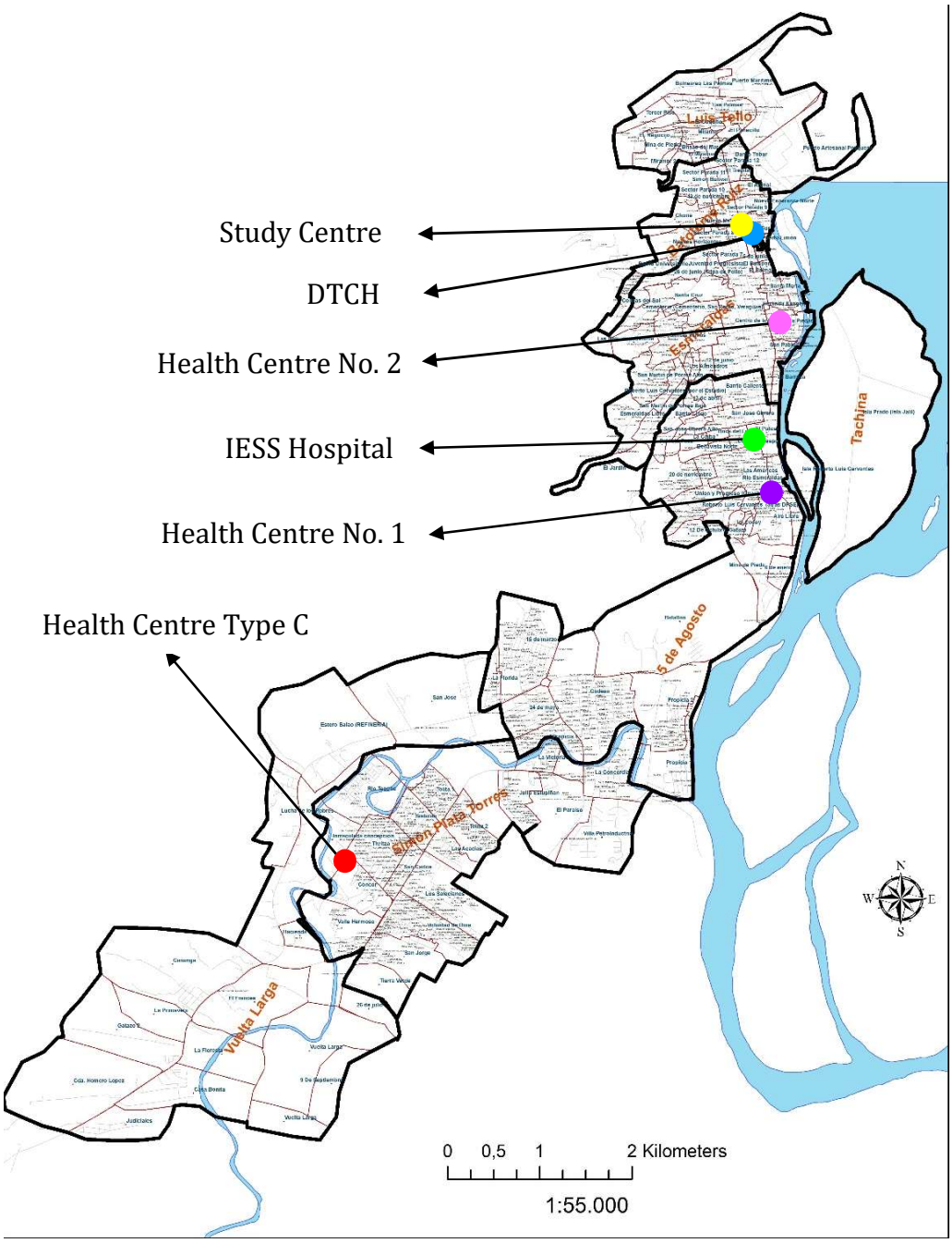
4.3.2. Recruitment and study centres

The city's public hospital, Delfina Torres de Concha Hospital (HDTC), belongs to the Ministry of Public Health, offers free attention and treatment at the point of care and is the only second-level Hospital in Esmeraldas province, receiving patients from throughout the province. The IESS (Instituto Ecuatoriano de Seguro Social, social security institute) hospital offers free treatment to people who contribute to national insurance (social security). Health centres offer universal free attention and treatment. Patients were recruited from these two hospitals, as well as from the two largest health centres in the city which had an emergency consultation room. Esmeraldas opened a specialised health centre (Type C) with a 24-hour emergency department in February

2015. Patients were recruited from this site for the study from February 15th, 2015.

Figure 4.2 represents the location of these centres.

Figure 4.2: Map of Esmeraldas city with the location of study and recruitment centres



DTCH: Delfina Torres de Concha Hospital; IESS: Instituto Ecuatoriano del Seguro Social (Social Security Institute of Ecuador).

Children were recruited and initially evaluated at the hospital's or health centres' emergency department. A basic laboratory and office was set-up close to the DTCH to process samples, perform pulmonary function tests, follow-up consultations, data entry, and study-coordination.

4.3.3. Study population:

All children aged between 5 to 15 years treated at the DTCH or IESS Hospital emergency department, or health centres, for an acute episode of bronchodilator-responsive wheezing over an 18-month period were invited to participate. We set the age limit between 5 and 15 years old, as older patients are no longer treated as paediatric patients. Children younger than 5 years old may sometimes present mild wheezing episodes secondary to viral respiratory infections that disappear around the ages of 5-10 years old. As many of the children that were included in the study did not have a previous doctor's asthma diagnosis, we excluded children younger than 5 years old to avoid including those with isolated viral wheeze. We also excluded children with other chronic diseases as their asthma characteristics may differ from other asthmatic patients.

Inclusion criteria:

- Age 5-15 years old.

- Treated at the DTCH or IESS Hospital emergency department, or health centres for an acute attack of bronchospasm: respiratory distress, coughing and wheezing, together with a clinical improvement after administration of nebulised β2 agonists (e.g. salbutamol).

- Parents or guardians willing to participate in the study and to sign the informed consent form.

Exclusion criteria:

- Parents or guardians unwilling to participate in the study or to sign the informed consent form.

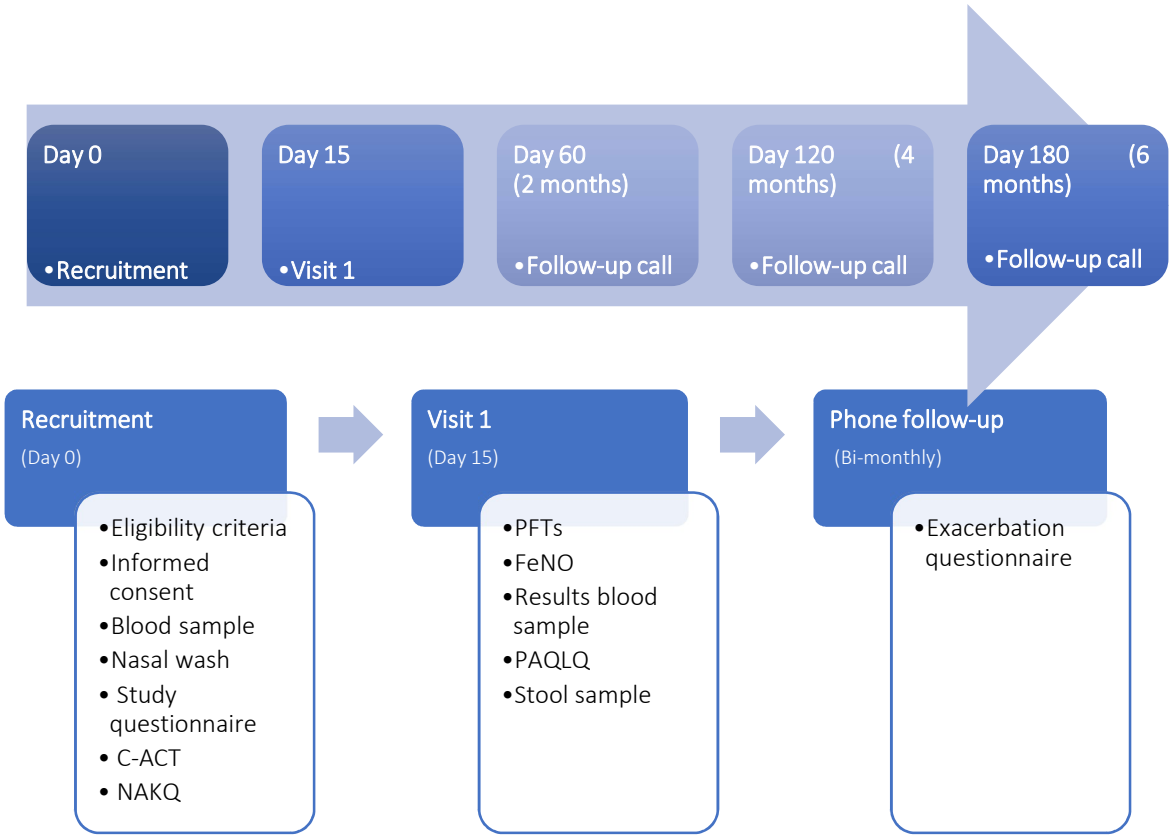
- Children with other chronic respiratory (cystic fibrosis, pulmonary hypertension, etc.), cardiac (congenital heart disease) or neurological (which may impair them from answering questionnaires, carrying out lung function measurements or accepting having samples taken) diseases.

- Parents/guardians and children who cannot commit to a minimum follow-up of 6 months.

4.3.4. Study design: prospective cohort study

We chose a cohort study design as such studies have the potential to provide strong scientific evidence, given the existence of a temporal framework to assess causality. This was a prospective study following up a cohort of children who present at the emergency department (ED) with an acute asthma attack. Exposures (risk factors) were assessed at the time of inclusion in the study and were followed-up to observe whether they had another acute asthma attack requiring emergency care or not, and in what time-frame. A cohort study design enabled analysis of the 'time to the next exacerbation' which is more clinically relevant as an outcome when compared to exacerbation 'yes' vs. 'no': e.g. a child having an asthma attack every 6 weeks may need more or a different intervention when compared with one who has an exacerbation every 6 months. Time to event analysis uses continuous data and therefore has greater statistical power than a binary outcome; it can also permit the inclusion of multiple attendances for one child.

Figure 4.3: Study plan and procedures



PFTs: Pulmonary function tests; FeNO: Fraction of Exhaled Nitric Oxide; C-ACT: Childhood Asthma Control Test; PAQLQ: Pediatric Asthma Quality of life Questionnaire; NAKQ: Newcastle Asthma Knowledge Questionnaire.

4.3.5. Study plan

Children were recruited during their visit to the emergency department. A description of the objectives of the study and the evaluations to be done were explained to the child's parent/s or guardian. The study procedures were described to the child at the time of informed consent and assent forms, in a simple language. If agreeing to participate, an informed written consent form was read out to the parent/guardian to be signed by them, as well as an assent form to be signed by children over 7 years. At the time of presentation, the treating doctor informed the caregiver of the existence of the study and if interested they left their contact number to be called on the following day by a member of the study team.

After agreeing to participate, study procedures were undertaken (see section below), including study questionnaires and a blood and nasal wash sample. They were also given a container to collect a stool sample.

Children and their caregivers were then asked to come back to the study clinic in 15 days' time, to allow for the acute asthma symptoms to disappear. In case the participant was still under medication that could alter the results of some of the procedures (such as corticosteroids), this visit took place another 7 days (21 days after recruitment). They received the full blood count results and a summary of findings from the other tests during this visit, and we carried out the following procedures: Fraction of Exhaled Nitric Oxide (FeNO) measurement, pre and post-bronchodilator spirometry and remaining study questionnaires.

Participants were recruited during an 18-month period to assure including asthmatic children who suffer exacerbations during different periods of the year (e.g. rainy and dry seasons) and to obtain the estimated sample size. Each participant was followed up for a minimum of 6 months from the time of recruitment with bimonthly telephone calls to enquire about asthma exacerbations (number, severity, duration and treatment received). They were also asked to contact the study team present at the study office (in person or by telephone) at each emergency care re-attendance due to an asthma exacerbation during the follow-up period. Hospital and health centres' records were checked twice a week to record any unscheduled visit for asthma exacerbation not already notified. To achieve the longest follow-up possible for each patient, those wishing to continue being followed-up in the study were contacted with bimonthly telephone calls to enquire about asthma exacerbations until the end of the study.

Future asthma management was discussed with each patient and their caregivers, according to the patient's asthma characteristics, their knowledge, and number and severity of asthma exacerbations suffered during the follow-up period. Participants'

asthma severity was classified by the Principal Investigator (a Paediatrician), using the Ecuadorian Asthma Consensus 2011[456]. They were offered available beta-agonists and/or inhaled corticosteroids for future exacerbations, in accordance with these guidelines that follow GINA recommendations[5]. Only medications available through the Ministry of Public Health were used in accordance with Ecuadorian law. The Principal Investigator also provided recommendations for future exacerbations and written asthma action plans.

4.3.6 Study procedures

The study procedures included collection of data by questionnaire (to design the study instrument) and data collected using objective clinical measurements to identify potential biomarkers, as well as to allow us to determine the phenotype of asthma in our study population and the populations to which our study findings were most relevant.

- *Weight and height:* Children were weighed using an electronic scale and height measured. Body Mass Index (BMI) was then estimated.

- *Questionnaire:* A questionnaire in Spanish modified from the ISAAC Phase II study[457] extensively field-tested[33,458] and previously used in Esmeraldas city by the same study team[34], was administered to the child's caregiver. It included the core asthma symptom questions of ISAAC and others regarding socio-demographic information, household characteristics and other environmental exposures, potential risk factors, severity of asthma and asthma triggers, and previous management and treatment for asthma.

- *Newcastle Asthma Knowledge Questionnaire (NAKQ)*[459]: To assess previous asthma knowledge, we used the NAKQ, a 31 item test (25 true/false items and six open ended questions) that provided a comprehensive assessment of: general facts about

asthma, triggers, symptoms, and asthma treatment and management. It has been extensively used in multiple studies, as well as translated to Spanish and validated in Spanish-speaking countries[460].

Figure 4.4: Study nurse undertaking study questionnaire with participant and his caregiver, at the study centre.

- *Childhood Asthma Control Test (C-ACT)*[4]: validated instrument included in the current Diagnosis and Management of Asthma Expert Panel Report 3 (EPR-3)[6] to assess asthma control in children 4 to 11 years old. A score of less than 20 from a total of 27 (obtained from 7 different questions) indicates poor asthma control. The Asthma Control Test (ACT)[3] (adult version) was used for children over 12 years old.

- *Blood sample:* 5ml of blood were obtained by venipuncture from the child into a Vacutainer tube containing EDTA as anticoagulant. A white cell and differential count for eosinophil counts was done manually at the research study clinical laboratory and plasma aliquoted and stored at -20C.

- *Nasal wash:* was done to determine the proportion of granulocytes (eosinophil vs. neutrophils). It was used as a surrogate of sputum cytology for determining airway inflammation[461]. This was done using a modification of a methodology designed by Dr Peter Heymann at the University of Virginia that allows

the collection of small volume samples to reduce dilutional effects[462]. With the child sitting straight on a high chair and breath holding, we instilled 2ml of phosphate buffered saline (PBS) at ambient temperature into one of the nostrils, using an intranasal mucosal atomization device, MAD NasalTM (Teleflex, USA) Wolfe Tory Medical, Inc., Salt Lake City, UT), after which the child blew his nose into a glass funnel and collection tube. The same process was repeated with the second nostril and the funnel was then washed with an extra 2ml of PBS into the collection tube, obtaining a total of 4-8ml.

Figure 4.5: Study lab technician obtaining a nasal wash sample from a participant, at the study centre.

Four 500µl aliquots were frozen for later respiratory virus analysis. Two slides were prepared for each sample using a cytospin to estimate the proportion of eosinophils present in the nasal wash.

- *Stool samples:* children were asked to collect a stool sample following recruitment. If found positive for intestinal parasites, caregivers were informed at the following visit and offered appropriate treatment.

- *Pediatric Asthma Quality of Life Questionnaire (PAQLQ)*[463]: Disease-specific questionnaire available in both interviewer and self-administered formats, designed for children aged 7 to 17 years of age. The PAQLQ has 23 questions in 3 domains (symptoms, activity limitation and emotional function). The activity domain

contains 3 'patient-specific' questions. Children are asked to think about how they have been during the previous week and to respond to each of the 32 questions on a 7-point scale (7 = not bothered at all - 1 = extremely bothered). The overall PAQLQ score is the mean of all 23 responses and the individual domain scores are the means of the items in those domains.

- *Lung function:* Standard spirometry was carried out to measure FEV_1 (Forced Expiratory Volume in the first second) and FVC (Forced Vital Capacity), before and after administering a β2 agonist to identify reversibility, using a portable Microloop spirometer (Micro Direct, UK). We followed the ERS and ATS criteria for a correct spirometry[131] (Miller 2005). The centile spirometry values predicted for age and height were estimated using Global Lung Initiative standards[464], using 'Afro-American' standards for Afro-ecuadorians, 'Other' for mestizos and 'White' for white, as reported in the parental questionnaire. An increase of FEV>12% was taken to be a positive bronchodilator reversibility test. FEV post-bronchodilator improvement was calculated by the formula: (Post FEV - Pre FEV / Pre FEV) x 100.

Figure 4.6: Study nurse supervising spirometry at the study centre.

- *Fraction of Exhaled Nitric Oxide* (FeNO) was measured using NObreath device (Bedfont Scientific, UK), at a fixed flow of 50ml/sec. Three measurements were taken to choose the best performed one or the mean of those with the highest quality.

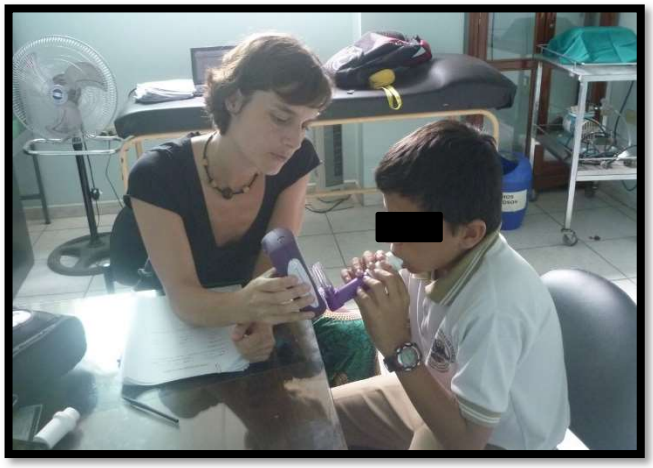


Figure 4.7: Principal investigator supervising FeNO measurements, at the study centre.

4.3.7. Laboratory procedures

Stool examinations

Single stool samples were analysed for geohelminth eggs and larvae by direct wet mount. They were then taken to the FEPIS (Fundación Ecuatoriana para Educación en Salud) laboratory in Quinindé, Esmeraldas, to do formol-ethyl acetate concentration analysis[465].

PCR for respiratory viral infections

Nasal wash aliquots were transported to the FEPIS laboratory situated at the Universidad Internacional de Ecuador (UIDE) in Quito, Ecuador, and stored at -80°C. Commercial kits (Qiagen) were used to extract RNA. Specific RNA for rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV) and parainfluenza viruses (PIV) 1–4 was converted to cDNA and amplified by reverse transcriptase real-time Polymerase Chain Reaction (PCR) (AgPath-IDTM One-Step RT-PCR kit, Invitrogen) using primer/probe combinations (Budge 2014) on a 7500 Fast machine (Applied Biosystems). A positive test was defined as Ct values ≤38.

IgE measurements

Plasma was shipped to Professor Tom Platts-Mills, Asthma and Allergy Center of the University of Virginia, Charlottesville, Virginia, USA, for measurement of total and specific IgE for *D. pteronyssinus*, *P. americana*, and *Ascaris* using the CAP system (Pharmacia Diagnostics). A positive assay for sIgE was defined as >0.70 kU/l. A sample of 33 plasma samples were shipped and analysed.

4.3.8. Study outcomes

Primary outcome:

- Time to an acute asthma exacerbation requiring emergency department attendance or systemic corticosteroid prescription during the 6 months following first attendance.

Secondary outcomes:

- Acute asthma exacerbation requiring emergency department attendance during the 6 months following first attendance.

- Acute asthma exacerbation requiring hospital admission during the 6 months following first emergency department attendance.

4.3.9 Definitions

a. Pets at home: Children were considered to have pets at home when the response to the question: '*Which of the following pets do you keep inside your child's home?',* was either: *'Dog, cat or other furry pets'.*

b. Humid household: Was defined as a positive response to the question: '*Does your child's home have damp spots on the walls or ceiling?*'

b. Urban setting: A child was considered to live in an urban setting when the response to the question: '*How would you describe the surroundings of your child's home?',* was: *'Urban with no parks or gardens.'*

c. Intense traffic near the house: A child was considered to have intense traffic near the house, when the response to the question: '*How intense is the traffic in the street where the child's home is located?',* was: *'Very frequent.'*

d. Exposure to tobacco smoke: Was defined as a positive response to the question: *Does anybody, at present, smoke inside your child's home?*

e. Severe attack in the last 12 months: was defined as a positive response to the question: '*In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?*'

f. Severe asthma attack: During the follow-up, a severe asthma attack was recorded as that needing emergency care attendance or systemic corticosteroid prescription. This is the definition included in the ATS/ERS 2009 statement[8].

4.3.10. Sample size calculations

We estimated that we would be able to recruit 350 children and expected to have a 50% emergency care re-attendance during the follow-up period, based on previous experience in this setting. This would represent around 50% of the total number of children treated for an acute asthma exacerbation at the HDTC emergency department in a year.

A cohort of 250-350 children would provide 80% power to detect factors that reduce the proportion of children re-attending the emergency room within 1 year from 50% to 31.4%% (hazard ratio of ≥1.46), and 90% power to detect factors that reduce the proportion of children re-attending emergency room within 1 year from 50% to 33.9% (hazard ratio of ≥1.37), using log-rank tests and actuarial statistical methods.

4.3.11. Statistical analysis

All statistical analysis was done using STATA 13.1, with confidence interval of 95%, and a level of significance of $p \leq 0.05$, to describe statistically significant results.

The primary outcome was an acute asthma exacerbation requiring emergency care, occurring between 2 weeks and 6 months after the index exacerbation. For children with more than one exacerbation during the study period, only the first exacerbation was taken into account. T-tests were used to examine continuous risk factors univariably. In the case of non-normal data, Mann-Whitney U-tests were undertaken. Categorical variables were compared using Fisher's exact test. Correlation between FeNO values and blood eosinophilia, as well as between the asthma control, asthma knowledge and quality of life tests, were estimated using simple linear regression. Multivariable logistic regression was used to evaluate the effects of multiple risk factors for emergency care re-attendance for acute asthma exacerbations. A time-to-event analysis was also performed, via a multivariable Cox proportional hazard model. Collett's method[466] of variable selection was used with a p-value threshold of 0.2, and confounding and interactions between variables were also assessed. The parsimonious logistic and Cox models were selected based on the explained variation (R^2). The proportional hazards assumption required by the Cox model was tested via the inclusion of time-dependent variables.

The predictive ability of the models was evaluated by estimating the area under the Receiver Operating Characteristics curve (ROC)[467], with 0.5 indicating a model with no discriminating power and 1.0 a perfectly discriminating model[468]. Internal validity was then assessed by bootstrapping techniques, using 200 random bootstrap samples with replacement, to evaluate potential upward bias (overfitting). Optimism in regression coefficients due to overfitting was estimated by measuring the difference between the

model's c-statistic (apparent c-statistic) and the c-statistic computed by nonparametric bootstrap resampling (internal bootstrap validation c-statistic)[469].

To investigate the effect of missing values for variables with greater than 5% of missing data we performed a sensitivity analysis using the "ice"[470] procedure for multiple imputation in Stata 13.1. The "mim" procedure in Stata[471] was then used to average the estimates of results across the 20 imputed data sets created, according to Rubin's rules[472]. The imputation models included all variables selected, the outcome of interest, and the Nelson Aalen estimator of the cumulative baseline hazard[473].

4.3.12. Data management, curation and storage

Information was collected directly from the child's parent or guardian by the study team, including only the participant's unique study number assigned at time of recruitment on the completed questionnaires. Consent forms, list of children's names with their study number and other identifiable data (contact details with detailed map of home location) were stored in a locked filling cabinet in the study clinic, with access limited to the site study team. They were then transferred to the FEPIS research unit in Quinindé where they are being stored in a dedicated secure facility.

Laboratory samples were labelled with the participant's unique identifier number at the collection or extraction point. Plasma was stored at -20°C in a secure facility at the FEPIS research unit in Quinindé with 24/7-back-up power from a dedicated generator.

All the information collected from the questionnaires and the different exam results were entered into a computer database, using double data entry. Data were entered daily, and any inconsistencies or missing information was checked with the participant's parents or guardians by phone or during the follow-up visit. The participant's study number was the only identifier included in this database. The study number accorded to each child was kept on a separate Excel File by the principal

investigator. The principal investigator's files were kept in a password protected computer, and backed-up in a password protected USB storage device and secure web-based files. All data collected, stored and shared complied with Good Clinical Practice (GCP) standards.

Access to the study database was password protected and limited to the principal investigator and PhD supervisors. Anonymised study databases were exported to SPSS/STATA to be analysed by the principal investigator with support from study supervisors and study statistician.

4.3.13. Ethical considerations

Studies with children

Children are always a vulnerable group, as it is their parents or guardians who decide what is best for them and they can also be easily manipulated. Our research included only children for the cohort study, as it is in this age group that we wished to study risk factors. A study of these characteristics in children is most urgently needed as they are the group least likely to receive preventive therapy, most likely to attend as an emergency, and are most vulnerable to loss of lung function (so they do not reach peak lung growth and have a longer duration of decline thereafter)[14].

The Declaration of Helsinki states that research should only be undertaken in vulnerable groups if "the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."[474]. This was the case of this study, which aimed to benefit the paediatric population with asthma in this setting. Asthmatic adult patients may not be used for this purpose, as their disease characteristics may differ greatly from those of children.

Even though it was the children's parents or guardians who signed the informed consent form, no child was forced to participate against their will, and those older than 7 years old, signed an informed assent form.

Studies in low and middle-income settings

It is indispensable for low resource settings to undertake research related to healthcare which addresses their burden of disease. However, they cannot always count on the necessary resources to do so, and for that reason, it is fundamental that externally-sponsored research that wishes to improve the health of the people living in these settings, is encouraged. Nevertheless, research in low and middle-resource settings poses many ethical challenges.

First, the research interest need to follow local priorities for research[475]. I designed my PhD project with the guidance of my supervisors, after I had been working in this setting for a year in the local public hospital and had understood the needs of asthmatic children and deficiencies in asthma care in this specific setting. As described in Chapter 2, asthma in Latin America is a public health problem and a research priority, and only through research undertaken in Latin American countries is that we may address this problem.

Second, we must prevent harm and exploitation of research participants[475]. Our study protocol was carefully designed and reviewed by two different Research Ethics Committees (local and the sponsor's), to assure that participants were not harmed or exploited in any way. It is vital that research undertaken in low-resource settings that is externally-sponsored, be independently reviewed in the sponsor's country as well as in the country where it will take place[475].

Third, according to the Council for International Organizations of Medical Sciences (CIOMS), the compensation offered to research participants, "should not be so large as

to persuade them to take undue risks or volunteer against their better judgment"[476]. In our study, participants were offered a small payment to cover travel costs when necessary, as well as guaranteed access to adequate management and treatment for the child's asthma, something which was not always available outside the study centre. Both incentives for individuals to participate were considered appropriate and did not constitute coercion for participation[477].

Fourth, a complete understanding of the informed consent may always be difficult to assure in a low-resource setting where health literacy may be limited[477]. Bearing this in mind, the informed consent form for our study contained detailed but simple and easy to understand information concerning the study objectives and procedures. We had used a very similar form in a previous study in this same setting[34], with a positive response from the research participants as to the level of understanding of the information transmitted. Similarly, children were given a simplified informed assent form using more elementary vocabulary, that was read out to them.

Finally, cultural differences should be always considered when undertaking research in a different country with a different culture, concept of illness and disease, doctor-patient relationship, traditional medicine and beliefs[475]. As mentioned already, I had lived and work in this same setting for over a year before undertaking the study. I tried to acknowledge all these cultural differences when designing the study to assure the success of the project and the respect of the research participants.

Offering additional research-supported services

The major ethical issue involved in this research is that the majority of the asthmatic children recruited for the study with an episode of acute asthma were not taking any baseline treatment such as inhaled corticosteroids (ICS), which are the most effective controller therapy, and are the recommended treatment for asthma for children of all ages[37]. The standard of care offered to research participants in a low-resource setting is

still under debate, as some believe they should be offered the same health care they would receive if treated in the sponsoring country to avoid exploitation[478]. Others allege that providing a universal standard (the best available treatment) would prevent sponsors from undertaking research in low-resource settings[475], as well as act as a coercion for research participants.

There is still controversy between guidelines on which children need to be started on ICS, given the different classifications of asthma severity and control. The 2017 GINA guidelines state that one severe exacerbation in the last year is enough to classify the child's asthma as persistent or not well controlled and should be therefore started on ICS[37]. On the other hand, the Expert Panel Report 3 Guidelines for the Diagnosis and Management of Asthma[6], include specific guidelines for management of children 5-11 years old who are not currently taking long-term control medication. They classify asthma as intermittent if they fulfil the impairment component and have 1 or no exacerbations per year (defined as those needing a short course of oral corticosteroids). In this case they only recommend short-acting beta-agonists as needed for symptoms[6].

Locally, the Ecuadorian Guidelines[146] include a specific section for childhood asthma, for which they follow the Spanish Asthma Guide (Guía Española de Manejo de Asma, GEMA 2009[479] guidelines (Spanish guide for Asthma Management). They classify asthma as occasionally episodic (5 or fewer episodes per year), frequently episodic (6-8 episodes per year), moderate persistent (1 episode per month) and severe persistent asthma (see definitions in Chapter 2). According to this, patients with occasionally episodic asthma do not need to be on daily ICS.

If we were to follow these national recommendations, we would only start children on ICS if we recorded 6-8 episodes of acute asthma during the study period. On the other hand, following Ecuadorian law, as we were working with the city's public hospital

patients, we were only able to offer the drugs available through the Ministry of Public Health. This is the approach we decided to implement for the study, to assure an adequate asthma management on one side, and so not to disrupt the usual management these children should be receiving in our absence and be able to explore the risk of re-attendance for acute asthma before any changes in management were implemented. However, even following the national guidelines and offering only the treatments available through the Ministry of Public Health (inhaled corticosteroids), the children were receiving a better asthma care than that normally offered at the hospitals and health centres from which they were recruited. At these centres, most doctors do not prescribe any baseline treatment for asthma[34] and patients are not regularly followed-up for their asthma, let alone educated on self-management and prevention. Therefore, during the cohort study, some patients varied their usual asthma care, as they received education sessions on asthma and written asthma action plans, together with their reliever and baseline treatment inhalers. Nevertheless, as the education and treatment offered was the same for all participants, the analysed predictors of re-attendance for acute asthma should not have been greatly biased.

4.3.14. Ethical approval

Every effort was made to safeguard the participants' confidentiality throughout the study. Stored laboratory samples were identified by the study number and date of collection. The study protocol was approved by the Bioethics Committees of the Liverpool School of Tropical Medicine Research Committee (Research Protocol 14.021RS2) and the Pontificia Universidad Catolica del Ecuador (PUCE). The latter has federal-wide assurance from the US department of Health and Human Services.

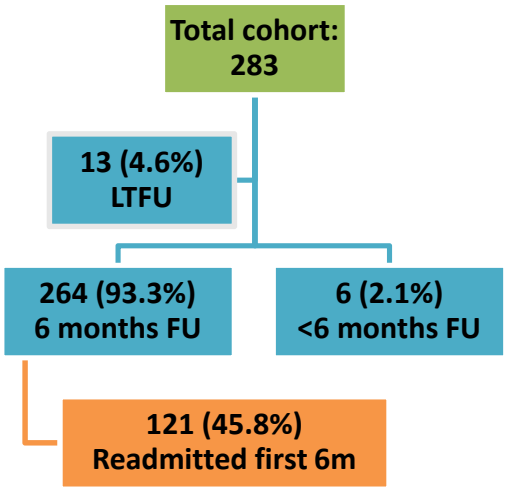
4.4 Results

4.4.1 Cohort characteristics

A total of 283 children were recruited over 18 months. After the first three months, the study recruitment location was extended to another hospital in the city managed by the government's national insurance (Instituto Ecuatoriano del Seguro Social (IESS) Hospital), and to three health centres with emergency services.

The number of potentially eligible participants could not be ascertained given the lack of an electronic record of children attended at the public hospital (HDTC) and the health centres. We did not record either the exact recruitment location of each participant, as some of them were seen at more than one location during the index asthma attack.

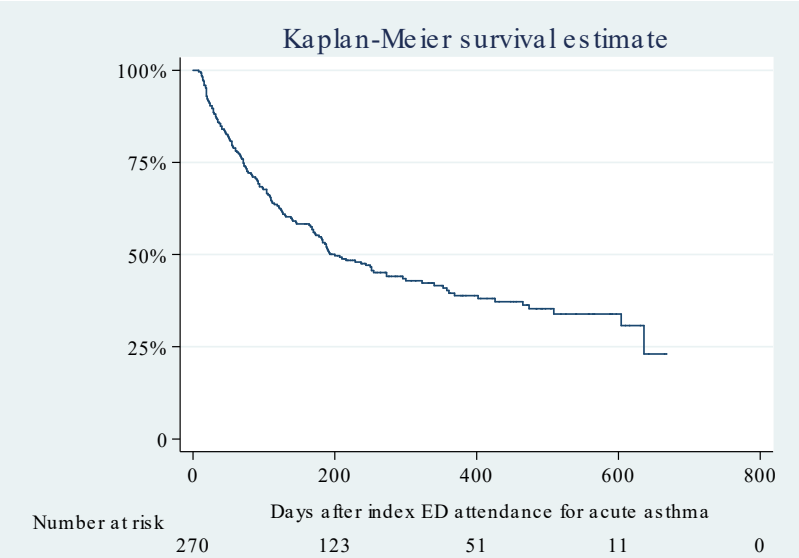
Figure 4.8: Number of participants recruited and completing 6 months follow-up.



Thirteen children (4.6%) were lost to follow-up after the initial recruitment visit, and 264 (93.3%) completed 6 months follow-up. Of these, 121 (45.8%) suffered a subsequent asthma exacerbation requiring emergency care during the first 6 months (Figure 4.8 and 4.9). The median follow-up time was 407.5 days (IQR: 265-541 days,

range 44-697 days) and the median time to a subsequent asthma exacerbation was 91 days (IQR: 39-178 days).

Figure 4.9: Kaplan-Meier curve of the cases of subsequent severe asthma attacks over time (requiring emergency care re-attendance or systemic corticosteroid prescription).



Sociodemographic, personal and family history

The sociodemographic, personal and family history for the whole cohort are shown in Table 4.1. The median age was 8 years old (range: 5-15), 59% were male and more than half (54%) self-reported as Afro-Ecuadorians. The median total years the mother and father had studied was 24 (range: 0-36), which is equivalent to finishing secondary education. Two thirds of the children lived in an urban setting and one third reported intense traffic near the house. The median household monthly income was 400 USD (range: 0-12000), slightly over the national minimum wage. Less than 20% reported being exposed to tobacco smoke, half of the houses had humid stains and 43% had pets at home.

Table 4.1: Socio-demographic characteristics, personal and family history of the whole cohort and divided by readmission status at 6-month follow-up.

		Total Cohort	Readmission by 6 months		
			Yes	No	P
Age (median, IQR)		8 (6-11)	7 (5-10)	9 (7-11)	<0.001
Sex male (%)		58.7	60.3	59.2	0.900
Ethnicity (%)	Afro-Ecuadorian	53.8	52.1	54.7	0.963
	Mestizo	42.9	44.6	41.7	
	White	1.5	1.7	1.4	
	Other	1.9	1.7	2.2	
BMI (median, IQR)		16.6 (15.1-19.4)	16.4 (15.0-19.2)	16.9 (15.1-19.7)	0.265
Siblings (%)		89.6	88.4	90.9	0.547
No. of years mother and father studied (median, IQR)		24 (18-28)	24 (18-28)	24 (19-29)	0.304
Early life respiratory illness (%)		48.7	58.5	40.1	0.013
Allergic rhinitis ever (%)		72..0	74.4	70.0	0.490
Allergic rhinitis diagnosis (%)		20.5	20.0	21.0	0.878
Eczema ever (%)		13.0	14.1	12.1	0.713
Eczema diagnosis (%)		4.2	6.6	2.1	0.119
Paternal/maternal asthma (%)		46.3	52.7	40.6	0.175
Paternal/maternal asthma/rhinitis/eczema (%)		68.4	69.9	66.4	0.788
Pets at home (%)		42.9	44.6	41.8	0.708
ETS (%)		18.3	16.5	20.6	0.474
Humid household (%)		46.6	41.3	51.1	0.137
Urban setting (%)		65.7	59.5	69.5	0.094
Intense traffic near house (%)		30.1	29.8	30.3	1.000
Monthly household income (USD) (median, IQR)		400 (255-700)	400 (260-700)	350 (250-700)	0.981

ETS: Exposure Tobacco Smoke; IQR: Interquartile range; USD: US Dollars; BMI: Body Mass Index.

As for the children's personal history, half of the cohort had a history of an early life respiratory illness associated with wheezing and difficulty breathing (bronchiolitis), and 72% and 13% reported symptoms of allergic rhinitis and eczema ever in life, respectively. Forty six percent of the children had a family history of asthma (either father or mother) and 68% had a family history of allergic disease (eczema, asthma or allergic rhinitis). Less than 7% of the children were recruited during their first ever episode of acute bronchospasm and less than 15% of the total 283 did not suffer any wheezing episodes during the previous year (Table 4.2). Thirty-six percent did not have a previous doctor's asthma diagnosis and 2% were receiving long-term treatment with inhaled corticosteroids.

Table 4.2: Asthma characteristics and history of the whole cohort and divided by readmission status at 6-month follow-up.

		Total Cohort	Readmission by 6 months		
			Yes	No	P
Wheezing ever (%)		93.5	97.5	90.1	0.021
Wheezing last 12m (%)		86.5	93.3	80.7	0.003
No. attacks last 12m (median, IQR)		3 (2-6)	5 (2-6)	3 (1-5)	<0.001
Days since last attack (median, IQR)		60 (30-120)	60 (30-120)	60 (30-150)	0.120
Wheezing at night last 12m (%)	Never	18.8	15.8	21.3	0.424
	<1 night per week	1.2	1.7	0.7	
	≥1 night per week	13.8	16.7	11.4	
	Only during acute attacks	66.3	65.8	66.7	
Severe attack last 12m (%)		36.0	44.2	29.8	0.014
Wheezing with exercise (%)	No	35.8	29.9	40.9	0.188
	Yes	40.2	44.4	36.5	
	Only during acute attacks	24.0	25.6	22.6	
Asthma diagnosis (%)		64.2	76.5	53.9	<0.001
Number of triggers		4 (2-6)	4 (3-6)	4 (2-5)	0.117
Food as trigger (%)		36.9	46.2	28.9	0.006
Doctor visit for acute asthma last 12m (%)	None	15.3	8.3	21.3	<0.001
	1-3	49.4	45.8	52.5	
	4-12	27.2	31.7	23.4	
	>12	8.1	14.2	2.8	
Doctor visit for asthma control last 12m (%)	None	68.2	65.0	71.1	0.592
	1-3	24.0	25.8	22.5	
	4-12	7.4	8.3	6.5	
	>12	0.4	0.8	0	
ICS treatment (%)		2.0	0.9	3.0	0.374
Emergency visits last 12m for asthma (%)		76.0	78.5	73.8	0.388
No. ER visits last 12m for asthma (median, IQR)		2 (1-4)	3 (1-6)	2 (0-3)	0.006
No. IV/IM CS courses last 12m for asthma (median, IQR)		0 (0-1)	1 (0-3)	0 (0-1)	<0.001
Ever admitted for asthma (%)		25.2	33.9	17.7	0.004
Admitted to hospital for asthma last 12m (%)		7.6	11.6	4.2	0.034
Ever admitted to ICU for asthma (%)		10.0	13.3	7.1	0.102

IQR: Interquartile range; m:months; ER: emergency room; ICU: Intensive Care Unit.

The median number of acute asthma attacks during the previous 12 months was three (range 0-24) and the median time since the last attack was two months (range 0-365 days). Markers for asthma severity in the last 12 months were reported as follows: wheezing ≥1 night per week 14%, wheezing with exercise 40%, and severe attack 36%.

Eighty-five percent of the children had visited a doctor at least once (35% more than four times) for acute asthma and 32% for a control visit (8% more than four times) during the previous 12 months. Three quarters of the cohort had visited the emergency department for an acute attack during the previous year, with a median number of 2 visits (range: 0-30) and 0 courses (range: 0-12) of intramuscular or intravenous corticosteroids courses in the last year. As for history of hospital admissions for asthma, 25% and 10% had been ever admitted to hospital and ICU, respectively, and 7.5% had been admitted to hospital in the previous 12 months.

Allergy and inflammatory markers

Table 4.3 includes the results from the allergy and inflammatory markers, as well as the lung function tests. The median percentage of blood eosinophils was 5.0% (range: 0-18%), the total count 372 cells/ml (range: 0-2368) and the median nasal eosinophils was 11% (range: 0-100%). One third of the children had blood eosinophilia (defined as 5% or higher), while 72% of them had nasal eosinophilia (defined as 5% or higher). The median FeNO was 33 ppb (range: 0-300) at a flow rate of 50ml/s (which is defined as high for children). There was no correlation between the proportion of nasal eosinophils and the FeNO measurements ($r=0.038$, $p=0.880$), nor between the proportion of blood eosinophils and FeNO ($r=-0.11$, $p=0.907$), using simple linear regression.

Table 4.3: Allergy and inflammation markers, and lung function parameters of the whole cohort and divided by readmission status at 6-month follow-up.

	Total Cohort	Readmission by 6 months		
		Yes	No	P
Haemoglobin (mean, SD)	13.0 (0.86)	12.9 (0.87)	13.1 (0.84)	0.032
Blood eosinophils (median, IQR)	372 (185-729)	306 (147-653)	449 (227-790)	0.061
Blood eosinophils (%) (median, IQR)	5.0 (2.0-8.0)	4.0 (2.0-7.0)	5.0 (3.0-8.5)	0.071
Blood eosinophilia (%)	33.0	28.1	37.1	0.148
Nasal eosinophils (%) (median, IQR)	11.0 (4.5-22)	9.5 (4.5-26)	13.3 (4.3-22)	0.595
Nasal eosinophilia (%)	72.1	72.7	71.6	1.000
FeNO measurements (ppm) (median, IQR)	33 (3-79)	31 (1-72)	40 (12-99)	0.095
Pre FEV_1 (% of predicted) (median, IQR)	97 (86-107)	94 (84-106)	98 (88-108)	0.112
Pre FEV_1 Z-score (median, IQR)	-0.24 (-1.09-0.51)	-0.46 (-1.26-0.44)	-0.18 (-0.92-0.70)	0.100
Pre FEV_1/FVC (median, IQR)	91 (85-97)	92 (87-98)	91 (84-97)	0.613
Pre FEV_1/FVC Z-score (median, IQR)	0.24 (-0.61-1.15)	0.27 (-0.57-1.07)	0.23 (-0.72-1.15)	0.658
Post FEV_1 (% of predicted) (median, IQR)	105 (93-115)	104 (93-114)	106 (93-115)	0.650
Post FEV_1 Z-score (median, IQR)	0.35 (-0.53-1.16)	0.33 (-0.58-1.06)	0.43 (-0.51-1.25)	0.526
FEV_1 improvement (%) (median, IQR)	6.3 (1.7-13.7)	6.4 (1.9-14.6)	5.7 (1.3-12.7)	0.286

SD: Standard deviation; IQR: Interquartile range; FeNO: Fraction of Exhaled Nitric Oxide; FEV_1: Forced Expiratory Volume 1st second; FVC: Forced Vital Capacity.

Total and allergen specific IgE were only measured for a subsample of 33 participants, given unexpected problems in transporting the samples from Ecuador to the US (Ecuadorian law changed during the study period). The median total IgE was 982 kU/l. Five of the 33 samples were negative for mite IgE (D. pteronyssinus and B. tropicalis IgE <0.70 kUA/l), which indicated that 85% of the children in the subsample were atopic to mite.

Respiratory viruses

The first 25 samples were tested for rhinovirus, respiratory syncytial virus (RSV), parainfluenza virus 1 and 3 (PIV 1 and PIV 3), human metapneumovirus (HMPV) and

adenovirus Hco2 HKU1, Hco3 N63. None of them were positive for adenovirus, PIV1 and PIV3, and only one of them was positive for HMPV. Given the very low prevalence of the PIV 1 and 3, HMPV and adenovirus, the rest of the available samples were tested for rhinovirus and RSV, alone. Of the total 243 samples, 84 (34.6%) were positive for rhinovirus and 11 (4.5%) were positive for RSV.

Intestinal helminths

Of the 147 stool samples obtained, 2 were positive for *Ascaris lumbricoides* and 1 for *Trichuris trichiura.* There were no other intestinal helminths in the analysed samples.

Lung function

The children had a median pre-bronchodilator FEV1 value of 78% (range: 48-122%) of predicted for age and size, a FEV1/FVC median ratio of 91% (range: 65-166%), and a post-bronchodilator FEV1 value of 86% (range: 53-138%) of predicted.

109 (40%) of the 270 children that underwent spirometry had a positive response to bronchodilator (FEV1 predicted improvement >12%).

Asthma control, asthma knowledge and quality of life

The results of other tests included in the preliminary child's study are shown in Table 4.4. Sixteen percent of the participating children had uncontrolled asthma according to the ACT and C-ACT scores. The median score for the Asthma Control Test was 16 (range: 10-24) for the adult version (ACT) (considered uncontrolled asthma if below 20) and 16 (Standard Deviation, SD: 3.75) the mean C-ACT (childhood version). Specific knowledge of asthma was low, with a median score in the Newcastle Asthma Knowledge Questionnaire (NAKQ) of 18 out of 31 (range: 9-27). The median score for the PAQLQ (Pediatric Asthma Quality of Life Questionnaire) completed by 222 children was 3.5 (IQR: 3.0-4.0), of a 1-7 scale, the lower score representing a poorer QoL. The

median scores for each PAQLQ domain were: symptoms 3.5 (IQR: 2.8-4.1); activity 3.4 (IQR: 2.6-4.0); emotional 3.7 (IQR: 3.1-4.5).

Table 4.4. Results for the Asthma Control Tests (ACT and C-ACT), Newcastle Asthma Knowledge Questionnaire and the Pediatric Quality of Life Questionnaire of the whole cohort and divided by readmission status at 6-month follow-up.

	Total Cohort	Readmission at 6 months		
		Yes	No	P
C-ACT score (mean, SD)	16.03 (3.75)	15.4 (4.05)	16.5 (3.41)	0.077
ACT score (median, IQR)	16.0 (13-18)	16 (14-18)	15.5 (13-18)	0.936
NAKQ score (median, IQR)	18.0 (16-20)	17 (15-20)	18 (16-21)	0.041
PAQLQ total score (median, IQR)	3.5 (3.0-4.0)	3.5 (2.9-4.0)	3.5 (3.0-4.2)	0.275
PAQLQ symptom score (median, IQR)	3.5 (2.8-4.1)	3.6 (2.8-4.0)	3.5 (2.8-4.2)	0.479
PAQLQ activity score (median, IQR)	3.4 (2.6-4.0)	3.4 (2.6-4.0)	3.4 (2.6-4.2)	0.525
PAQLQ emotional score (median, IQR)	3.7 (3.1-4.5)	3.5 (3.0-4.2)	3.9 (3.2-4.6)	0.030

SD: Standard deviation; IQR: Interquartile range; C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; NAKQ: Newcastle Asthma Knowledge Questionnaire; PAQLQ: Pediatric Asthma Quality of Life Questionnaire.

We studied the correlation between asthma knowledge, asthma control and asthma related quality of life using simple linear regression. There was no correlation between asthma knowledge and asthma control or quality of life. Asthma control as measured by ACT (taken by children older than 12 years old) was positively correlated with quality of life as measured by the PAQLQ total score (r= 0.297, p=0.041).

4.4.2. Risk factors for emergency care re-attendance

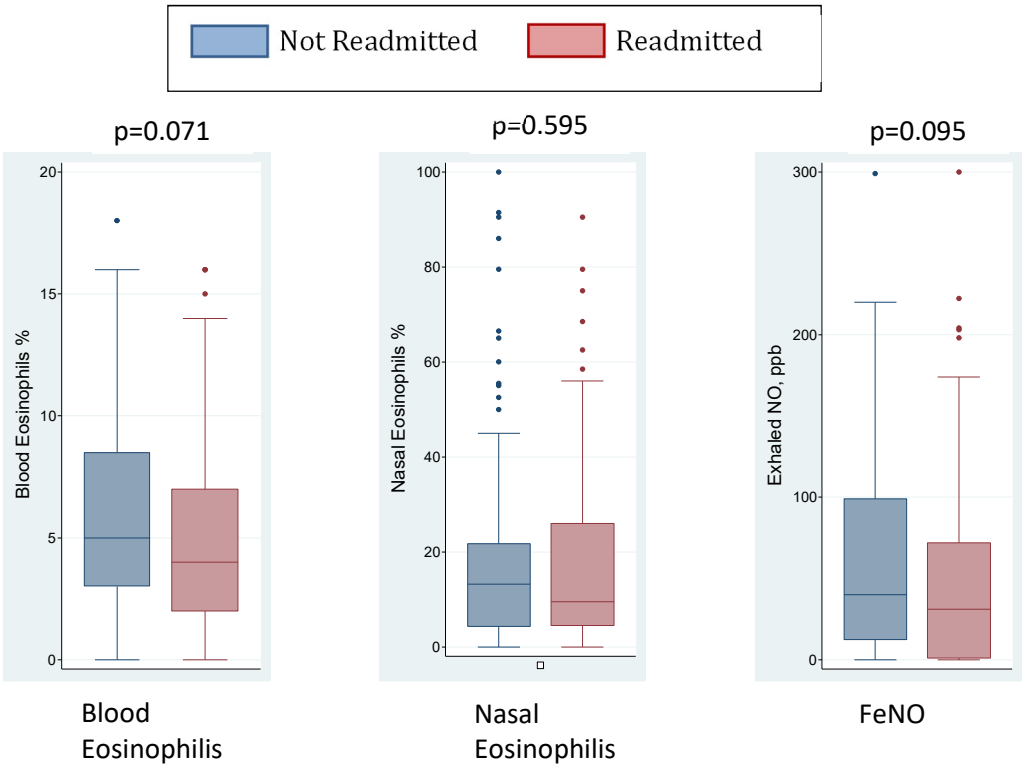
Re-attendance by six months

Tables 4.1-4.4 show the results of the socio-demographic, personal and family history, asthma characteristics, the allergy and inflammatory markers divided by readmission status after the first 6 months of follow-up following the initial emergency care attendance for acute asthma. In univariable analyses, risk factors for recurrence were: younger age, early life severe respiratory illness, food triggers, previous asthma

diagnosis, number and severity of previous attendances for asthma and lower haemoglobin levels.

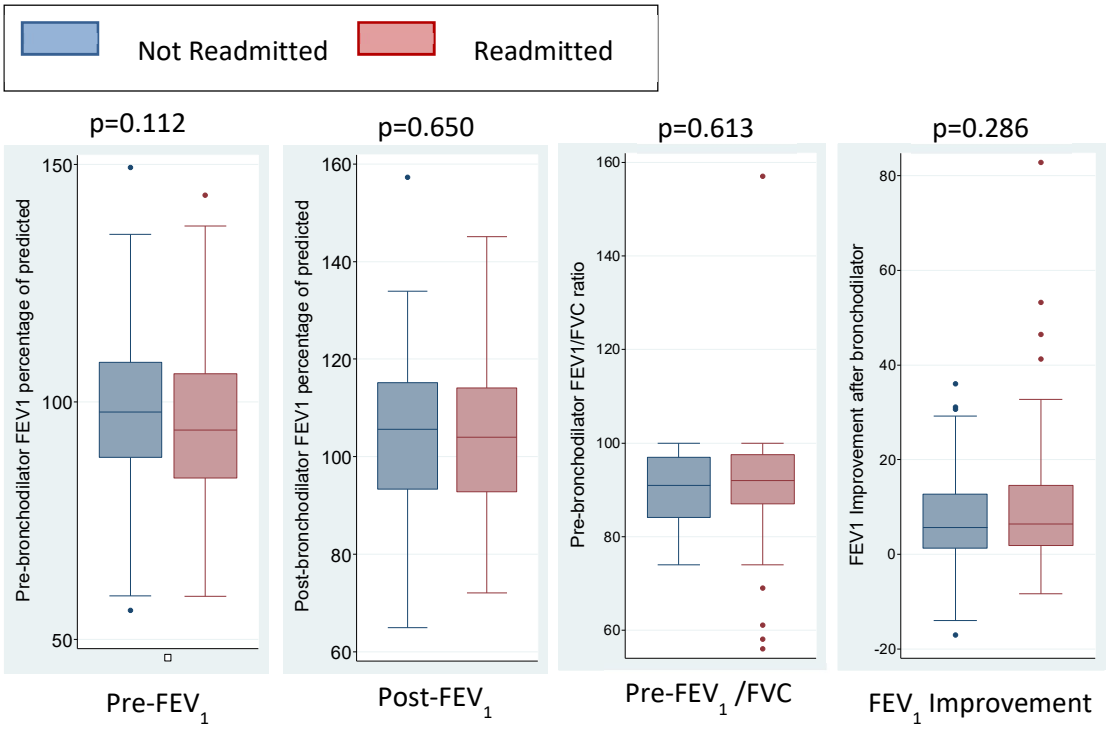
a. Allergy and inflammatory markers and lung function: There were no differences in the blood and nasal eosinophilia or FeNO measurements between those that were readmitted during the first 6 months and those that were not (Table 4.3 and Figure 4.10). The same was true of the different lung function parameters (Table 4.3 Figure 4.11).

Figure 4.10: Allergy and Inflammatory Markers Box Plots. P values represent the differences between the medians and the distribution of the data of those readmitted vs those not readmitted as measured by Mann-Whitney U-test.



FeNO: Fraction of Exhaled Nitric Oxide

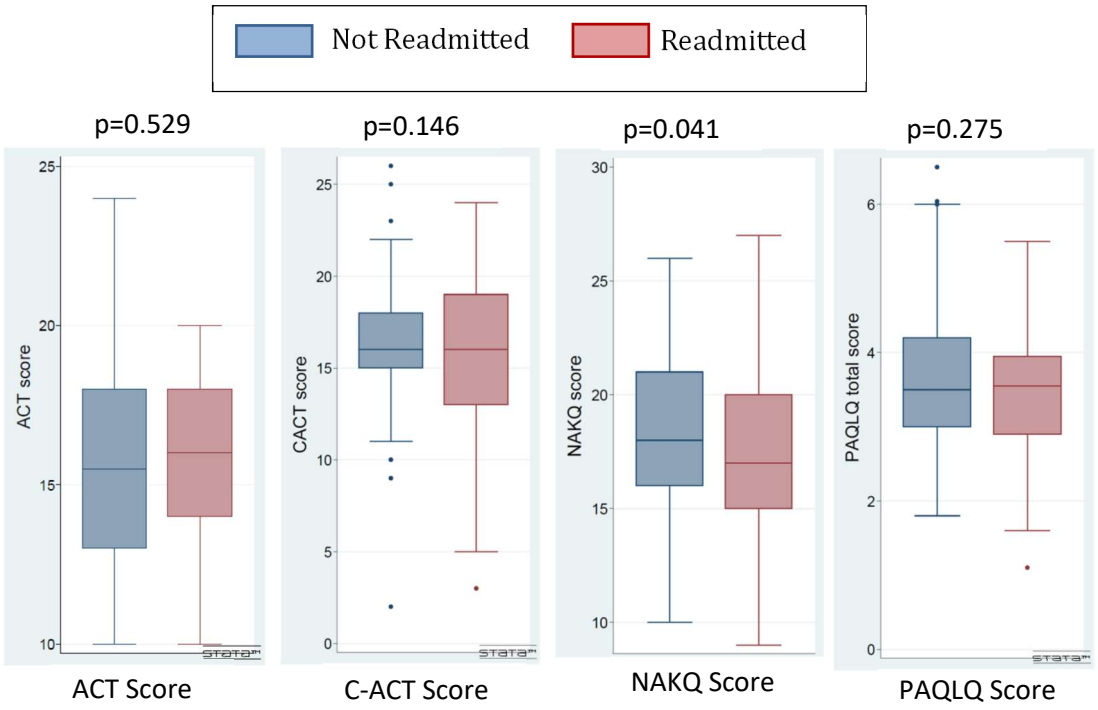
Figure 4.11: Lung Function Parameters Box Plots. P values represent the differences between the medians and the distribution of the data of those readmitted vs those not readmitted as measured by Mann-Whitney U-test.



FEV_1: Forced Expiratory Volume 1st second; FVC: Forced Vital Capacity

b. Asthma control, asthma knowledge and quality of life: The parents of children who were readmitted at 6 months for acute asthma, showed less specific asthma knowledge (NAKQ score). There were no differences in the level of asthma control (ACT and C-ACT scores). A high NAKQ (OR: 0.91, 95% CI: 0.85-0.98) and PAQLQ emotional domain (OR: 0.72, 95% CI: 0.55-0.94) score were associated with a lower risk of subsequent asthma attacks requiring emergency care. We found no significant association between PAQLQ total score, symptoms or activity domain, and future risk.

Figure 4.12: Asthma control tests, asthma knowledge (NAKQ) and quality of life (PAQLQ) Box Plots. P values represent the differences between the medians and the distribution of the data of those readmitted vs those not readmitted as measured by Mann-Whitney U-test.



C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; NAKQ: Newcastle Asthma Knowledge Questionnaire; PAQLQ: Pediatric Asthma Quality of Life Questionnaire.

c. Respiratory viruses: The proportion of children with a positive sample for rhinovirus and RSV did not differ between those that suffered a subsequent severe asthma attack and those that did not during the first 6 months follow-up (Table 4.5).

Table 4.5. Results for the respiratory viruses analysed by PCR from the nasal wash samples, of the whole cohort and divided by readmission status at 6 month follow-up.

	Total Cohort (229)	**Readmission by 6 months**		
		Yes	No	P
RSV (number, %)	10 (4.4)	5 (4.9)	5 (4.0)	0.757
Rhinovirus (num, %)	79 (34.5)	39 (37.9)	40 (31.8)	0.402

RSV: Respiratory Syncytial Virus.

Multivariable analysis

In the final multivariable logistic regression model, younger age, an existing asthma diagnosis, food triggers, number of intravenous or intramuscular corticosteroid courses

for acute asthma in the previous 12 months, and previous eczema diagnosis, were associated with a higher risk of subsequent asthma exacerbations requiring emergency care in the 6 months following the index ED attendance (Table 4.6). The area under curve (AUC) of the model was 0.73 (c-statistic) and the model explained 13% of the variation. After internal validation (bootstrapping), the AUC reduced to 0.72 and the R^2 to 14%, indicating little overfitting of the regression coefficients. This was estimated by measuring the difference between the model's c-statistic (apparent c-statistic) and the c-statistic computed by nonparametric bootstrap resampling (internal bootstrap validation c-statistic)[469].

Table 4.6. Multivariable logistic regression for the risk of ER re-attendance for acute childhood asthma during 6 months follow-up.

	Crude OR	95% CI	P value	Adjusted OR*	95% CI	P value
Age	0.87	0.79-0.95	0.001	0.87	0.79-0.96	0.006
Existing asthma diagnosis	2.78	1.62-4.76	<0.001	2.17	1.19-3.94	0.011
No. IV/IM CS courses last 12m for asthma	1.36	1.15-1.61	<0.001	1.28	1.08-1.53	0.006
Food as trigger	2.11	1.25-3.55	0.005	1.99	1.11-3.55	0.020
Eczema diagnosis	3.26	0.84-12.6	0.086	4.22	1.02-17.54	0.048

*: Adjusted Odds Ratios were adjusted for all other variables in the model. OR: odds ratio, CI: confidence interval; IV: intravenous; IM: intramuscular; CS: corticosteroids. P values to 3 decimal places.

Cox regression analysis

Table 4.7 shows the final Cox regression model. Children of a younger age, with an existing asthma diagnosis, a greater number of intravenous or intramuscular corticosteroid courses for acute asthma in the previous 12 months, and not living in an urban setting showed a higher rate of recurrent acute asthma exacerbations requiring emergency care over time. The AUC of the model was 0.65 (c-statistic) and overfitting of the model was estimated as <1% after bootstrapping. This was estimated using the same method as for the logistic regression model (see above). The proportional hazards assumption was valid for all included variables.

Table 4.7. Multivariate Cox regression model for the risk of ER re-attendance for acute childhood asthma.

	Crude HR	95% CI	P value	Adjusted HR*	95% CI	P value
Age	0.92	0.87-0.97	0.002	0.93	0.88-0.98	0.009
Existing asthma diagnosis	1.78	1.26-2.53	0.001	1.66	1.15-2.39	0.007
No. IV/IM CS courses last 12m for asthma	1.17	1.10-1.24	<0.001	1.13	1.06-1.20	<0.001
Urban residence	0.65	0.47-0.89	0.007	0.69	0.50-0.95	0.023

**: Adjusted Hazard Ratios were adjusted for all other variables in the model. HR: hazard ratio, CI: confidence interval; IV: intravenous; IM: intramuscular; CS: corticosteroids.*

4.4.3. Post-hoc analysis

Differences urban vs rural

As living in a rural environment was found to be a risk factor for emergency care re-attendance for acute asthma, we aimed to undertake a post-hoc analysis to explore any possible differences between the children living in rural or sub-urban, compared to those living in urban environments. The only differences observed are shown in Table 4.8.

Table 4.8. Results for the exposures that differed between the children residing in an urban vs. rural area.

	Urban (176)	Rural (92)	P value
Humid household	90 (51.4%)	35 (38.0%)	0.040
Days since last attack	75 (30-135)	44 (30-90)	0.0031
FeNO	29 (1-73)	43 (14-97	0.0316
NAKQ	19 (16-21)	17 (16-21)	0.0270

It was more common to have evidence of humidity in the household for children living in an urban environment than those from a rural one. This factor was not associated with the risk of future acute asthma attacks requiring emergency care. Additionally, the time elapsed between the acute asthma attack and the current one at which children were recruited was shorter for rural than urban children (Table 4.8). As before, this was not identified initially as a predictor for emergency care re-attendance for acute

asthma, though it may be an indicator that the population of rural children attended at the city's ER suffer more frequent attacks than those coming from the urban area and may be therefore at a greater risk of suffering subsequent attacks. Rural children also had a higher median FeNO value, which indicates a greater lung eosinophilic inflammation, and their caregivers obtained a lower score on the asthma knowledge questionnaire (NAKQ). This latter factor was initially identified as a predictor for future severe acute asthma attacks, though the association disappeared when adjusted for other related factors in the multivariable analysis.

Sensitivity analysis

To investigate the effect of missing values for variables with greater than 5% of data missing we performed a sensitivity analysis using multiple imputation. There were no differences in the final logistic regression and Cox regression multivariable models obtained when using the multiple imputation dataset compared to the original dataset (data not shown).

4.5. Summary of findings

There were two relevant and important findings in this cohort study: i) we characterised a cohort of asthmatic children with acute asthma recruited from an emergency care room in a low-resource setting in tropical Latin America; and ii) we identified independent predictors for emergency care re-attendance for severe asthma attacks among children treated at an emergency room in Ecuador.

Many of the children treated at an emergency room for an episode of acute bronchodilator-responsive wheezing were previously underdiagnosed, inadequately managed and had received no formal asthma education, as reflected by the low asthma knowledge of the caregivers, the poor asthma control and the deficient baseline treatment. This cohort of children appears representative of a Latin American urban

population, of low socioeconomic status, with atopy (family history, concomitant allergic rhinitis, nasal eosinophilia and positive allergen specific IgE to mite) and frequent severe asthma exacerbations.

Forty six percent of the children suffered a subsequent severe asthma requiring emergency care during the first 6 months after the index attack. From the identified predictors for emergency care re-attendance for severe asthma attacks, previous severe asthma exacerbations was the most reliable predictor of future risk: each acute corticosteroid course received during the previous year for acute asthma increased the odds of a subsequent attack requiring emergency care by a factor of 1.28. Other factors relating to the risk of attack and the time to the next attack were similar, though not the same, and included: younger age, an existing asthma and/or eczema diagnosis, food triggers for asthma attacks and rural residency. In this unselected cohort, none of the biomarkers or lung function parameters, were useful for predicting future risk of severe attacks. These predictors could be combined into a user-friendly risk assessment tool to be used at the emergency room by the treating doctor of the child with an acute asthma attack. Even though such risk assessment tool has not yet been formally developed and validated, here is a representation of how it might look:

Table 4.9 Initial model of the risk assessment tool

<table>
<tr><th></th><th>LOW RISK</th><th>AVERAGE</th><th>HIGH RISK</th></tr>
<tr><td>Age: 5-6 years old</td><td rowspan="4">Answered Yes to ≤ 1 question</td><td rowspan="4">Answered Yes to 2 questions</td><td rowspan="4">Answered Yes to ≥ 3 questions</td></tr>
<tr><td>Previous asthma diagnosis</td></tr>
<tr><td>Received at least one IV/IM corticosteroid course during previous 12m for asthma</td></tr>
<tr><td>Lives in a rural setting</td></tr>
</table>

According to this classification, 68% of the children from this cohort classified as high risk suffered a subsequent asthma attack requiring emergency care in the following 6 months, compared to the 28% classified as low risk.

4.6. Strengths and limitations of the study

This study included a relevant number of children treated for acute bronchospasm at the ED in Esmeraldas and attained a high follow-up rate and an accurate record of subsequent asthma attacks by keeping continuous contact with the study participants. The comprehensive questionnaire and laboratory tests together with the lung function and FeNO measurements were designed to explore a broad range of potential risk factors that could be associated with the risk of subsequent severe asthma attacks, including those normally available or measured in high income country paediatric practice, though not routinely used in Latin America. Furthermore, the study represented real-life asthma attending emergency rooms, by including all the bronchodilator-responsive wheeze, irrespective of their previous asthma diagnosis or their lung function parameters.

However, the study has several limitations. First, the fact that this cohort of asthmatic children were actively followed-up, educated and offered a written asthma action plan, may have modified their asthma knowledge, treatment adherence and self-efficacy in treating asthma attacks. However, all the children were treated alike and in accordance with local and international guidelines, so the predictors we identified likely represent the reality of the setting.

Second, the study population has certain specific characteristics (race, socioeconomic status, asthma knowledge, etc.), which may differ from other Latin American settings, given its large geographical area and population diversity. Nonetheless, Latin American cities, where asthma is more prevalent, share common characteristics such as

overcrowding, air pollution and greater exposures to dirt (e.g. an unhygienic environment) in low-resource areas.

Third, we were only able to recruit an estimated 60% of all bronchodilator-responsive wheeze episodes treated at the ED during the study period. However, this is only an estimation, as we did not record the potential number of eligible participants for two reasons. First, during the first months in the public hospital (HDTC) and during the whole study in the health centres, there was no electronic records of patients seen at the ED and the paper record system was very incomplete and unreliable, therefore we did not know the total number of patients seen with an acute asthma exacerbation. Second, the initial diagnosis recorded in the paper records was not ascertained in those patients who were not contacted or who did not come the study clinic to participate in the study. We could therefore not be sure whether the patients were eligible or not.

In addition, we do not have data to assess differences between those included and those not included in our analysis, other than the age of the child, his/her caregivers name and address available at the hospital's record. Reasons for not being recruited were: i) did not wish to leave a contact number with the study team to call them; ii) not having a contact number (mobile phone or land line); iii) providing incorrect contact details; iv) not wishing to participate when contacted later by the study team; and v) not being available for an appointment during office hours, or missing the scheduled appointment on at least 3 occasions (after which we did not arrange another appointment unless the participant's caregiver demanded it). Non-participation may have introduced some form of selection bias in the final study sample. For example, not having a contact number is a proxy for low socioeconomic status and such children could have been underrepresented in our sample. However, they were given an information sheet at the emergency department and told they could visit the study office the next day without a scheduled appointment.

Fourth, we did not have the opportunity within the restricted time of the study to increase the sample size further or validate a possible risk-assessment tool such as that shown above in a different setting. We managed to increase patient recruitment initially, by including further health centres and hospitals in Esmeraldas, increasing the number of children recruited to attain the minimum sample size. We then made arrangements to augment the sample by inclusion of health centres in two other cities, Guayaquil and Santo Domingo, but were unable because of bureaucratic impediments. Although a prediction model has not been validated, the predictors identified could be used to guide the decision-making process at the ED when treating a child with an acute asthma exacerbation.

Finally, we did not classify the severity of the asthma attacks, other than they were being treated at the ED. Although perception of severity may vary depending on the treating doctor or triage nurse, as well as the acute asthma management skills and knowledge of the caregivers, a severe asthma attack has been defined at the ATS/ERS joint statement[8] as an attack requiring systemic corticosteroids (and for at least 3 days if oral). The prescription of systemic corticosteroids was not used to define asthma attacks in our study for several reasons including a lack of national guidelines for the management of acute asthma exacerbations, a very variable approach to asthma management between different doctors, and low prescription rates of oral corticosteroids. Additionally, we were aiming to assess a real-life situation to obtain predictors to allow us to design a risk-assessment tool to be applied at the ED for any child treated for a bronchodilator-responsive wheeze.

4.7. Findings related to other studies

4.7.1. Baseline cohort characteristics

Most children with a severe asthma exacerbation participating in this study were not adequately managed: few (2%) were taking inhaled corticosteroids as controller treatment and only 32% were being regularly followed-up for their asthma. Only 64% of the children had had a doctor diagnosis of asthma, while 76% had visited the emergency department for a severe bronchodilator-responsive wheezing episode during the previous year. This reflects the inadequate management of asthmatic children in many Latin American settings where asthma is treated as an acute disease during acute exacerbations in emergency rooms with no follow-up or long-term treatment offered (estimated at <6% of asthmatic patients in certain Latin American regions)[24].

A high proportion (85%) of children with acute asthma in our study who were tested, displayed atopic sensitization to mite (*D. pteronyssinus* and *B. tropicalis* IgE >0.70 kUA/l). As discussed in Chapter 2, the predominance of atopic or non-atopic asthma in Latin American countries is still under debate due to contradictory study findings. In a clinic-based study in Quito, Ecuador, 67% of adults and children with allergic respiratory diseases (asthma and/or rhinoconjunctivitis) had a positive skin reaction to at least 1 mite species[480], while in a population-based survey in Esmeraldas, a third of schoolchildren with current wheeze living in either rural or urban settings had a positive SPT for any allergen or a specific IgE to dust mites[300]. We measured mite-specific IgE measurement on a sample of this cohort (33 participants) and showed that 85% had mite atopy, a similar finding to our previous case-control study of 120 children with acute asthma from the same setting[34]. It would, therefore, be reasonable to assume that the majority (~85%) of the cohort would have had mite atopy. Such a predominance of atopic asthma contrasts with the findings of the ISAAC phase II study

which showed variable rates of atopy (measured by SPT) between non-affluent and affluent settings, varying predominance of non-atopic wheeze (with atopy measured by SPT) in non-affluent settings from 4.7% in Ghana to 86% in Hong-Kong and from 21% to 25% in the participating Latin American countries[30]. These disparities may be explained by differences in study populations: our study was clinic-based and recruited acute asthmatics while the ISAAC study was a population survey of school children irrespective of asthma symptoms, where they used 'current wheeze' as the outcome definition. More severe disease has been associated with a greater prevalence of atopy, eosinophilia and concomitant allergies[297].

Lung function of the children included in our cohort was similar to that found in asthmatic children in other Latin American countries. For example, in a cohort of 6-7 year olds in Pelotas, Brazil, the mean FEV_1 (% of predicted), FVC (% of predicted) and FEV1/FVC ratio were 100%, 108% and 105% respectively[481]. Of these, children with current asthma had lower lung function volumes (-6.5% for FEV1, -0.3% for FVC and -6.4% for FVC/FEV1 ratio) as did those children with more than 4 episodes of wheezing episodes in the last year (-5.4% for FEV1, -4.3% for FVC and -10% for FVC/FEV1 ratio)[481]. Median lung function (of predicted for age and size) of the children included in our study (78% FEV1, FVC and 91% FEV1/FVC) are comparable to the Pelotas cohort[481].

Forty percent of the children who underwent spirometry, had a positive response to bronchodilator (FEV1 %predicted increase >12%), as described by international guidelines[37]. This was the only objective measure we could use to identify children with a definite asthma diagnosis, so we could argue that only 40% of our study sample had a definite asthma diagnosis according to guidelines. However, and even lower proportion of positive BDR has been previously described among controller naïve asthmatic children (19%)[482]. This may well be due to an overdiagnosis, though some of our patients did show improved clinical symptoms and/or lung function during trial

inhaled or oral corticosteroids and bronchodilators. According to international guidelines[37], these patients may still be diagnosed with asthma. We were not able to record in our study a clinical or lung function improvement after the use of asthma treatment, as spirometry was only undertaken at the study initiation and not during the follow-up.

Asthma control, as measured by the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) for children 12 or older, was low in our study sample. This was expected, as the test was taken at the moment of an asthma exacerbation. In the bivariate analysis, there was no difference in the initial level of asthma control between the children who suffered a subsequent asthma exacerbation requiring emergency care over the following 6 months and those who did not and neither C-ACT nor ACT scores were associated with future severe exacerbations in multivariate analysis, as children with well-controlled asthma may still be at risk of suffering acute asthma exacerbations[7].

The caregivers' asthma knowledge of the children who participated in the study, as measured by the NAKQ score was relatively low, with a median score of 18 out of the 31, when a score under 21 is considered inadequate asthma knowledge. Other studies measuring asthmatics parents' or caregivers' asthma knowledge using this same questionnaire obtained median scores between 16 and 20[483-486], all under the 21-point cut-off score for adequate knowledge. These studies were undertaken in different countries (Spain, Australia, Brazil), and on different study populations (children admitted to hospital or ICU for a severe asthma attack or being followed-up by a pulmonologist) and still showed a similar degree of parental asthma knowledge. This was not a surprising finding in our study, given the lack of asthma education programmes and adequate follow-up, though we expected it to be lower compared to other more resource-rich settings. This is therefore a reflection of the general disinformation and lack of knowledge concerning asthma that caregivers of affected

children have worldwide, as their score was very similar to that obtained from parents of non-asthmatic children in Brazil (median score 17.2)[485] or from school teachers in Spain (median score 15.7)[487].

We assessed the children's quality of life as referred to their asthma disease using the Pediatric Asthma Quality of Life Questionnaire, divided into 3 domains: activity, symptoms and emotions, all evaluated using a Linkert scale from 1 to 7. The results were very similar between the three domains (median scores of 3.4, 3.5 and 3.7 respectively) lying in the middle of the scale. It is difficult to interpret these scores in an isolated manner, as this questionnaire was developed to evaluate the variations in a child's asthma quality of life, for example after the implementation of an intervention, rather than to evaluate a specific score at one point in time[463]. For example, Yilmaz et al.[488] reported a 2-point increase in the total PAQLQ total score (from 4.5 to 6.5 median scores) and the different domains, 4 months after the initiation of regular follow-up for recently diagnosed children who were started on controller medications. Similarly, 4-12-year olds with asthma PAQLQ median scores improved 6 months after the implementation of a small group educational intervention (from 5.9 to 6.5)[489]. In both these studies, the initial quality of life of the participating asthmatic children was higher than in our study. Once more, this difference may have been due to the timing of the questionnaire (in our study the children had just suffered a severe asthma exacerbation whilst in the other studies children were recruited from a consulting room), as well as for the more severe asthma profile of the children included in our study, as PAQLQ scores have been shown to be correlated with asthma control[463,490]. However, in our study only the asthma control measured in children 12 or older using the ACT was positively correlated with the PAQLQ total score, but not the C-ACT score (used for children under 12 years old). This may be due to the C-ACT not being completed only by the children, but by also caregivers who have a different perspective of the child's diseases severity[491].

4.7.2. Emergency care re-attendance for severe asthma exacerbation predictors

Forty six percent of the 264 children who completed the 6-month follow-up suffered a subsequent severe asthma attack that required emergency room treatment during the first 6 months after the index attack. This was the proportion we had expected, based on the results obtained from our previous case-control study in this same setting, where 53% of children with acute asthma had suffered at least 4 episodes of acute wheezing during the previous year[34]. In similar studies from US and Canada, ED re-attendance for acute asthma attacks rates varied from 15% to 39% 12 months after the index ED admission or between 11% and 30% after the first 3 months of follow-up[399,414,422,427,428,435,437,440]. These proportions of re-attendance were all lower than the one we registered, even after extending the follow-up time to 12 months compared to our 6-month follow-up. Our study sample had therefore a greater number of severe exacerbations probably due to poor asthma control and inadequate management, as the proportion of children receiving baseline treatment in the North American studies mentioned, was much higher than in our study[399,414,422,427,428,435,437,440].

A history of severe asthma attacks during the previous year has been found to be the most strongly associated factor with severe future attacks in this and several other studies[414,424,435,440]. This may be measured as previous ED attendances, number of systemic corticosteroid courses or unscheduled contacts for acute asthma. All these factors were associated with future risk in our study, though, due to the characteristics of this setting (low oral corticosteroid prescription and variable degree of severity of asthma attacks attended at the ED), the number of intramuscular or intravenous corticosteroid courses resulted to be the predictor included in the final model.

Younger children in this study were found to have a greater risk of suffering subsequent asthma attacks requiring emergency care, as was the case in similar studies carried out in high income countries[414,422,435]. Further, younger children are also at risk

of hospital readmission for acute asthma[414,415,428]. This is especially true for children younger than 5 years old[398,409,414], who were not included in our study in order to exclude pre-school wheezers in whom asthma may not be an appropriate diagnosis. Younger children are more exposed to viral upper respiratory infections, such as rhinovirus, which have been found to be important triggers for asthma attacks[11,12].

Atopic asthma may be present as part of the 'atopic path', which includes eczema, allergic rhinoconjunctivitis and atopy. Previous studies[410,412,432] have shown that children with concomitant allergic diseases may have a higher risk of future severe asthma attacks, as was the case in our study with children with an existing eczema diagnosis. Even though the proportion of children with an eczema diagnosis was low, they had a 4 times greater odds of suffering subsequent asthma attacks requiring emergency care. Eczema was also associated with poor asthma control (one hospitalization for asthma or high frequency of symptoms in the last year) among children in urban Brazil[492]. Individuals with allergic asthma appear particularly susceptible to exacerbations from viruses, and other studies have shown that suppression of allergic mediators reduces virally-mediated attacks[493]. Further studies are necessary to better understand the nature of this association.

Similarly, there was a greater risk of repeated severe asthma attacks among children who described having some kind of food as a trigger for their attacks. These included both children with food allergies and those who identified food colorants or cold foods and drinks as triggers. It is a difficult factor to interpret due to its variable perception, although food allergies are definitely a risk factor for severe asthma attacks, especially in a population where these children and their families are not adequately diagnosed, followed-up and informed.

Children living in an urban area had a lower risk of subsequent severe asthma attacks than those from a rural area, a finding which has not been described previously. The

hospitals and health care centres included in our study were situated in urban Esmeraldas, therefore the distance to the ED may have biased the severity of asthmatic children treated for an asthma attack depending on their residency, towards a more severe asthma in those living in a rural setting. On the other hand, there are many other factors that vary depending on the place a child lives, such as education and socioeconomic factors, which have been associated with the risk of severe asthma attacks[400,422,428]. However, these factors were considered when designing the final multivariable model.

Interestingly, two highly relevant characteristics that have been previously identified as risk factors for repeated asthma attacks did not appear to predict future risk in our study: low socioeconomic status[400,422,428] and African-American ethnicity[399,422]. The population in which we worked in Esmeraldas is predominantly from a low SES (median monthly household income 400 USD, range: 0-12 000 USD) and Afro-Ecuadorian (58% of the total cohort), resulting in a relatively homogeneous cohort, perhaps reducing power to identify such factors as predictors. Monthly household income was sometimes difficult to estimate due to the frequency of informal employment with highly variable incomes. We therefore also included the number of years the parents had studied as a measure of SES, which was also not associated with future asthma attack risk. Recently, black ethnicity was found to act as a confounder for risk of subsequent severe asthma attacks when careful adjustment was made with other socioeconomic factors which may be associated with ethnicity[403]. This may be the reason why we did not identify Afro-Ecuadorian ethnicity as a predictor in our study. Further studies in similar low and middle-income settings appear necessary to clarify the role of SES and ethnicity in severe asthma attack risk beyond high income countries.

4.8. Implications for future studies

Poor asthma control, inadequate management and frequent severe asthma exacerbations are all very serious issues that need urgent attention. This cohort study was designed as an attempt to improve this situation by identifying asthmatic children at high risk of frequent severe exacerbations from those already attending an emergency room for acute asthma in a low resource setting. This should aid health care workers in the decision-making process of initiating baseline treatment and/or referring to specialist care where available. The next natural step would be to design a validation study for the risk assessment tool both in the same setting where it was elaborated, as well as in other national and international settings, to be able to implement the risk-assessment tool into daily practice. Two different aspects would need to be evaluated. First, risk factors or a prediction model would need replicating. Second, the questions themselves would need validating and refining to make sure people would use and understand them, as well as the algorithm or flowchart that would indicate health care workers who to apply the risk model too and what to do with the results. Only then we would be able to assess its efficiency and cost-effectiveness.

However, there are many other steps in asthma management that still need to be further studied to improve asthma outcomes. Understanding the patient's, caregivers' and health care workers perspectives on acute asthma and its management is essential, as they are the main actors involved. This was addressed through a qualitative study presented in the following chapter, together with the caregiver's and health care workers' understanding of the barriers and facilitators to health care and home care access for asthma, as well as their opinion regarding the risk-assessment tool.

Novel interventions to improve all steps that lead to an adequate asthma management are a research priority, as it is still an unsolved long-time problem occurring

worldwide. These include: the proportion of asthmatic children with access to basic asthma medicines (both relievers and controller medications), the number of children prescribed baseline long-term treatment, and finally, adherence to treatment. Reasons for low adherence and effectiveness of interventions may differ between high and low resource settings. Studies addressing these issues should be undertaken in both types of settings.

4.9. Conclusions

To conclude, around half of the children treated at a public ED for a bronchodilator-responsive wheeze in a tropical city in Ecuador, suffered a subsequent exacerbation requiring emergency care over the following six months. Those who had suffered severe exacerbations during the previous year had a higher risk of a new asthma attack, as is the case in a range of settings in high-income countries. A combination of a few predictors in a questionnaire could be used as an effective and simple risk-assessment tool in EDs to identify asthmatic children at a higher risk of recurrent severe asthma attacks. Biomarkers appeared to be less useful in this context. A simple risk assessment tool for emergency consultations based on data such as this may prove extremely useful to target resources towards those most in need of continuing support and treatment. Further studies are now necessary to confirm these predictors as relevant in other settings, both within and outside Latin America.

5. Acute asthma significance, barriers and facilitators to health care access for asthmatic children, and opinions regarding the use of a recurrent asthma attack risk assessment tool, from health care workers' and caregivers' perspective: a qualitative study

5.1. Introduction

The prospective cohort study described in the previous Chapter analysed potential predictors for emergency care re-attendance for acute asthma, with the future aim of combining them to design a risk assessment tool to be implemented in emergency departments. This tool would aid decision-making concerning treatment and follow-up of children treated for an acute asthma attack.

Even though further studies are necessary to refine and validate this tool before it is implemented, it is also vital to understand what is the significance of a childhood acute asthma attack, both for the caregivers and the health care workers, as well as what are their perceptions of the current barriers and facilitators for adequate asthma care. Similarly, it is important to hear their opinions regarding the use of a recurrent asthma attack risk-assessment tool and whether understanding the future risk of a subsequent asthma attack would modify in any way their attitude and management of the asthmatic child. Making a context sensitive risk assessment tool may ensure its utility.

With this background, we designed a qualitative study to better understand the significance of acute asthma attacks and recurrent asthma attacks, the barriers and facilitators for health and home care access, generated from the social construction of

health care workers and caregivers of asthmatic children, as well as their opinions regarding the use of a recurrent asthma attack risk assessment tool**.**

5.2. Research question and objectives

5.2.1. Research questions

- What is the significance of acute asthma attacks and recurrent asthma attacks, generated from the social construction of health care workers and caregivers of asthmatic children?

-What are the barriers and opportunities to diminish the gaps in health care access and home care, in asthmatic children?

-What are the opinions regarding the use of a recurrent asthma attack risk assessment tool**?**

5.2.2. Objectives

General objective

Our aim was to describe the significance of acute asthma attacks and their recurrence, the barriers and facilitators for health and home care access, generated from the social construction of health care workers and caregivers of asthmatic children, as well as their opinion regarding the use of a recurrent asthma attack risk assessment tool**.**

Specific objectives

1. To explore the meanings of acute asthma attacks and their recurrence, in children from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador.

2. To describe the barriers that limit health care access and home care and opportunities, in children with recurrent asthma exacerbations, from the caregivers'

and health care workers' perspective, in Esmeraldas, Ecuador, following Tanahashi's model.

3. To describe behaviours and beliefs towards the use of a recurrent asthma attack risk assessment tool in asthmatic children with recurrent asthma attacks, from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador.

5.3. Methods

5.3.1. Study design

This was an interpretative qualitative study, based on phenomenological approach, to identify and interpret discourses (health care workers and caregivers) on individual experiences in asthma care expressed through language, and conducted at the end of a cohort study on asthmatic children in the city of Esmeraldas.

The phenomenological focus assumes that there are one or more essential experiences that represent key meanings, and that these are shared. These experiences on a phenomenon are related, analysed and compared, to identify the essence of the event studied and to show how the important meanings are constructed from the direct experiences[494,495]. The researcher must become detached of his/her own experiences to avoid the thought that he/she understands better what it is for a person to experience the phenomenon studied. He or she must keep a reflexive and critical attitude, dialoguing with him/herself and practice active listening[496].

This strategy enables quick access both to health care workers and caregivers, based on the idea that the characteristics of a qualitative study with a phenomenological approach is crucial to understand and address the symbolic construction of asthma and recurrent asthma attacks.

5.3.2. Study setting

The study took place in Esmeraldas city, Esmeraldas, Ecuador. The details of this setting have already been described in Chapter 4. For the qualitative component, we considered doctors and respiratory therapists, as well as caregivers of asthmatic children.

There are two different kinds of doctors treating asthmatic children in Esmeraldas: specialists (paediatricians in this case) and general doctors in training (named residents in this setting). The latter are less experienced, are usually younger and are either training in a specific medical speciality or applying for a training programme outside Esmeraldas. There are no specialty training programmes in Esmeraldas now.

It is important to understand the role of Respiratory Therapists to understand our choice of study sample. Asthmatic patients in this population are diagnosed, treated and managed exclusively by doctors in this setting. Respiratory Therapists act as a bridge between the asthmatic patient and the doctor, by applying the medication and/or respiratory therapy prescribed by the doctor, and have therefore a close contact with the asthmatic patients and their families.

On the other hand, caregivers of asthmatic children are normally their mothers or fathers, though on occasion they may also be other family members such as grandparents. Caregivers are responsible for the child's care at home during the asthma attack, of taking him/her to be seen at the health care service, to deliver the prescribed medicines and on many occasions of buying these, as there is a lack of asthma drugs in the public health system. Sociodemographic characteristics of asthmatic children caregivers in Esmeraldas, have been described in the Results section of the cohort study in Chapter 5.

5.3.3. Study sample

The study population was defined by purposive criteria, using pragmatic and feasibility criteria. We included health care workers (both doctors and respiratory therapists) from the city of Esmeraldas, Ecuador, as well as the carers of asthmatic children (caregivers) who had previously participated in the cohort study.

5.3.4. Heterogeneity criteria

These were the criteria used to compare the discourses (heterogeneity criteria):

Health care workers

The health care workers' profile was initially proposed according to three criteria: sex (men and women), work description (doctors and respiratory therapists) and level of training and experience (just graduated vs experienced). We included professionals working in the two main city's hospitals (Hospital Delfina Torres de Concha, HDTC, and Instituto Ecuatoriano de Seguro Social Hospital, IESS), as well as those working in large and specialised health centres. Some of these health care workers also work part-time in private clinics in Esmeraldas. We aimed to include both highly and inexperienced doctors, as well as respiratory therapists.

Caregivers

The caregivers' participant profile initially proposed followed three criteria of heterogeneity: sex (men and women), degree of kinship to asthmatic child (mother/father, aunt/uncle, grandparent), and socioeconomic status (low vs high resources).

We collected other further information from the participants, such as age, degree of education, workplace, age of child with asthma, to describe the characteristics of the study participants, although they did not constitute part of the heterogeneity criteria.

5.3.5. Inclusion and exclusion criteria

We used the following inclusion and exclusion criteria.

Inclusion criteria

Health care workers:

- Involved in the treatment and/or management of asthmatic children.
- Willing to participate.

Caregivers:

- Carers of children who participated in the asthma cohort study.
- Available contact number.
- Carers of children of any age.
- Willing to participate.

Exclusion criteria

Health care workers:

- Not involved in the treatment and/or management of asthmatic children.
- Not willing to participate.

Caregivers:

- Carers of deceased children.
- No available contact numbers.
- Not willing to participate.

5.3.6. Study sample recruitment

The health care workers were invited to a presentation of the study findings of the previous cohort study. At the end of the presentation, they were informed of the existence of a qualitative study and a list was passed around the assistants for them to

write their name and contact number if they were interested in participating. Three presentations were organised at the two main hospitals and the specialised health centre in the city of Esmeraldas, Ecuador.

The participant profile criteria were used to identify those to be selected for the study from the ones that appeared on the contact list. Given the small number of health care workers initially available, all of them were contacted by telephone to arrange an interview time and place, to the convenience of the interviewee. To increase the number of participants, the snowball technique was also implemented, by asking the health care workers that participated to inform other colleagues of the study.

All the carers of the asthmatic children of any age who participated in the cohort study with updated contact numbers, were contacted by telephone and invited to assist an informative session to present the findings from the previous prospective cohort study. Two general meetings were held. At the end of these meetings, we informed the assistants of the existence of a new qualitative study and a list was made available for those interested in participating to leave their names and contact numbers.

Purposive sampling of caregivers interested in participating was then undertaken and individuals were contacted and invited to participate in focus group discussions. As with the health care workers, snowball technique was also used, and we encouraged the participants of the focus group discussions to inform other possible carers of asthmatic children of the study we were undertaking.

5.3.7. Methods for collecting qualitative data

The methods for collecting qualitative data in this study were in-depth interviews (ISI) and focus group discussions (FGD) (Annex C: Interview Guide). The ISI were undertaken with the health care workers involved in the management of children with asthma.

The FGD were composed of asthmatic children's caregivers. We tried to include fathers and mothers, as well as other relevant caregivers such as grandparents or aunts/uncles.

5.3.8. Participant coding

Table 5.1 represents the coding system we used to identify the study participants, both for the ISI and the FGD.

For the ISI, we used the coding for the sex of the participant (man or woman), the training (medical resident, paediatrician or respiratory therapist) and the number of the interview for that specific training level. For example, the number IT2W represented the interview of the second respiratory therapist, who happened to be a woman.

For the FGD, participants were identified for the number of the focus group discussion (1-5), and the degree of kinship to the asthmatic child, which already represented the sex of the participant. For example, the number F3G represented a participant from the focus group discussion number 3, who was a grandmother. There were no grandfathers in our study sample.

Table 5.1: Participant coding

In depth interviews		**Focus Group Discussions**	
Work description	R= Resident doctor T= Respiratory therapist P= Paediatrician	Degree of kinship	M= Mother F= Father G= Grandmother
Sex	M= Man W=Woman		

5.3.9. Study procedures

We applied ISI for health care workers and FGD for caregivers. Before the ISI and FGD, participants completed a short questionnaire to collect sociodemographic information

(age, sex, level of studies, occupation, work place, degree of kinship with asthmatic child, age of onset of asthmatic symptoms in child).

In-depth semi-structured interviews (ISI) with health care workers

We organised a total of 12 interviews: 3 paediatricians, 3 respiratory therapists and 6 general doctors (medical residents). Given the limited number of paediatricians and respiratory therapists in the city of Esmeraldas, we were unable to undertake more interviews for these two groups of health care workers. The 6 general doctors and the 3 respiratory therapists were considered as the less experienced health care workers.

Most of ISIs took place in a private room at the hospital or health centre where the health care worker worked, together with one interview which took place at the study office and one other at the health care worker's home, depending on the interviewee's preference. They lasted between 35-55 minutes and refreshments were offered depending on the time and location of the interview.

A topic guide was used to briefly explore the health care workers' perspective regarding asthma exacerbations, as well as their perception of transmission of information to caregivers concerning the future risk of suffering subsequent asthma attacks. To explore the significance of the future risk of recurrent asthma exacerbations, we worked with the risk assessment tool presented below. The in-depth interviews were undertaken by the PI (Principal Investigator). (9 interviews) and Dr Natalia Romero (Universidad Internacional de Ecuador, UIDE) (3 interviews), an experienced qualitative researcher. Data saturation was achieved, that no more new themes were emerging.

Focus group discussions (FGD) with caregivers

We organised a total of 5 groups of 6-8 people, though the final number of participants was 4 in three of the groups and 5 and 3 in the other two groups. Both men and women

were invited equally to the discussions, though of the 20 participants who attended the discussions, only 2 were men.

The discussions took place in a wide room in a private health centre very near the city's public hospital (HDTC), where the study office for follow-up of the asthmatic children participating in the previous cohort study had been set up. The discussions lasted for around 1 hour and refreshments were offered at the end. The FGD were facilitated by the P.I (3 FGD) and Dr Natalia Romero (2 FGD), an experienced qualitative researcher.

A topic guide was used to briefly explore the caregivers' perspective and experience regarding acute asthma exacerbations, as well as their understanding of future risk of subsequent asthma exacerbations. To explore the significance of the future risk of recurrent asthma exacerbations, we worked with the risk assessment tool presented below. Data saturation was achieved.

Opinion regarding the use of a recurrent asthma attack risk assessment tool

As shown in Chapter 5, as a result of the prospective cohort study we obtained specific predictors of recurrent severe attack requiring emergency care using Cox regression analysis. These predictors could be easily combined to design a risk assessment tool. In the Table 4.9 an example is provided of how this risk assessment tool might look. Even though it has not been validated, we used this design to explore the health care workers' and caregivers' opinions regarding its hypothetical use.

It is a tool to be used at the emergency department by health care workers who are treating a child for an acute asthma attack. This tool will hopefully identify children at a greater risk of coming back to the emergency department for acute asthma, to assist with decision-making regarding appropriate treatment and tertiary referral, as well as to inform the patient and his family so they may undergo necessary lifestyle modifications. As the model has not yet been validated, all we discussed is whether the carers participating in the discussion could understand the information this tool is

trying to show and whether this information would change their attitude towards their children's asthma in any way.

Following our third objective, we included in the ISI and FGD a moment to capture the HCWs and CGs perceptions concerning the use of this risk assessment tool, from a global perspective. We did not pretend to acquire such an insight into the participants point of view as to see it with their own eyes, but to gain the participants' perspective, understand their mental categories, their interpretations, their perceptions and the motives behind their comments concerning the use of the proposed risk assessment tool.

Recording and transcriptions

The audio from the ISI and FGD were digitally recorded, prior participant's consent and transcribed verbatim by expert transcriptors. The transcriptions were compared with the recordings for accuracy, and any errors in transcription were corrected.

5.3.10. Ethics and informed consent

The study was approved by the Ethics Committees of the Liverpool School of Tropical Medicine (Research Protocol 17001) and the Universidad Internacional de Ecuador (International University of Ecuador) (UIDE). Once the carer or health care worker had been contacted, the interviewer introduced herself and explained briefly why they had been contacted. A description of the objectives of the study and the evaluations to be done were then explained. If agreeing to participate, an informed written consent form was handed out to the participant to be signed by them. The informed consent form included a summary of the importance of the study, its objectives, the procedures and when they will be carried out, the risks and benefits of participating in the study, and the options and rights they had as participants. They were able to ask as many

questions as needed to completely understand all the points included in the informed consent forms.

5.3.11. Emerging design

The design of the study was subject to an emerging design, enabling an iterative development of a thematic framework to explore experiences of, and barriers and facilitators to, asthma management in general and future risk of asthma attack understanding in particular. Following development of the initial thematic framework, the data were reanalysed to assess appropriateness of the fit, to allow modification and to highlight deviant cases. To construct the emerging design, we included verbatim notes, field notes, a diary, the researcher's reflective notes made during the research, and the transcribed recordings of the first 4 ISIs and the first FGD.

We evaluated: a) the heterogeneity criteria, b) procedures, c) the a priori categories and sub-categories, and d) the use of the topic guide.

Heterogeneity criteria:

Among the criteria used for the health care workers, we modified the classification by including two groups: one for the more experienced HCWs, and another for the younger, inexperienced HCWs. We excluded the initial criteria of sex (male and female) and work description (doctors and respiratory therapists) based on the analysis of the first ISI. There were no more respiratory therapists and Paediatricians in the city of Esmeraldas that treat asthmatic children, apart from those contacted, therefore it would not have been possible to reach data saturation for the criteria of sex and work description.

Among the caregivers, we did not consider an equitable presence of participants by sex, degree of kinship to asthmatic child, or socioeconomic status, as there was no variability of these conditions among the cohort study participants.

Procedures

To reduce the bias that my presence may have introduced in the opinions obtained by the caregivers, the last two FGD were undertaken by Dr Natalia Romero, who the participants had not met previously. I had had a very close contact with the caregivers participating in the FGD, as they were all part of the previous cohort study, and this may have conditioned or influenced the caregivers.

A priori categories and sub-categories

Table 5.2 shows the categories and subcategories initially planned.

Table 5.2: Initial thematic framework before study was started

Categories	Subcategories
Acute asthma attack perception	- Meanings - Behaviours
Gaps in health and home care	- Barriers - Opportunities
Perceptions of the use of a recurrent asthma attack risk assessment tool	- Perceived susceptibility - Perceived severity - Perceived benefits - Perceived barriers - Cues to action - Self-efficacy

At this point, we used an inductive analysis that enabled us to re-define once more the thematic framework to include the emerging categories and subcategories. We discarded the use of the Health Belief Model to subcategorise the perceptions of the use of a recurrent asthma risk assessment tool for a simpler 'benefits' and 'barriers', as the data did not suit this sub-categorisation. Similarly, we classified divided barriers and opportunities to asthma health and home care in two separate groups, and we subcategorised each of them using Tanahasi's[379] classification of measurements of health care coverage. These 4 categories were implemented in a qualitative systematic review analysing barriers and facilitators to health care access[378], and include:

- Acceptability: social, cultural, or religious factors, beliefs, cultural norms and values that may influence the health services perception and its use.

- Accessibility: physical and geographic location of the health service in relation to the population served, as well as administrative requirements.

- Contact: Characteristics and quality of the health care service, treatment continuity, including doctor-patient relationship.

- Availability: Available health care services and programmes for the population served.

The emerging design process was supervised and guided by an experienced qualitative researcher (Dr Natalia Romero) to refine the chosen approach to determine the categories and subcategories, which are described in Table 5.3.

Table 5.3: Final thematic framework following emerging design

Category	Subcategory
Acute asthma significance	
Asthma health and home care access barriers	Acceptability Accessibility Contact Availability
Asthma health and home care access facilitators	Acceptability Accessibility Contact Availability
Emergency care Re-attendance risk assessment tool	Benefits Barriers

Topic guide

We noted that the responses that we were obtaining from the ISI were on some occasions very short (yes/no answer or no details, descriptions or feelings) and very technical. We therefore modified the topic guide accordingly to obtain the perceptions

of the health care workers and facilitate the development of skills, vision, and integrity of the researcher team.

5.3.12. Analysis strategy

We analysed the data using the analysis strategy suggested by Pope et al.[497]. The analysis took place sequentially, starting with the first ISI and FGD, and continuing with the following transcriptions, in a systematic and rigorous manner. Once all the data were obtained, all the ISI and FGD transcriptions were read in detail (to familiarize ourselves with the collected data) and then were analysed inductively, using content analysis guided by the categories and subcategories, considered as key issues, concepts and themes by which the data could be examined and referenced. Qualitative software for analysis (QDA Miner) was used as an aid to organise the data.

Each interview was individually coded (by the PI) by organizing the text into codes (sub-categories) and group codes (categories), using an open coding process. Each data segment could be indexed against one or more code or category. We therefore undertook a thematic analysis approach to describe and analyse the data obtained. Dr Natalia Romero read some of the ISI and FGD, and met with the writer on several occasions to discuss and agree upon the coding system and the thematic framework, to triangulate the analysis.

The final thematic framework included the different contextual, social, psychological and behavioural aspects that may influence the significance of acute asthma exacerbations in children and adolescents from the health care workers' and caregivers' perspective.

Once the data were analysed and organised, they were summarised under the key categories and sub-categories and related the data to the objectives of the study, using quotes from the participants to illustrate the findings discussed.

5.3.13. Quality control and credibility

The PI was trained in qualitative interview techniques and focus group discussion. She is a Paediatrician who has been working during the last 3 years with asthmatic children and their families in Esmeraldas, Ecuador. She was directly supervised by Dr Natalia Romero Sandoval, an experienced qualitative researcher in Ecuador

The ISIs and FGDs took place in a comfortable and private setting, to ensure an interactive and reliable atmosphere.

There were frequent meetings with the study group during the interviews and analysis, to agree upon the coding used and the categorization. Data saturation was reached, as now more themes emerged during the last interviews. Triangulation was assured by the participation of experts and the review of published literature.

5.4 Results

5.4.1 Participants characteristics

Health care workers (ISI)

A total of 12 health care workers participated in the in-depth, semi-structured interviews (ISI), 3 of them experienced paediatricians (more than 10 years of clinical experience) and the younger, less experienced (8 years or less of experience) respiratory therapists (three) and medical residents (or general doctors, 6 of them). Most participants were currently working at the city's public hospital (HDTC), except for 3 from the social security hospital (IESS) and one from a rural, specialised health centre. The less-experienced health care workers were between 26 to 35 years old, while the more experienced ones were over 40. There was a mixture of female and male, as well as of Afro-Ecuadorian and Mestizo workers. The characteristics of health care workers participating in the in-depth, semi-structured interviews are shown in Table 5.4.

Table 5.4: Characteristics of health care workers participating in the in-depth, semi-structured interviews (ISI)

Participant Code	Gender	Age	Ethnicity	Formal education	Place of work	Years experience
IR1	F	30	Af	GD	HDTC	3
IR2	F	31	Af	GD	HC (rural)	5
IR3	M	34	M	GD	HDTC	6
IR4	M	32	M	GD	HDTC	<1
IR5	F	28	Af	GD	HDTC	<1
IR6	F	26	M	GD	HDTC	1
IT1	M	35	Af	RT	HDTC	8
IT2	F	35	Af	RT	HDTC	8
IT3	F	32	M	RT	IESS Hospital	6
IP1	F	40	Af	Paediatrician	IESS Hospital	12 (6 as a Paediatrician)
IP2	M	64	M	Paediatrician	IESS Hospital	27
IP3	M	62	M	Paediatrician	HDTC	26

F: female; M: male; Af: Afro-Ecuadorian; M: Mestizo; GD: general doctor; RT: respiratory therapist; HDTC: Delfina Torres de Concha Hospital; HC: Health Centre; IESS: Instituto Ecuatoriano del Seguro Social (Ecuadorian Social Security Institute).

Caregivers (FGD)

Twenty caregivers participated in the 5 focus group discussions (FGD). All of them were mothers of asthmatic children, except for two grandmothers and two fathers, with an age between 25 and 63 years old. Only four of them were mestizos (the rest were Afro-Ecuadorian) and 13 worked in their homes. Four of them had received only primary education, 8 some level of secondary education, and the following 8 had attended the university. The age of the asthmatic child they cared for was between 7 and 12 years old.

Table 5.5: Characteristics of caregivers participating in the focus group discussions

Partici-pant Code	Gen-der	Age	Ethni-city	Asth-ma*	Years** Formal Education	Job	Relation asthmatic child	Age asthmatic child#
FG1-1	F	32	Af	Y	6	House	Mother	12/9
FG 1-2	F	25	Af	N	12	House	Mother	7
FG1-3	F	35	Af	N	12	Nursery	Mother	9
FG1-4	F	35	Af	Y	6	House	Mother	12
FG2-1	F	45	Af	N	6	House	Mother	8
FG2-2	M	43	Af	N	11	Own business	Father	8
FG2-3	F	43	Me	N	6	House	Mother	7
FG2-4	M	50	Me	N	16	Secreta-ry	Father	9
FG3-1	F	63	Af	N	15	Retired (auxiliar y nurse)	Grandmot her	7
FG3-2	F	37	Me	N	16	Mana-ger	Mother	7
FG3-3	F	31	Af	Y	14	House	Mother	8
FG4-1	F	60	Af	Y	9	House	Grandmot her	12
FG4-2	F	32	Af	Y	12	House	Mother	7
FG4-3	F	61	Af	N	9	House	Grandmot her	12/10
FG4-4	F	47	Af	N	15	House	Mother	14
FG4-5	F	48	Af	Y	16	School teacher	Mother	12
FG5-1	F	30	Me	Y	16	House	Mother	10
FG5-2	F	45	Af	N	12	House	Mother	11
FG5-3	F	42	Af	N	16	Nurse	Mother	11
FG5-4	F	33	Af	N	12	House	Mother	11

**: If the participant had suffered asthma him/herself; **: total number of years the participant had studied (6= primary school; 12= secondary school; >12= university); #: When two different ages appear, there are two different asthmatic children. F: female; M: male; Af: Afro-Ecuadorian; Me: Mestizo; Y: Yes; N: No;*

5.4.2. Acute asthma significance

Health care workers

Health care workers expressed that for them, acute asthma attacks represent a scenario in which they clearly experience their relationship with life, illness and death, and put into practice their professional disciplining.

> *"You are responsible for what could happen with that child in the future. Let´s say that, if he doesn´t recover from the attack, […] then the attack could become more*

severe. Then, one feels such commitment […] I mean, the life of the patient depends on me." [IR5]

"It is a severe disease, it is a disease that can cause your death, and there are some attacks that are pretty strong." [IR2]

The more experienced health care workers reported not feeling fear when dealing with a child with an acute asthma attack nor mistrust towards the medications used to treat these cases. They expressed a sense of superiority and confidence in themselves when contacting an asthmatic child, as well as feeling the responsibility of being adequately prepared to manage them.

"My experience, ours, tells me that if I see a child who is tremendously distressed I don´t make a big deal, I mean I don´t get scared. I mean come on, nothing at all; I mean I know I will reverse the attack. Easily." [IP3]

"I think it is a controllable disease. Yes, of course, it is a controllable disease. I am not afraid of inhaled corticosteroids." [IP1]

"We must be very – very well prepared to provide care to any child. […] So, when someone shows up, I mean, you must assume that situation as a great responsibility. The mum does not want to let go of the child, but they do give it to you. So, one must be tremendously ready to solve those cases." [IP2]

However, another experienced health care worker discussed feeling worried about other associated complications or consequences of asthma in children, such as loss of school days and obesity.

"School dropout, they miss a lot of school-days, they miss class, that child […] if they don't go to school, they fail to learn." [IP1]

"I also see often that they have a tendency to obesity, I mean, I am concerned about the curve rising and rising" [IP1]

On the other hand, young health care workers reported feeling fear and despair when treating a child with an acute asthma attack, as well as concern and caution when using medications for asthma. On some occasions, they also felt helpless towards the caregivers' questions regarding their child's asthma. When informing about an asthma diagnosis, young health care workers felt sorry for the patient and their family.

"That he requires mechanical ventilation, so… it is my greatest fear, that the child comes here in acidosis, I don´t know, and he… and he goes to mechanical ventilation at once. Then it, it is the… the greatest fear. When he comes… a child comes with a severe attack and I can´t reverse it." [IT2]

"Going there and feeling a little bit – a bit of despair, I mean, seeing the mother feeling helpless and upset; sometimes the medicine doesn´t work immediately. Then, one feels discomfort […] Many times it does cause despair." [IR5]

"And that shouldn´t be given in an excessive amount because it provokes a com… more complications. The Salbutamol. Then it causes tachycardia and… and sometimes even the respiratory distress increases." [IR3]

"As a doctor, you want to have the answer for everything, and always reassure the parent. But there are cases in which the doctors – and not only for asthma – we don't know what to say to them. It's infuriating, even for oneself." [IR6]

"Giving a child, an asthma diagnosis is not something that makes me glad, because it is a chronic disease, and many times with an extended course." [IR6]

Health care workers explained that, in general, they have the necessary skills and knowledge to act quickly when facing a child suffering asthma and that their job is to administer medications.

> *"Well, thanks – thanks to the gained experience and, now, to the safety and handling of medicines, to be able to reverse the attack, we are a little more prepared and not so scared as we were some time ago when I was starting, it was catastrophic." [IP2]*

> *"We end up getting used to it. So, asthma attack –ok– medication, oxygen and try to calm her down, because the mum arrives in a desperate state and all that, so we say to them –please calm down–. And then we're done." [IT3]*

They believe they should keep a cool head to control the situation and act effectively.

> *"Though the doctor should keep a cool head, shouldn´t he? […] To act well. […] I mean, cold in the sense – at the moment of acting, not cold to the family or patients. I mean, cold at the moment when it's necessary, I don´t know, to do one more procedure – intubation – it is, for procedures, isn´t it? But not in the other sense, I mean he must be warmer with – with the families." [IP2]*

Besides, experienced health care workers discussed feeling concerned regarding the inadequate management of asthmatic children that some young and non-specialised doctors offered. Young health care workers did not comment on similar or contradicting perceptions.

> *"I do feel worried or restless about the inadequate handling that sometimes resident doctors have during asthma attacks in the emergency department" [IP1]*

Health care workers commented on the importance of informing and educating the child's caregivers when treating him/her for an acute asthma attack. They frequently

used terms such as 'raising awareness' or 'scaring', when referring to educating families about asthma, as seen in the representative extract. They described the caregivers as being scared and not knowing anything about what is happening to the child and the management needed, so the health care worker should act as a guide for them.

> *"We tell them: "Next time, your child may arrive in a worse state, and he is not going to arrive walking, he will arrive with a tube in his mouth." […] At least, in that way, they will become a little afraid." [IR3]*

> *"But you are the one who has to come to talk to him. You are the one who must tell him/her that he must buy this, apply this, use this. He/she doesn´t know [the caregiver]. He/she has no idea when he/she gets there, he/she is afraid. So, that is the issue, it´s a responsibility to guide him/her." [IP3]*

Another experienced health care worker indicated that what is really important is to establish a good patient-doctor relationship to be able to convey the information to the caregivers.

> *"In general, there has to be a good interrelation with both [father and mother]… you have to be very charismatic." [IP3]*

Finally, some health care workers expressed feeling satisfied, fulfilled and relieved when the child improves after being treated for an acute asthma attack.

> *"I mean, a child who arrives with respiratory insufficiency and who, with medicine, inhalers, the use of spacers, it´s really satisfying to see how they react. They recover immediately." [IP2]*

> *"I feel fine, I feel relieved [seeing that the patient responds to the treatment of an asthma attack]." [IR5]*

Caregivers:

Caregivers described feeling fear, despair and anxiety towards their child's acute asthma attacks. They expressed how asthma affects not only the child, but also the caregivers and the family.

> *"Gosh, it is worrying, because one thinks that one can die that very moment." [FG4M]*

> *"It is such a horrible thing… you feel that you choke, you can't breathe, and, at times, it seems that you are going to die." [FG1M]*

> *"So yes, as parents we feel grief. We feel lost and sometimes do stupid things because we want to help our children, right? And, of course, it is a disease that does affect us, parents, very much, and I don´t know, I mean, seeing our children suffering at that moment." [FG3M]*

They believe that the disease is unpredictable, that it will be present during a long period of time and that it may bring some associated complications, as well as death.

> *"[…] that sickness, in the long term, becomes chronic and it is like death approaching. You don´t get to know when you choked. And, if you don't have anyone to look after you, you may die. Because if it starts during adolescence… ok, it affects the child, in the adolescence it stops, but when you are a grown up, it comes back again." [FG1M]*

> *"[…] we have to be careful because it develops, and it brings complications later." [FG2F]*

A mother who had suffered asthma herself, expressed a divergent opinion, reporting that she took her child's acute asthma attacks calmly.

> *"Take it easy, I have also suffered from that disease." [FG4M]*

According to the caregivers, acute asthma attacks are situations when they feel forced to take immediate action, and for which they usually contact the formal health care system.

> *"[…] once she even fainted, we had to rush to the hospital in the middle of the night. […]. You must run to the hospital or clinic. But run." [FG2F]*

> *"[…] he has already gotten to the extreme where he couldn't breathe, there is a lot of effort in - the muscle of the chest, of the abdomen, it already started to hurt him/her and that moment, let´s run to the hospital […]" [FG3M]*

> *"She got sick and I took her to the emergency room at the hospital and she received treatment, she got oxygen because she couldn´t breathe and all that, she even got an injection." [FG5M]*

They expect that their child will be given a fast and appropriate treatment that will get him/her better.

> *"[…] we are pretty sure that taking him there will make him get better, because she is the doctor for that." [FG4G]*

> *"[…] that´s why I went to the doctor, so he can give him the medicine, so the kid can get better." [FG4M]*

However, some caregivers feel fear, deception, frustration and defeat when taking their child to be treated for an acute asthma attack to the hospital or health care centre.

> *"I had another granddaughter who had asthma and she got horribly bad, and my husband said: 'No, you aren´t going to take her there, she will get traumatized because she will get an injection', that when taking – taking her to the hospital she was going to get an intravenous fluid and she was going to die there." [FG4G]*

"It´s only that Salbutamol is a medicine that you have to be careful about. Exactly what must be given is exactly what the doctor gives, because if you administer too much Salbutamol, forget that, he can even die! It is very dangerous." [FG3G]

"But Salbutamol, that bromide, it doesn´t even tickle him. Because I go to the clinic, they nebulize him, I get back home, and three hours later he is again [with respiratory distress]. And as a mother, you worry." [FG5M]

Some caregivers described how they prefer treating their own child at home when suffering an acute asthma attack.

"No, I do it at home. I don´t take her to the hospital. I don´t take her. I have my own supplies, the same that I have right here, I have at the hospital." [FG2M]

Caregivers also brought up how their child's asthma limits the life of the child and the whole family, as they are afraid that certain activities or foods may trigger an acute asthma attack. Similarly, they reported how the children miss school days during the acute asthma attacks.

"He/she couldn´t go the beach, he/she couldn´t have ice cream" [FG4M]

"Many times, I haven't sent her to school, because she woke up very sick because of that [asthma]." [FG5M]

Some caregivers discussed the lack of knowledge concerning their child's asthma and how to treat their acute asthma attacks.

"Because I really – I mean, I have always heard about asthma, asthma, but I really don´t know what it is, no." [FG4M]

"Because many times, eh, at the beginning I didn´t – didn´t have medicines at home. No, I didn´t know who – eh, then that´s why I went to the doctor, so they can give him the medicine, so the child can get better." [FG4M]

"I don´t know about my little girl either because she looks fine to me. Sometimes she gets a cold. Sometimes she goes to the doctor but no… I don´t know much about asthma. [FG2F]

On occasions, caregivers felt guilty for their child's acute asthma attack, as if it were their sole responsibility.

"It did happen to me once because I went out with him and – I mean – it was cold, and I got home at night. And he had – he had a little cold, not much. And the night came and – and when we arrive, it seems that the cold, because we were travelling, it seemed to hurt him and that – that made him agitated. So yes, I really felt guilty at that moment because I said if I had taken him home at a different hour, or – or if I had gone there earlier." [FG4M]

5.4.3. Barriers to Asthma Health Care and Home Care Access

We classified the reported barriers into 4 categories, based on Tanahashi's model[379] (see Methods section).

Acceptability

a. Health Care Workers

The caregiver's educational and socioeconomic level was described as a perceived barrier by health care workers, together with carelessness and neglect towards the disease.

"First, the educational level of the parents […] I think it is crucial. Um, illiterate mothers or fathers can sometimes have the intention, but they don´t carry it out in a correct way. Second, the socio-economic level they belong to. It has too much to do too. I think that mainly they both – they are the barriers to do it [follow the doctor´s instructions]." [IR6]

> *"Then I try to talk and explain them everything. Then […] it seems that there are caregivers […] who don´t listen to us. Then, they get […] the medical consultation, they talk to a specialist, then things are explained to them, then eh, parents start to have […] a good management with their children. But there are others who sometimes, eh, the same culture is a barrier, …the indifference, and they come again, and they recur with an attack again." [IR4]*

A second relevant barrier for health care workers, in the context of cultural factors, was the use of traditional or natural remedies for their child's asthma, and the reliance on friends' or neighbours' advice by the caregivers.

> *"But here they are used to visit – this – let´s use the right words – a witchdoctor or a healer around the corner. It is very common." [IP2]*

> *"You tell the patient that he/she has to take that medicine for some time, don´t you? And that he/she must return before finishing. He/she doesn´t, the neighbour tells him that the sap of a tree cures asthma and they change and take that, and after 2-3 months you see that… 4 months, 5 months, that they have another asthma exacerbation." [IT1]*

Similarly, health care workers believed that caregivers were told (by non-health care workers) of certain false side effects of the medication prescribed for the child's asthma.

> *"[…] I was told that if I gave it to him, I mean the Salbutamol, they become addicted or they start with heart problems […]" [IT2]*

Health care workers also brought up the issue of caregivers' poor adherence to their child's long-term medication.

> *"Here the idiosyncrasy makes people live from… from aromatic teas, from a certain plant´s tea, from the tea of… the preparation of … the witchdoctor who massages children. Then, a person here can´t adhere to medication." [IR3]*

Another barrier some health care workers reported was that caregivers only take asthmatic children to be treated once they are severely ill. Consequently, asthmatic children were treated solely at the emergency department during acute asthma exacerbations.

> *"In the area where we live there are many parents whose child starts with a common cold, and only when the child situation becomes complicated, that's when they go to the doctor." [IR2]*

Young doctors referred that on some occasions they felt rejected as general doctors (vs. specialists), by the caregivers, and this created a barrier between them, hampering understanding and confidence.

> *"Sometimes parents […] create a barrier between the doctor and the – and the parent – the patient´s parent, and that barrier prevents them from understanding the information correctly […] they refuse to be assisted by a general doctor, they prefer to get the treatment from a specialist immediately." [IR6]*

There were no other differences in the social and cultural factors, as well as in the norms, beliefs and values between young and experienced health care workers, related to acceptability barriers to health and home care access for asthmatic children.

b. Caregivers

Caregivers admitted using a variety of natural remedies and following other people's advice in respect to asthma medication, as part of their beliefs in alternative medicine and how much value they give to it, and justified in the search for a solution for their child's asthma, which they do not find in doctors and biological medicine.

"And do you know how it stopped [my child´s asthma]? Cockroach tea" [FG2M]

The use of natural remedies, however, did not always interfere with the adherence to acute asthma medication (like relievers), though it may have done so with baseline long-term treatment (such as inhaled corticosteroids).

"Because a woman told me…not to let my girl use the inhaler too often, because eventually it will end up hurting her lungs." [FG1M]

Some caregivers were reluctant to expose their children to a large amount of medication or for a long period of time and preferred more 'natural' remedies.

"The norm would be for a person, regardless being sick or not, he/she is not going to spend his/her whole life taking medication. Because our body is not going to be under medication all the time; this medication has effects on certain parts of our organism and our defences. For us, growth, intelligence, a lot of medication, or how we call it here, too many drugs, because it makes them become fool." [FG1M]

Some caregivers expressed fear towards the hospital care and mistrust of the doctors and medications prescribed or given for free at the hospital. This led them to seek advice outside the health care services, not to attend at all, or to buy over-the-counter medicines.

"[…] that when taking him to the hospital, he would get an intravenous treatment and that he would die there." [FG4M]

"But one had to buy them, because those medicines that they prescribed him did nothing to him. Instead, the medicine that I used to buy over the counter, eased his discomfort." [FG5M]

"I don´t trust all doctors […]. In fact, I go there, or I come here, because he has social security cover, he, I don´t like to take him to IESS [social security hospital].

And, I have him in the [public] hospital, I lie to get in […] I don´t trust the IESS." [FG3M]

Accessibility

a. Health Care Workers

A common complaint among the health care workers was the lack of a specialist doctor to follow-up asthmatic children in the City of Esmeraldas. The process of referring a patient to be followed up by a specialist, was described as slow and complicated. They had to be sent to one of the larger cities that are 8-9 hours away (Quito or Guayaquil), with long waiting lists and associated costs (both for the caregivers and the health system).

"Sometimes one wants, or the patient is already diagnosed, and you need them to be evaluated by specialists, paediatricians or allergists. The – the time that, eh, is used or needed to generate that referral and for the patient to be treated is also a delay." [IR6]

"but our [Esmeraldas's public hospital] level is second level, then I shouldn´t have to start, of course that I can replicate and to refer to a third level, but this issue is a bit more complicated, I can help you get an appointment with the allergist and all. It isn´t that easy." [IP3]

"Here in the city we don´t have a specialist in – in – in respiratory diseases, and in – and in asthma and – it is a little far." [IR5]

Health care workers discussed the economic difficulties some of the caregivers encountered to buy the medicines that were not freely available through the hospital, to access the health centre or hospital, or to transfer the child to be seen and followed-up by a specialist in another city.

> *"And if the families are low-income and they can´t obtain the medication, it is like they are tying our hands, us, the professionals." [IR6]*

> *"It could be that – that they don´t have the economic resources. I mean, one thinks of some things – difficulty to get to the health centre, eh, the access depending on where you come from." [IP2]*

> *"[…] then that patient must go to another third level, I don´t know if he has the economic capacity to get there." [IP3]*

Similarly, health care workers blamed the economic situation that forced both parents to work outside the house and leave the child under the care of a third person who may not be as thorough in the management of the child's asthma.

> *"No parent wants a child to suffer like that, but unfortunately due to the economic situation they have to go out [to work] and to leave them with people who they don´t know." [IT1]*

In addition to this, an experienced doctor raised her concern about caregivers only being given days off work when their child was acutely ill, and not when they had to attend necessary follow-up visits.

> *"They don´t give them authorization to be absent [from work] to have a medical check-up, just if the child is sick they get permission." [IP1]*

On the health workers side, some felt that in the private practices, doctors are more worried about obtaining economic benefits than in improving the asthmatic child's quality of life. In this sense, they reported that some private health care workers do not want to prevent the child's future asthma attacks to receive more visits.

> *"Unfortunately, here we are very commercial, so the doctor: 'Ah! The more attacks he has, the more he comes for a medical consultation'. But that is not… I mean, that is not the objective that the health staff should have." [IT2]*

Some young doctors commented on the long working hours and the little time they could dedicate to each patient, which, in their opinion, reduced the quality of the service provided and the amount of information and explanations they could offer the caregivers concerning their child's asthma.

> *"There is a large demand from patients, and because we provide care to all of them, and we try to generate quantity, numbers, we don´t generate good quality care." [IR6]*

> *"Doctors who work exhaustingly for many hours and who don´t have, eh, enough time to rest adequately, obviously, they won´t generate correct work. So, I think that it is another – another cause why some doctors can simply say: 'Take this medication and leave'. Right? For fatigue, physical exhaustion." [IR6]*

Another barrier some young doctors reported was that they were told by the caregivers that, on some occasions, they were denied access to the emergency department or they were referred to the health centre when they attended with their child for an acute asthma attack. This may cause the caregivers to lose their trust in the health services provided and stop attending when their child is suffering an acute asthma attack.

> *"Most of my patients say that. In fact, they really say that – I mean, they say: 'They didn´t – didn´t want to see me'." [IR5]*

Finally, some health care workers expressed the impression that the health authorities, at least at the provincial level, did not give the necessary relevance to the problem of asthma. This resulted in a lack of specific preventive and follow-up programmes.

"It is a serious public health problem [asthma], as well as an indefinite number of pathologies that exist, but in our province, it is no… it is not being taken with the importance that it deserves." [IT1]

b. Caregivers

The participant caregivers reported several barriers when accessing the health care services for their asthmatic child. First, they mentioned the difficulties faced when trying to arrange an appointment, second the service hours available, and third the waiting hours before their child is seen for an acute asthma attack. Because of these downsides, some of the caregivers had a negative opinion of the quality and accessibility of the health services provided.

"To get an appointment sometimes you get an answer, sometimes you don´t and it is a chaos. One goes there, but they tell you: 'Wait for your turn'. Then you stop giving him/her the medication." [FG1M]

"You get to the hospital at 10 at night and they don´t… don´t open the door. They send you to the medical dispensary, the health sub-centre to get an appointment again" [FG2F]

"You get to the clinic at 6 in the morning and they see you at 12. It is the same at the hospital." [FG2F]

"If you go to the health sub-centre, you have to wait and wait and wait." [FG1M]

As the health care workers had reported, caregivers described the economic hardships experienced when having to buy prescribed drugs not available at the hospital, to go to a private specialist, or the struggle to find transport to get to the hospital at certain times of the day.

"They prescribe him/her a medicine and sometimes there is, in one way or another, there are times… when there is no money to get it." [FG1M]

"This moment he only has… I bought the blue one [salbutamol inhaler] for him. Because I didn´t have money for the other. I was broke." [FG1M]

"I took him but in [name of the clinic] the medical appointment was very expensive. One got there and waited, all the medicines the doctor prescribed were expensive at that moment, but I bought them the same." [FG5M]

"Anything that is unexpected, and it affects you at night. And there isn´t money to take a cab, it´s a problem:" [FG2F]

Some caregivers reported logistic difficulties, especially when having their child admitted to hospital or referred to a specialist in another city.

"Once she was about 4 or 5 days at the hospital. I was working, my wife was with the little child at home. I…left from my work, I prepared the food, I got back to attend home. So, it was a problem." [FG2F]

"After that I was sent to Quito, and I was going there constantly, I went to Quito for one year, for a year I was going up and going down, every month with him." [FG5M]

Time off work was sometimes complicated to obtain, as explained by some caregivers. They felt that employers do not understand the importance of the situation or the time needed when their child was going through an acute asthma attack. This is even more a problem when dealing with a chronic and recurrent disease such as asthma.

"Sometimes at work they don´t –don´t understand, at work they don´t understand that you have a sick relative and if you don´t get a medical certificate, they think it is a lie." [FG4M]

> *"And sometimes they called me from work, and I said: 'I am going to the hospital'. I used to work 24 hours at that time. It was not possible to leave, I had no one to cover for me, no. So, it's a problem. Um…It´s like I tell you, it has you thinking about…3 parts: work, home and hospital. Where should I run to first? And sometimes you ignore something. I remember one day I said: 'If you want to, fire me'. Because I am not going to lose my daughter over work. I can get a job tomorrow or the day after tomorrow." [FG2F]*

Caregivers also felt that asthma was not taken seriously enough by health authorities in their country and even more in their city.

> *"In the first place, something is missing, as you said, in the first place they need to take it [asthma] more seriously here, in our country, over all. Here in our city, in Esmeraldas city." [FG1M]*

Contact

a. Health care workers

Health care workers complained that caregivers did not follow the indications given and did not adhere to the entire treatment. They thought this occurred because of caregivers not being aware of the importance of their child's asthma and not taking it seriously.

> *"No, they are not very aware of the disease. I don´t think they realize it – from what I have seen, no they don´t." [IP2]*

> *"They don´t care too much about environmental measures, to eliminate the source of mites." [IP1]*

"They stop the treatment, because as they know it always happens, a treatment is always applied to them, then they say: 'No, I, I am already healed', and they simply leave." [IT3]

"Sometimes, I explain it to parents and I give it written to them, and they don´t give the child the medicine as it is written." [IR1]

As for the doctor-patient relationship, some health care workers expressed that on some occasions, the caregivers did not even listen or pay attention to what they were told, while on other occasions they did not seem to fully understand the indications or explanations given. This would also explain the lack of adherence to treatment and lifestyle indications.

"There are caregivers who don´t listen to us." [IR4]

"Sometimes I feel that they don´t understand me. Sometimes I feel that – that they don´t understand what I tell them, no – they don´t, although I like to be very clear." [IR6]

Another reason why health workers thought that caregivers did not adequately treat their asthmatic children or alter their lifestyles to reduce the child's risk of future asthma attacks, was complete ignorance or lack of knowledge concerning their child's asthma management. This was therefore a consequence of them not being informed of their asthmatic child's treatment and necessary care at home. Health care workers also reported that, even if the main caregiver of the child knew about the child's treatment and care, they did not share this with the rest of the cohabitants in the house, who may take care of the child at some point.

"[…] from the caregivers' part there is total lack of knowledge too, eh…real lack of knowledge of the management, of the life style that patients must have, in this case the caregiver ignores all this." [IT2]

"They don´t inform at home. For example, the mother can know his/her trigger, let's see, she is, I drinking soda, eh… the colorants, right? But maybe his/her cousins, uncles, siblings, even his/her father, ignore it." [IT3]

Some health care workers discussed the fact that caregivers only take the asthmatic child to be seen and treated during the acute asthma attacks, but not for the follow-up visits. They blamed it on the caregivers' customs and culture, as they think are not used to visiting a doctor when not feeling ill. They even felt that caregivers wait too much before taking the child to the emergency department with an acute asthma attack, until they are severely ill. The following phrases show the health care workers' perception of how they believe that the child's asthma care is their responsibility, and when they are not able to establish a continuous and close relationship with the child's caregivers, they take them for being responsible for the child's poor asthma control.

"The cultural aspect, thinking that it is only when the patient is ill that he has to go to the doctor." [IP1]

"There are many parents who, when the attacks are over they don´t go to follow-up consultations." [IR2]

"In the area where we are there are many parents who see their child to have a light flu but only when the child gets worse, that moment they take him to the doctor." [IR2]

Another barrier to offer a high-quality health care service reported by some young doctors, was the fact that there is sometimes a lack of organization and cooperation among the health care workers' team, especially at the emergency department.

"Sometimes, we are supposed to be a team, aren´t we? And there they are, and there are people who don´t do things quickly, who don´t hurry up. And then the patient gets more complicated." [IR5]

There were no other differences in the social and cultural factors, as well as in the norms, beliefs and values between young and experienced health care workers, related to contact barriers to health and home care access for asthmatic children.

b. Caregivers

Most of caregivers described having been ill-treated or even abused by health care workers, on some occasions, when attending the emergency department or health centre with their child for an acute asthma attack. Caregivers expressed that a perceived poor doctor-patient relationship may result in the children or the caregiver not wanting to attend that particular health service again.

> *"And after that she said no, they didn´t want to give him the medicine. Then, I had to tell them that: 'I am not a nurse, but here where I am standing, I can hear my son [the wheezing], look at his abdomen'. So, she had to call another nurse to observe him, and the other nurse said that he needed attention." [FG3M]*

> *"Once I got there with – with my child with an attack and a nurse put a thermometer, I was there with the child, and she sat down, I swear that she took a nail polish, and she started to paint her nails." [FG1M]*

> *"My child almost didn´t want to come, because he says that the other doctor is different. […] He said that the doctor is kind of angry." [FG1M]*

Another barrier that some caregivers discussed was that their children were not followed-up by the same health care worker, but that it changed at every visit. This may hamper an adequate doctor-patient relationship, as well as the child's management, as their treatment may be interrupted.

> *"If you are not seen by the same doctor, one sees you then another." [FG1M].*

Some caregivers reported being afraid of the side effects of the medications their children were prescribed for their asthma. On the other hand, other caregivers commented that on some occasions they did not give their children the complete treatment as recommended by the health care worker. They explained that once the child was feeling better, they would stop the treatment.

> *"I heard that when you take Salbutamol, your heart beats a little faster." [FG3M]*

> *"One took her to the doctor and she had some medicine and then we knew that on the fourth day she was better so I didn´t finish all the medication." [FG2M]*

> *"When I see him better, I don´t give him anything more. I stop worrying. […] There is medicine left." [FG2M]*

Together with these fear and mistrust, caregivers seemed not to be aware of the effect and duration of the effect of certain medications used for their child's asthma. For example, they did not know that after 3-4 hours, the effect of salbutamol (an acute bronchodilator) wore out and another dose should be administered.

> *"But that Salbutamol, that bromide, it doesn´t even tickle him. Because I go to the clinic, they put a nebulizer on him, I get back home and after three hours he is sick again." [FG5M]*

Availability

a. Health care workers

Both young and experienced health care workers commented on the lack of diagnostic tools, such as spirometry, human resources and drugs for treating asthmatic children at the hospital or health centre. They felt this precluded them offering an adequate management for these children.

"And not really – we don´t have all the medicines, an appropriate stock of medicines in hospitals." [IP2]

"There aren´t even enough human resources. It has happened to me sometimes that just one doctor oversees all the emergency area, and he doesn´t attend just one patient, but there are some patients who are less severe." [IR6]

"[I am used to diagnosing children with asthma] Clinically only. I don´t have, any methods, spirometry, nothing like that." [IP1]

This was especially noted at the health centre, were health care workers reported there were no drugs or professionals to take care of the follow-up of asthmatic children. The reason why this happens is because of how health care is organised by the Ministry of Health, as health centres (primary level) do not have access to drugs for 'specialised' diseases, such as asthma.

"It is a big problem too because in the health centre, for example, in the first level unit there isn´t any treatment for asthma, for the long term." [IR4]

Similarly, some health workers explained that because their hospital was only a 'second' level hospital, they could not have access to certain diagnostic tools.

"I can´t carry out immunology tests here, if there is deficiency of IgA or, the deficiency of alfa – 1 – antitrypsin, either of these things, I couldn´t do it. Then I have to think about the third level." [IP3]

Another barrier that health care workers reported was the lack of follow-up and educational programmes for asthmatic children. They mentioned that this kind of programme exists for other chronic diseases (hypertension or diabetes) or for pregnant women, which even include home visits. Young doctors who only work shifts

at the emergency department (ED) expressed the difficulty of following-up a child they may have treated at the ED for an acute asthma attack.

> *"There are TAPS [physician assistants], who are technicians that help, they visit people at home, they follow-up the patient. But overall in pathologies, it is like… more about morbidity, about diabetic and hypertensive patients, but following-up patients with asthma, no." [IR2]*

> *"That´s what we are lacking, education programmes for asthmatic patients." [IT2]*

> *"I would like to see them [asthmatic patients] again, but here unfortunately we have work in shifts, I don´t get to see them." [IR3]*

Experienced doctors complained about the lack of training programmes for the general doctors that work at the emergency department and health centres treating and managing children. They referred that young doctors sometimes treated acute asthma attacks inadequately and that they thought they felt unsure given their lack of specific knowledge concerning paediatrics in general and paediatric asthma in particular. Even worse, experienced doctors reported that some young doctors base their practice on their own experience, instead of clinical guidelines or scientific recommendations.

> *"When the general doctor sees a child closely, he is already scared." [IP3]*

> *"The norm that residents in training need to come here to learn Paediatrics hasn´t been set up. To become a clinical paediatrician. They think that with the experience of repeating things gives them the reliability to do it, they say: 'I have repeated it'. It is not science; you can repeat things wrongly." [IP3]*

Other health care workers reported that, on occasions, asthmatic children and their caregivers receive incomplete or even misleading information regarding their child's

management. As an example, they described how some health care workers impose unnecessary limitations to the child's life, such as, those referred to sports activities.

> *"Some doctors can simply say: have this medication and leave." [IR6]*

> *"Then we have […], lack of knowledge about the management, and wrong information, I think, given to the patient´s caregivers." [IT2]*

> *" 'You can´t eat, […] strawberry. You can´t play, you can do nothing.' So, it becomes a strong taboo, and they [health care workers] scare the caregivers so much […], that they have created such carelessness and fear towards the asthmatic patient." [IT2]*

Some young doctors also brought up the mistrust they felt when using certain drugs to treat asthmatic children, given their side effects. These fears were sometimes based on certain beliefs that did not coincide with guidelines recommendations.

> *"The corticosteroids, for me, all of them the inhaled as well as the injections, oral, all of them have their faults since… they leave sediments, deposits and…in the long term you will see negative results, let´s say, in other organs." [IT2]*

> *"Salbutamol has its risks; besides we have to know how to use it, how to explain […]. Patients who aren´t asthmatic, have received this medication and they end up badly – to the extreme that, they even, […] have a tachycardia and they end up dying." [IR4]*

<u>b. Caregivers</u>

Caregivers discussed the unclear and insufficiently detailed information they received from the health care workers concerning their child's asthma management and home care. They believed this information was sometimes incorrect. In addition to this they

reported receiving contradicting information or criteria from different health care workers.

> *"Yes, it is very rare for a doctor to explain, more detailed." [FG2F]*

> *"No, in general here doctors only tell you that it is an allergy. 'No stuffed toys'. But here we realized that it is not only that." [FG2F]*

> *"But they never told him or explained to him: 'This medicine is good for this or for that'. But they gave it to him and they told him: 'Take this medicine', nothing else." [FG4M]*

As the health care workers did, caregivers also commented on the lack of medicines and medical supplies at the hospital and health centres to treat their child's asthma.

> *"But we took the control of the medicine ourselves, because they [at the public hospital] didn't have anything. They didn´t even have disposable masks [to nebulize]." [FG2]*

Caregivers explained that their children were diagnosed with asthma without having had any specific tests or samples taken. This led them to mistrusting the diagnosis.

> *"You go there, and the doctor tells you: 'The child has this'. But never before he was checked up, he didn´t have any tests done, to say that this [asthma] is what the child really has." [FG4G]*

Some caregivers expressed that, on some occasions, the health care workers had told them that they did not have the necessary training to manage their child's asthma and that they should take them somewhere else.

> *"He told me: 'Definitely your child needs another type of medicine and another kind of doctor who can attend him, take him to another place'." [FG5M]*

Other caregivers reported that they were not aware of any other treatment available for their child's asthma, except for the relievers (bronchodilators, such as salbutamol).

> *"I only knew about Salbutamol, and no more." [FG3M]*

Finally, female caregivers discussed how the burden of the asthmatic child's care falls on the women in the house (mothers and grandmothers), with an absence or a low participation from the father.

> *"They [fathers] aren´t awaken at night, I say, well, there aren´t many cases. But in most of them, mothers are the ones who stay awake, and we don´t sleep when the child is sick. But the father sleeps, and then he asks: 'How is he?', 'He is ill', 'Ah, OK'. And he leaves and falls asleep, right? I say: 'How can he be sleeping when he sees his child like that?'" [FG3M]*

5.4.4. Facilitators to health care and home care access

Both caregivers and health care workers discussed facilitators to health and home care access for asthmatic children. We have also included in this section ideas they expressed of how health and home care could be improved to reduce barriers to access.

Acceptability

a. Health care workers:

Both young and experienced health care workers believed that certain taboos and myths about asthma could be easily eliminated through specific community asthma education programmes. They reported that caregivers have a sufficient cultural and educational level as to understand what health care workers explain to them about their child's asthma.

> *"Education programs and health programs that teach what asthma is and that can remove all the taboos that we have about asthma." [IT2]*

"One explains them, because mothers or caregivers don´t have such a low cultural level as to not understand." [IT3]

Some experienced health care workers explained that certain caregivers do follow the indications given and attend their regular follow-up appointments. They even offered caregivers their personal mobile number in case they need some guidance or help.

"Some of them do. Some come, even… and I give my cell number to those asthmatic patients. Some of them call me: 'Doctor, my medicine is finished, help me with an appointment'." [IP1]

Some young health care workers expressed feelings of affection towards the asthmatic children and their caregivers, and were willing to help them in whatever way they could.

"Sometimes one as I have just told you, one tries to be neutral, as a doctor I try to be neutral so not to create feelings. But sometimes, you get to feel some affection towards them [asthmatic children]." [IR6]

"They already know that they can support us and that we are ready to help them." [IR4]

Young health care workers discussed the difference they observed in the degree of implication in the care of the asthmatic child among the fathers in the urban compared to the rural area. In the city, on some occasions, both parents are present at the emergency department and they both show the same level of interest towards their child's disease, according to young health care workers.

"Yes, there are changes [in the urban setting compared to rural setting]. Both of them are usually here. So far in – in a month that I am here, both of them come, the father and the mother. And they both say: 'Do you know what´s going on?' The

mother leaves and the father comes:' I want to know what´s wrong with my baby'." [IR5]

b. Caregivers:

Some caregivers explained that they do follow the doctor's indications and give their asthmatic children the medicine such as it was prescribed. This is especially so, if they believe it is going to make them get better.

"Because if the doctor tells me: 'Give it to him for seven days and it has to finish all of it [the medication]'. I do." [FG2M]

"'[…]Take the medicine, you will feel fine with this. If you don´t take it, you won´t feel good'. Sometimes I de-stress and he de-stresses, because if he doesn´t take the medicine all the time, then he won´t be fine. And, if there is a medicine that will have an effect on him, I mean, using it for 1, 2, 3, 4 days and the attack won´t affect him until after 6 months, or 4 months, then, I would feel good." [FG1M]

"Then, yes, I would be interested if there were a treatment like that, that can change it, eh, I don´t know, the frequent attacks, I would do it. Whatever the cost." [FG3M]

Another facilitator some caregivers expressed is that they trust the medications prescribed and the doctors' criteria, given they have undertaken scientific studies to develop such drugs. Some, even trust them more than traditional or natural remedies, which were shown to be of no use in some cases.

"If they know that it is a medication that they first must research, many people, many doctors, and that is why they prescribe it for asthma. And that´s why, as she says, many people say that at in the long term it hurts him… and why can it hurt him… what is the reason why it can hurt the lungs, will it be too much air or what?" [FG1M]

> *"My daughter is 23 years old, the oldest of my children. My daughter did suffer from this disease [asthma], and we only gave her home remedies. But now…this… those remedies have no effect on my boy. It does nothing." [FG2M]*

However, some caregivers also suggested a more holistic approach to asthma care from the health care workers, to include other recommendations or therapies apart from the use of drugs, as some of them do not believe it is good for the body to take medications for a long time.

> *"It could be another… another methodology, not always taking medicine." [FG1M]*

Finally, some caregivers commented on the possibility of making older children and adolescents responsible of their own asthma care, as they are old enough to understand the implications and the importance of an adequate follow-up, management and prevention.

> *"A ten-year old child, he can be aware. For instance, my daughter – she knows. Then when she tells me: 'Oh, mom, I want a little [of something that may trigger her asthma]'. I say to her: 'You decide if you take it, because you can take a little now, but your body will be affected'. Then she, when I say that to her, she doesn´t take it." [FG5M]*

Accessibility

a. Health care workers:

Another facilitator health care workers reported was the availability of necessary drugs and equipment at the hospital, for free.

> *"I mean we have a type of bronchodilators. But in the private clinic they need to buy those in private drugstores. But, here in the hospital, we are well-equipped. We have bronchodilators." [IP3]*

"At least, we have in the hospital all the necessary supplies to attend the patient." [IR4]

"No, because here, we give all the medication to them. We give them what the doctor prescribes. At least, for respiratory diseases, we provide them with all the medication. It is never missing. Supplies, materials, disposable masks and other things too. So, it's not about missing medicines or supplies." [IT3]

On the other hand, experienced health care workers working in the private practice, commented that they try to help caregivers that may not have the economic resources to buy prescribed medication, by maybe inviting him or her to visit the hospital where he may be offered the drug for free.

"I don´t let him be without the medicines. I mean, if people tell me that they don´t have any money to buy it, I tell him that I will wait for him in the hospital tomorrow. I help that patient. I give everything to him, I give the pills to him. I give it to all the patients." [IP3]

Similarly, other experienced health care workers discussed that certain caregivers can buy the medication that may not be available at the hospital without problems, and that some way or other they end up obtaining the prescribed drugs.

"They can buy the medicine perfectly, what…the only thing we don´t have here is what I have just told you, the Montelukast, they buy it without problem." [IP1]

"In general, they do get it. It takes one day, maybe, but they get it." [IP3]

Both experienced and young health care workers expressed several ideas of ways to improve asthmatic children's asthma, such as organising periodic home visits or a specific team to take care of these children, what they call an 'Asthma Club'. Some health care workers believe this is the responsibility of the Ministry of Health or the

local health authorities, who should implement specific public health programmes for asthma.

> *"Having coverage, a better health coverage, and the existence of health promoters who get to the houses and who are constantly educating them." [IP2]*

> *"We could improve if we could visit mothers, be in touch with them by phone, I mean, creating an…an Asthma Club. An institution which is kind of an Asthma Club. Like that, we could follow-up that baby, visit his house, see the conditions, and have a complete dedicated team." [IP1]*

> *"That could be solved with a public health programme, right? To have the patients identified and carry out home visits." [IT1]*

b. Caregivers:

Caregivers commented that in general they found no difficulties in obtaining days off school for their asthmatic child.

> *"We give you the time-off you want." [FG4M]*

As for health care workers, some caregivers also believed that health care for asthmatic children could be improved by organising specific areas in the hospital for their management.

> *"Here at the hospital there should be an area for that system only [asthma]." [FG1M]*

Contact

a. Health care workers:

Some health care workers felt that communicating with asthmatic children's caregivers was not difficult, especially if they had a higher educational level, and that by using

repetition, most of caregivers would easily understand the information they were trying to convey to them. On occasions, they reported meeting caregivers who were very cooperative, understanding the indications given and following them.

> *"It´s an advantage to work here, because the type of patient that comes here is not always the public patient. Here we have many mothers who have a higher level of education, isn´t it? I mean, they ended high school, or they are professionals. Then, that facilitates the message getting across." [IP1]*

> *"I liked it because the mother was very cooperative, in this case. She understood me, I explained to her what we had to do, what we were going to do with him. […] She understood because she started to give the medication to him properly." [IR6]*

Other health care workers described how they use different methods such as drawings or games to help children and their families understand asthma. They also commented that being honest and direct was sometimes useful to engage caregivers in the management of their child's asthma.

> *"Mainly, I would have to search the way to help these children. Telling them, teaching them, by motivational speeches, games. Maybe, with my hands, taking their little hands, showing them, organizing workshops, motivating them to do all that we have explained and doing it with interest." [IR6]*

> *"[…] you have to explain it all, drawing IgE, the hypersensitivity. It is the fastest way […] In general, if one guides and tells them what the topic is about, they will get to know it." [IP3]*

> *"I mean, making the parents aware, telling them the truth, being honest: 'These are the conditions, and this is what may happen if you don´t do this', and this kind of stuff." [IR5]*

Some young health care workers felt motivated and happy when caregivers turned up to inform them that their child was getting better thanks to their indications.

> *"So, when a child or a mother tells me: 'Doctor, he is much better with your indications, with the specialist´s indications, he is fine.' One feels happy. I mean, it is motivating." [IR6]*

The same happened when the health care workers in a department worked together as a team, cooperating and giving feedback to improve asthma management.

> *"What makes me feel good? Well. That I and all my co-workers talk in the same way, that we understand each other with the same diagnosis, that if we fail we correct each other, that there is always a good feedback in the cases of patients. That is what induces a state of well-being." [IR6]*

b. Caregivers:

Some caregivers reported having received an adequate care when taking their child to be treated for an acute asthma attack to the hospital. They describe specific moments when they were nicely treated, explaining that even if the child does not improve as much as they expected, they still felt satisfied with the care received if they treated them promptly and with respect.

> *"The times that I've been to the hospital I´ve received good attention." [FG4G]*

> *"He was attended, he received first aid, but, no, he didn't get better, but he was taken care of. I mean, I leave happy." [FG4M]*

> *"In general – in all the places where I have taken my son to get nebulized or receive attention, they have always – always treated him very well." [FG5M]*

Caregivers also expressed gratitude for the guidance received from some health care workers.

> *"We have to feel good for it, thankful because we have received advice, they have helped us in that aspect, to have that responsibility, that aid, what they have offered us. Because they have given us advice for a reason, haven´t they? It is for us to know how to cherish that. We have to learn from what the doctor offers us." [FG4G]*

Similarly, they discussed how some health care workers recognise the emergency of acute asthma attacks and try to treat them quickly.

> *"Once, I got there and my child was – was very distressed with the fever. And the nurse said: 'Sit down and wait – wait for your turn'. […] And – and then a doctor showed up […], and he – he made me get in immediately." [FG4M]*

Another facilitator that caregivers brought up is that certain health care workers do follow up their asthmatic children more closely.

> *"In December, I had an appointment with my son. Instead, the doctor this time did tell me to get an appointment because he told me that my son needs to be followed-up month by month." [FG1M]*

Finally, some caregivers commented on the effect the specific asthma programme (the cohort study during which they were followed up by phone every two months) had on them and the home care of their asthmatic children, by reminding them the importance of the disease and its prevention. On the other hand, a father also expressed how participating in the focus group discussion had made him realise the relevance of his daughter's asthma and how he now felt he should be more involved in the management of her asthma.

> *"[…] From here, from the asthma centre [asthma study centre] they always call me at home. And when they call me I feel so grateful, and I remember, and I start cleaning, […] So, it is like they are telling me: 'Clean, clean." [FG4M]*

"But, sometimes I receive phone calls telling me that she is in the hospital, that the girl has a headache or something else. Then, well, at least what I do is to provide money for the doctor, buy the prescribed medicine. But, it is important that I came [to the focus group discussion] to ascertain all these things well." [FG2F]

Availability

a. Health care workers:

Health care workers did not report any facilitator for increasing availability of health and home care access for asthmatic children. However, they expressed many different opinions and ideas of how this could be improved. For instance, they gave great importance to the increasing asthma knowledge of caregivers and the general population using media or specific education campaigns in schools, for example.

"Improving the knowledge of the ones who suffer from the disease, right? And not only the affected should be educated but also all the general population." [IP2]

"Keep educating the family, educating at school, creating education programmes there… there at school, educating." [IT2]

"It would be a matter of prevention, of communication, I don´t know, with speeches for people who are proactive in this management. To use the media, I don´t know, radio, television." [IP2]

Once more, the concept of organising a 'Club of Asthma' to improve asthma knowledge and management at home. Some health care workers also highlighted the importance of broadening this education and training to the extended family and friends who may be in charge of the asthmatic child at some point.

"They should do the same, shouldn´t they? A mothers' club, for asthmatic people, mothers whose children have asthma." [IP2]

"I don´t know if it could be with greater, I mean, organizing something like a more aggressive campaign for the families, of education, explaining them." [IT2]

"I think that teaching all the [extended] family and the closest friends. I believe that way we can avoid, [asthma] attacks." [IT3]

Experienced health care workers also discussed how to improve asthma knowledge and management among young doctors, by specific lectures and daily training.

"I do really think that the topic should be managed. It can be. A lecture, prepared for the residents [general doctors], about this topic. It is the only way, if not they [general doctors] will continue. […] It must be on a daily basis, daily. To learn and to train them […]." [IP3]

Some young health care workers felt motivated to study more about asthma and allergies, following the end of the cohort and qualitative study on asthma at the hospital, for which they had collaborated.

"It is motivating for me that you are, doing this. Thank God, in the long term, well, I also continue with my studies, studying this [asthma] in more depth. I like it very much – Allergology - I'm interested in it, a lot." [IR6]

b. Caregivers:

Caregivers also discussed how an enhanced asthma knowledge would improve their child's management and care. Some caregivers felt empowered to treat their child during an acute asthma attack.

"The thing is, if I know what the cause is, I would be more careful, making him not to – not to be in contact with what hurts him, trying to keep him away. But if I don´t know, how am I supposed to know what I should protect him from? Because I really don´t know what it is." [FG4M]

> *"If he gets sick in the middle of the night, or if he doesn´t have the pills here, we soon give him one, two or three puffs [salbutamol inhaler]. We would do it, so the child could – could get better – be fine the next day. It ends quickly - doing that [salbutamol inhaler]." [FG4G]*

Some caregivers believed their asthma knowledge and skills could be improved with education sessions or lectures.

> *"It could be possible that we can do something. That´s why I say… with lectures, attending good seminars. [FG1M]*

5.4.5. Use of recurrent asthma attack risk assessment tool

Benefits

a. Health care workers

Health care workers discussed the usefulness of the risk assessment tool and described it as being simple, easy to use, clear, ideal, excellent, practical and didactic. They expressed it would be very helpful and important.

> *"It would really be of great help. A clear, simple and understandable tool." [IR6]*

> *"So, they are very valid tools and if they are implemented, they are of good help." [IP2]*

> *"It is something very didactic, very practical and very simple and it is a very important tool." [IT1]*

Both experienced and young health care workers described how it would improve their daily practice, by helping them identify the children at a higher risk of suffering a subsequent asthma attack. They reported how this would facilitate the decision-making

process regarding treatment, necessary follow-up and level of health care needed (primary vs tertiary).

> *"It would be useful to know which of them will be coming back, and which won´t […] To know who requires more attention and who doesn't." [IR1]*

> *"To know when to follow-up a patient at a first level [health centre], or when he needs to be treated at a more advanced level of care […] it would be good to follow-up those of low-risk at a primary level of health care, while the high-risk patients need a […] They come to emergency room with these attacks constantly, they go directly to the specialist." [IR4]*

> *"We would identify them. We would call them. We would have a more direct control over high-risk and low-risk patients." [IT1]*

> *"It would also help us a lot to know when to start using or not the corticosteroids and all that stuff." [IR2]*

> *"We would communicate to the mother that [her child] has a higher risk of triggering another attack in the future. Then, the medical check-ups for that child will be stricter, or the follow-up, or the treatment or the – physical examination […] First, the treatment, I mean, I would have to see what kind of inhaler to use, how frequent it will be used […]. I would see for how long, I would schedule the appointments much better." [IP1]*

Some health care workers even thought it might reduce the number of severe acute asthma attacks, the number of deaths due to asthma and it would increase the adherence to asthma treatments and life-style modifications.

> *"Then yes, with this tool and explaining it to the professional appropriately, and then applying it correctly on the population, I think we would find or we would have*

fewer cases of children who have asthmatic attacks that could be the cause of some types of serious and acute illnesses that could even lead to death."[IP2]

"Yes, yes, yes. In fact, it would. [It would help fathers and mothers to become aware of the importance of the treatment]. Of course [it improves the treatment compliance]." [IP1]

"I do think that it would change [the parents´ attitude a little if they could see something as visual as this tool]." [IT1]

Another benefit health care workers discussed was how it would enable the transmission of information to caregivers, concerning the child's asthma, especially their future risk of severe acute asthma attacks. They commented on how they would change the amount and type of information they would offer caregivers, depending on the predicted future risk.

"The tools which are used are great instruments for the doctor, for sure. And if they are understandable or correctly and simply explained to the doctor, obviously much clearer for the patient, so the doctor may convey that information to the patient, it would be much better." [IR6]

"Yes, it [the tool] is easy to use. I would say: 'Madam, it´s important that you come back after a certain time and to manage this amount and frequency of medication because that child has a high-risk or medium-risk to have it again…or let´s not do much because he has a low-risk of experiencing an attack so frequently.' It does work for me." [IP1]

"It would be more specific [the advice given to patients], wouldn´t they? I won´t give the same - treatment to the ones who are in the high risk zone as to the ones who have recently started, right? Well, it does change the attitude." [IP2]

Experienced health care workers also brought up that the risk assessment tool would be especially useful for young health care workers, trainees and students, to decide upon specific treatment and follow-up needs.

> *"It is a very important aid for one and for […] the residents [general doctors], the interns. To be able to give these tools to them so they can assess and try to cure the patient." [IP2]*

> *"And also for the resident [general doctor], they would know which patient they need to refer to me that moment and which not." [IP1]*

Finally, some health care workers had specific ideas of how the risk assessment tool could be implemented in the health care system, for example at the emergency department, to initiate a whole management team including social workers to assure that high risk children are given the necessary information, treatment and follow-up.

> *"It would be very useful for emergencies: admitting the child to hospitalization, making sure that parents understand that he is a high-risk patient, that the social worker has to be in touch with this patient, right? Finding out who is the most responsible of the family members: his extended family, his father or his mother; knowing which is their nearest health centre." [IT1]*

<u>b. Caregivers</u>

As the health care workers did, caregivers felt the risk assessment tool was easy to understand, simple, good and important. They commented on the familiarity of the traffic-light colours (green-yellow-red) and how visual the tool was.

> *"Because you can see it there, like the traffic lights. Because red is danger and everything. It is fine for me like that, because one is able to understand like that, because you know what the dangers are, and that's how the colours are." [FG1M]*

"I find it simple. If you have made it so, then some of your experience is integrated here. So, I find it easy to understand for lay language. It quickly found out that I am here [pointing at one of the risk areas in the tool]." [FG2F]

"Red means high-risk, yellow is medium-risk and green is low-risk, almost nothing." [FG3M]

Some caregivers discussed how the risk assessment tool helped them understand their child's future risk and how this would affect their degree of concern and worry regarding their child's asthma. They reported how they would be more prepared for the next acute asthma attacks.

"For me, it´s fine too. Because with it, one knows what he has and what he hasn't; and the risk you are taking." [FG1M]

"If you tell me that he/she is in the green zone [of the tool], then it means that…I shouldn´t worry that… that much, right? Because I know that it would take some more time [for the asthma attack to recur] […], right? And if he/she is in the yellow, I must be a little more [worried], but not much. But if he/she is in the red, it means that I must be there with that person because I don´t even know if at what moment he/she stay there [die], and not come back." [FG1M]

"I think it would even be a good method for me because I would know the truth, because a doctor can say: 'Your child is in this stage and he/she has this risk or he/she doesn´t', then I am facing a disease with a risk and I know it for sure, if not – the doctor sends us the medicine, we take care of him, but we don´t know what the risk is and how the illness may progress." [FG5M]

"We have to be more careful. We know that in 4-5 months the [asthma] attacks will return, then we already have to be aware of what will happen." [FG2F]

"[…] Because if he/she is in red I have to pay attention […]. In yellow, a little. In green, well, when it is green then, the concern is less. […] He is out of danger. But if it is red or yellow we must be a little careful, but if it is green, then the danger exists but it is lower." [FG3M]

As a consequence, some caregivers explained that being more worried due to their child's high risk of recurrence, would mean they would increase their adherence to doctor's indications and treatment prescriptions, would be more vigilant of the child's home care, and would take extra care of the high-risk child.

"For me, yes, it would [change my life style a little or the use of the medicine prescribed to them]. Because I wouldn´t see my child daily, or every day. I would also say: 'Take the medicine because you will feel fine with this. If you don´t take it, you won´t feel good'. Sometimes I de-stress and he de-stresses, because if he doesn´t have the medicine all the time, then he won´t be fine. And, if there is a medicine that will have an effect on him, I mean, using it for 1, 2, 3, 4 days and the attack won´t affect him until after 6 months, or 4 months, then, I would feel good." [FG1M]

"I would. I would take control every day and I would follow-up my son to see how he is doing." [FG2M]

"If I would see that, for instance, he/she is in yellow. Then, I want him/her to be lower, right? […] So, yes, I would be interested if there was a treatment like that, so it could change him [the level of risk in the tool], the frequency of the attacks, I would do it, whatever the cost." [FG3M]

Finally, some caregivers discussed how they would rely on the risk assessment tool, as it comes from a research study. They commented on how this instrument was developed to help them (caregivers of asthmatic children) and how they believed it was an example of a medical advance.

"In any of the three stages, we must follow the methods, because it is supposed that thanks to this research which is being done and which is being done through the university and all that stuff, well, it means that it is to improve… so our children can get better and we can also get some well-being for ourselves, as parents." [FG1M]

"Through this, you help us." [FG1M]

"I find it to be very good and a medical advance, as medicine is progressing little by little, and gaining more knowledge." [FG4G]

Barriers

a. Health care workers

Some health care workers believed that all the patients seen at the emergency department would be classified as high-risk patients according to the risk assessment tool, making no difference between them.

"Here everybody would be high-risk patients because here everybody has been under treatment using corticosteroids, most of the patients are from the rural area." [IR1]

"Because here everybody is high-risk patients. Most of them. Most of them if you realize. Because they get here when they have been under many treatments and since they can´t reverse the mild attacks… they can´t and they realize it and then, they come here." [IT1]

Other health care workers commented that there were some important or relevant questions missing from the risk assessment tool, or they did not completely understand how the tool should be used or the information it offered.

"I think that we have to include more questions." [IR1]

"At first glance we could add […] the time since his/her last attack. We could add something there." [IT2]

"It could say: 'Living in a rural or urban area'. I would add: 'or urban.' And about the ones who use inhalers, I would expand it. I would." [IP1]

Another barrier some health care workers brought up regarding the implementation of the risk assessment tool in their daily practice, was that it would not change their management of the asthmatic child nor the caregivers' attitude, regardless of the risk group the child was assigned to.

"As for the treatment, no…my attitude would be the same because if I neglect these, the low-risk ones, they will end up on the other side. So, I would continue in the same way. All of them would be kept in the level they are, avoiding them to pass to another." [IT1]

"I wouldn´t change my attitude [when informing the patients]." [IR3]

"If they are recurrent patients, well, they know they already know about their disease and we tell them: 'It will last for a certain time, until…or that they will always have factors that trigger the attacks', I mean, I don't think that telling them: 'You are in a group, or not'… I don´t consider that they will go, or they will get more motivated to continue with the treatment." [IT3]

Finally, some young health care workers highlighted the importance of the risk assessment tool being adequately explained to the health care workers that will be using it, before it is implemented.

"Obviously with the right instruction and training. […]Some tools get here, we have a demonstration, but we don´t get an explanation or it is not understandable for the doctor or the doctor might not be here – it's difficult to understand for the doctor

the assessment of such tools. Then, if the doctor cannot understand the evaluation, how can he/she explain this to a caregiver?" [IR6]

b. Caregivers

Some caregivers reported that they would not change their attitude towards their child's care regardless of the level of future risk they were informed of, according to the risk assessment tool. Other had even doubts of the effectiveness of the risk assessment tool.

"I would continue in the same way. Let´s suppose that he/she is here and when I don´t give him/her the medicine, he/she gets here [to a higher risk] due to my carelessness. So, I continue in the same way." [FG1M]

"I don´t know if it will work." [FG2F]

Another barrier that some caregivers brought up concerning the risk assessment tool was that once some time has passed by, and their child is asymptomatic, then they would stop worrying and taking the medication. The same would happen in the case of caregivers who have some experience with the disease, because of other siblings or themselves suffering asthma and surviving it.

"It is about a year, and I don´t…I told you…it is almost a year that he she doesn't have… [asthma attacks]. Imagine I have the inhaler they gave me, and it's not been used. I've got two inhalers, and both are brand-new. Then, no, there's no reason to stop [taking care of him/her]." [FG2F]

5.5. Main findings

This qualitative study offers novel and relevant findings by including the opinions and experiences of both HCWs and CGs of asthmatic children, concerning acute asthma significance, and asthma health and home care access.

The main finding related to acute asthma significance is how CGs and HCWs experience this event from their perspective, and how this could also be observed between experienced and less experienced HCWs.

HCWs focus on improving the child's situation during the acute attack and feel responsible for them, a moment that young, inexperienced professionals may endure with fear and uncertainty, while more experienced workers are confident on their skills and knowledge.

For the CGs, acute asthma attacks are troublesome and urgent events that they live with fear, desperation and resignation in some cases. They affect the family's economy, organisation and activities. Both CGs and HCWs feel responsible for the child and are aware of the possibility of the attack resulting in his/her death.

HCWs and CGs identified multiple barriers to health care access for asthmatic children, and a few related to home care. The barriers are summarised in Table 5.6, divided into the 4 categories of Tanahashi's model[379]. Some of them were shared by both HCWs and CGs, with contradicting opinions on others.

Table 5.6: Barriers to health and home care access for asthmatic children according to HCW and CG.

Category	Health care workers (HCWs)	Caregivers (CGs)
Acceptability	- Use of natural remedies and other people's advice by CGs - Poor adherence to medication and indications - Education and SES CGs -Rejection by CGs (Y)	- Natural remedies and other people's advice - Reluctant to expose children to long-term medications - Fear and mistrust towards doctors and hospitals - Seek advice outside health service
Accessibility	- Cost of medicines, transport and specialist consultations. - CGs not given days off-work for follow-up appointments. - Lack of specialists and slow and complicated referral system. - Child cared by a third person - Health authorities not interested in asthma, not taken seriously. - CGs not given access to emergency department (ED) when child with acute asthma attack. (Y)	- Economic hardship (drugs, transport) - Difficult to obtain days off-work - Logistic difficulties (hospitalizations) - Difficulties in obtaining appointments. - Limited office hours and long waiting times.
Contact	- No adherence to treatment and indications, CGs not aware of importance of asthma. - CGs do not listen or pay attention. - Lack of knowledge in CGs (not informed adequately) - CGs take childsren when severely ill. - Private HCW looking for profit (no prevention strategies) - No sense of team work at ED (Y)	- Afraid of asthma drugs side-effects. - Stop treatment if no symptoms. - Ill-treated and abused by HCWs. - Not aware of effects and duration of the effect of asthma drugs.
Availability	- Lack of diagnostic tools, human resources and drugs. - HC have no access to asthma controller medicines - Lack of follow-up and asthma education programmes. - Long working hours, short time per patient. (Y) - Misleading and incomplete information to CG (Y) - Mistrust in asthma drugs based on beliefs (Y) - Lack of training for GDs (E) - Inadequate management by GDs (E)	- Lack of medicines and medical supplies (nebulizing masks). - Not aware of asthma controller drugs. - No diagnostic tests for asthma. - Unclear, insufficient and incorrect information from HCW - Contradicting information and criteria - GDs do not have necessary training to manage asthma. - Burden of care on women

HCWs: Health care workers; CGs: Caregivers; SES: socioeconomic status; Y: young, inexperienced HCWs; E: Experienced HCWs; ED: Emergency Department; HC: Health centre; GD: general doctor.

Table 5.7: Facilitators to health and home care access for asthmatic children according to HCW and CG.

Category	Health care workers	Caregivers
Acceptability	- CGs that do follow indications, treatment and control appointments. - CGs have sufficient cultural and educational level to understand explanations. - Taboos and myths easily eliminated with asthma education. - HCW offer private mobile number for CGs to call when needed. - Affection towards children and CGs - Greater implication of fathers in the city.	- Follow HCWs indications and treatment. - Trust HCWs and drugs prescribed (over natural remedies). - Possibility of making older children responsible of their asthma management. * Prefer a more holistic approach.
Accessibility	- Free drugs and equipment available. - HCW help low-resource families in private practice. - Families that can buy prescribed medicines. * Periodic home visits, 'Asthma Club', public health asthma programmes.	- Easy to get days off from school for children. * Organization of a specialised area for asthma in the hospital /HC.
Contact	- Easy to communicate with CGs. - Cooperative CGs, follow instructions. - Use of alternative methods to convey information (pictures, etc.). - Being honest and direct with CG - Some HCW are motivated and happy when children improve or there is a feeling of team work. (Y)	- Adequate care by HCW, kind and quick. - Feel gratitude for guidance offered. - Close follow-up by certain HCWs. - Importance of specific asthma programmes that increase awareness.
Availability	- Feel motivated to study asthma further. (Y) * Increase asthma knowledge for CGs and general population. * Organise an 'Asthma Club' for patients and families. * Education for extended family. *Improve GD's knowledge. (E)	- Feel empowered to manage their child's asthma (self-efficiency). - Enhanced knowledge improves child's management. * Education sessions or programmes for patients and CG to improve asthma knowledge.

HCWs: Health care workers; CGs: Caregivers; SES: socioeconomic status; Y: young, inexperienced HCWs; E: Experienced HCWs; ED: Emergency Department; HC: Health centre.
* Ideas or suggestions to improve health and home care access for asthmatic children.

A small number of facilitators for health and home care access for asthmatic children were reported by either HCWs or CGs, represented in Table 5.7. On the other hand, several ideas and proposals of how to overcome the discussed barriers were brought up. These proposals included both changes in the way they (HCWs and CGs) behaved in front of an asthmatic child or how they managed their asthma attacks, as well as how

other people or institutions could modify the health services' structure and organization.

Finally, when shown a preliminary design of a risk-assessment tool for recurring severe asthma attacks, HCWs and CGs felt quite positive about its usefulness in improving asthma management, transmission of information to CGs, and adherence to indications and treatment. They could understand the information it provided and found it simple and easy to use. However, some HCWs and CGs felt reluctant towards the tool, and expressed their doubts about the use of the tool resulting in a change in CGs' or HCWs' behaviours and attitudes towards asthmatic children.

5.6. Strengths and limitations

The main strength of this study is the inclusion of both HCWs and CGs of asthmatic children, at the same time and addressing the same topic, to be able to contrast their opinions, beliefs and experiences. Similarly, the involvement of both specialist doctors, respiratory therapists and young general doctors added value and richness to the data obtained, facilitating once more the analysis of the difference between experienced and inexperienced HCWs. We were also able to obtain a wide picture of the childhood asthma experience by exploring the significance of acute asthma on one side, and the perceived barriers and facilitators to health and home care access. This enabled us to reflect the importance of the disease for the patient's CGs and HCWs, as well as perceptions of why asthma management is not as adequate as it should be, and opportunities to overcome these barriers. Finally, by discussing the use of a hypothetical risk assessment tool of recurring severe asthma attacks, we could describe whether this tool could act as a facilitator to improve asthma management from the CGs' and HCWs' point of view.

In qualitative research, authors should first explain their own background and context before presenting the study findings, as these may be influenced by the researcher's subjectivity. I am a paediatrician who has been working in the setting where the study was undertaken for over two years, having a close working relationship with some of the HCWs that we interviewed. I also conducted the previous cohort study from which the CGs were recruited, therefore they had all already met me before and some had had a close contact with me concerning their child's asthma, as I had been following them up for between 6 months to over a year.

The cohort study enabled nearly 300 children to access asthma-specific follow-up and treatment, which otherwise was not available in the city of Esmeraldas, therefore some of CGs and some HCWs had previously expressed their gratitude to the study team in general and to me in particular.

Bearing in mind that I conducted 9 of the 12 in-depth interviews and 3 of the 5 FGD, my presence may have influenced the answers obtained from both the HCWs and the CGs. However, most of the HCWs I interviewed, I had not worked with before. As for the CGs, I focused the discussion towards the use health care services outside the study centre, for which they could speak freely as they knew I had no connection with any of the hospitals or health centres they referred to.

I also had several preconceived ideas and assumptions of the underlying barriers and facilitators concerning asthma management in Esmeraldas, given my clinical experience in this setting. Nevertheless, during the analysis of the data, Dr. Natalia Romero's guidance, precluded me from introducing my preconceptions when interpreting the data.

This study presented some other limitations. First, men (fathers) were underrepresented in the CGs' FGD, as only 2 out of 20 participants were male. The same happened with other degrees of kinship apart of mothers, as there were only 2

grandmothers and no grandfather or aunts/uncles. This was due to the mothers and grandmothers being the ones who are normally in charge of the child's asthma care, and they are therefore the ones who attended the invitation to the FGD, even if this was directed specifically to the father. However, we could at least recollect the opinions and experiences of two fathers, and on the other hand, it reflects the real situation as the women in the house are the ones responsible for the asthmatic child's care in most of the households in this setting.

There was a small number of experienced HCWs (3 out of the 12 interviews), though they were all the available specialists (paediatricians in this case) that treated asthmatic children in the city of Esmeraldas. However, we did seem to reach data saturation in the opinions and experiences expressed by this subgroup of HCWs.

Second, it was undertaken in a setting, the city of Esmeraldas, with a specific socio-cultural environment that may differ significantly from other settings, such as rural population or a city in a high-resource country. On the other hand, it may have some characteristics in common with other similar settings in Latin American countries, where qualitative studies have not been undertaken addressing this topic in both CGs of asthmatic children and HCWs. Many Latin American countries share a similar cultural background (indigenous and Spanish/Portuguese) as well as socioeconomic context.

Third, when studying barriers and facilitators to health care access, it is important to include people that, having suffered the same condition, did not access health care services, as they may have encountered different barriers than those that finally accessed health care. This was not the case in our study, given that all the participant CGs had been previously recruited from an emergency room for the cohort study. Even though this is the ideal procedure to include a sample as heterogeneous as possible, it was not feasible in our setting, as there is no available record of asthmatic children in

the city and we did not have the resources, nor the time to conduct a previous populational survey to search for CGs of asthmatic children that had not accessed any health care service. However, it is also true that this thesis is focused around severe asthma attacks, that by definition are those that require an unscheduled appointment with a doctor (or emergency room) and the prescription of systemic corticosteroids.

Fourth, due to time constraints, we were unable to share our findings and interpretations with the study participants, an important step to add credibility to our findings. Nonetheless, we did contrast our findings with first participants and my own previous experience and knowledge as a Paediatrician living and working in this same setting with asthmatic children, and having a very close contact with both CGs and HCWs, often having discussed with them similar issues as those addressed in the current study. These observations and discussions were registered in the field diary that was completed during the study. We were also able to triangulate our findings with those from the cohort study, where we collected data on use of health care services for asthma during the previous year and treatment prescribed, and finally with the literature reviewed.

5.7. Findings in relation to other studies

5.7.1. Asthma acute attacks significance

HCWs perceive severe paediatric asthma attacks as urgent events that need to be overcome, and that it is their responsibility to do so by applying the necessary treatments. To do so successfully, they need to keep a cool head and avoid feelings to distract them from their objective: to improve the child's health during that acute episode. This situation is lived with fear and uncertainty by the young, inexperienced HCWs, as they are afraid the child might suffer severe complications or even death.

On the other hand, the more experienced, specialised doctors feel confident that the child will improve as a result of their knowledge and skills. This contrasts with the asthma management reality in Latin America, with a high asthma morbidity[24,25] and mortality[275] when compared to other regions. However, it is the young and inexperienced HCWs that need to manage the children with severe asthma attacks at the ED, while the specialised doctors only treat them once they have been stabilised and are admitted to hospital or seen for follow-up at the consultation room. Nevertheless, the more experienced doctors expressed worry for other associated consequences of acute asthma attacks in children, such as lost school days and obesity, secondary to exercise avoidance.

Only once the child had improved did HCWs concentrate on information transmission and education of CGs on asthma, which they considered highly relevant to avoid future severe exacerbations. In this sense, they regarded the CGs as the sole responsible for an inadequate management of the child's asthma in case of a recurrent asthma attack. Similarly, HCWs from primary and secondary care in the UK also reported the CGs being responsible for the child's acute exacerbation following a withdrawal of controller therapy after symptom improvement, and that this was due to the caregiver's lack of understanding of asthma treatment[498].

To increase the CGs' awareness, the HCWs in our study reported the use of strategies to improve the physician-patient relationship, as well as frightening or even intimidating CGs by exaggerating or lying about their child's future risk. Patient and caregiver education was also highlighted as essential by HCWs participating in a qualitative study on interventions to increase physical activity in asthmatic children[499].

Severe asthma exacerbations in children are experienced by CGs with anxiety, fear, helplessness and despair, affecting not only the child, but the whole family. The disease is part of their lives, limiting their activities and commanding the family's organization.

They perceive these attacks as unpredictable and asthma as a chronic disease which may improve, but not disappear completely. The inevitability of the attacks, the burden on the families and the feelings of fear and frustration have been mentioned in other similar qualitative studies with CGs of asthmatic children undertaken in very different high-resource settings[363-366,500,501], as well as in other Latin American countries reflecting the universality of these findings[371-373].

In contrast, feelings of rejection, denial and anger that were also brought up in these other qualitative studies[364,367,372], were not expressed by the CGs from Esmeraldas. Interestingly, CGs in our study also felt guilty of their child's asthma attack on occasions, as if it occurred because of their inadequate care towards the child. This feeling of guilt was also reported by Peruvian mothers of asthmatic children admitted to hospital[372]. In addition to these, CGs may also feel blamed by other family members who think the asthma is caused by a lack of care, as described by South-Asian mothers living in the UK[500].

During the acute asthma attacks, CGs relied on the health care services, for which they seek a fast and effective solution, as they are afraid of complications or even death. However, during the encounter with the HCWs, they often feel frustration, deception and defeat, as they do not receive the treatment or the results they expected. CGs of asthmatic children in other studies expressed annoyance and anger towards HCWs, a feeling that they did not meet their expectations and that they were not taken seriously[500,501].

These experiences of frustration may also appear when not being believed by the child's teacher or the staff in nursery or school[501]. CGs in our study also felt fear and mistrust towards the doctors or the medications prescribed, due to the side effects or their beliefs. Even though some CGs prefer treating their child's asthma attack at home, it was often expressed that they lacked the necessary knowledge to do so.

As we will discuss later, this is a recurrent barrier reported by CGs of asthmatic children[499,500]. In this sense, CGs were afraid of not being able to identify when their child was suffering an acute asthma attack, either because the child was trying to hide his/her symptoms or because these are difficult to recognize. This issue has been already been mentioned by CGs in other studies, in relation to distinguishing the symptoms of asthma in comparison to those of breathlessness due to physical activity[498].

It was interesting to note that neither HCWs nor CGs barely mentioned the asthmatic children involved, as if they were not part of the significance of acute asthma for them. Several studies have reflected how asthmatic children play a passive role when accessing health care services, with their parents or CGs being the ones voicing their concerns and describing their symptoms, and the HCW discussing asthma drug risk with them rather than with the children[354-356,358,498].

5.7.2. Health and home care access barriers for asthmatic children

When analysing the barriers to health and home care access for asthmatic children identified by HCWs and CGs, we realise the similarity with those included in the Systematic Review of barriers and facilitators to health care access, for any disease[378]. Participants in our study reported barriers for all the 4 subcategories.

Acceptability

There were several coincidences and overlap in the barriers expressed by HCWs and CGs, while there were also differences between them, as well as between more and less experienced HCWs. For example, both CGs and HCWs discussed that CGs' beliefs, their mistrust in hospitals and doctors, together with the advice they received from non-medical people, led them to use natural remedies over prescribed drugs. The myths

regarding side effects of asthma drugs, such as that it may damage the hurt or cause addiction were very similar to those reported by caregivers in Peru and Colombia[371,382].

This is a common acceptability barrier in asthma, as well as other chronic diseases, causing poor adherence to asthma medications[365-368,380,500]. The CGs' scepticism towards doctors and hospitals was also perceived by young, non-specialised HCWs who reported feeling rejected by CGs.

On the other hand, HCWs believed that the CGs' beliefs and trust in medical establishment, depended on their level of education and socioeconomic status. In this sense, it is important to note that the level of education (median of having studied high school) and socioeconomic status (median monthly household income of 400 USD) of CGs in this setting, together with the strong African influence in their culture with a frequent use of natural remedies and 'traditional medicine', are relevant characteristics that may affect acceptability of health care services and that may not be present in other similar settings.

Accessibility

The cost, logistic impediments, administrative complications and difficulties in obtaining days off-work made it challenging for CGs of asthmatic children to access asthma medications and medical appointments, even more when referred to medical specialists. These accessibility barriers were discussed by both HCWs and CGs and appeared frequently in the revised literature[361,365-368,372,383,384].

The lack of specialised HCWs who may adequately manage asthmatic children in the city of Esmeraldas resulted in a problematic situation for many asthmatic families, not only for the slow, bureaucratic process of the referral system, but for the necessity of travelling to a city that was 7-9 hours away just for an appointment, with its associated costs and days off-work and off-school needed. For some families, this was not a feasible solution to follow-up their asthmatic child, with an appointment every 2-3

months in a distant city. The lack of a specialised doctor was one of the reasons Mexicans reported for changing the hospital where they treated their asthmatic child[361].

Lack of specialist doctors for asthmatic children was also reported by HCWs in secondary care in the UK[498], therefore it may not only be a problem affecting low-resource settings. HCWs in Esmeraldas, claimed that some of these accessibility barriers were caused by the lack of interest in asthma of the health authorities, who did not take the disease seriously enough. It is worrisome that some inexperienced HCWs reported having been told by the CGs that they were denied access to the ED when arriving with their child suffering an acute asthma attack, though CGs themselves only mentioned that they were made to wait for a long time before being seen by a doctor. This may be a consequence of not having a professionally trained triage nurse at any of the emergency rooms in Esmeraldas, who may classify the emergency of the patient to be treated according to their severity. Long waiting times were also reported by Colombian and Mexican caregivers[361,371].

Contact

As contact barriers, HCWs reported lack of interest of the CGs of asthmatic children in what HCWs had to say, poor adherence to medication and indications, taking the children to be seen by a HCW only when he/she was severely ill, and how they thought this happened because of the lack of awareness CGs had about asthma and its consequences. Brazilian CGs reported taking the child to the emergency department when he/she is very ill, as before that, they try to treat him/her at home[373]. This could also be secondary to the lack of knowledge that CGs have, according to HCWs in our study, due to not being informed correctly.

Poor CGs asthma knowledge was documented in our previous cohort study and was also mentioned by both CGs and HCWs in qualitative studies from high-resource

settings[498-500]. On the other hand, CGs admitted stopping their child's treatment once the acute symptoms had disappeared, as well as being afraid of the side effects of the asthma medications prescribed, and some were unclear about the effects and duration of the effects of the different asthma drugs (both relievers and controllers).

Adhering to asthma medications only during the acute exacerbations, not being aware of the seriousness of the disease, and fear to side-effects, addiction or tolerance to drugs are common contact barriers that threaten adherence to medications, and have been previously reported in in high[364,365,367,368,383,500,502] and low income countries[371,382]. These could all be consequences of inadequate or incomplete information on asthma, as HCWs had claimed in our study.

Special attention should be brought to the provider-patient relationship, as it is the key to most of the contact barriers identified. While the HCWs in our setting felt ignored by the CGs, the CGs on their side reported having been ill-treated by HCWs in different circumstances, especially when attending due to an acute asthma attack. Lack of a shared-decision process, discrimination, mistrust, and apportioning blame on the CGs are all aspects of the provider-patient contact that have been previously reported by asthmatic children's CGs to hamper the establishment of a good and trustful relationship[365-368], and these were all mentioned by the CGs in our study.

As highlighted before, none of the HCWs and CGs participating in our study mentioned the asthmatic children when discussing communication issues, therefore excluding them completely from the patient-provider relationship. On the contrary, HCWs from the UK believed that including the child in this process was essential[498].

Interestingly, some HCWs discussed that in private practice, doctors were more worried about obtaining economic profit than about the patient's wellbeing, avoiding establishing preventive strategies or prescribing preventive treatment, as this would cause the children to stop attending the clinic for acute asthma episodes.

We did not include any HCWs who worked only in private clinics, as all the doctors in Esmeraldas work in the public sector and some in both public and private. None of the CGs mentioned this barrier that may clearly affect the quality of the health service received, and we found no referral to it in the revised literature either, though there were remarks about the general low quality or inadequate care received[364,367].

Availability

The most reported availability barriers by both HCWs and CGs were the lack of asthma drugs, medical supplies, human resources and diagnostic tools, something commonly acknowledged in other qualitative studies[361,384]. The fact of the CGs receiving unclear, insufficient, incorrect and sometimes contradicting information and criteria depending on the HCW, made them feel unprepared and insecure to manage their child's asthma and not being knowledgeable about the existence, for example, of asthma controller drugs.

Scarce (and contradicting) information and education for CGs and patients, and them not having a clear understanding of the effects and indications of the asthma drugs, is one of the availability barriers identified by Hirmas et al.[378] in the Systematic Review, together with other qualitative studies on asthma[365,367,368,371,380,498,500]. This situation was worsened by the uncertainty the CGs felt towards their child's asthma diagnosis, as they had not been offered any kind of specific diagnostic test for asthma.

This same issue was discussed by South Asian families of asthmatic children residing in UK, who reported that a lack of clear diagnosis led to a poor adherence to asthma medications[500], together with CGs in Sweden who complained about delayed diagnosis[501]. We did not find any reference diagnosis uncertainty as a barrier to health care access in the qualitative studies undertaken in Latin America[361,371-373,382]. The fact that HCWs and CGs did not talk about written asthma action plans (WAPs) was a reflection of the complete absence of these in Esmeraldas, an even worse situation than

that described in other qualitative studies where HCWs reported barriers to implementing them (time, space, updating)[384,385] and CGs reported not receiving them, not using them, or the WAP not being updated[500]. Similarly, caregivers from other Latin American studies did not mention asthma action plans[361,371-373,382].

Both CGs and experienced HCWs reported that general doctors did not have the necessary training to manage asthmatic children adequately, as an availability barrier. This lack of specific asthma knowledge was described in a Mexican study undertaken with general practitioners (GPs) and doctors with a leadership role (managers)[503]. Barriers described by the GPs to access continuing education and advance training were the lack of support from the hospital managers and the long distance to training centres, while managers believed the problem was the GPs' lack of motivation and interest[503]. This inadequate asthma knowledge could be ascertained by the mistrust or even fear, that some young and inexperienced HCWs in our study expressed towards certain asthma drugs (mainly salbutamol), which was based more on beliefs or personal experience than on clinical guidelines.

General practitioners from the UK reported requiring more time and resources to receive extra training on asthma[384] and CGs wished to be referred to an 'asthma specialist'[361,500,501], as did the CGs in our study. It was interesting that only inexperienced HCWs in our study brought up the issue of long working hours and high demand, with short times available per patient, as availability barriers that hampered an adequate patient and CG asthma education. This barrier was also reported by GPs and health professionals in secondary care in the UK, a group of HCWs that, similar to young doctors working in the emergency department, are frequently time-pressured irrespective of the setting[384,498].

5.7.3. Health and home care access facilitators for asthmatic children

Acceptability

An acceptability facilitator that contrasted with what was discussed as barriers to health care access for asthmatic children, was that both HCWs and CGs reported that some CGs did follow the indications and treatment prescribed by HCWs. This was possible because of the trust some CGs had in HCWs and the asthma drugs prescribed, and the involvement of the older children in the management of their own asthma.

Trust in the medication prescribed was one of the facilitators identified in the systematic review by Hirmas et al.[378]. Some caregivers (both from high income and low income countries) of asthmatic children also described using the drugs as prescribed by HCWs, as they feared their child could worsen if they did not[371,500].

HCWs believed that the CGs in Esmeraldas had the sufficient cultural and educational level to be able to understand the information provided and manage their child's asthma adequately, and that existing beliefs and myths could be easily eliminated with asthma education sessions. Some of the HCWs interviewed felt affection towards the asthmatic children and their family, and even offered their private mobile numbers for them to call whenever they needed., showing that they cared for these children.

Accessibility

As for the accessibility facilitators, HCWs claimed that all necessary drugs and equipment are available at the health care services where they work. The public health system in Ecuador has a list of basic medicines that should be available for free at the public hospitals. This list includes acute bronchodilators (salbutamol and ipratropium bromide), systemic corticosteroids (oral prednisone, intramuscular or intravenous dexamethasone or hydrocortisone) and inhaled corticosteroids (budesonide)[312]. However, at the moment there were no inhaled corticosteroids available at the health

centres, nor at the public hospital (HDTC), only at the social security hospital (IESS hospital), and there were no combined ICS with long acting beta-agonists or leukotriene receptor antagonists (LTRA) (montelukast) available for free.

On the other hand, HCWs claimed that families are normally able to buy the medicines needed (if not available for free) and that they tried to help low-resource families who could not afford them, in different ways. Reinforcing patient's access to asthma drugs and health care services was one of the facilitators mentioned by general practitioners in the UK[384].

The only accessibility facilitator that CGs mentioned in our study was that it was easy for the children to obtain days off-school during their asthma attacks and for control appointments. Both HCWs and CGs believed that the establishment of a specialised area for asthmatic patients, an 'Asthma Club', home visits or public health asthma programmes would facilitate the accessibility of asthmatic children to health care, improving their asthma management. Access to free asthma drugs and to health care professionals through an asthma control programme were described as facilitators to improve asthma control in children in Brazil[386].

Contact

In the contact category of facilitators, some of the HCWs found it easy to communicate with CGs of asthmatic children, who could be very cooperative on occasions and follow the indications given. To make sure CGs did understand the information given on asthma, several HCWs in our study reported using alternative methods such as drawings, and they expressed that being honest and direct helped in the transmission of information to CGs. CGs of asthmatic children in other settings perceived their child's asthma as well-managed and were satisfied with the care received, the drugs prescribed or the review appointments[367,368,500].

Similarly, CGs of asthmatic children in Sweden held in high regard the asthma nurses that worked at the outpatient clinics, who they considered knowledgeable, competent and able to manage their children's asthma treatment[501]. Mothers of children hospitalized for asthma in Peru also spoke well of the nurses, both for their medical and humane quality[372]. In this sense, some of the participant CGs in our study reported having been treated kindly and adequately by HCWs when attending with their child suffering an asthma attack and they expressed gratitude for the guidance and close follow-up offered by certain HCWs.

Building a good patient-provider relationship is essential to improve asthma management, and being followed by the same professional who may establish a patient-centred approach with a shared decision-making process and who includes the child in these conversations, is vital for this[367,368,498]. However, none of the participants in our study discussed the decision-making process, as it is common in this setting to apply a more paternalistic, controlling and directed approach by the HCWs who do not rely on the CGs' knowledge and criteria. Additionally, when follow-up by one same provider is not possible, special care should be taken at standardisation of prescribed treatment and indications given to asthmatic patients, as differing recommendations make patients lose faith in the doctors and in there being a clear and consistent plan of action, as was mentioned in this study.

This is an issue that should be discussed and worked with the HCWs, as shared decision making has proved to reduce the number of severe asthma exacerbations in children[504]. The improvement of a child's condition and a sense of team work were two situations that made some HCWs in our study feel motivated and happy, a facilitator to improve patient-provider relationship and asthma management quality.

Availability

Finally, several availability facilitators were mentioned. CGs in our setting felt empowered to manage their child's asthma and believed that increasing their knowledge on asthma would further improve their self-efficacy. To address this, both HCWs and CGs exposed several proposals to enhance asthma knowledge for CGs, extended family and general population, a proposal also shared by general practitioners from the UK[384]. The desire to increase their asthma knowledge was frequently described by CGs of asthmatic children in other qualitative studies[363,367,380], though some also felt confident in their current asthma knowledge and management skills, understood asthma and its medications, and trusted their children in alerting them of exacerbation symptoms[365,367,368,498].

Experienced doctors in our study also proposed improving general doctors' asthma knowledge and management, while some young and inexperienced HCWs reported feeling motivated to study asthma further. Similarly, general practitioners in the UK were willing to attend training sessions to improve their knowledge on all aspects of asthma management[384]. They also suggested increasing the time available for each asthmatic child and reviewing patients regularly by the same HCW[384], a facilitator that was not mentioned by the HCWs interviewed in this study.

5.7.4. Emergency care re-attendance acute asthma risk assessment tool

When presented with the risk assessment tool for emergency care re-attendance for acute asthma, the first reaction of both HCWs and CGs was quite positive, as they found the tool easy to use and understand and quite visual, due to the use of traffic-light colours to inform of the risk. They also emphasized the importance of such a tool both to facilitate the transmission of information related to future risk to asthmatic children's CGs, and to facilitate the organization of the children's need of referral to specialised doctors and initiation of controller asthma therapy. CGs believed it would

make them be more aware of the severity of their child's disease, and therefore increase their adherence to the HCWs indications and prescribed medications.

Nevertheless, some HCWs and CGs discussed that the use of the tool would not alter the CGs' or HCWs' attitude towards the child's asthma management, something that would completely defy the aim of such a tool. It may well be that certain HCWs feel reluctant to follow guidelines (such as a risk-assessment tool) as it may challenge their position of knowledge and authority, a position that was expressed by the experienced HCWs in this study. Standardising data capture allows benchmarking between staff and units and between staff and gold standards, something that some HCWs may not be willing to do. None of the management tools, educational instruments or interventions used in medicine are always effective in the totality of patients and HCWs, and still may improve the overall outcomes of a specific disease. The same thing may happen with the risk assessment tool if it is implemented in the daily practice, as there will always be a proportion of HCWs that will not make use of it, some CGs that will not take it seriously, and another proportion of HCWs and CGs that will continue the same attitude irrespective of the risk assessment tool's information.

There are relatively scarce qualitative data on the use of risk assessment tools[505]. The most studied risk assessment tools are the ones analysing fall risk, and in a systematic review of qualitative studies analysing factors influencing implementation of fall-prevention programmes, health care professionals from the US included in three different studies had reported not being reimbursed for the time required to complete the fall risk assessment and that time restrictions per patient were a barrier for the implementation of such a tool[506].

This might not be a problem with the risk assessment tool for subsequent severe asthma attacks, as it includes only 4 questions and may be completed in less than 5 minutes. However, the issue of time availability should always be considered, especially

if the tool is to be implemented in emergency rooms where HCWs are normally overwhelmed and fully occupied with severely ill patients. This could be maybe overcome if the tool was completed by an administrator, as it does not need to be done by a HCW.

Pay-for performance-programmes are designed to assess quality of care by adherence to protocols and clinical guidelines for specific diseases and offer economic rewards accordingly. Hospitals where pay-for-performance programmes have been introduced in the UK have shown an association with a clinically significant reduction in mortality[507]. Similar programmes could improve adherence to risk-assessment tools implementation in emergency rooms.

5.8. Implications for future studies

We have identified several barriers and facilitators for health care access for asthmatic children as perceived by HCWs and CGs. However, as discussed in the limitations section of this study, all the CGs interviewed had already accessed health care services at some point. It would now be interesting to interview CGs of asthmatic children who have not accessed such health services, to explore further the perceived barriers that may differ in this population of asthmatic children and families. For this, we should first identify such families through a cross-sectional household survey. Such a study has already been undertaken in certain areas of the city of Esmeraldas and surrounding villages by our study team[508].

Similarly, male CGs were underrepresented in the present study, and even though they may be a minority of the usual CGs of asthmatic children in this setting, their opinions and experiences are still as relevant, as they may influence the attitude of the main female caregiver in the house. In-depth semi-structured interviews with fathers and

grandfathers would add relevant data and validity to the information already collected and could be analysed with a gender perspective.

An Ecuadorian study analysing the implications of the feminisation of the medical profession, from a gender perspective, found that female doctors who do not have a social and economic capital, and that have children, have fewer probabilities of reaching the ideal of the Ecuadorian doctor: be recognized and have money[509]. This reality poses the following question: how does feminisation of the medical profession affect asthmatic children's care?

On the other hand, older children and adolescents influence asthma management at home and adherence to indications and medications prescribed. Their relationship with the HCW may also alter adherence to appointments. In this sense, it would be desirable to undertake focus group discussions to address the same points that were discussed with HCWs and CGs, as they are also part of the process studied.

The impressions and opinions around the risk assessment tool for severe asthma attacks recurrence were only based on a hypothetic situation, as it is not being currently used in the emergency rooms. Once the tool has been validated and implemented in the daily practice, it would be necessary to design a new qualitative study to assess the experiences of its implementation, both from the HCWs' and the CGs' point of view, and desirably from the asthmatic children's too.

The numerous barriers to health care access for asthmatic children identified by HCWs and CGs highlight the need to undertake research studies assessing interventions that may address these barriers. These interventions could be based on the facilitators reported in this study, as well as on the proposals from CGs and HCWs.

Some of these have already been extensively studied, such as the use of written asthma action plans or asthma educational interventions that have shown to reduce the number of severe asthma exacerbations[510,511]. Others, such as home visits, the

organization of an 'Asthma Club' for asthmatic patients and CGs, or the use of media to increase the general public's awareness on asthma are examples of interventions to be further studied in this setting.

Similarly, the establishment of a specialised centre for asthmatic patients with access to free medication and regular follow-up has been shown to reduce adult hospitalizations for asthma in Salvador, Brazil[304]. A study of the effect on the patient's asthma morbidity and quality of life, as well as the cost-effectiveness of such an intervention for asthmatic children in Esmeraldas would be highly relevant.

5.9. Conclusion

This study has shown that asthma attacks in children are perceived and experienced differently by CGs, inexperienced and experienced HCWs, resulting in a distinct significance. Experienced HCWs perceive asthma attacks as opportunities to demonstrate their experience, and specific knowledge and skills mastery; it is a routine aspect of their professional activity; and they are annoyed by the attitude they perceive some caregivers to show. On the other hand, for inexperienced HCWs, asthma attacks mean fear and self-doubt, while they hope to act correctly, an aspect that is reflected on the comprehensive attitude towards the CGs' fear and anxiety from whom they expect cooperation. Both experienced and inexperienced HCWs need to keep a cool head and avoid feelings to distract them from their objective. HCWs and CGs perceive asthma attacks as urgent events that need to be overcome, and that it is their responsibility to do so. All of them feel responsible for the asthmatic child and are aware of the possible complications and risk of death of the event.

Multiple barriers were identified by CGs and HCWs which limit asthmatic children's access to an adequate health and home care. While some of these barriers refer to economic and health service organisational issues, others such as fear of side effects of

medication or ineffective self-management could be overcome through educational interventions, both for CGs and HCWs, as was mentioned when discussing facilitators to health care access.

Increasing CGs' and HCWs' asthma knowledge as well as HCWs' communication skills, to establish a patient-centred approach with a shared decision-making process could mean a difference in the quality of the asthma care in this setting. The use of the described recurrent risk assessment tool could proof useful in this process, and it would be largely acceptable, as reported by the participants in this study.

6. Summary, recommendations and conclusions

6.1 Summary of rationale, objectives and key findings

Asthma prevalence in children worldwide is still rising, especially in certain regions of Latin America. Despite the development of new asthma drugs and of strategies to improve asthma control, such as asthma education, shared decision-making and promotion of self-management, severe asthma attacks continue to occur among asthmatic children. These attacks lead to increased direct and indirect economic costs, loss of lung function in patients, anxiety and panic, risk of complications and even death. These consequences do not only affect the asthmatic child, but the whole family too. For these reasons, there has been an increased interest in asthma attacks, with their inclusion in asthma guidelines to assess future risk in patients, and growing research to develop interventions and treatments that may prevent recurrent attacks. As an example, current randomized clinical trials for new asthma drugs are now assessing severe asthma attacks as one of the outcomes to be studied, together with daily asthma symptoms. However, there is still no clarity around predictors of recurrent severe asthma attacks to enable the identification of asthmatic patients at risk who may require medication or lifestyle alterations.

In Latin America, asthma is a growing public health problem, not only because of the increasing prevalence, but also because of the high level of associated morbidity, when compared to other high prevalent countries such as the UK. Reasons for this include inadequate asthma management with limited access to specialized care and timely diagnosis, low prescription rates for controller medications because of cost or poor health care worker training, and poor adherence to long-term controller medications. Consequently, asthma is treated as an acute disease, through unscheduled appointments or emergency care visits for acute attacks and limited follow-up. This

combination of factors results in high health care costs, indirect costs for the patient and family, and low quality of life for the asthmatic patient.

To address this problematic situation, we aimed to:

- Identify the asthmatic children at risk of suffering subsequent severe asthma exacerbations requiring emergency care in the City of Esmeraldas, Ecuador.
- Explore the significance and experiences of severe asthma exacerbations in children, as well as the perceived barriers and facilitators to health and home care access in asthmatic children from both caregivers' and health care workers' perspectives, in Esmeraldas.

A mixed-methods research approach was adopted to answer these aims: a quantitative study to analyse predictors for emergency care re-attendance for acute asthma and a qualitative study to explore the caregivers' and health care workers' experiences regarding acute asthma attacks and its recurrence. The use of both quantitative and qualitative methods adds richness to the study findings, as they analyse different aspects of the same problem, which in isolation may not be sufficient to improve our understanding of the current situation of asthmatic children in this low-resource setting.

The cohort study followed children who had been treated for an episode of bronchodilator-responsive wheeze at an emergency room and showed: i) high rates of re-attendance (46%) with a severe attack in the following 6 months; and ii) high rates of under-diagnosis (only 77% had received a previous doctor's asthma diagnosis) and undertreatment (just 2% were taking inhaled corticosteroids). Several predictors were identified using different statistical methods, some of which had not been described previously. A higher risk of re-attendance with a severe attack during the next 6

months after the initial ER attendance was observed in: younger children (especially those aged 5-6 years old); those with a previous doctor's asthma diagnosis; and those who had received systemic corticosteroid courses for acute asthma during the previous year. Other predictors were: rural residency, previous doctor's eczema diagnosis and having food or drink triggers. Interestingly, none of the inflammatory markers and lung function parameters were useful in identifying children at future risk of severe asthma attacks in this setting. This is the first study to analyse predictors of severe asthma attack recurrence in a low-resource setting. The novelty of this study relies on the children being recruited from the emergency room, often the only place where asthmatic children are seen in settings where there is no follow-up or control of asthmatic patients. The predictors identified have the potential to be combined into a risk-assessment tool to be used in ERs to select high risk asthmatic children that require specialised care and long-term treatment. This may prove extremely useful in low-resource settings, especially as it does not require the use of expensive and unavailable complementary tests.

The linked qualitative study revealed how caregivers experience severe asthma attacks with fear and despair, and how it affects the whole family at different levels (work, finance, activities, etc.). The health care worker's perspective of severe asthma attacks varied in relation to their experience, as fear of death and complications disappeared in more experienced health care workers who felt more confident and reassured. This may affect the way health care workers act towards children with recurrent severe asthma attacks. Multiple barriers and scarce facilitators to acceptability, accessibility, contact and availability of health care services for asthmatic children were described by health care workers and caregivers. Some of them were common to both caregivers and health care workers, while others differed completely. Although this is the first study of childhood asthma of its kind undertaken among caregivers and health care workers in a low-resource setting in tropical America, some of the barriers and facilitators

identified have been described also in high-resource settings, a finding that reveals the multiculturality and generalizability of certain problems concerning asthma worldwide. Finally, there was a general positive opinion and acceptance towards the use of a risk-assessment tool to inform caregivers and health care workers of the child's future risk of subsequent severe asthma attacks. It was the opinion of some of the caregivers that being informed about their child's risk of recurrence of severe asthma attacks, would change their attitude towards their child's asthma management and enhance their adherence to asthma medications and lifestyle alterations. Given that adherence to long-term medications is a common barrier to adequate asthma control, an intervention that could improve this would proof extremely useful.

6.2 Recommendations and future directions

6.2.1 Increasing asthma diagnosis in children

Under-diagnosis of asthma is a major barrier to adequate control and management in Latin America and other low-resource settings [28,512]. From the cohort study, we ascertained that one third of the children treated at an emergency room for an acute episode of bronchodilator responsive wheeze had not received a previous asthma diagnosis from a doctor. Even though not all of these children had asthma, most probably did, given that 76% had suffered a similar episode requiring emergency care during the previous 12 months.

In the qualitative study, caregivers were concerned that their children had not taken any specific tests for their asthma, making them doubt the diagnosis. An uncertain diagnosis may reduce adherence to asthma treatment, especially to medication with possible side-effects such as inhaled corticosteroids (ICS), and to lifestyle modifications[500]. This stresses the importance of obtaining an asthma diagnosis from a

doctor, and the need to avoid some frequently used terms such as 'early asthma' or 'bronchitis' when managing children with recurrent severe wheezing episodes.

Through the qualitative in-depth interviews, we learned that health care workers in this setting were reluctant to diagnose asthma in children. One of the reasons for this was that they do not have access to specific tests such as spirometry, allergen-specific IgE or skin prick tests, to diagnose reversible bronchoconstriction or atopy. Even though these are very useful and important tools that may aid and guide a physician in the diagnostic process for asthma and in treatment decisions, they are not essential to obtain a diagnosis. A comparison of prevalence rates of doctor diagnosis of asthma and asthma symptoms indicates that up to 50% of asthma cases may be missed in low resource settings[513,514]. Similarly, primary care doctors' asthma diagnosis has been shown to be highly inaccurate, with 54% of under-diagnosis and 34% of over-diagnosis[515]. For this reason, and given the unavailability of spirometers and professional training in spirometry, WHO has proposed the use of peak expiratory flow (PEF) meters to confirm airflow limitation, by including them in the list of essential tools for low-resource settings[37,516]. The combination of asthma symptoms together with PEF measurements before and after a therapeutic trial with ICS and as-needed short acting beta-agonists, could enable the confirmation of an asthma diagnosis prior to the start of long-term treatment[517]. This could be easily implemented in primary care health services in Esmeraldas, Ecuador, or at least in the Paediatric consultation rooms in the public and social security hospital. Nevertheless, a spirometer should still be available for children with a more severe asthma, who do not respond to ICS or whose asthma diagnosis may be in doubt. The respiratory therapists working in the public and social security hospitals in Esmeraldas have been trained to do lung function tests and could take responsibility for this procedure.

6.2.2 Increasing number of asthmatic children receiving baseline long-term treatment and follow-up

Regular follow-up and long-term baseline treatment for asthma for those in need, are the next two key elements to achieve an adequate asthma control. As explained in Chapter 2, asthma in many Latin American settings is managed at emergency rooms during acute attacks and not as a chronic condition[24]. This was reflected in the cohort study, with only one third of the children visiting a doctor for a regular check-up of their asthma at least once during the previous year, and just eight per cent at least on four occasions or one appointment every three months. As a result, nearly half of the children participating in the study had recurrence of severe asthma exacerbations within the first 6 months after the initial emergency care attendance at recruitment. The consequences of this inadequate management may be serious for the children, affecting lung function[14], quality of life[330] and educational attainment due to missed school-days.

Health care workers in Esmeraldas did report the lack of follow-up as a current barrier to adequate asthma care. Reported explanations were lack of asthma specialists, lack of training in asthma management of general doctors, excessive demand (large number of asthmatic children) and poor adherence of child caregivers to follow-up appointments. Each of these issues are equally relevant and should be dealt with using different strategies.

There is currently no pulmonologist or respiratory specialist in the city of Esmeraldas and certainly no paediatric pulmonologist. One strategy could be to employ a pulmonologist in the city's public hospital that may be feasible given the presence of other specialists such as a neurosurgeon, dermatologist and cardiologist. The contracting of a paediatric pulmonologist would have to be requested at a regional and central level in Ecuador and pressure from patients' and doctors demands in the

context of local epidemiological data (such as that provided by the present study) would be important lobbying tools. Further, data are now available by disease for emergency and hospitals admissions through electronic records that show a high rate of presentations in children with respiratory diseases. Another possible need identified by health care workers would be to train general doctors and paediatricians in asthma management. The paediatricians participating in the in-depth interviews, although confident on their asthma knowledge and management of patients, likely require additional training on the importance of controller treatment for asthma[384], given that only 2% of children were taking inhaled corticosteroids at the time of recruitment. This way, paediatricians in Esmeraldas would be able to follow-up and manage children with mild and moderate asthma or those with a good or partially controlled asthma, and only those children not responding to long-term maintenance therapy would require referral to a specialist in a tertiary centre in Quito or Guayaquil. Similarly, in more rural settings, general doctors could be trained to manage asthma patients with non-complicated and easy to treat asthma. These measures would avoid significant economic costs to families of asthmatic children and the healthcare system, and missed school and work days, associated with referrals to tertiary centres in other cities, an important barrier reported by both caregivers and health care workers.

Nevertheless, for these changes to occur, asthma should be identified as a priority by both local and national health authorities, something that is currently not the case. Health care workers and caregivers interviewed reported a lack of interest in asthma by health authorities resulting in an absence of specific programmes, currently available for other chronic diseases such as diabetes or hypertension. There are no official national clinical practice guideline or protocols for asthma in Ecuador, something that would be of great help for general doctors[518]. In this sense, non-communicable diseases are now the major cause of death, even in low and middle-income countries[519], and asthma is the most important chronic disease in children

(14% of the world's children)[1]. The disability adjusted life years (DALYs) caused by asthma are comparable to those of hypertensive heart disease, being the 14th most important disorder in terms of extent and duration of disability[1]. These, together with the high asthma prevalence in Esmeraldas, Ecuador, are sufficient reasons for a prioritisation of asthma by health authorities. This would enable some important organisational changes, such as extending availability of controller medication (ICS) to health care centres as is the case now for medications for other chronic diseases. Lack of availability of asthma medications in health care centres was another barrier reported by health care workers in the present qualitative study.

There is a limited number of paediatricians in the City of Esmeraldas despite the significant burden of asthma disease in children. General doctors working at the emergency rooms have neither the time nor training to start children on ICS after stabilization for an attack in ERs as expressed in the in-depth interviews. However, not all the children treated for a bronchodilator-responsive wheeze at the emergency room may merit the initiation of ICS. First, because presenting to the ER in this setting does not necessarily indicate a severe attack, given the inability of caregivers to treat even a mild asthma exacerbation and a lack of salbutamol inhalers and spacers at home. Second, because they may not suffer another asthma exacerbation in the following year, according to the recommendations of the Ecuadorian Respiratory Association, children with intermittent asthma do not need to start controller treatment[146]. Third, because controller long-term treatments have associated side-effects[160-162,341] and costs (see Chapter 2). Identifying a group of asthmatic children at high risk of suffering subsequent severe asthma attacks among those presenting to the emergency room with a bronchodilator-responsive wheeze, would prove very useful at addressing these issues. This subgroup of children could be identified using a simple risk-assessment tool which includes the predictors analysed in the cohort study. This subgroup of high-risk children could be then referred to a paediatrician for regular follow-up and to start

baseline long-term treatment with ICS. Those at low risk could also be referred to the paediatrician or to the general doctor at the health centre for less frequent follow-up. Likewise, the demand on the health care system and paediatricians would decrease and still, the children most in need would be receiving a regular follow-up and the necessary medications. As a result, the child's quality of life would improve, and the direct and indirect costs caused by their asthma would decrease by reducing the number of severe asthma attacks requiring emergency care. This will be possible once the risk-assessment tool is validated in a future study. In the meantime, children with a history of emergency care admissions for acute asthma in the previous year should be managed more closely and prescribed ICS.

The establishment of specific asthma programmes to provide follow-up and treatment to adults with severe asthma inside the public health system in Brazil, has been shown to be effective in reducing asthma hospitalizations, increasing patient's quality of life and reducing costs for the health care system and families[304]. A pilot study of a similar programme in Esmeraldas, together with the use of the risk-assessment tool for severe asthma attack recurrence would be highly informative on the cost-effectiveness of such an intervention and would provide the necessary data to implement such a programme in the public hospital in Esmeraldas and other cities in Ecuador.

6.2.3 Enhancing adherence to baseline long-term treatment for asthma and follow-up

Increasing asthma diagnosis, regular follow-up and controller long-term treatment prescription would all prove useless if the asthmatic patients or their caregivers do not adhere to the medication prescribed. Poor adherence to medication is a constant issue affecting around 50% of patients[520-522] especially those with chronic diseases. Similar adherence rates have been described for asthma - less than 50% in children[523] and 30 to 70% in adults[524-526]. In the cohort study, we were not able to assess adherence to

baseline long-term treatment, given the low initial proportion of children receiving controller medication and the absence of data for adherence to the medication prescribed during the study. However, both health care workers and caregivers identified poor adherence (specially to long-term treatments) as a barrier to adequate health care. The reasons reported for poor adherence during the qualitative study were multiple and included: cultural background and beliefs, lack of information regarding asthma medications and side-effects, preference for natural remedies, fear of side-effects, and cost and difficulty to attend regular check-ups to obtain more medicines.

Asthma education programmes for asthmatic patients and/or their caregivers, have been shown to reduce severe asthma exacerbations and hospitalizations[225,510]. Caregivers in our setting were willing to receive further information on asthma, to increase their knowledge and their self-management skills as they described in the focus group discussions (FGD). On the other hand, their asthma knowledge was inadequate, and similar to that of a non-asthmatic person[487] as shown by findings from the Newcastle Asthma Knowledge Score instrument administered during the cohort study. Educating asthmatic patients and their families should therefore be a priority in this setting, and it could be part of the specific asthma programme proposed above. This education could be undertaken privately, during the doctor's regular follow-up visits, as well as through groups sessions and through written information. We should highlight also the importance of completing and regularly updating a personalised written asthma action plan for each patient, something completely absent in this setting and that has been shown to be effective in reducing severe asthma attacks[442]. Improving the caregivers' asthma knowledge would decrease their fear of side-effects from medications, increase their trust in the treatment and relay their cultural background and beliefs, increasing adherence.

However, it is important that health care workers are well trained in asthma management before they inform and educate asthmatic patients and their caregivers.

They should not only be trained in asthmatic medications, but also in other non-therapeutic interventions that are recommended for adequate asthma control, such as exercise, avoidance of exposure to tobacco smoke and other irritants, healthy (Mediterranean style) diet, etc[37]. The lives of asthmatic children should not be limited by their disease as recommended by some health care workers in Esmeraldas in the qualitative study. A more holistic approach may be the key for asthmatic patients and their caregivers to adhere and trust the recommendations of health care workers[365,367], as caregivers reported in the qualitative study to prefer natural remedies, and by implementing other interventions apart from drugs. A good patient-provider relationship, and a patient-centred approach should also be attained, as they increase the caregivers' trust in the health care workers and empower them to take responsibility of their child's asthma improving self-management and adherence[367,368,498].

The use of the described severe asthma attack recurrence risk assessment tool, could also enhance caregivers of asthmatic children adherence to prescribed treatment, as reported in the qualitative study. If patients and caregivers knew their risk score, they could maybe help drive the change in treatment prescription and adherence by asking for treatment themselves to reduce their risk. Additionally, media (posters, television, radio, etc.) could be used to encourage asthmatic patients to get to know which is their own risk score.

6.3 Conclusion

The application of a mixture of methods (prospective cohort and interpretative qualitative study) enabled the identification of strategies to improve the currently inadequate paediatric asthma management in a low resource setting. This thesis confirms the high proportion of emergency care re-attendance for acute asthma among children presenting to the emergency room for an asthma attack. It also shows how it is

possible to identify those children at a higher risk of suffering subsequent severe asthma attacks using simple questions and without the need of complementary tests. This could maybe aid the decision-making process regarding asthma follow-up and controller treatment prescription in a low resource setting, and may therefore stop the revolving door in which these children are found: they are treated at the emergency room and then go back to the same high-risk situation (no controller treatment and inadequate home management) that leads them back to the emergency room with a subsequent asthma attack. As we have seen in the qualitative study, such a tool would be possibly acceptable to HCWs and CGs. However, other strategies such as asthma education programmes for caregivers and health care workers, close and frequent follow-up of asthmatic children and provision of free controller treatment, should all be implemented in parallel to increase the effect of the risk stratification provided by the risk assessment tool. Further research is now needed to validate and assess the effectiveness of the presented risk-assessment tool to allow its implementation into daily practice.

Appendix A: Supplementary materials for systematic review and meta-analysis

1. Search strategy

(risk OR predic* OR associat* OR probabil*) OR "Risk Factors"

AND

(((((asthma) AND hospital admission)) OR ((((asthma AND exacerbation)) OR ((asthma) AND "Disease Progression")) OR (asthmatic AND exacerbation)))) OR (asthma AND "Patient Readmission")

AND

child OR children OR childhood OR pediatr* OR paediatr*

2. Search report

Supplementary Table 1: Search report Asthma exacerbation risk factors in children searches. January 2017

Search No.	Date	Database searched	Hits (before duplicate removal)
1	9/01/2017	Medline (Pubmed)	1835
2	9/01/2017	Cinahl (EBSCOhost)	353
4	9/01/2017	PsycInfo (EBSCOhost)	90
5	9/01/2017	Embase (OVID)	2603
6	9/01/2017	AMED (EBSCOhost)	3
7	9/01/2017	WHO clinical trial registry platform (WHO ICTRP)	8
FINAL NUMBER OF REFERENCES IN ENDNOTE AFTER DELETING DUPLICATES = 3259			

Appendix B: Supplementary materials for prospective cohort study

1. Informed consent form for caregivers of participating children (English translation)

Informed Consent Form

"THE CHILDHOOD ASTHMA RE-ATTENDANCE ASSESSMENT (CARA) STUDY"

Title of Research: ***"Emergency care re-attendance for acute childhood asthma in a low-resource setting: The Childhood Asthma Re-attendance Assessment (CARA) Study "***

Date: 15 /January /2014

Organization: "FUNDACIÓN ECUATORIANA PARA INVESTIGACIÓN EN SALUD" and PONTIFICIA UNIVERSIDAD CATÓLICA DEL ECUADOR.

Name of Principal Investigator: Dr. Philip Cooper, Laboratorio de Investigaciones FEPIS, Calle A S/N, Barrio Fundo Limon, Nuevo Quinindé, Quinindé, Provincia de Esmeraldas, Ecuador.

Co-investigators: Dra. Cristina Ardura, Dra. Maritza Vaca

Principal Investigator contact details: Tel: 59362737158. e-mail: pcooper758@puce.edu.ec

1. Introduction

We are inviting you and your child to participate in this research where we will study the characteristics of asthmatic children with acute attacks of difficulty breathing and wheezing requiring emergency care. The purpose of this research is to identify the asthmatic children with a greater risk of suffering severe acute asthma attacks.

Your decision to have your child participate in this study is entirely voluntary. Take as much time as you need to take the decision and discuss it with other members of the family. This form includes a summary of the research, which we will analyse with you. If you decide to have your child to participate, you will receive a copy of this form. You may ask ask many questions and request as many explanations as you need to any member of the study team about all the different study activities and procedures.

2. Why are we carrying out this research?

We are carrying out this research because asthma is the most frequent chronic disease in children and we do not have much information regarding the risk of acute asthma

attacks in children, especially in Latin American cities like Esmeraldas. Understanding a child's risk of suffering future acute asthma attacks will enable us to offer a better management and treatment for asthmatic children.

3. What are the benefits of participating in this study?

Each participant will receive an individual diagnosis and recommendation according to the test results (for example: treatment for intestinal parasites, referral to another specialist, lifestyle recommendations, etc.) Each participant will be closely followed-up by the study team during his/her participation in the study. If judged necessary, he/she will be referred to a specialist doctor.

Asthmatic patients from Esmeraldas will benefit from this study, as it will make health workers aware of the importance of asthma and the large number of patients who suffer from this disease. This will hopefully improve asthma management and treatment.

4. How many children will participate in the study?

Around 350 asthmatic children between 5-15 years old will participate in this study.

5. What are the study procedures?

If agreeing to participate, we will carry out:

- Three questionnaires: (a) The first one covering general questions about the child (personal and family history, home characteristics, etc.), the child's asthma characteristics, and the previous treatment and management received. (b) A second one to assess the parent's or guardian asthma knowledge. (c) A third one to study the child's quality of life.

- Blood sample: A small amount of blood, equal to about a teaspoon will be taken from your child's arm to carry out different exams, like: blood cell count and identifying allergy makers (total IgE and allergen specific IgE for house dust mite, American cockroach and Ascaris). These tests for allergy markers will be carried out at the University of Virginia, US, where a small sample of blood will be shipped to. Another small sample of this blood will be stored for future genetic analyses of genes associated with asthma and allergy.

- Stool sample: To diagnose whether you child has intestinal parasites or not. A small simple will be also stored for future studies on intestinal parasites and bacteria.

- Lung function: Your child will be asked to blow through a machine to study the inflammation present in his airways by measuring a substance called nitric oxide. He/she will also be asked to blow through another machine to measure his/her lung function, both before and after receiving an inhalation of a drug (salbutamol) to expand his/her lungs (a bronchodilator).

- Nasal wash: We will finely spray in each side of the child's nose a small amount (2ml) of a liquid similar to water with a nasal atomization device, while he/she is sitting down. We will then collect the liquid that comes back out. A small

sample of this liquid will be stored to study the inflammation present in his nose at that moment.

6. How long will my participation in the study take?

We will take the blood sample and nasal wash as soon as your child has been treated for his asthma attack and is stable, and you have agreed to participate in the study. You may bring the stool simple when it is more convenient for you. We will then set an appointment for a visit in two weeks' time, to carry out the questionnaires and the lung tests, and give you your child's blood and stool results.

We will then follow-up your child for 6 months, during which we will contact you by telephone every 2 months, to ask about any other acute asthma attack your child might have had. We will also invite you to contact us (by phone or in person and the study office) each time your child needs emergency care for an acute asthma attack (at the DTCH or any other place).

After the 6 months follow-up, we will set another appointment to repeat some of the questionnaires and the lung function tests. According to your child's progress, we will recommend a specific treatment, follow-up and we will offer an asthma action plan for future acute asthma attacks. The recommended treatment will be that available at the DTCH in Esmeraldas through the Minsitry of Public Health.

If you wish to, your child may continue to be followed-up after the first 6 months, until the end of the study (September 2015). In this case, we will continue to contact you by phone every 2 months. You will also be able to contact us every time your child has an acute asthma attack.

7. What are the risks of participating in this study?

A nurse or lab technician will obtain a blood sample from your child's arm. This is a simple procedure that the nurse and lab technician carry out every day. Your child will feel some discomfort when the needle stick goes into her/his arm, there may be slight bruising and very rarely your child may faint.

Your child may feel a little discomfort during the nasal wash, with nose itch and watery eyes.

The lung function tests may proof a little but difficult for small children and require the child's cooperation. They do not produce any discomfort. For one of the tests, we need to give your child an inhaled rug (salbutamol) to expand the lungs (bronchodilator), the same one he/she usually takes for his/her acute asthma attacks. This drug may increase the heart rate o cause shakiness in your child. These effects will disappear after 4-6 hours maximum.

The rest are non-invasive procedures with no other associated risks. Some of the questions present in the questionnaire may be slightly discomforting to answer, as we may require details about the child's home characteristics and how proper it is. The study team will explain to you that all the questions included only seek to study the child's environmental

exposures, in order to better understand the risk factors of acute asthma attacks and to advise of possible changes they may make in their homes and lifestyles, as to minimise the child's risk.

8. Are my child's samples and information given confidential?

Your privacy is very important to us. We will keep all your information absolutely confidential and will only be accessed by the health workers involved in the project, and not by any other members of your family or neighbours. To protect your child's privacy, each questionnaire will be identified by a unique code. The same will happen with all the samples, including those sent outside Ecuador, which will not be identified with your child's name, but only the code. Only the project's researchers will know which code belongs to each child. The remaining samples will be kept in the FEPIS laboratory in Quinindé and will not be used for other purposes different to those already explained. Once the study results are ready, they will be published in scientific journals or presented at scientific meetings, without including any names or identifiable information which will be kept in absolute confidentiality. The data collected will be entered into a computer and handled only by the project's researchers and study team.

9. What other options do I have?

It is very important for you to understand that your and your child's participation in this study is voluntary, so you may decide not to participate. If you accept to participate, you may also drop out of the study whenever you wish to. The treatment your child will receive at this moment will not depend on your participation in the study.

10. How much will it cost me to participate in this study?

Participants will not have to pay for anything. The study researchers will pay for all the costs and materials necessary for the study.

11. Will I be paid to participate in this study?

Participants will not receive any payment for participating in the study.

12. What are my rights as a study participant?

Your participation in this study is voluntary, that is, you may decide not to participate and may retire at any time. There will be no negative consequences if you decide not to participate or if you drop out before the end of the study. You may discuss with, ask or request information to any of the study team members.

13. Who should I call if I have questions or problems?

If you have any questions regarding the project, you may contact the study doctor: Dr. Cristina Ardura, at the Hospital Delfina Torres de Concha Hospital emergency department, or by telephone: 0985021194. If you have any questions regarding the informed consent form, you may contact Dr. Arturo Donoso, PUCE Bioethics Committee Secretary, by phone: 2991-700 Ext. 1533 or by email: ajdonoso@puce.edu.ec

14. Informed consent

I understand the purpose of my child participating in this study, and the risks and benefits of doing so. I have been informed of the study procedures and I accept the explanations I have received. I consent voluntarily for my child to participate as a participant in this study.

Parent/guardian Surnames and Names_____

Child's Surnames and Names:_____

---------- ----------
Mother's Signature Date

---------- ----------
Father's Signature Date

---------- ----------
Guardian´s Signature Date

GUARDIAN'S RELATIONSHIP WITH CHILD: _____

Name of Researcher taking the consent _____

---------- ----------
Signature of Researcher taking the consent Date

---------- ----------
Signature of a Witness (where applicable) Date

2. Child assent form (for participating children older than 12, English translation)

Child Assent Form (7-15 years old)

"THE CHILDHOOD ASTHMA RE-ATTENDANCE ASSESSMENT (CARA) STUDY"

Title of Research: ***"Emergency care re-attendance for acute childhood asthma in a low-resource setting: The Childhood Asthma Re-attendance Assessment (CARA) Study "***

Date: 15 /January /2014

Organization: "FUNDACIÓN ECUATORIANA PARA INVESTIGACIÓN EN SALUD" and PONTIFICIA UNIVERSIDAD CATÓLICA DEL ECUADOR.

Name of Principal Investigator: Dr. Philip Cooper, Laboratorio de Investigaciones FEPIS, Calle A S/N, Barrio Fundo Limon, Nuevo Quinindé, Quinindé, Provincia de Esmeraldas, Ecuador.

Co-investigators: Dr. Cristina Ardura, Dr. Maritza Vaca.

Principal Investigator contact details: Tel: 59362737158. e-mail: pcooper758@puce.edu.ec

1. Introduction

I am Dr. Cristina Ardura from the Ecuadorian Trust for Health Research (FEPIS) and my job is to study asthma in children. I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/guardian and they know that we are also asking you for your agreement.

You may discuss anything in this form with your parents or friends. You can decide if you want to participate or not after you have talked it over. You do not have to decide now.

There may be some words you don't understand or things that you want me to explain more about. Please ask me to stop at any time and I will take time to explain.

2. Why are you doing this research and why are you asking me?

I am doing a study to figure out why some asthmatic children suffer more frequent severe acute asthma attacks than others, and how to help these children better. We are asking you to take part in the research study because you have come to the emergency department with an acute asthma attack today.

3. What is going to happen to me?

For this research:

- we will ask some questions about you and your family which may be related to asthma
- we will ask you to bring a small stool sample to check if you have any parasites
- we will take a small blood sample (equal to about a teaspoon) from your arm to study your defence system and if you have allergies
- we will wash your nose with a small amount of a liquid similar to salty water and collect what comes out
- we will carry out some tests to measure how well your lung is working.

We will then follow you up during at least 6 months, calling your parents or guardians every 2 months to ask them about any asthma attack you may have had, and we will ask you to come and visit us at the end of the 6 months to repeat some of the questions and the lung tests.

4. Is this bad for me? Will it hurt?

We don't think that any big problems will happen to you as part of this study, but you might:

- feel some discomfort while we take the blood sample,
- feel a nose itch and watery eyes while we wash your nose, and
- feel upset if you are not able to carry out the lung tests correctly and have to repeat them more than once.

Also, for one of the lung tests we will give you a medicine to breath, the same you are given when you have an asthma attack. This medicine may make you feel a little bit nervous, but this effect will disappear after a few hours.

5. Is there anything good that happens to me?

During the study we will follow you up and help you and your parents learn how to treat your asthma attacks and how to stop them from happening so often. You can feel good about helping us to make things better for other children with asthma like you.

6. Is everybody going to know about this?

We will keep all your answers and test results private, and will not show them to other members of your family or friends. Only people working on the study will see them.

7. Can I choose not to be in the research? Can I change my mind?

You should know that:

- You do not have to be in this study if you do not want to. You won't get into any trouble with your parents, the doctors or you teachers if you say no.
- You may stop being in the study at any time.
- Your parent(s)/guardian(s) were asked if it is OK for you to be in this study. Even if they say it's OK, it is still your choice whether or not to take part.

8. Who can I talk to or ask questions to?

You can ask any questions you have, now or later. If you think of a question later, you or your parents can contact me at the Delfina Torres de Concha Hospital emergency department, at the study office or by telephone: 0985021194

9. Certificate of Assent

Sign this form only if you:

- have understood what you will be doing for this study,
- have had all your questions answered,
- have talked to your parent(s)/legal guardian about this project, and
- agree to take part in this research

I agree to take part in the research.

OR

I do not wish to take part in the research and I have not signed the assent below._____(initialled by child/minor)

Only if child assents:

_____

Your Signature Printed Name Date

_____

Name of Parent(s) or Legal Guardian(s)

_____

Researcher explaining study

Signature Printed Name Date

Appendix C: Supplementary materials for qualitative study

1. Interview guide

1.1 In-depth interviews

Initial Question
What does the word 'asthma' mean to you?

Asthma Attacks Perception
- What dose a child's asthma attack mean to you?

- Please tell me about the last time you treated child with an asthma attack

Recurrent Risk Perception
- What does it mean to you that a child is 'at risk' of suffering a new asthma attack?

- Please tell me about the last time you thought about the possibility of a child suffering a new asthma attack.

Barriers and facilitators to health and home care access for asthmatic children
- What do you think about the health and home care that asthmatic children receive?

- Please tell me about the last time you had contact with an asthmatic child's caregiver.

- What do you expect from an asthmatic child and his/her caregiver when you are treating them?

Perception of recurrent asthma attack risk assessment tool use
- Do you think some people may have a greater risk of suffering an asthma attack? Why?

- Do you think there is something you can do to reduce that risk? What things do you know do work and what other things have you heard do not work?

- What do you think about this tool?

- How would your attitude towards a child's asthma change after obtaining the information this tool offers?

- Do you think there is anything you could do to reduce a child's risk of suffering new asthma attacks?

- Anything else you would like to say?

1.2 Focus group discussions

Initial Question
What does the word 'asthma' mean to you?

Asthma Attacks Perception
- What do your child's asthma attacks mean to you?

- Please tell me about your child's last asthma attack

Recurrent Risk Perception
- What does it mean to you that your child is 'at risk' of suffering a new asthma attack?

- Please tell me about the last time you thought about the possibility of your child suffering a new asthma attack.

Barriers and facilitators to health and home care access for asthmatic children
- What do you think about the health and home care that asthmatic children receive?

- Please tell me about the last time you had contact with a health care worker concerning your child's asthma.

- What do you expect from health care workers when you visit them for your child's asthma?

Perception of recurrent asthma attack risk assessment tool use
- Do you think some people may have a greater risk of suffering an asthma attack? Why?

- Do you think there is something you can do to reduce that risk? What things do you know do work and what other things have you heard do not work?

- What do you think about this tool?

- How would your attitude towards your child's asthma change after obtaining the information this tool offers?

- Do you think there is anything you could do to reduce your child's risk of suffering new asthma attacks?

- Anything else you would like to say?

2. Informed consent form

2.1 In-depth interviews

INFORMED CONSENT FORM

UNIVERSIDAD INTERNACIONAL DEL ECUADOR
CLINICAL, HEALTH AND LIFE SCIENCES FACULTY
SCHOOL OF MEDICINE

INFORMED CONSENT TO PARTICIPATE IN HUMAN BEING RESEARCH

TITLE OF RESEARCH: **IN-DEPTH INTERVIEWS**

"Understanding the significance of acute asthma exacerbations in children and adolescents from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador: A Qualitative Study "

RESEARCH TEAM

NAME	ACADEMIC TITLE	INSTITUTION	CONTACT DETAILS
Cristina Ardura García	MD, MSc, MRes	Liverpool School of Tropical Medicine,	Tlf: 0997756251 Email: crisardura@gmail.com
Philip Cooper	PhD	Universidad Internacional de Ecuador	pcooper@sgul.ac.uk
Natalia Romero Sandoval	PhD	Universidad Internacional de Ecuador	nromero@internacional.edu.ec

I- INTRODUCTION

We are inviting you to participate in this research where we will study the experiences of asthmatic children's carers and the health care workers, regarding the management and treatment of asthma. The purpose of this research is to explore the understanding of future risk of asthma attacks, and the best way to inform about it.

Your decision to participate in this study is entirely voluntary. Take as much time as you need to take the decision and discuss it with other members of the family. This form includes a summary of the research, which we will analyse with you. If you decide to have your child to participate, you will receive a copy of this form. You may ask as many questions and request as many explanations as you need to any member of the study team about all the different study activities and procedures.

II- PURPOSE OF THE STUDY

We are carrying out this research because asthma is the most frequent chronic disease in children and we do not have much information regarding the experiences and understanding of asthma from the children's carers

and health care workers' point of view. In this study we will talk to asthmatic children's carers and health care workers about their experiences regarding asthma, including management and treatment, and especially looking into the risk of suffering asthma attacks in the future. We will invite them to share their knowledge and perception with us so that we can find ways of helping them understand the importance of the disease and how to minimise their risk of asthma attacks.

III- STUDY PARTICIPANTS

Around 30-50 adults will participate in this study.

IV- PROCEDURES

You will take part in an in-depth semi-structured interview, guided by me, which will last for 30-60 minutes.
At the start of the interview I will answer questions about the research that you might have. Then we will talk about how your experience regarding treatment and communication with families of asthmatic children during an acute attack, especially regarding the risk of future recurrent asthma attacks. These are the types of questions I will ask. We will not ask you to share personal stories or anything that you are not comfortable sharing.
The interview will take place where ever it may suit you best. The entire interview will be tape-recorded, but no-one will be identified by name on the tape. The tape will be kept in a locked filling cabinet in the study office. The information recorded is confidential, and no one else except the study team involved in the project will be allowed to listen to the tapes.

V- BENEFITS AND RISKS

V- BENEFITS

There will be no immediate and direct benefit to you, but your participation is likely to help us find out more about how to help asthmatic children and their carers understand more about asthma management and future risk of asthma attacks.

VI- COSTS AND COMPENSATIONS

There is a risk that you may feel uncomfortable talking about some of the topics. However, we do not wish for this to happen. You must know that you do not have to answer any question you feel are too personal or if talking about them makes you uncomfortable.
Participants will not have to pay for anything. The study researchers will pay for all the costs and materials necessary for the study. You will not be provided with any payment to take part in the research.

VII- PRIVACY AND CONFIDENTIALITY

Your privacy is very important to us. We will keep all your information absolutely confidential and will only be accessed by the study team involved in the project, and not by any other members of your family or neighbours.

Once the study results are ready, they will be published in scientific journals or presented at scientific meetings, without including any names or identifiable information which will be kept in absolute confidentiality. The data collected will be entered into a computer and handled only by the project's study team.

VIII- VOLUNTARY PARTICIPATION AND WITHDRAWAL

It is very important for you to understand that your participation in this study is voluntary, so you may decide not to participate. If you accept to participate, you may also drop out of the study whenever you wish to. There will be no negative consequences if you decide not to participate or if you drop out before the end of the interview.

IX- OPTIONS TO QUESTIONS AND ANSWERS

You may discuss with, ask or request information to any of the study team members.

X. ETHICS COMMITTEE CONSULTANT FOR THE STUDY

XI. NAME AND SIGNATURE OF PRINCIPAL INVESTIGATOR FOR THE STUDY

Cristina Ardura Garcia

INFORMED CONSENT

The study: "Understanding the significance of acute asthma exacerbations in children and adolescents from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador: A Qualitative Study" has been explained to me**.** I understand the purpose of me participating in this study, and the risks and benefits of doing so. I have been informed of the study procedures and I accept the explanations I have received. I consent voluntarily to participate as a participant in this study.

I_____
_____, wish to participate voluntarily in this study and I give my authorisation to Universidad Internacional de Ecuador to use my information given for the described purposes in the informed consent form. By signing this informed consent form I do not renounce any of my legal rights.

_____ _____
Name of participant /Tutor Signature of participant /Tutor
Date (Place, day/month/year) _____

I confirm that the information give in this informed consent form was clearly explained and understood by the participant or tutor. The participant or tutor agree to participate voluntarily in this research study.

_____ _____
Name of Witness Signature of witness
Date (Place, day/month/year) _____

_____ _____
Name of Researcher Signature of researcher
Date (Place, day/month/year) _____

2.2 Focus group discussions

INFORMED CONSENT FORM

UNIVERSIDAD INTERNACIONAL DEL ECUADOR
CLINICAL, HEALTH AND LIFE SCIENCES FACULTY
SCHOOL OF MEDICINE

INFORMED CONSENT TO PARTICIPATE IN HUMAN BEING RESEARCH

TITLE OF RESEARCH: **FOCUS GROUP DISCUSSIONS**

"Understanding the significance of acute asthma exacerbations in children and adolescents from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador: A Qualitative Study "

RESEARCH TEAM

NAME	ACADEMIC TITLE	INSTITUTION	CONTACT DETAILS
Cristina Ardura García	MD, MSc, MRes	Liverpool School of Tropical Medicine,	Tlf: 0997756251 Email: crisardura@gmail.com
Philip Cooper	PhD	Universidad Internacional de Ecuador	pcooper@sgul.ac.uk
Natalia Romero Sandoval	PhD	Universidad Internacional de Ecuador	nromero@internacional.edu.ec

X- INTRODUCTION

We are inviting you to participate in this research where we will study the experiences of asthmatic children's carers and the health care workers, regarding the management and treatment of asthma. The purpose of this research is to explore the understanding of future risk of asthma attacks, and the best way to inform about it.

Your decision to participate in this study is entirely voluntary. Take as much time as you need to take the decision and discuss it with other members of the family. This form includes a summary of the research, which we will analyse with you. If you decide to have your child to participate, you will receive a copy of this form. You may ask as many questions and request as many explanations as you need to any member of the study team about all the different study activities and procedures.

XI- PURPOSE OF THE STUDY

We are carrying out this research because asthma is the most frequent chronic disease in children and we do not have much information regarding the experiences and understanding of asthma from the children's carers and health care workers' point of view. In this study we will talk to asthmatic children's carers and health care workers about their experiences regarding asthma, including management and treatment, and especially looking into the risk of suffering asthma attacks in the future.

We will invite them to share their knowledge and perception with us so that we can find ways of helping them understand the importance of the disease and how to minimise their risk of asthma attacks.

XII- STUDY PARTICIPANTS

Around 30-50 adults will participate in this study.

XIII- PROCEDURES

You will take part in a discussion with 4-7 other participants. This discussion will be guided by me.
The group discussion will start with me making sure that the participants are comfortable. I will also answer questions about the research that you might have. Then I will ask questions about asthma. We will talk about your experience regarding asthma, your beliefs and concerns relating to your risk of suffering an asthma attack. These are the types of questions we will ask. We will not ask you to share personal stories or anything that you/they are not comfortable sharing.
The discussion will take place at the study office, and no one else but the people who take part in the discussion and I will be present during this discussion. The entire discussion will be recorded, but no-one will be identified by name on the tape. The digital recording will be kept in a locked filling cabinet and the digital file will be saved to a password-protected computer. The information recorded is confidential, and no one else except the study team involved in the project will be allowed to listen to the recordings.

V- BENEFITS AND RISKS

I- BENEFITS

There will be no immediate and direct benefit to you, but your participation is likely to help us find out more about how to help asthmatic children and their carers understand more about asthma management and future risk of asthma attacks.

II- COSTS AND COMPENSATIONS

There is a risk that you may feel uncomfortable talking about some of the topics. However, we do not wish for this to happen. You must know that you do not have to answer any question you feel are too personal or if talking about them makes you uncomfortable.
Participants will not have to pay for anything. The study researchers will pay for all the costs and materials necessary for the study. You will not be provided with any payment to take part in the research. However, a light lunch will be provided for all the participants, as well as a small stipend to cover travel expense if needed.

III- PRIVACY AND CONFIDENTIALITY

Your privacy is very important to us. We will keep all your information absolutely confidential and will only be accessed by the study team involved in the project, and not by any other members of your family or neighbours.

We will ask you and others in the group not to talk to people outside the group about what was said in the group. We will, in other words, ask each participant to keep what was said in the group confidential. You should know, however, that we cannot stop or prevent participants who were in the group from sharing things that should be confidential.
Once the study results are ready, they will be published in scientific journals or presented at scientific meetings, without including any names or identifiable information which will be kept in absolute confidentiality. The data collected will be entered into a computer and handled only by the project's study team.

IV- VOLUNTARY PARTICIPATION AND WITHDRAWAL

It is very important for you to understand that your participation in this study is voluntary, so you may decide not to participate. If you accept to participate, you may also drop out of the study whenever you wish to. There will be no negative consequences if you decide not to participate or if you drop out before the end of the discussion.

V- OPTIONS TO QUESTIONS AND ANSWERS

You may discuss with, ask or request information to any of the study team members.

X. ETHICS COMMITTEE CONSULTANT FOR THE STUDY

XI. NAME AND SIGNATURE OF PRINCIPAL INVESTIGATOR FOR THE STUDY

Cristina Ardura Garcia

INFORMED CONSENT

The study: "Understanding the significance of acute asthma exacerbations in children and adolescents from the caregivers' and health care workers' perspective, in Esmeraldas, Ecuador: A Qualitative Study" has been explained to me**.** I understand the purpose of my child participating in this study, and the risks and benefits of doing so. I have been informed of the study procedures and I accept the explanations I have received. I consent voluntarily for my child to participate as a participant in this study.

I_____
_____, wish to participate voluntarily in this study and I give my authorisation to Universidad Internacional de Ecuador to use my information given for the described purposes in the informed consent form. By signing this informed consent form I do not renounce any of my legal rights.

_____ _____
Name of participant /Tutor Signature of participant /Tutor
Date (Place, day/month/year) _____

I confirm that the information give in this informed consent form was clearly explained and understood by the participant or tutor. The participant or tutor agree to participate voluntarily in this research study.

_____ _____
Name of Witness Signature of witness
Date (Place, day/month/year) _____

_____ _____
Name of Researcher Signature of researcher
Date (Place, day/month/year) _____

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