GLOBAL ATLAS OF ASTHMA

EAACI
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FOREWORD

An estimated 36 million deaths, or 63% of the 57 million deaths that occurred globally in 2008, were due to noncommunicable diseases including chronic respiratory diseases. 80% of deaths (29 million) due to noncommunicable diseases occurred in low- and middle-income countries.

Global efforts to tackle the challenge of noncommunicable diseases including asthma have gained momentum since the 2011 United Nations Political Declaration on the prevention and control of noncommunicable diseases. The World Health Organization is developing a Global Plan of Action, for 2013-2020, to provide a roadmap for country-led action for prevention and control of noncommunicable diseases including chronic respiratory diseases. It will be submitted for consideration to the 66th World Health Assembly this year.

Premature death, disability, loss of income and health-care expenditure due to asthma take a toll on families, communities and national health finances. In low- and middle-income countries many people cannot access treatment for asthma, because it is prohibitively expensive. Households often then spend a substantial share of their income on hospitalization to treat exacerbations and complications of asthma.

I wish to congratulate the European Academy of Allergy and Clinical Immunology for developing the Global Atlas of Asthma. It provides simplified and useful information on a range of topics related to prevention and control of asthma including magnitude of the problem, risk factors, associated diseases, barriers to treatment and sustainable strategies to address asthma in resource constrained settings.

I hope that the knowledge prevention and control of asthma, imparted by this document to decision makers, health workers, the civil society, private sector and the public will benefit people in all countries.

Dr. Oleg Chestnov, Assistant Director General
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PREFACE

Asthma is a major public health problem affecting the lives of several hundred million people around the world, with an increasing prevalence in developing countries. Governments, and the general public, face huge direct and indirect costs, with major effects on macroeconomics due to health-care costs, loss of productivity and the absenteeism of patients. Unfortunately, a high number of unmet needs remain to be resolved, due to gaps in current scientific knowledge in pathophysiology and in patient care, and as a result of the global social determinants of health.

To tackle this huge global health problem, we at the EAACI decided to develop a "*Global Atlas of Asthma*". With this Atlas, our aims were: to gather evidence to call attention to the burden of asthma, to warrant its recognition as a main concern in national health strategies; to demonstrate its priority as an issue for research; to describe risk factors for asthma; to evaluate the best ways to prevent and control it; to provide guidance on how to overcome barriers; and to alert political bodies to the issue of asthma to ensure a global management approach.

The "*Global Atlas of Asthma*" has been developed as an essential reference source for multi-sectoral use, covering all aspects of asthma, from epidemiology, risk factors and mechanisms to phenotypes and management, to major current problems in asthma, associated diseases, and asthma prevention and control. With 59 chapters written by 80 contributing authors, and containing 147 illustrations and 46 tables, the Atlas will also be a comprehensive educational tool and desktop reference for medical students, allied health workers, primary care physicians, medical industry, policy makers, patient organizations and specialists dealing with asthma and other comorbid diseases.

I would like to thank all of the authors for their contributions, the EAACI Executive Committee Members, and particularly Prof. Dr Ioana Agache, with whom working on this highly exciting project was a great pleasure, and Costel Agache and Macarena Guillamon for their focus, devotion and proficiency.

Cezmi A. Akdis
President of the
European Academy of Allergy and Clinical Immunology

Section A

ASTHMA FROM EPIDEMIOLOGY, RISK FACTORS AND MECHANISMS TO PHENOTYPES AND MANAGEMENT

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* History of asthma
* The asthma epidemic - Global and time trends of asthma in children
* The asthma epidemic - Global and time trends of asthma in adults
* Death and disability due to asthma
* Socio-economic costs of asthma
* Natural history of asthma
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* Pharmacogenetics of asthma
* The pathogenesis of asthma
* The underlying mechanisms of asthma
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* Environmental risk factors for asthma
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* Infections and asthma
* Emerging risk and protective factors for asthma
* Perinatal and early life influences on asthma development
* Psychological factors and asthma
* The complex network of asthma risk and protective factors
* Asthma in childhood
* Asthma in the elderly
* Asthma in the elite athlete
* Asthma in pregnancy
* Work-related asthma
* Asthma management
* Asthma monitoring

1 WHAT IS ASTHMA

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KEY MESSAGES

- Asthma is one of the most common chronic inflammatory disorders
- Asthma affects patients of all ages and is a serious challenge to public health and has large effects on school and work performance of patients
- Asthma symptoms can be treated effectively in many patients however, at considerable costs
- There is no cure and many patients remain uncontrolled despite available treatment
- Combined efforts in public health, basic and clinical research need to be upscaled to fight this highly prevalent and increasing disorder

Epidemiologically asthma is a very common chronic condition. Its prevalence varies worldwide but more than 5% of any investigated population suffer from asthma. In some regions this percentage is much higher. Asthma affects all ages: it is the most common chronic disease of childhood, adolescence and adulthood and affects patients in their most productive years. Everybody is either personally affected or will know someone who suffers from asthma. Every physician will see patients with asthma during his/ her career. Asthma is a serious challenge to public health. Its direct and indirect costs are high, but the costs of not treating asthma are even higher. It has detrimental influences on school and work performance and productivity. About 10% of all asthma is caused by or occurs in the workplace. As more people reach old age it is also an important disease of the elderly. Asthma not only leads to limitations in daily life, but can end fatally in some cases, especially if untreated.

Pathophysiologically asthma is an inflammatory disorder of the lungs. It leads to widespread airflow limitation. The resulting signs and symptoms are dyspnea, discomfort, wheezing, anxiety and panic and occasionally fatal respiratory arrest. The pathogenesis of asthma is highly complex and as of today incompletely understood. Based on clinical and laboratory findings different phenotypes have been suggested (Figure 1). Whether they all represent different features or severities of a single disease or are separate diseases within the syndrome of asthma remains unclear. The majority of asthma occurs on an IgE-mediated background with sensitisations to inhaled allergens called allergic asthma. Asthma which occurs on a non-allergic background is termed intrinsic asthma. Asthma often results in chronic persistent airway inflammation unrelated to allergen contact and has features of autoimmunity. Long term chronic inflammation has been associated with airway remodelling with an increasingly fixed airflow limitation as a result of "scarring" of the airways.

Clinically signs and symptoms of asthma vary from patient to patient. Episodic shortness of breath, wheezing and the sensation that inspiration is no longer possible due to hyperinflation of the lungs are common. The pathophysiological equivalent in pulmonary function tests is a reduced FEV1 (Forced Expiratory Volume of the first second)

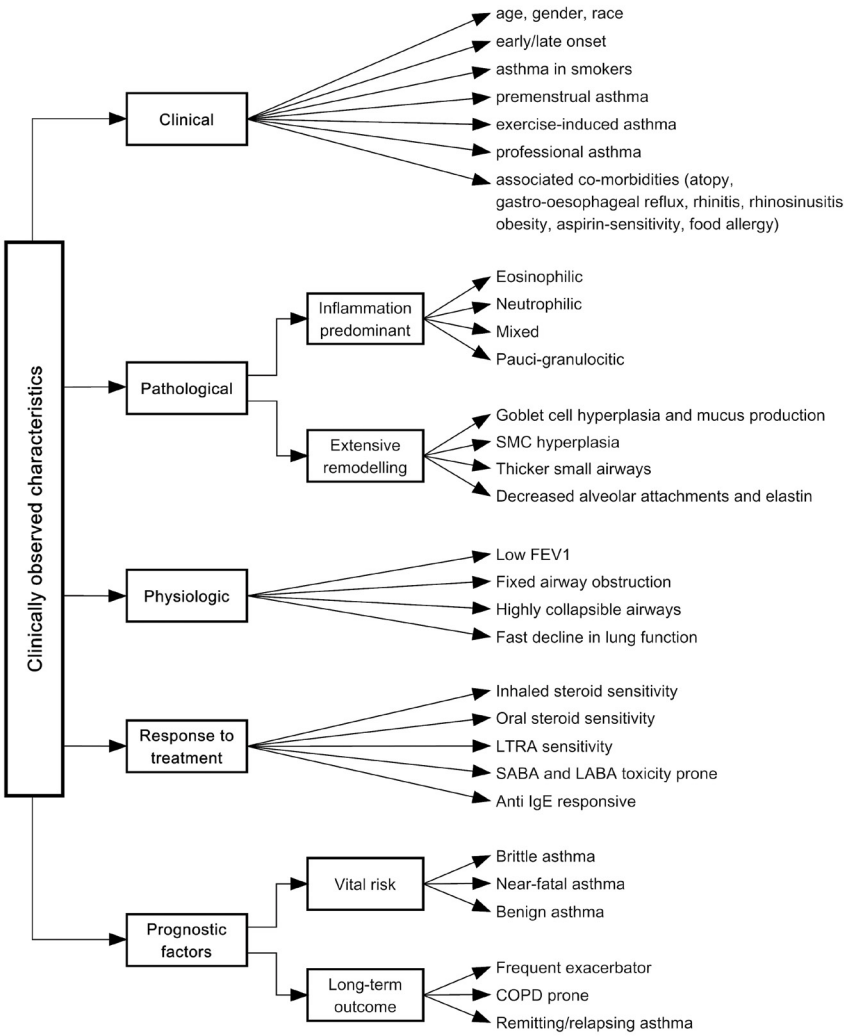

Figure 1 Clinically observed characteristics and asthma phenotypes.
(Reproduced from Agache I, Akdis C, Jutel M, et al. Untangling asthma phenotypes and endotypes. Allergy 2012; 67:835-846; with permission from Wiley-Blackwell.)

and PEF (Peak Expiratory Flow). A circadian peak of symptoms in the early morning hours is typical. Bronchial hyperresponsiveness to non-specific airway irritants such as smoke, cold air, odours, etc. is characteristic and can be tested with bronchoprovocation test with histamine or methacholine. Allergic asthma is associated with increased levels of circulating total and specific IgE. Elevated numbers of eosinophils can be found in the blood, the airway mucosa and the bronchoalveolar lavage fluid. Asthmatic symptoms and/or asthma attacks increase following inhalation of allergens, but can also persist in the absence of allergenic triggers. The fraction of NO in exhaled breath (FeNO) can be elevated in asthma. Many patients experience worsening airflow obstruction and symptoms following exercise. Some suffer from severe attacks upon ingestion of non-steroidal anti-inflammatory drugs (Aspirin Exacerbated Respiratory Disease). None of these signs or symptoms, however, is characteristic. Asthma therefore remains a clinical diagnosis.

Therapeutically there is no cure for asthma available. Most patients profit from inhalation therapy with little if any side effects. However, many patients with more severe asthma or failure to adhere to treatment remain uncontrolled. Brief attacks of asthma usually respond well to the inhalation of β2-agonists. Persistent asthma responds to inhaled corticosteroids. Leukotriene-antagonists, theophylline, anti-IgE-antibodies and anticholinergic drugs can be added in more severe or therapy refractory cases.

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2 HISTORY OF ASTHMA

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KEY MESSAGES

- The term "asthma" has been in use for millennia, but the description of the condition that now bears that name has been in place since the writings of Aretæus the Cappadocian about 2000 years ago
- Both attacks and chronic dyspnea are characteristic of asthma
- Treatments of asthma based on bronchial smooth muscle relaxation have been in use for over 200 years, with sympathomimetic reliever treatment introduced in the early 1900s
- The use of glucocorticoids to treat asthma was introduced in the mid-20th century; inhaled corticosteroid treatment was started in the late 1960s

THE TERM "ASTHMA"

The term "asthma" is derived from the Greek *aazein*, which means to pant. Before the writings of Aretaeus in the 2nd century and well into the 20th century, many physicians and lay people alike used the term "asthma" to refer to any condition characterized by acute nonphysiologic shortness of breath. For example, acute congestive heart failure would often be termed "cardiac asthma." Aretaeus's and, much later, Floyer's (1698) descriptions of asthma largely match those in use today (Figure 1).

CLINICAL DESCRIPTIONS

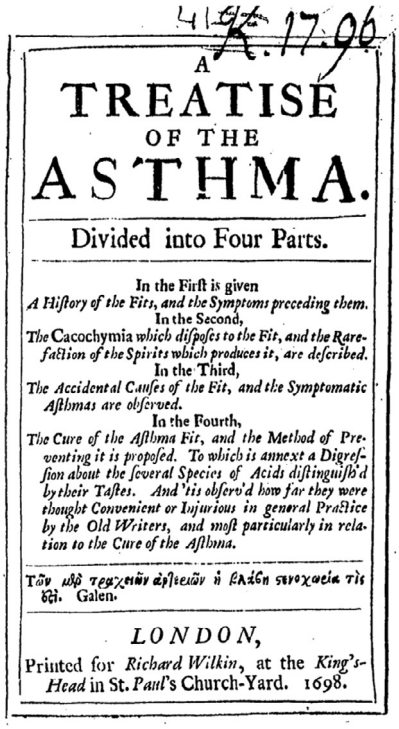
There are two key components of the clinical description that have survived two millennia. The first is the acute asthmatic episode, also known as an asthma attack. This is the sudden onset (as quickly as seconds, but more usually minutes to hours) of shortness of breath often accompanied by wheezing audible to the patient and those close to him or her; this resolves spontaneously or as a result of treatment. The second is dyspnea of much less severity between these episodes. Exercise and allergen exposure have been recognized as causes of asthma attacks over this entire recorded history.

The physicians examining patients with asthma were able to appreciate wheezing long before Laennec's treatise on diseases of the chest was published in 1819. With Laennec's work, it became clear that there were many other conditions characterized by wheezing other than asthma.

ASTHMA TREATMENTS

Anticholinergic asthma treatment was known to Floyer. At that time, patients were instructed to inhale smoke from the burning of certain plant's containing belladonna alkaloids. The three most commonly used plants were known as the "sinister sisters" because, if taken in excess amounts, they could have severe side effects including death. These were *hyoscyamus, stramonium, and belladonna* (Figure 2). After a century of disuse, long-acting muscarinic antagonists are being re-introduced into asthma treatment.

Sympathomimetic treatment of asthma dates from the original use of *ma huang* in traditional Chinese medicine, likely over 5000 years ago. The active ingredient in *ma huang* is ephedra, and epinephrine, first by injection and later by inhalation, became the standard of care for acute asthma treatment. In the 1950s, inhaled isoproterenol (isoprenaline) was introduced for over the counter sales for asthma therapy, but high potency isoproterenol use was associated with asthma deaths (Figure 3). Restriction of



A
TREATISE
OF THE
ASTHMA.

Divided into Four Parts.

In the First is given
A History of the Fits, and the Symptoms preceding them.
In the Second,
The Cacochymia *which disposes to the Fit, and the Rarefaction of the Spirits which produces it, are described.*
In the Third,
The Accidental Causes of the Fit, and the Symptomatic Asthmas are observed.
In the Fourth,
The Cure of the Asthma Fit, and the Method of Preventing it is proposed. To which is annext a Digression about the several Species of Acids distinguish'd by their Tastes. And 'tis observ'd how far they were thought Convenient or Injurious in general Practice by the Old Writers, and most particularly in relation to the Cure of the Asthma.

Τῶν μὲν τραχειῶν ἀρτηριῶν ἡ βλὰξη συνοχωκὸν τὶ ἔχει. Galen.

LONDON,
Printed for *Richard Wilkin*, at the *King's-Head* in St. *Paul's* Church-Yard. 1698.

Figure 1 Title page from Floyer's classic monograph on asthma published in 1696. This contains a clear description of the condition we now recognize as asthma.

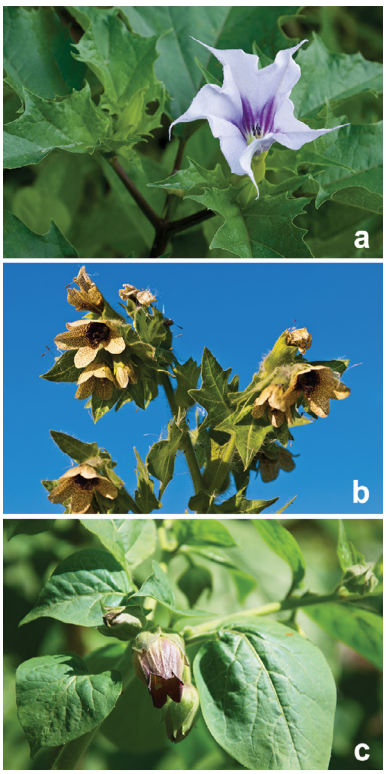


Figure 2 "Sinister sisters" plants. Smoking the leaves from these plants has been used as an asthma remedy for decades. a - *Datura stramonium*; b - *Hyoscyamus niger*; c - *Atropa belladonna*.

this treatment led to a reversal in asthma deaths. In the 1960s, selective β_2 agonists (Figure 4), such as albuterol, became available for inhalation and now have become the standard of care. The introduction of inhaled beta agonists with duration of action of over 12 hours occurred in the 1990s. Although these are highly effective therapies, there has been concern about their long-term safety. Large safety studies are ongoing at this time.

GLUCOCORTICOIDS AND ASTHMA

The use of adrenocorticotropic hormone (ACTH) or injections of biologically derived or synthetic steroids as an asthma therapy was introduced in the early 1950s. Because of the severe side effects of systemic steroid use, inhaled glucocorticoids were introduced in asthma treatment in the 1960s (Figure 5).

TARGETED ASTHMA TREATMENTS

Leukotriene modifier treatments -- both antagonists of the action of leukotriene D_4 at the CysLT1 receptor or inhibitors of the action of the enzyme ALOX-5 were introduced into the market in the mid-1990s. Although their impact on lung function is less than inhaled glucocorticoids, they have a minimal adverse event profile and their oral action has led to their reasonably common use. Anti-IgE therapy was approved about the turn of the 21st century.

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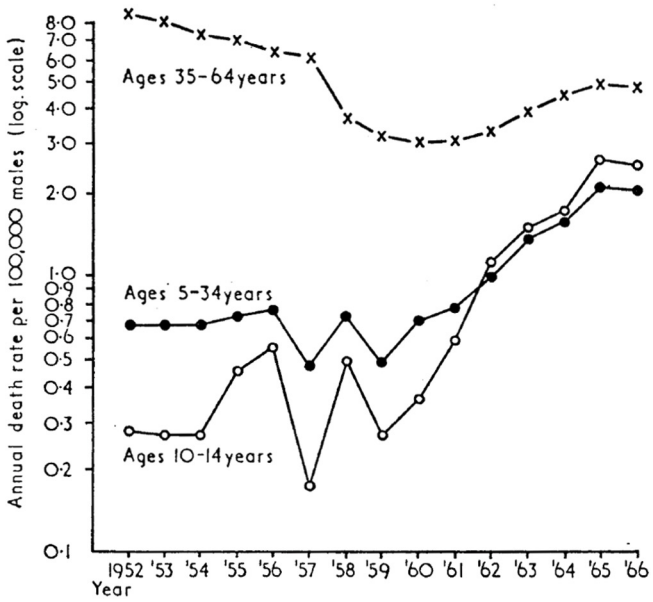

Figure 3 Asthma deaths in Britain from 1952 to 1966 showing the impact of high potency isoproterenol inhalers, introduced for over the counter sales in the late 1950s and subsequently limited to prescription use in the late 1960s. *(Reproduced from Br Med J, Speizer FE, Doll R, Heaf P, 1, 335-339, Copyright 1968 with permission from BMJ Publishing Group Ltd.)*

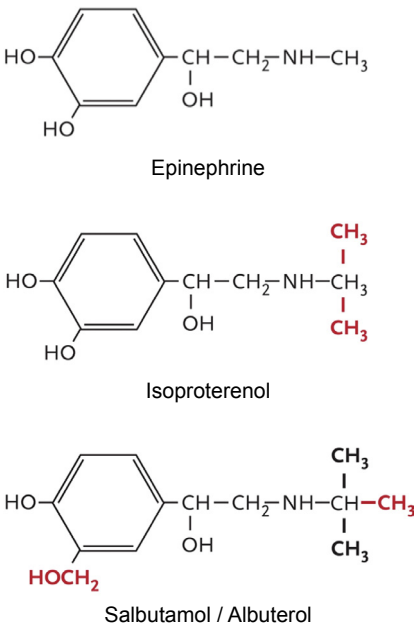

Figure 4 Chemical structures of epinephrine, the nonselective beta-adrenergic agonist, isoproterenol (isoprenaline), and the selective beta2-agonist, albuterol (salbutamol). The components of the structure in red show the differences from the preceeding structure.

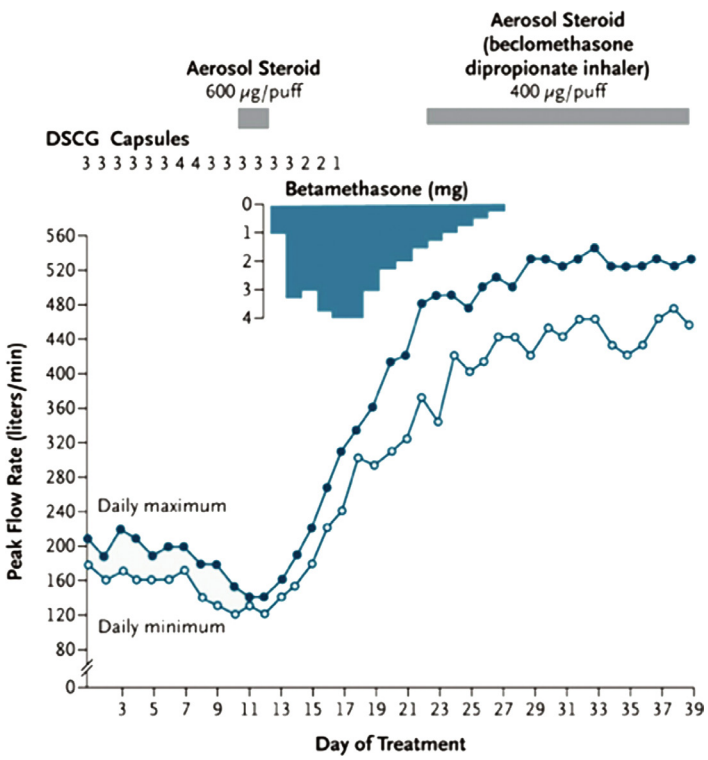

Figure 5 Data from an early case report of the effects of inhaled glucocorticosteroids in asthma. DSCG denotes disodium cromoglycate. *(Adapted from Br Med J, Brown HM, Storey G, George WH, 1, 585-590, Copyright 1972 with permission from BMJ Publishing Group Ltd.)*

3a

THE ASTHMA EPIDEMIC - GLOBAL AND TIME TRENDS OF ASTHMA IN CHILDREN

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KEY MESSAGES

- Asthma in children is a disease of low and middle income, as well as high income countries
- Asthma in children is more severe in low and middle income countries
- Asthma in children is on the increase in many countries especially in low and middle income countries
- Further asthma surveillance and research is needed

ASTHMA CONTEXT

Asthma has been recognized for more than 3000 years but it is only in the last three to four decades that it has become a serious public health concern. This was precipitated by a new epidemic of asthma deaths in 1977, affecting New Zealand, more than any other country, that stimulated a great deal of research which continues to this day. About the same time admissions to hospital for asthma were increasing dramatically in New Zealand, Australia, The United Kingdom, Canada and USA and the highest rates were in New Zealand children. Until two decades ago scientists in these countries believed that asthma affected predominantly people in high income countries and was negligible in developing countries.

GLOBAL VARIATION

The International Study of Asthma and Allergies in Childhood (ISAAC) was formed to examine variation around the world in asthma and allergies by development of the necessary standardized methodology. At the time ISAAC started (1991), there were fewer than 30 centres in the world where the prevalence of asthma in children had been studied at all, and most had used different methodologies. Through ISAAC, which, in the third phase included 237 centres in 98 countries, we now know that asthma occurs in all countries studied, with striking variations in the prevalence of asthma symptoms throughout the world, up to 15-fold between countries (Figure 1). Although asthma symptoms were more common in some high income countries, some low and middle income countries also had high levels of asthma symptom prevalence. Among children with asthma symptoms, asthma is more severe in low and middle income than high income countries (Figure 2).

TIME TRENDS

Studies from English-language countries in the 1990s reported increases in asthma prevalence from the 1980s, and therefore continuing increases in prevalence were expected. Indeed, ISAAC found that asthma in children was on the increase in many countries from 1993 to 2003. However, in most high prevalence countries, particularly the English-language countries, the prevalence of asthma symptoms changed little during that time, and even declined in some cases. In contrast, prevalence increased in many countries over that time, especially low and middle income countries with large populations (Figure 3). The overall percentage of children and adolescents reported to have ever had asthma increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice.

CONCLUSION

The 20-year ISAAC programme

has shown that childhood asthma is a common disease in both high income and lower income countries. It is relatively more severe and increasing in prevalence in many lower income countries. It is vital to continue surveillance of asthma, research its causes and reach all asthma sufferers with good management as summarised in The Global Asthma Report 2011. These are the aspirations of the new Global Asthma Network.

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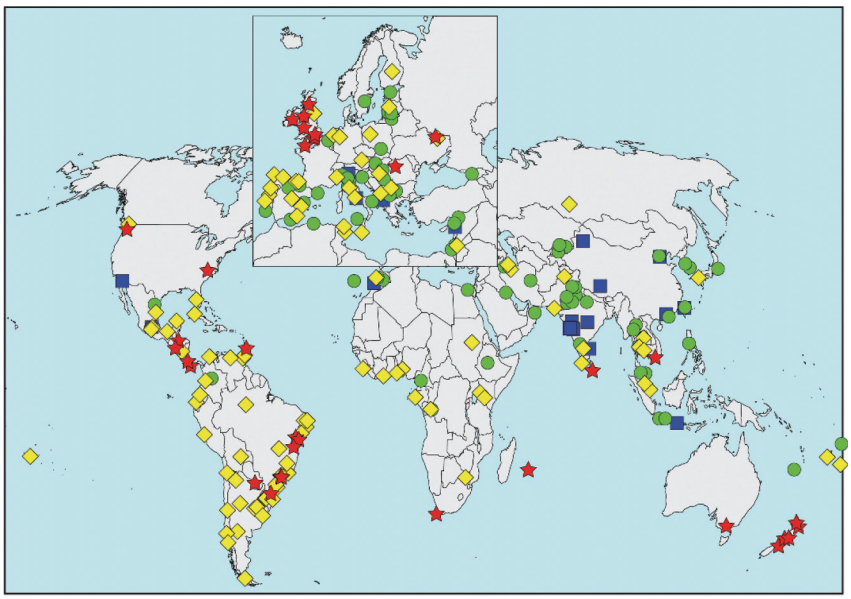

Figure 1 Prevalence of current wheeze according to the written questionnaire in the 13–14 year age group. The symbols indicate prevalence values of <5% (blue square), 5 to <10% (green circle), 10 to <20% (yellow diamond) and >20% (red star). *(Reproduced from Thorax, Lai CK, Beasley R, Crane J, et al, 64, 476-483, Copyright 2009 with permission from BMJ Publishing Group Ltd.)*

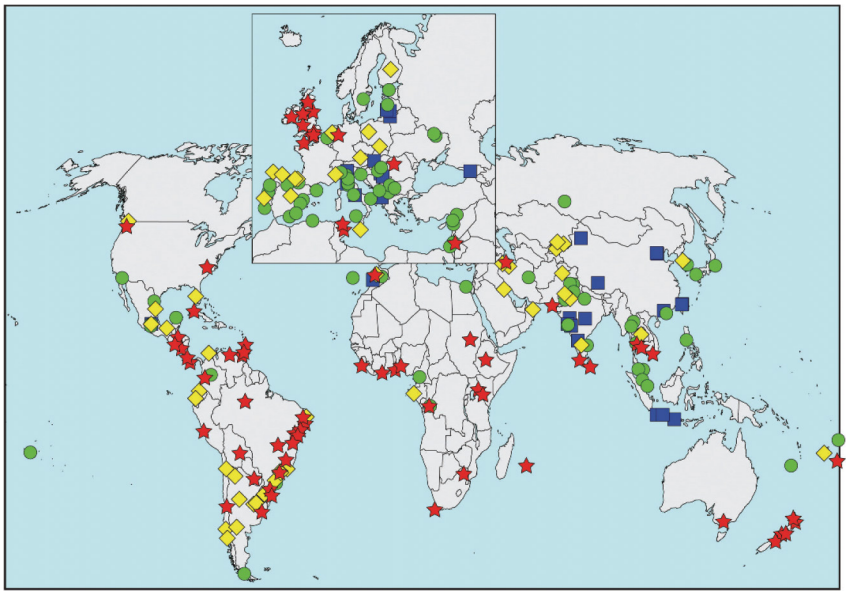

Figure 2 Prevalence of symptoms of severe asthma according to the written questionnaire in the 13–14 year age group. The symbols indicate prevalence values of <2.5% (blue square), 2.5 to <5% (green circle), 5 to <7.5% (yellow diamond) and >7.5% (red star). *(Reproduced from Thorax, Lai CK, Beasley R, Crane J, et al, 64, 476-483, Copyright 2009 with permission from BMJ Publishing Group Ltd.)*

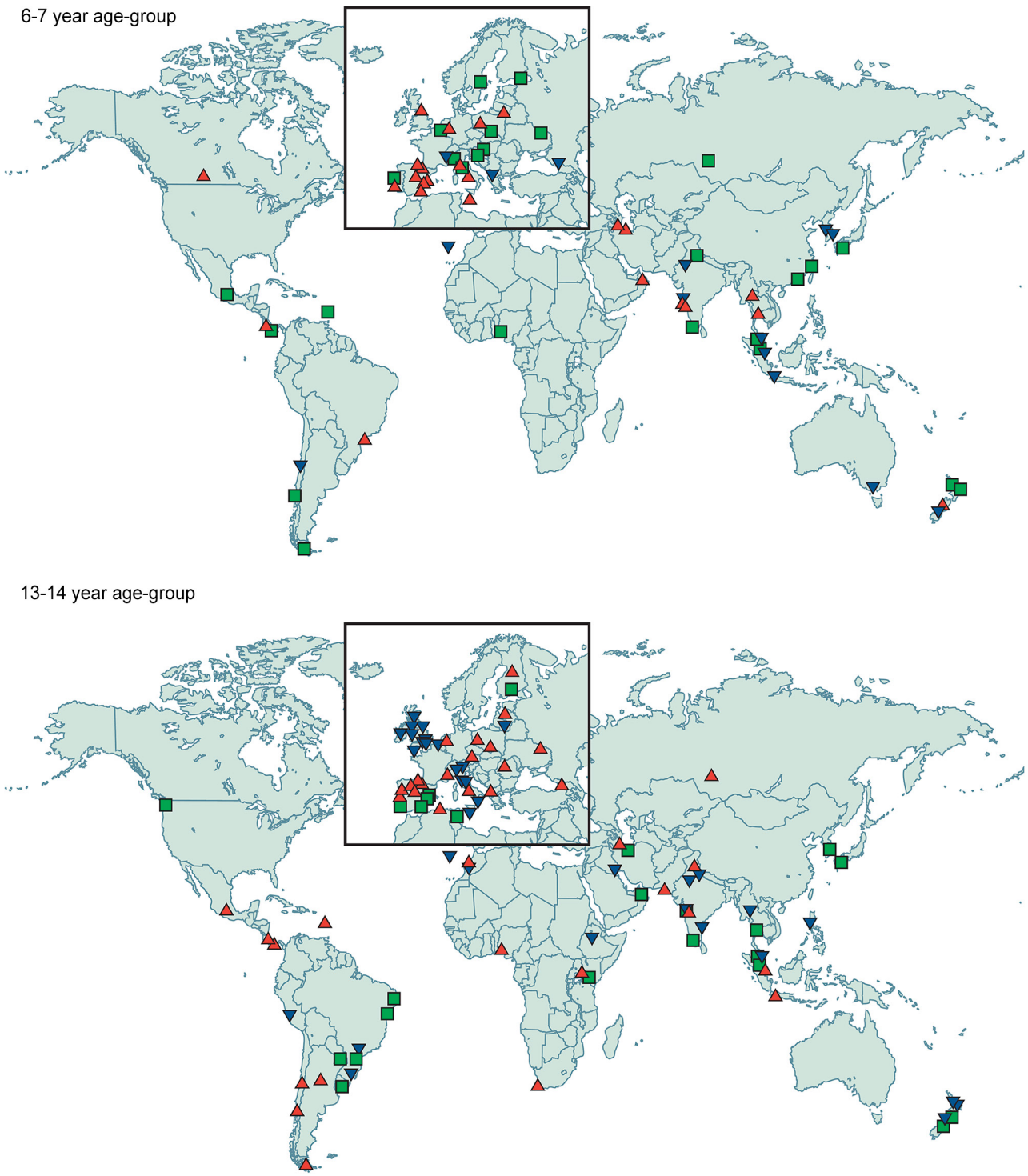

Figure 3 World map showing direction of change in prevalence of asthma symptoms for 6-7 year age-group and 13-14 year age-group. Each symbol represents a centre. Blue triangle=prevalence reduced by ≥1 SE per year. Green square=little change (<1 SE). Red triangle=prevalence increased by≥1 SE per year. *(Reprinted from The Lancet, 368, Asher MI, Montefort S, Björkstén B, Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis,and eczema in childhood: ISAAC Phases One and Three repeat multicountry crosssectional surveys, 733-43, Copyright 2006, with permission from Elsevier.)*

3b THE ASTHMA EPIDEMIC - GLOBAL AND TIME TRENDS OF ASTHMA IN ADULTS

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KEY MESSAGES

- Three large international surveys on adult asthma have been conducted: ECRHS I (1991-1994), WHS (2002-2003), and GA²LEN (2008-2009)
- Comparison of prevalence estimates across the surveys is difficult due to the different methods and disease definitions
- Each survey suggests substantial geographical variation in adult asthma prevalence between countries
- Analysis of the ECRHS and information from the GA²LEN survey provides some evidence of cohort-related increases in adult asthma
- Repeat surveys need to be conducted to reliably assess global time trends of adult asthma prevalence

MEASURING ADULT ASTHMA FOR GLOBAL COMPARISON

The assessment of adult asthma in epidemiological studies is difficult. Use of objective markers, such as bronchial hyperreactivity, is usually impracticable in large, international population-based surveys, which therefore primarily rely on the reporting of asthma symptoms like wheeze and/or a physician-diagnosis. A complicating factor is the lack of a commonly agreed terminology for asthma symptoms across languages. Even if this could be overcome, the perception and reporting of asthma symptoms differs between subjects, who come from diverse socio-cultural backgrounds. In addition, diagnostic criteria vary between physicians, for instance as a result of working in different health care systems. Furthermore, reported asthma symptoms in the elderly are difficult to distinguish from symptoms of chronic obstructive pulmonary disease (COPD). To date three large international surveys have provided data to make international comparisons.

THE EUROPEAN COMMUNITY RESPIRATORY HEALTH SURVEY (ECRHS)

The ECRHS assessed the prevalence of asthma symptoms, asthma attacks, and the use of asthma medication in the general population aged 20 to 44 years. It was conducted at different sites, mostly in Western Europe, between 1991 and 1994. Information from 48 study centres in 22 countries showed wide variations in the prevalence of wheeze and 'diagnosed asthma', the latter being defined as a report of an asthma attack or current use of asthma medication (see Table 1).

THE WORLD HEALTH SURVEY (WHS)

The WHS was conducted among adults (aged ≥18 years) in 70 countries in 2002/2003. The prevalence of respiratory symptoms was assessed in 68 countries, and of asthma diagnosis in 64. The WHS adds to the ECRHS because it provides information on adult asthma in low-income countries. The survey showed that there are wide variations in the prevalence of wheeze (Figure 1) and asthma (Figure 2) regardless of overall national income.

THE GLOBAL ALLERGY AND ASTHMA NETWORK OF EXCELLENCE (GA²LEN)

The GA²LEN survey was conducted among adults aged 15-74 years in 15 European countries in 2008/09. The data on asthma prevalence

TABLE 1

Prevalence (in %) of 'wheeze' and 'diagnosed asthma' in the European Community Respiratory Health Survey (ECRHS) and the Global Allergy and Asthma Network of Excellence (GA²LEN) *

Country	Centre	ECRHS		GA²LEN
		wheeze[1]	dg asthma[2]	asthma[3]
Iceland	Reykjavik	18.0	3.4	
Norway	Bergen	24.6	4.3	
Sweden	Göteborg	23.2	5.8	7.1
	Stockholm			8.6
	Umeå	19.8	6.8	11.2
	Uppsala	19.2	6.0	9.5
Finland	Helsinki			7.8
Estonia	Tartu	26.8	2.0	
Denmark	Aarhus	24.1	4.0	
	Odense			8.6
Poland	Katowice			5.2
	Krakow			7.1
	Lodz			6.0
Netherlands	Amsterdam			6.4
	Bergen op Zoom	19.7	4.7	
	Geleen	20.9	4.4	
	Groningen	21.1	4.3	
Belgium	Antwerp city	20.6	4.6	
	Antwerp south	12.8	2.7	
	Ghent			7.6
Germany	Brandenburg			6.3
	Duisburg			10.1
	Erfurt	13.3	2.1	
	Hamburg	21.1	4.4	
Austria	Vienna	14.3	3.1	
France	Bordeaux	15.7	5.5	
	Grenoble	14.6	3.5	
	Montpellier	14.4	5.0	10.3
	Nancy	13.6	3.7	
	Paris	14.5	5.1	
Macedonia	Skopje			5.1
UK	Caerphilly	29.8	8.0	
	Cambridge	25.2	8.4	
	Dundee	28.4		
	Ipswich	25.5	7.8	
	London			11.4
	Norwich	25.7	7.5	
	Southampton			14.2
Ireland	Dublin	32.0	5.0	
	Kilkenny-Wexford	24.0	5.4	
Greece	Athens	16.0	2.9	
Italy	Palermo			10.7
	Pavia	8.5	3.3	
	Turin	10.7	4.5	
	Verona	9.7	4.2	
Spain	Albacete	25.0	3.9	
	Barcelona	19.2	3.1	
	Galdakao	16.2	2.1	
	Huelva	29.2	6.3	
	Oviedo	21.0	3.6	
	Seville	22.6	5.0	
Portugal	Coimbra	19.0	6.0	16.8
	Oporto	17.7	4.3	
Algeria	Algiers	4.2	3.0	
India	Bombay	4.1	3.5	
New Zealand	Auckland	25.2	10.1	
	Christchurch	26.7	11.2	
	Hawkes Bay	24.2	9.0	
	Wellington	27.3	11.3	
Australia	Melbourne	28.8	11.9	
USA	Portland, Oregon	25.7	7.1	

** Reproduced with permission of the European Respiratory Society. Eur Respir J April 1, 1996 9:687-695 and from Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA²LEN survey in Europe. Allergy 2012;67:91-98, Wiley-Blackwell.*

[1] Age and sex standardized prevalence of a positive response to 'Have you had wheezing or whistling in your chest at any time in the last 12 months?' in 20-44 year olds.

[2] dg asthma = diagnosed asthma. Age and sex standardized prevalence of a positive response to at least one of the following: (i) 'Have you had an asthma attack in the last 12 months?', or (ii) 'Are you currently taking medication for the treatment of asthma?' in 20-44 year olds.

[3] Age and sex standardized prevalence of reporting 'ever had asthma' AND reporting at least one of the following symptoms in the last 12 months (i) wheeze or whistling in the chest, (ii) waking with chest tightness, (iii) waking with shortness of breath, and (iv) waking with an attack of coughing in 15-74 year olds.

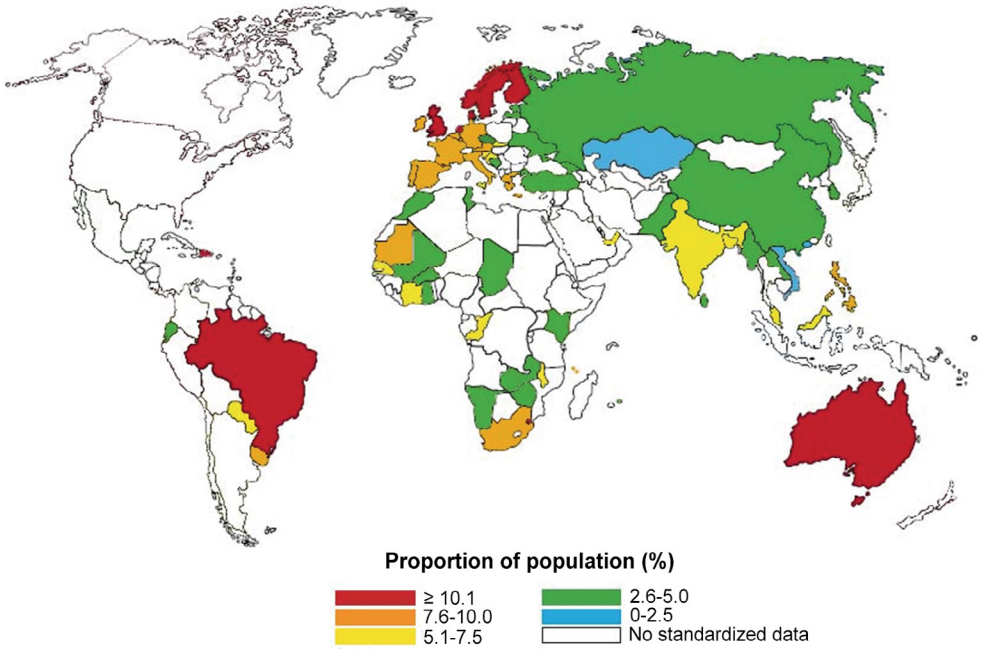

Figure 1 World map of the prevalence of 'current wheezing symptoms' [1] among 20-44 year olds in the WHS.
[1] positive response to at least one of the two options in the following question: 'During the last 12 months, have you experienced any of the following: (i) attacks of wheezing or whistling breathing? or (ii) attacks of wheezing that came on after you stopped exercising or some other physical activity?' *(Reproduced with permission of the European Respiratory Society. Eur Respir J February 2010 35:279-286; published ahead of print September 9, 2009, doi:10.1183/09031936.00027509.)*

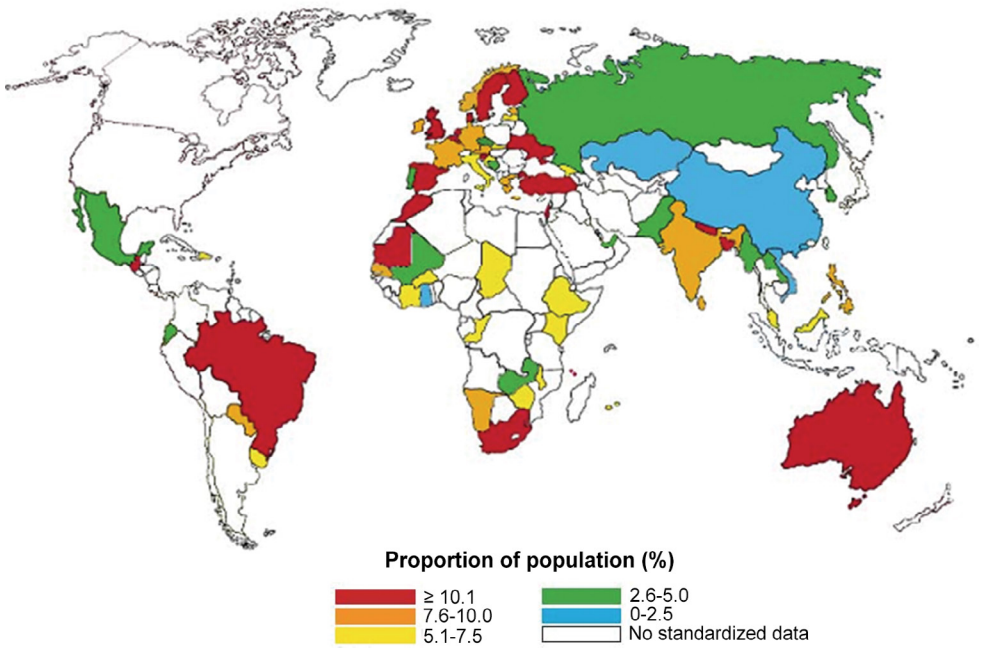

Figure 2 World map of the prevalence of 'diagnosed asthma' [1] in the WHS.
[1] positive response to any of the following: (i) 'have you ever been diagnosed with asthma (an allergic respiratory disease)?'; (ii) 'have you ever been treated for it?'; (iii) 'have you been taking any medications or other treatment for it during the last 2 weeks?' *(Reproduced with permission of the European Respiratory Society. Eur Respir J February 2010 35:279-286; published ahead of print September 9, 2009, doi:10.1183/09031936.00027509.)*

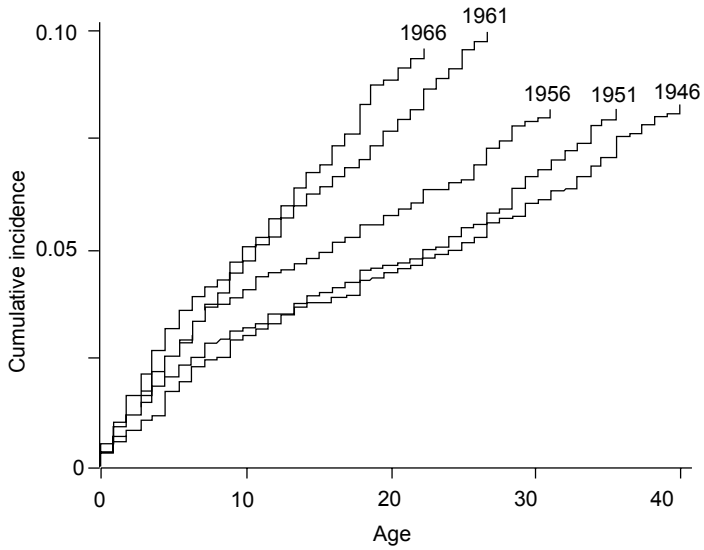

Figure 3 Cumulative incidence of 'asthma' [1] by age at first asthma attack and birth cohort.
[1] positive response to 'Have you ever had asthma?'
(Reproduced with permission of the European Respiratory Society. Eur Respir J October 1, 1999 14:885-891.)

from 19 centres (12 countries) following the full study protocol are displayed in the table.

COMPARABILITY BETWEEN THE SURVEYS

The WHS used different sampling methods to ECRHS and GA²LEN, and ECRHS (unlike WHS and GA²LEN) studied only young adults. Different questions were employed to define the prevalence of asthma. The footnotes to the table and figures explain some of these differences.

TIME TRENDS IN ADULT ASTHMA PREVALENCE

Neither of these three surveys has been repeated on an international level to assess time trends in adult asthma prevalence. At single sites, repeat surveys have been conducted using the ECRHS methodology. In two examples from Italy and Sweden the prevalence of diagnosed asthma increased. Somewhat contradictory, over the same period, the prevalence of wheeze decreased in Sweden but increased in Italy.

Over the last sixty years there has been a well documented cohort related increase in asthma in children, and we would expect this to be reflected in higher asthma prevalence in adults as the affected cohorts have aged. Consistent with this, there is evidence from GA²LEN that the prevalence of asthma in younger adults is higher than in older adults in most (although not all) parts of Europe. An alternative explanation could be that asthma remits with aging. Within the ECRHS, data from 15 industrialized countries on age at first asthma attack were used to estimate the incidence of asthma within birth cohorts represented in the study population, suggesting that the cumulative incidence of asthma increased progressively across the birth cohorts from subjects born in 1946-1950 (Figure 3). However, the retrospective assessment of age at onset of asthma may be subject to recall bias and secular changes in labelling of asthma may additionally affect the results.

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4 DEATH AND DISABILITY DUE TO ASTHMA

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KEY MESSAGES

- Asthma mortality rates rise rapidly with age and are higher in boys and men
- Asthma mortality rates vary widely across different regions of the world and are highest in Oceania and lowest in the developed economies
- Since 1990 mortality rates from asthma have been falling in all regions of the world
- Disability associated with asthma is highest in uncontrolled asthma
- Uncontrolled asthma is associated with more disability than is moderate angina pectoris, but less disability than moderate COPD or Parkinsonism
- Undertreated asthma is associated with a heavy economic and social burden
- Although many areas where asthma is common also have a high prevalence of "severe" disease, there are areas such as sub-Saharan Africa where severe asthma is relatively more common
- The relative importance depends on the prevalence of other pathologies; in Australia and New Zealand, where mortality rates are relatively low, asthma is the 15th most common cause of disability adjusted life years (DALYs) lost, whereas in South Asia where mortality rates are higher, it is the 25th cause of DALYs lost

Recorded asthma mortality rates vary very widely across age groups rising (as with most causes of death) exponentially with age, rates being slightly lower among women than men at all ages (Figure 1). Death rates are also very uneven between different regions. In 2010 the highest death rates from asthma were experienced in Oceania with high rates also in south and south-east Asia southern and central and east sub-Saharan Africa and in north Africa the middle east and central Asia. Much lower mortality rates were observed in Australasia, Europe and North and South America (Figure 2).

Over the last two decades mortality rates have been falling. In 1990 the global mortality rate for asthma (age adjusted) was around 25/100,000 men and around 17/100,000 women, by 2010 these figures had fallen to around 13/100,000 for men and just over 9/100,000 for women (Figure 3). This downward trend was universal, though some regions, such as Australia/New Zealand, experienced a relatively more rapid decline.

The disability associated with asthma varies with the amount of control of the condition. Well-controlled asthma has relatively little effect on daily life, but uncontrolled asthma has a serious impact, estimated to be considerably more disabling than, for instance, moderate angina pectoris (Figure 4).

In many parts of the world access to medication is severely limited and lack of access to inhaled corticosteroids severely reduces the chances of asthma being adequately controlled. This may explain in part why in areas such as in sub-Saharan Africa, where access to medication may be poor severe asthma is more common than would otherwise might be predicted from the prevalence of asthma (Figure 5).

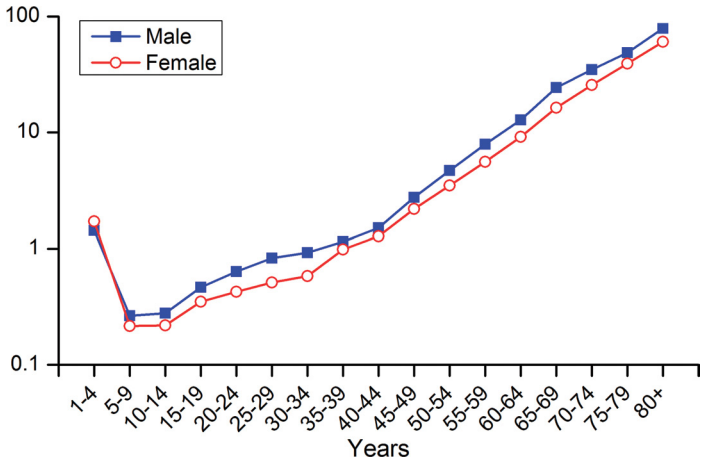

Figure 1 Global death rates/100 000 from asthma by age in 2010. *(Data from Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-2223.)*

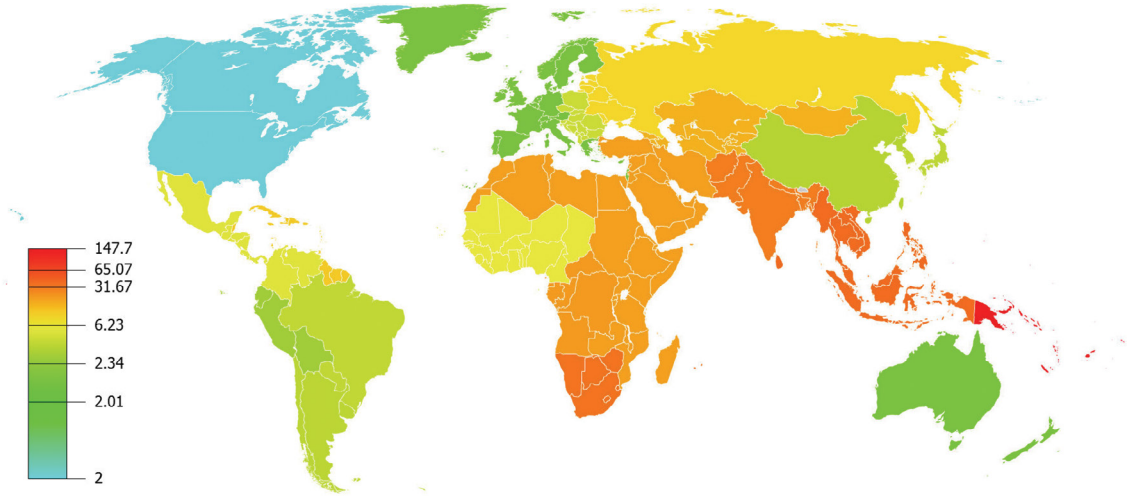

Figure 2 Male Asthma Mortality/100 000 by Global Burden of Diseases Region (2010). *(Data from Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-2128.)*

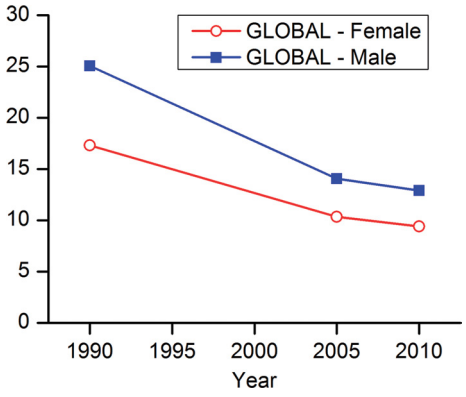

Figure 3 Global trends in age standardised mortality from asthma by sex.

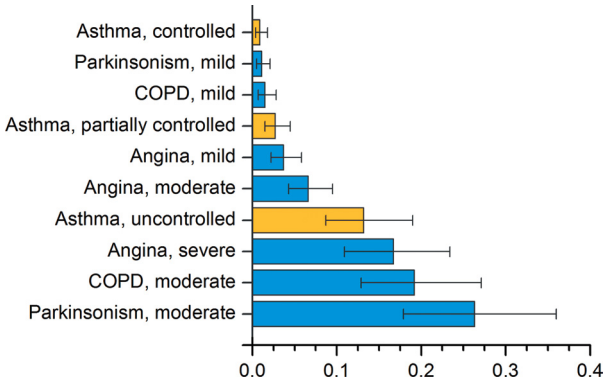

Figure 4 Disability score in various chronic diseases. *(Data from Salomon JA, Wang H, Freeman MK, et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet 2012;380:2144-2162.)*

The implications of this for patients and for the economy can be substantial. Figure 6 shows results from a study of patients attending emergency rooms for asthma, mostly in low and middle income countries. The patients' level of treatment was compared to that recommended for the severity of their disease and they were asked how much work they had missed in the previous weeks. Over 50% of those taking two or more steps below the recommended treatment had missed over a day a week of work, compared with about 5% of those who were on the appropriate treatment.

There are however other determinants of asthma control, and these are partly unknown. In Europe the proportion of patients on inhaled corticosteroids who have uncontrolled asthma is fairly constant at around 10%-20%, but there is wider variation in the proportion of patients who are taking inhaled corticosteroids and who are still uncontrolled, and this varies from 20% to 65% (Figure 7).

Because asthma is a common condition and one that in many instances starts very young and persists throughout life, its impact is substantial, and this impact, relative to that of other diseases, is paradoxically higher in some regions with relatively low mortality (Figure 8). Asthma ranks in the top 20 conditions affecting the disability adjusted life years in Australasia as well as in Oceania, South East Asia and tropical Latin America, and ranks in the top 25 in North America and Western Europe as well as in North Africa and the Middle East, Southern Africa and Southern Latin America. Conversely, in some places, where severe disease is common, it still falls further down the rank of conditions causing loss of disability adjusted life years, as in Central and East Africa. Although sub-Saharan Africa has consistently higher death rates from asthma compared with Western Europe, asthma is relatively less important there when compared with other causes of death and disability.

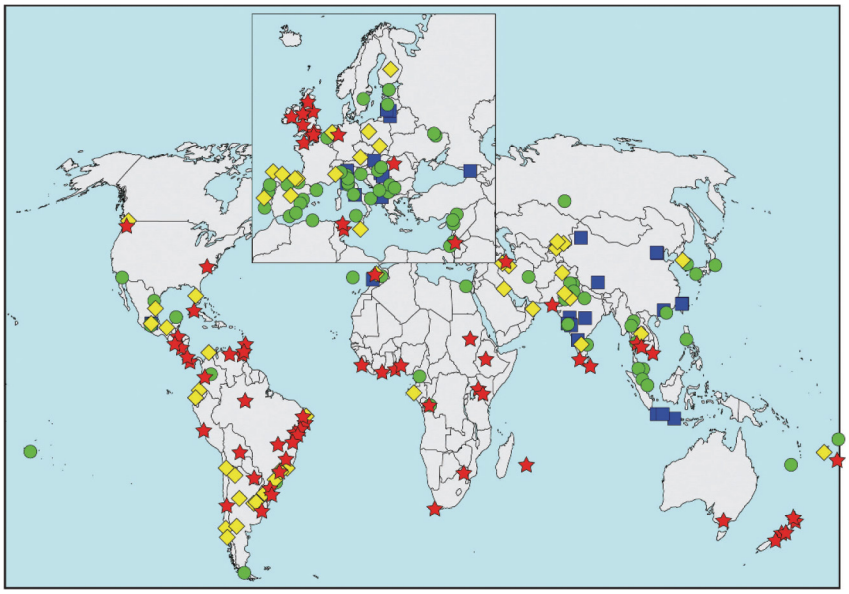

Figure 5 Prevalence of "severe" asthma in 13-14 year olds in the ISAAC studies. The symbols indicate prevalence values of <2.5% (blue square), 2.5 to <5% (green circle), 5 to <7.5% (yellow diamond) and >7.5% (red star). *(Reproduced from Thorax, Lai CK, Beasley R, Crane J, et al, 64, 476-483, Copyright 2009 with permission from BMJ Publishing Group Ltd.)*

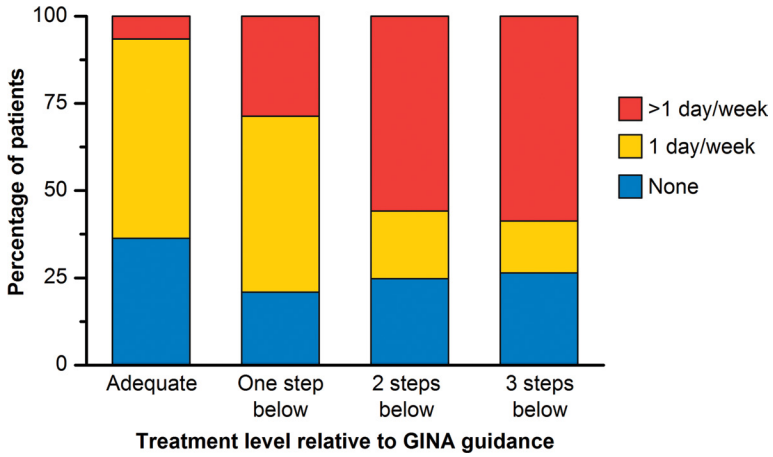

Figure 6 Loss of work related to asthma treatment in the GASP study. *(Data from Burney P, Potts J, Aït-Khaled N, et al. A multinational study of treatment failures in asthma management. Int J Tuberc Lung Dis 2008;12:13-18.)*

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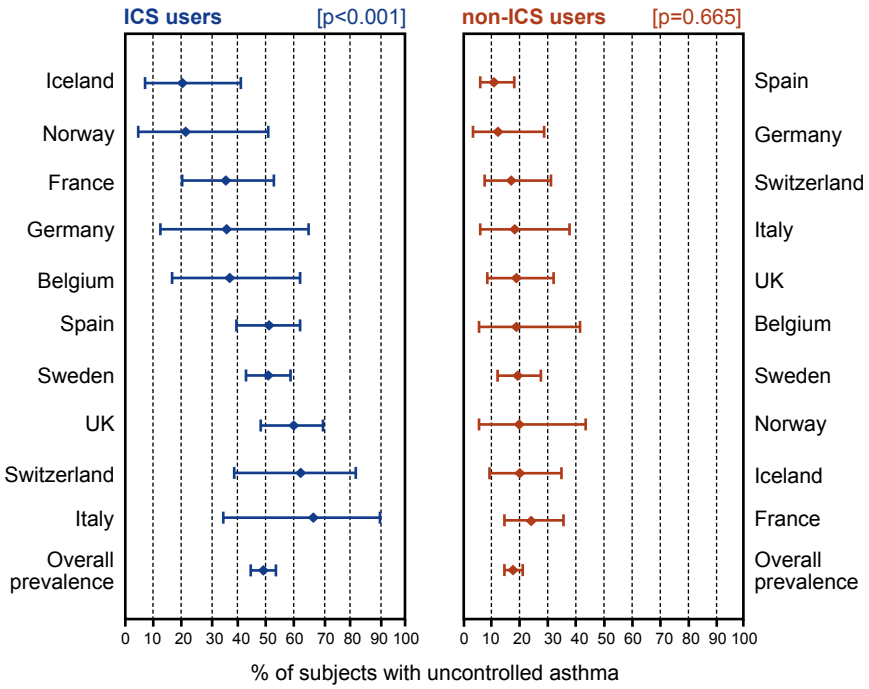

Figure 7 Percentage of patients with asthma in the European Community Respiratory Health Survey who were uncontrolled according to use of Inhaled Corticosteroids (ICS). *(Reprinted from J Allergy Clin Immunol, 120/6, Cazzoletti L, Marcon A, Janson C, et al, Asthma control in Europe: a real-world evaluation based on an international population-based study, 1360-1367, Copyright 2007, with permission from Elsevier.)*

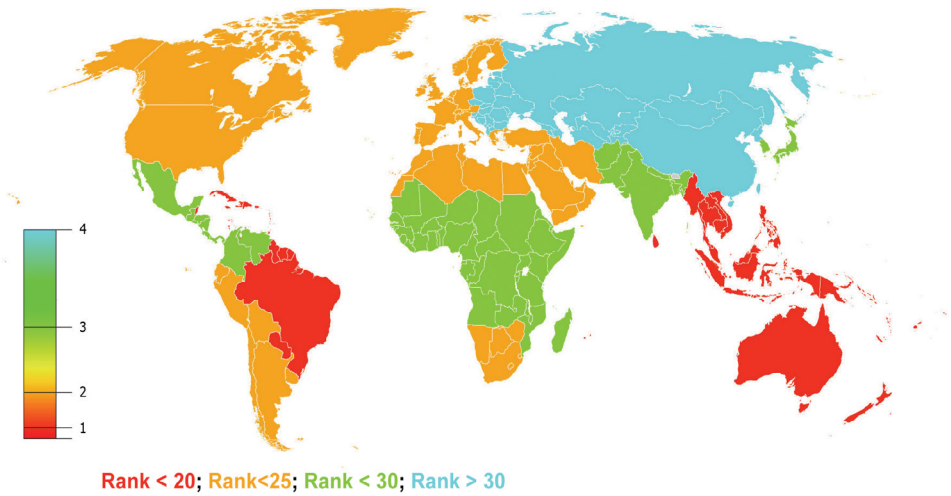

Figure 8 Importance of asthma relative to other conditions. Rank of disability adjusted life years by region (2010). *(Data from Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-2223.)*

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5 SOCIO-ECONOMIC COSTS OF ASTHMA

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Asthma is characterized by a major impact on patients in terms of impairment of quality of life, work and school performance. Patients may experience sleep disorders, impairment of cognitive function, depression and anxiety. The high and increasing prevalence of these disorders in particular allergic rhinitis and asthma may lead to substantial direct and indirect costs of disease.

KEY MESSAGES

- The economic burden of asthma is substantially high
- Uncontrolled asthma is an important cost-enhancing factor
- Hospital admissions and medication costs are the major components of direct costs
- A national approach may be useful in reducing the burden of asthma
- Indirect costs of asthma are substantial and for a major part caused by productivity losses
- Increase of asthma prevalence and costs of medication are responsible for the rise in the cost of illness

ECONOMIC IMPACT OF ASTHMA

In a Global Initiative of Asthma (GINA) report on the burden of asthma, it has been estimated that asthma is one of the most common chronic diseases in the world: 300 million people in the world have asthma. The number of disability-adjusted life years (DALYs) lost due to asthma worldwide has been estimated to be currently about 15 million per year. Worldwide, asthma accounts for around 1% of all DALYs lost, which reflects the high prevalence and severity of asthma. The number of DALYs lost due to asthma is similar to that for diabetes, cirrhosis of the liver, or schizophrenia. When ranking chronic diseases, asthma was the 25th leading cause of DALYs lost worldwide in 2001 (Figure 1).

An analysis of the burden of asthma in the US estimated the annual costs per patient at $ 1907 and the total national medical expenditure at $ 18 billion. The ERS White book, published in 2003 estimated the total costs of asthma in Europe at approximately € 17.7 billion per annum. The countries with the most asthma related consultations were the UK, followed by Greece and Germany. The countries with the least consultations were Poland and Turkey. A 2012 analysis derived from the European Community Respiratory Health Survey II (ECRHS II) estimated the annual costs per patient in Europe at € 1583.

An estimate of the costs of asthma in children in 25 EU countries has been published in 2005. The total costs of asthma for the 25 countries of the European Union are estimated at € 3 billion. The use of wheeze as definition of asthma leads to considerable higher costs of € 5.2 billion. Annual costs for childhood asthma per country vary widely (Figure 2).

DIRECT AND INDIRECT COSTS

The direct costs of disease comprise the health care expenditure associated with hospitalizations, emergency visits, physician visits, diagnostic tests and medical treatment, whereas indirect costs include the impact on employment, loss of work productivity and other social costs. The most impor-

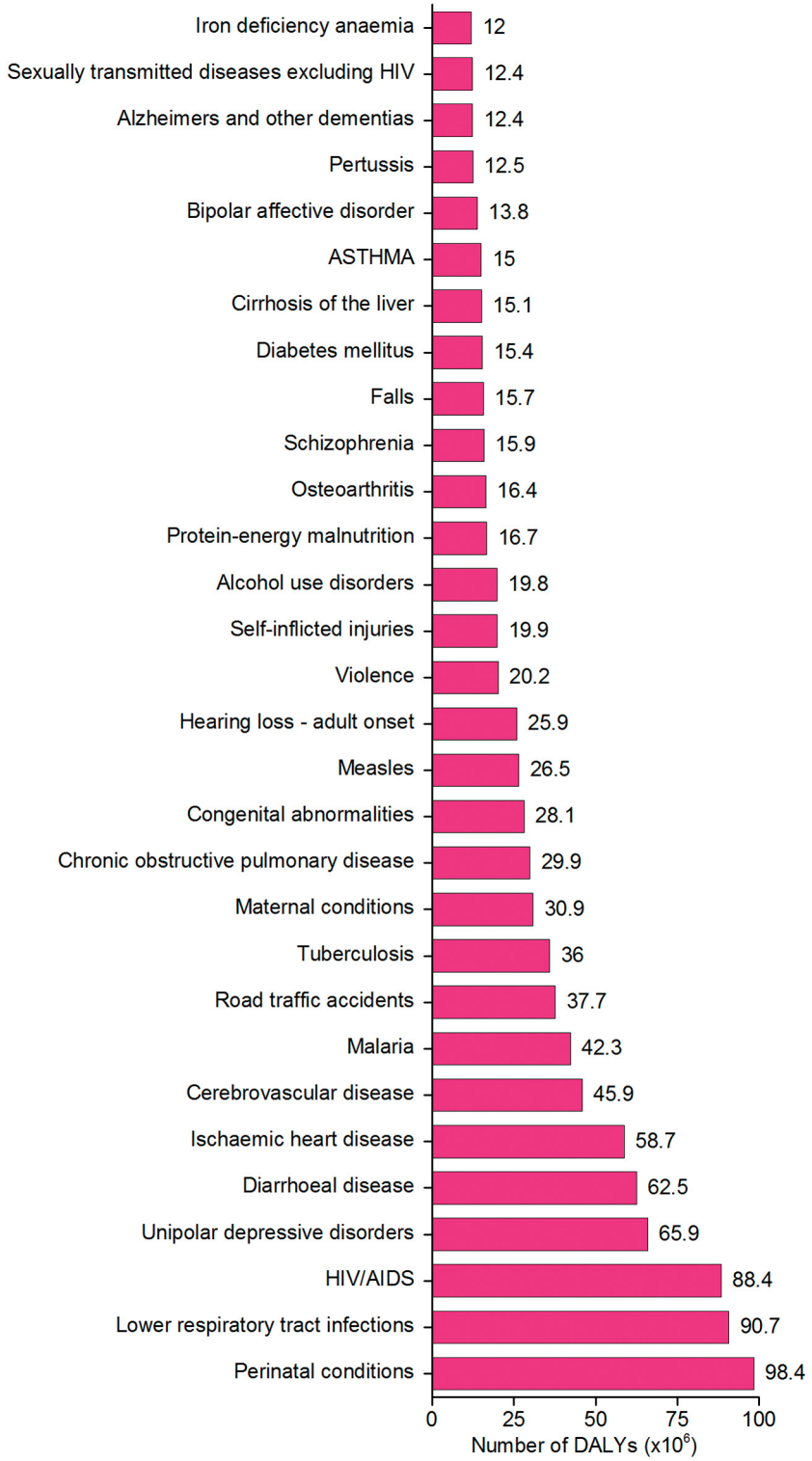

Figure 1 Disability-adjusted life years lost due to asthma worldwide – ranking with other common disorders. GINA report Global burden of asthma 2001. *(Data from Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-478.)*

tant cost components are hospital admissions and asthma medication. Australian, US and Canadian studies found that direct costs account for the greatest part of the total costs. However, the American TENOR study focusing on severe and difficult to treat asthma demonstrated higher indirect than direct costs. Also, several European studies among of which a large German study demonstrated that up to 75% of the total costs of asthma could be attributed to indirect costs. An analysis of adult asthma in 11 ECRHS countries showed that 62.5% of the total costs were caused by working days lost and days with limited, not work related activities. These studies underwrite that the indirect costs of asthma are substantial (Figure 3).

COST-ENHANCING FACTORS

More than 20 studies suggest that more severe disease is a major factor influencing the increase in asthma-related costs. Comparisons between mild and severe disease may result in 1.3 - 5 fold differences. Other cost-enhancing factors comprise poor asthma control, comorbidity, and disability status (Figure 3).

TRENDS IN COSTS

The costs of asthma are rising. For instance, in Canada the costs of asthma increased due to a rise in prevalence and cost of medication. The increase was observed in spite of a reduction in hospitalizations and physician visits. In contrast, the National Asthma Programme in Finland has been proven to be effective in reducing the costs per patient per year by 36% in ten years.

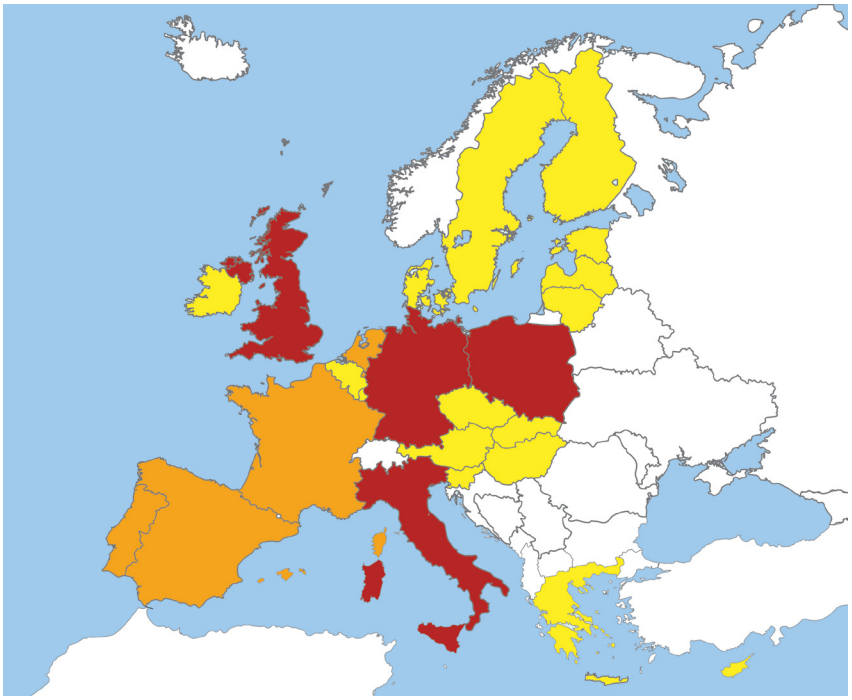

Figure 2 Annual costs of childhood asthma per country. Yellow: less than 100 million €; orange: between 100 and 300 million €; red: more than 300 million €. *(Data from van den Akker-van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: assessing the burden to society of asthma in children in the European Union. Allergy 2005;60:140-149.)*

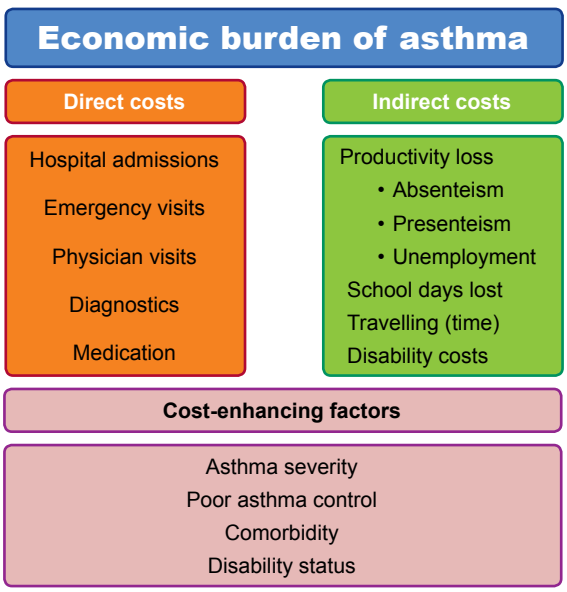

Figure 3 Direct and indirect costs of asthma and cost-enhancing factors.

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6 NATURAL HISTORY OF ASTHMA

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KEY MESSAGES

- Most children with recurrent wheeze in infancy will grow into remission
- Long term outcome may be influenced by early exposure to certain viruses (Rhinovirus, RSV)
- Early domestic exposure to indoor allergens together with early sensitization may lead to impaired lung function in school-age
- Tobacco smoke exposure during pregnancy increases the risk for long-term asthma
- Atopic sensitization to indoor allergens in preschool age is a risk factor for persistence of asthma
- Strategies trying to prevent asthma up to now have not been successful
- Future initiatives for asthma-prevention should focus on viral-triggers and tolerance-induction to indoor allergens

The highest annual incidence of wheeze is observed during infancy. Long-term longitudinal cohort studies have clearly demonstrated that the vast majority of wheezy infants will not grow into a chronic asthma during the following decades. However, early exposure to certain viruses like Rhinovirus or Respiratory Syncytial Virus (RSV) increase the risk of recurrent asthmatic wheeze in school-age and adolescence. In preschool-age different clusters of asthmatic children are emerging. The natural history of asthma is strongly determined by parental phenotypes: asthma and atopy in father and mother is associated with higher prevalence of asthma during the first two decades of life. During the first years of life asthma prevalence is higher in boys. Between the age of 12 to 14 years old girls are catching up so that after adolescence most studies find higher prevalence rates in females.

A number of environmental factors have been shown to significantly contribute to a poor outcome of childhood asthma. Among them domestic tobacco-smoke exposure, particularly during pregnancy and infancy, is clearly one of the most important risk factors. In many adolescents asthma is associated with sensitization to indoor-allergens, particularly house-dust mites and cats. For children who acquire this sensitization during the first three years of life it has been demonstrated that the chance for long-term asthma remission is significantly reduced (Figure 1), and long function will be impaired by school-age.

Future challenges for paediatric allergists and chest physicians include the need to find appropriate strategies for asthma prevention. After a variety of pharmacotherapeutical approaches like inhaled corticosteroids, antihistamines or calcineurin inhibitors have failed, it appears likely, that future activities will have to address the role of viral infections in infancy as well as the mechanism of early sensitization or tolerance induction to indoor allergens (Figure 2).

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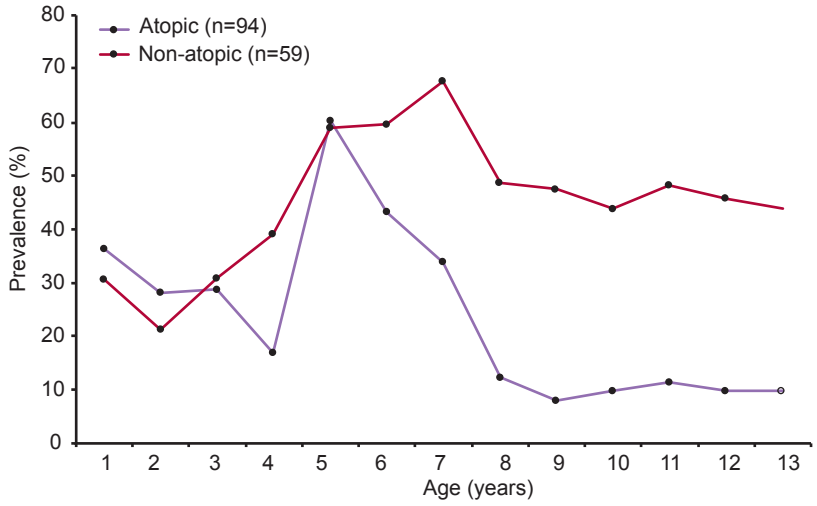

Figure 1 Prevalence of current wheeze from birth to age 13 years in children with any wheezing episode at school-age (5-7 years), stratified for atopy. *(Reprinted from The Lancet, 368, Illi S, von Mutius E, Lau S, et al, Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study, 763-770, Copyright 2006, with permission from Elsevier.)*

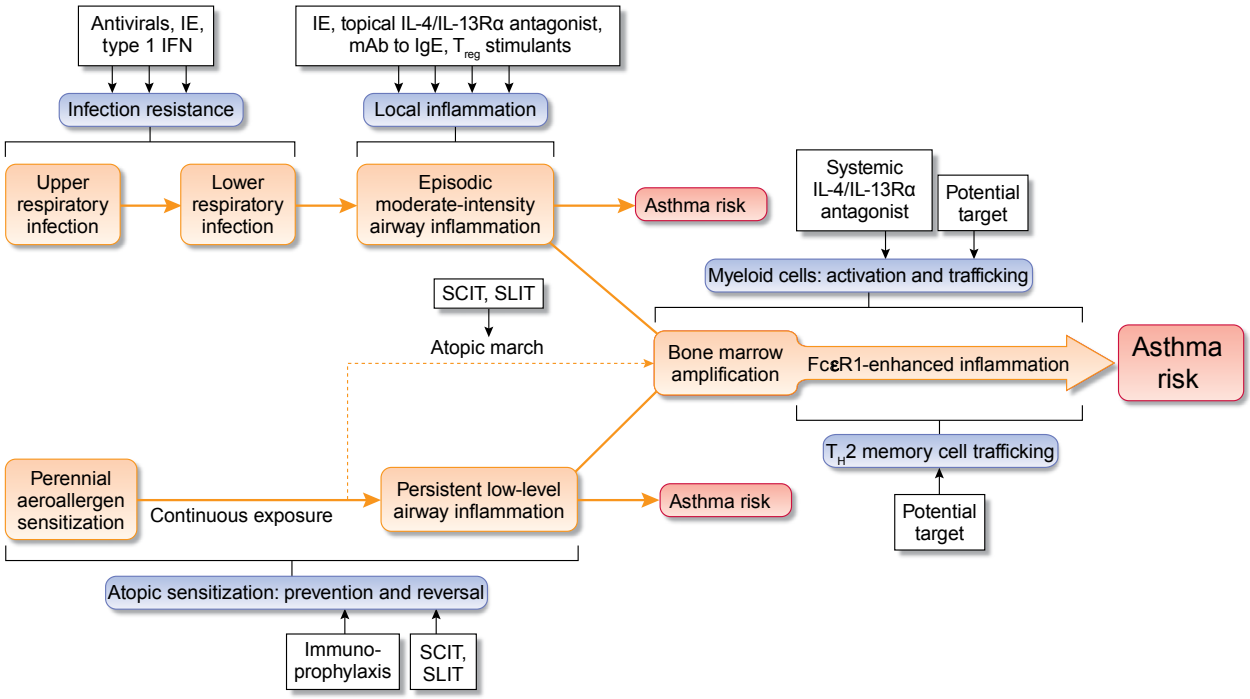

Figure 2 Strategies for Asthma Treatment and Prevention. *(Reprinted by permission from Macmillan Publishers Ltd: Nat Med, Holt PG, Sly PD, Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment,18, 726-735, copyright 2012.)*

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7 GENETICS OF ASTHMA

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KEY MESSAGES

- A precise definition of the clinical phenotype and biological endotype is required as a base for genetic investigations
- Asthma is a polygenetic disease with many genes involved in different biological mechanisms
- Identifying genes responsible for the individual differences in response to asthma drugs is essential for improving treatment outcomes
- Gene-gene interactions: different genes interact with each other in the pathogenesis of asthma. While the effect of one single polymorphism may be modest, the combined effect of different genes may be substantial
- Gene-environment interactions: genes interact with environmental exposures in determining the risk for asthma
- Epigenetic mechanisms are likely to play a role in the development of asthma and may be activated by environmental exposure

HERITABILITY OF ASTHMA

Children of asthmatic mothers have an odds ratio (OR) of approximately 3 to suffer themselves from asthma. The fathers' influence is slightly smaller, but still sizeable (OR about 2.5), according to a meta-analysis aggregating data from 33 studies. For adult-onset asthma less data are available, but the results point towards the same direction. Thus, hereditary factors clearly do play a role in the development of asthma.

During the last one or two decades asthma research has identified an impressive number of the parts of the puzzle: many genes, gene-gene interactions, gene-environment interactions, epigenetic modifications. The next challenge is to assemble the puzzle in order to see the bigger picture.

GENES ASSOCIATED WITH ASTHMA

In the early days of asthma genetics the hope was to find one single gene explaining asthma. Meanwhile, using candidate-gene approaches and linkage studies followed by positional cloning many genes have been linked to asthma; in 2008 over 30 candidate genes have been listed. During the last decade, using whole genome sequencing many more genes have been added to the list which keeps growing.

Asthma is a complex disease with several clinical phenotypes and different endotypes, as defined by various biological mechanisms, which, in turn, involve different genes. For example STAT6, a gene encoding a transcription factor involved in Th2 cell differentiation has been described to be associated with total serum IgE levels. Atopy is a component of asthma, however, it is neither required nor sufficient to explain asthma; thus, different variants of the STAT6 gene will only explain a part of the genetic basis of asthma. Polymorphisms of the ADAM33 gene (A Disintegrin And Metalloproteinase gene family-member), to give another example, are associated with diminished lung function and relate to another part of the pathogenesis of asthma.

Genes found to be associated with asthma can be grouped according to different criteria. March et al have proposed several functional categories (Table 1).

TABLE 1

Functional categories of genes associated with asthma		
Th2-mediated cell responses	GATA3 IL-4 STAT6 IL-13	TBX21 IL-4RA IL-12B FcεR1
Inflammation	IL-18 TNFα Leukotriene C4 synthase	IL-18R1 ALOX-5
Environmental sensing, innate immune receptors for microbes	CD14 TLR-4 TLR-10 HLA class II genes	TRL-2 TLR-6 NOD1/CARD4
Airway remodeling	ADAM33 DPP10	COL6A5 GPRA
Bronchoconstriction	CHRNA3/5 NOS1	PDE4D
Epithelial barrier dysfunction	Filaggrin (FLG) CC16 Chemokines CCL-5, 11, 24, 26	DEFB1

ASTHMA PHARMACOGENETICS

Of note in asthma genetics, research has also identified genes responsible for individual differences in response to treatment. Polymorphisms in the β2-adrenoreceptor encoding gene have been implicated in the variable response to treatment with β2-adrenoreceptor agonists. Other genes such as CRHR1 (corticotrophin-releasing hormone receptor 1) or GLCCI1 (glucocorticoid-induced transcript 1 gene) have been suggested to modify responses to corticosteroids. Such observations may pave the way to personalized treatment of asthma, but remain to be confirmed.

GENE-GENE INTERACTIONS

In a given patient not only one gene will determine whether or not the patient will suffer from asthma. Rather, variants of different genes will interact, enhancing or attenuating each other's effect on the disease development. As an example, for the participants in a large German birth cohort study the effect of polymorphisms of IL-4, IL-13, IL-4RA and STAT 6 each had a modest effect on the children's risk to suffer from asthma. However, when combined, the asthma risk increased 16.8 fold. This example illustrates the effect of the interaction of genes involved in one aspect of asthma pathogenesis, such as regulation of Th2-mediated cell responses. There are, however, many more biological processes involved in the development of asthma, such as inflammatory responses or epithelial barrier function, and variants in each of the genes involved in these processes will likely interact with other genes leading to or protecting from disease.

GENE-ENVIRONMENT INTERACTIONS

For some asthma risk or protective genes, conflicting results have been described in different studies. One explanation is that the effect of a genetic variant may depend on environmental exposures and vice versa. Well studied examples for this are effects of polymorphisms in the endotoxin receptor CD14 or in the TLR2 genes that depend on the microbial load in the environment. When assessing the effect of a gene on the development of asthma one thus always has to consider potentially interacting environmental exposures.

EPIGENETICS

The effect of environmental exposures has been shown to have long-lasting effects on immune responses related to allergic disease, and even prenatal exposures have the potential to modify the development of atopic diseases during childhood. Recent data suggest that epigenetic mechanisms such as modifications in methylation of different genes might explain such observations.

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8 PHARMACOGENETICS OF ASTHMA

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KEY MESSAGES

- Pharmacogenetics is the study of how heredity influences medication response
- There are three major medication classes used in asthma treatment - short acting beta-agonists, inhaled corticosteroids, and leukotriene modifiers
- As many as one-half of all patients do not respond to one or more of the classes of asthma medications, supporting a role for pharmacogenetics
- Familial studies have demonstrated a genetic component to corticosteroid and beta-agonist medication response
- Pharmacogenetic studies have identified genetic variants associated with response to each asthma medication class
- The future of asthma pharmacogenetics lies in personalized therapy for a given patient

Pharmacogenetics is the study of the role of genetic determinants in the variable, inter-individual response to medications (Figure 1). Numerous examples of heritable differences in pharmacokinetics (drug distribution and metabolism) in individuals resulting in varied clinical response to medications have been described. Other mechanisms underlying the genetic response to drugs include alterations in pharmacodynamics (changes in the drug target), idiosyncratic associations (unintended side effects in predisposed individuals), and genetic predisposition to the disease in which the treatment is to be instituted. The two main categories of asthma drugs are commonly referred to as "reliever" drugs that target acute bronchoconstriction and "controller" drugs that reduce the severity of airway inflammation and frequency of obstruction. The main reliever drugs are rapid-acting β_2-agonists (e.g., albuterol, metaproterenol, pirbuterol, levalbuterol) that are also referred to as bronchodilators, since they relax the bronchial smooth muscle by activating β_2-adrenergic receptors. This is the treatment of choice for mild intermittent asthma. For mild persistent, moderate, and severe asthma, reliever treatment is usually combined with controller treatment, such as inhaled corticosteroids (ICS) and the leukotriene modifiers. ICS (e.g., budesonide, beclomethasone, flunisolide, and fluticasone) and leukotriene modifiers (e.g. montelukast and zileuton) target the inflammatory micro-environment of the airway to reduce airway obstruction and hyper-responsiveness.

It has been estimated that as many as one-half of asthmatic patients do not respond to treatment with β_2-agonists, leukotriene antagonists, or inhaled corticosteroids (Figure 2), suggesting a potential role for pharmacogenetics in defining treatment response. Family and twin studies have demonstrated that endogenous levels and exogenous administration of glucocorticoids, as well as bronchodilator response are heritable and hence genetic in origin. Pharmacogenetics began by looking at candidate pathway genes and drug treatment response. Prior to 2004, genetic variants in five genes had been associated with altered therapeutic response to four classes of asthma drugs: the β_2-adrenergic receptor (ADRB2) for the beta

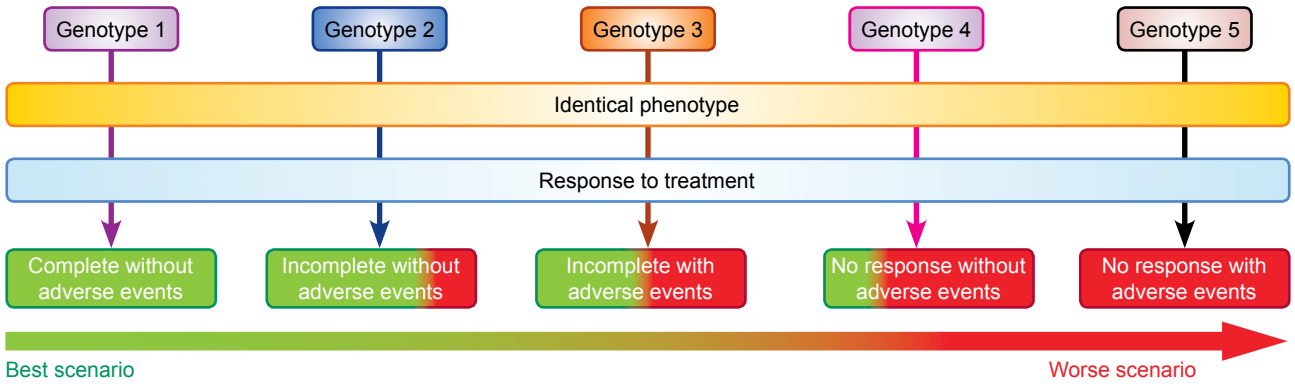

Figure 1 Pharmacogenetics is the study of genetic influences on the response to medications. The overarching goal of pharmacogenetics is the personalized prediction of who will respond to medications in a safe and effective fashion.

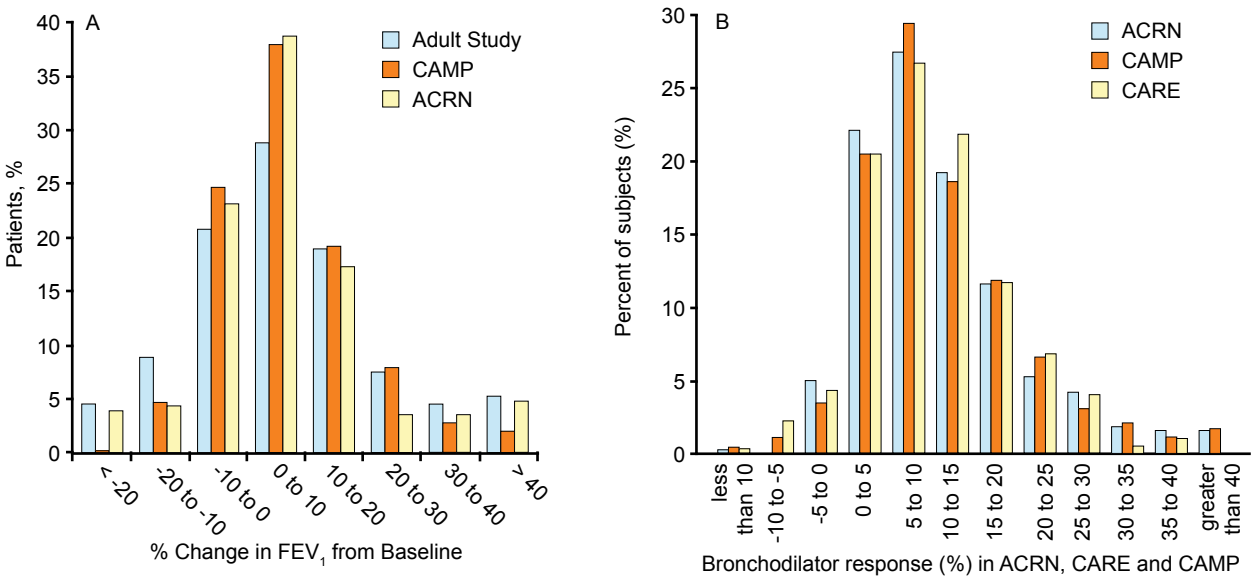

Figure 2 Population response to inhaled corticosteroids (A) and short acting beta-agonists (B). For both medications, there is wide inter-individual variability in response that is consistent across multiple populations; both good and poor responders can be readilty identified. *(A reproduced from Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet 2004;13:1353-1359 with permission from Oxford University Press; B reprinted by permission from Macmillan Publishers Ltd: Pharmacogenomics Journal, Tse SM, Tantisira K, Weiss ST. The pharmacogenetics and pharmacogenomics of asthma therapy. Pharmacogenomics J 2011;11:383-392, copyright 2011.)*

agonist pathway, 5-lipoxygenase (ALOX5) and leukotriene C4 synthase (LTC4S) for the leukotriene pathway, corticotropin releasing factor receptor type 1 (CRHR1) for the steroid pathway, and cytochrome p450 1A2 (CYP1A2) for the methylxanthine (e.g. theophylline, which is no longer first line therapy for asthma) pathway. Since 2004, additional novel replicated candidate genes for various steroid response phenotypes (STIP1, TBX21, DUSP1, and FCER2) (Figure 3) and beta-agonist response phenotypes (AC9, CRHR2, ARG1, and GPCR5) have been published. Most recently, investigators have used genome-wide association studies (GWAS) where drug response phenotypes are related to single nucleotide polymorphisms across the genome in a genomic approach to Identify novel genes. Tantisira and coworkers utilized this approach to identify a functional polymorphism in the promotor region of GLCCI1 as a predictor of change in lung function in response to inhaled corticosteroid and were able to replicate this finding in several other asthma populations (Figure 4). Two other asthma

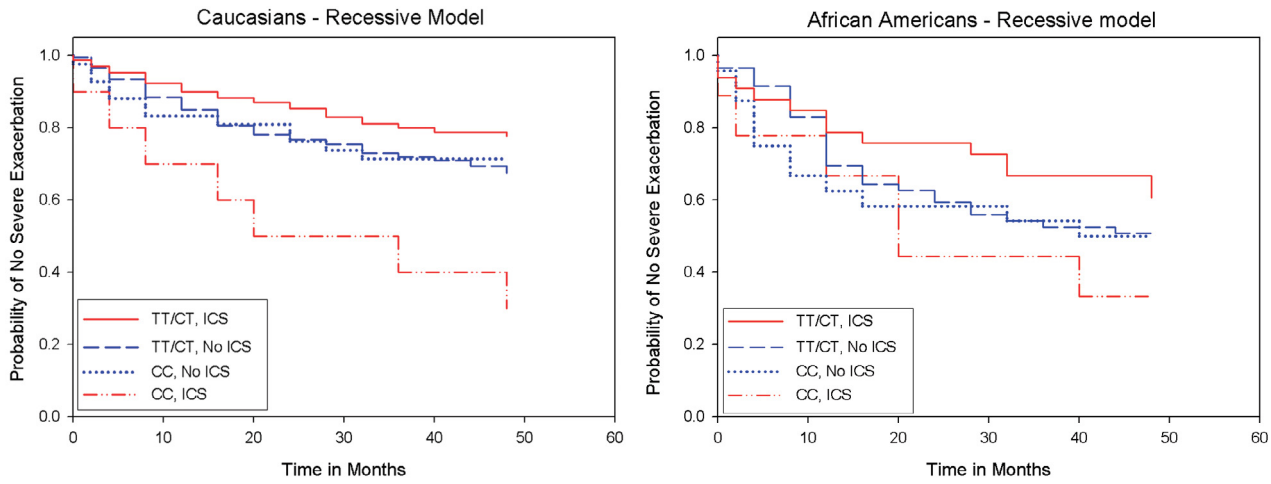

Figure 3 Association of a genetic variant in the FCεR2 (low affinity IgE gene) with risk of subsequent asthma exacerbations (emergency room visits or hospitalizations) while on inhaled corticosteroids, which generally are protective against exacerbations. The variant has no effect on those not taking the medication. However, in both Caucasians and African Americans, subjects with two copies of the genetic variant in their DNA were 3-4 times as likely to have an exacerbation compared to those with zero to one copy of the variant. *(Reprinted from J Allergy Clin Immunol, 120/6, Tantisira KG, Silverman ES, Mariani TJ, et al, FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma, 1285-1291, Copyright 2007, with permission from Elsevier.)*

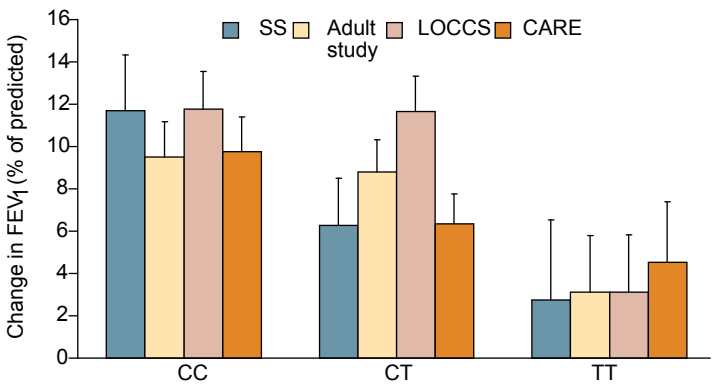

Figure 4 Association of a variant (rs37973, where the C allele is common and the T allele is rarer) in the GLCCI1 gene with reduced lung function response to inhaled corticosteroids in four independent populations. The variant was identified through genome-wide association testing. *(From N Engl J Med, Tantisira KG, Lasky-Su J, Harada M, et al, Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma, 365, 1173-83, Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)*

pharmacogenetic GWAS genes have been reported: SPATS2L for acute short acting beta-agonist response and the T gene for inhaled corticosteroid response. Recent trends in the field have been to aid in the identification of individual genes by GWAS to identifying regulatory variants via the expression quantitative trait locus approach (eQTLs) using human immortalized cell lines treated with the drug of interest, as well as to move away from individual genes toward a systems approach of identifying biologically interacting genes through the aid of computational networks aimed at predicting drug treatment response. The overarching goal of these studies is to eventually identify a set of genetic variants that together will allow the personalized prescription of asthma therapies that will avoid side effects and optimize therapeutic response.

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9 THE PATHOGENESIS OF ASTHMA

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KEY MESSAGES

- Asthma is a heterogeneous disease consisting of multiple different pathogenetic subgroups with different cellular and molecular characteristics
- Th2-like immune response and peripheral blood and lung eosinophilia represent a consistent and dominant subgroup
- Molecular and cellular mechanisms of non-Th2 associated asthma are poorly defined
- Allergy and IgE play a role in the pathogenesis of a majority of pediatric and approximately half of adult patients
- Remodeling characterized by smooth muscle hypertrophy, goblet cell hyperplasia, subepithelial basement membrane thickening and angiogenesis is a key pathogenetic feature
- Recent studies have demonstrated an essential role of permissive bronchial epithelial tight junctions and leaky epithelium
- Small molecule mediators such as leukotrienes, adenosine, ATP that affect cellular chemotaxis, smooth muscle relaxation and tissue inflammation play roles

Allergic inflammation can lead to several diseases, including asthma, allergic rhinoconjunctivitis, anaphylaxis, urticaria and atopic dermatitis, which are all complex disorders with several disease variants caused by different underlying cellular and molecular mechanisms. Our understanding of asthma mechanisms are emerging from direct analyses of human biopsies, bronchoalveolar lavage, sputum, peripheral blood cells and serum, clinical response to drugs and biologicals that target a specific molecular mechanism. The mouse model of allergic lung inflammation has similarities with human Th2 and eosinophilic inflammation, but drugs which suppress allergic inflammation in this model have failed in clinical trials in humans. Asthmatic airway inflammation through the infiltration of cells and release of potent inflammatory mediators and remodeling of the airway wall represent the essentials of the disease pathogenesis. Asthmatic bronchial wall shows altered wound repair response with secretion of growth factors that induce remodeling during chronic inflammation. Remodeling involves almost all elements of the airway wall and occurs throughout the bronchial tree. It is characterized by smooth muscle hypertrophy, goblet cell hyperplasia, subepithelial basement membrane thickening and angiogenesis. Airway remodeling increases the thickness of the airway wall and leads to irreversible airflow obstruction and airway hyperresponsiveness, and is associated with increased disease severity.

The recently identified innate type-2 immune effector leukocyte, the nuocyte, provides a missing link between the innate and adaptive Th2 response for the recruitment of T cells and eosinophils. During initial allergen sensitization of the airways, Th2 lymphocyte differentiation from naive T cells takes place and requires IL-4 to activate the transcription factors signal transducer and activator of transcription 6 (STAT6) and GATA-binding protein 3 (GATA3). Induced sputum from asthmatic airways and peripheral blood contain increased numbers of both plasmo-

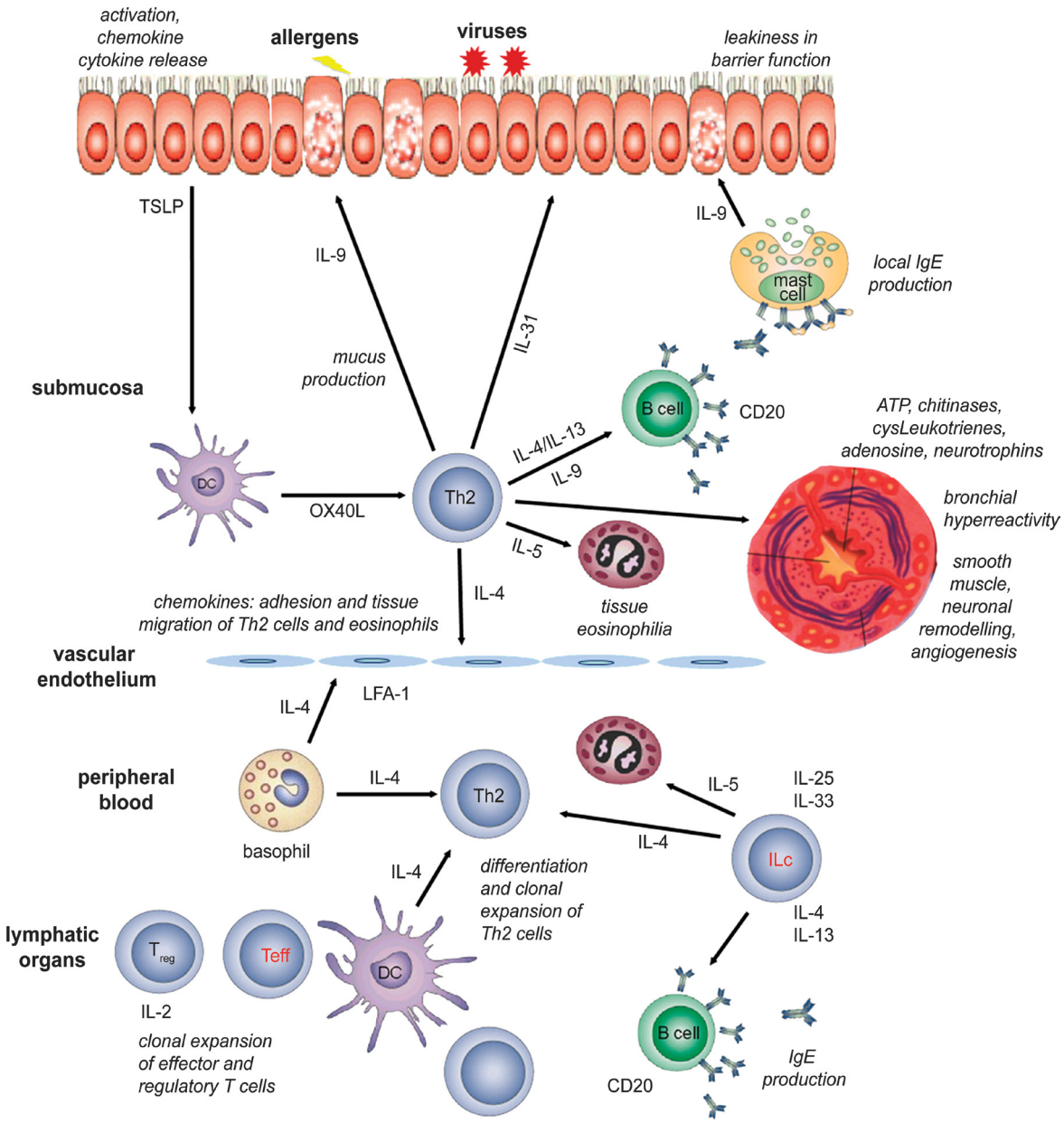

Figure 1 Pathogenic mechanisms in asthma. Epithelial leakiness and activation and their proinflammatory cytokines and chemokine production that induces inflammation and contributes to Th2 response: TNF-α, IL-13, TSLP, IL-31, IL-33. Highly activated epithelial cells undergo apoptosis and shedding takes place. Cell migration and chemokines are essential players for the recruitment of inflammatory cells, which is followed by survival and reactivation of migrating inflammatory cells and their interaction with resident tissue cells and other inflammatory cells. Innate lymphoid cells (ILC2) play a role on T and B cell activation and recruitment and are early providers of Th2 cytokines and T cell recruitment. Th2 type of an immune environment is characterized by IL-4, IL-5, IL-9, IL-13, IL-25, IL-33 production coming from Th2 cells and tissue cells. Eosinophilia is induced by IL-5, IL-25, IL-33. Local and systemic IgE production takes place in allergic patients with the involvement of IL-4, IL-13. Other effector T cell subsets, such as Th9, Th17 and Th22 cells also play partial roles in inflammation, mucus production, tissue healing. Smooth muscle, myofibroblasts activation and bronchial hyperreactivity is related to IL-4, IL-9, IL-13, IL-25, IL-33. Several chemokines, and arachidonic acid pathway molecules and other small molecules play roles in the inflammatory cell recruitment and further augmentation of the inflammatory cascades. *(Modified from Papadopoulos NG, Agache I, Bavbek S, et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. Clin Transl Allergy. 2012;2:21)*

cytoid and myeloid dendritic cells, which further increase in number upon allergen challenge. Myeloid dendritic cells represent an inflammatory subset of dendritic cells in the asthmatic lungs, whereas several studies have shown a role of plasmocytoid dendritic cells targeted more towards the humoral immune response, suppression of lung inflammation as well as allergen tolerance. Th2 cytokines such as IL-4, IL-13 play a role in IgE synthesis and IL-5, IL-25 and IL-33 induce airway eosinophilia in animal models of asthma. IL-9 expression is also increased markedly in response to allergen challenge. In studies using IL-9 transgenic and knockout mice, direct IL-9 instillation into the lungs and blocking monoclonal antibodies, it has been shown that IL-9 drives mucus production, both by a direct effect on airway epithelia and also by interacting with IL-13. Th17 cells are a distinct T cell lineage suggested to be involved in asthma and corticosteroid insensitivity. In humans, a subset of Th2 and Th17 memory and effector cells, producing Th17 and Th2 cytokines at the same time may be more important compared to single Th2 cells. The role of regulatory T cells in suppression of allergic inflammation has been shown in allergen-immunotherapy and high dose allergen exposure models such as cat owners with asthma. Recently, an IL-10 secreting regulatory B cell subset joined the family of regulatory cells that play a role in allergen tolerance and IgG4 production.

Eosinophilic asthma is a distinct phenotype of asthma that is associated pathologically with thickening of the basement membrane and pharmacologically with corticosteroid responsiveness. In contrast, neutrophilic asthma includes patients with severe disease, and appears to be relatively corticosteroid resistant. Neutrophils accumulate in the airway in more severe forms of asthma, and neutrophil numbers are associated with chronic airway narrowing. In addition, neutrophils are prominent during acute severe asthma exacerbations, suggesting roles for both the initiation and resolution of attacks. Current knowledge on the mechanisms of neutrophilia in asthma, and clinical consequences of decreasing airway neutrophilia is very limited.

The asthmatic epithelium is intrinsically defective in its physical barrier function with incomplete formation of tight junctions, thereby facilitating penetration of inhaled allergens into the airway tissue. Related to this defect, a proportion of the asthma-related allergens have intrinsic biological properties that increase their capacity to penetrate the epithelial barrier and trigger an inflammatory signal in submucosal cells and tissues. Beyond proteolytic allergens, additional environmental stimuli such as respiratory viruses and air pollutants also disrupt tight junctions and impair barrier function in addition to activation of a whole inflammatory cascade leading to early development and exacerbations of asthma. TSLP, IL-33 and IL-25 are generated by the airway epithelium in response to activation of pattern recognition receptors such as Toll-like receptors or following cytotoxic epithelial injury. These three epithelial cytokines have the potential to bridge innate and adaptive immunity to sustain the Th2 response toward a more chronic state that is characteristic of asthma. Intensive research in the area is essential to fully uncover the molecular pathways of inflammation and link pathogenesis to clinical phenotypes to find better treatments.

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10 THE UNDERLYING MECHANISMS OF ASTHMA

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KEY MESSAGES

- Asthma is characterized by persistent chronic inflammation and remodeling of the airways
- Airway inflammation is initiated by a dysregulated immune response to inhaled allergens
- Several inflammatory effector cells contribute to development of asthma including mast cells, eosinophils, basophils, macrophages, T lymphocytes as well as airway epithelial cells and smooth muscle cells
- Mediators produced by inflammatory cells induce acute constriction of the bronchi, airway edema, increased mucus production as well as epithelial damage and smooth muscle proliferation
- Chronic inflammation and structural remodeling of the airways are responsible for progressive deterioration of lung function

Asthma is a chronic inflammatory disease of the airways that involves multiple pathophysiological mechanisms leading to recurrent attacks of bronchial narrowing and to structural alterations of the bronchi (Figure 1). In the majority of patients the primary cause of inflammation is sensitization to airborne allergens such as plant pollens, dust mites or pet danders. In genetically predisposed individuals, these allergens are taken up by dendritic cells in the airways, processed and presented to T lymphocytes. This triggers the immune response of the so-called Th2 type with production of specific cytokines such as IL-4, IL-5, IL-13 by T lymphocytes (Figure 2). Th2 type cytokines promote the formation of specific antibodies of the IgE class that are subsequently fixed on the surface of mast cells and basophils. Mast cells, which are very abundant in the airways, and basophils, which are recruited in the bronchial mucosa from the blood, are subjected to rapid and massive activation after inhaled allergens crosslink their surface IgE. Degranulation of mast cells and basophils results in the release of very potent mediators of bronchoconstriction such as histamine, cysteinyl leukotrienes, prostaglandins and platelet-activating factor (Figure 3). Within minutes after allergen inhalation these mediators induce a strong constriction of the airways, generate edema of the airway walls and enhance the production of mucus. In addition to these acute responses, cytokines produced by both Th2 lymphocytes and by mast cells and basophils induce the recruitment of eosinophils from the blood into the airways. Infiltration of eosinophils in the bronchial mucosa is a hallmark of allergic asthma and it persists even when symptoms of asthma are not present. While these are considered the early mechanisms of allergic asthma in the majority of asthmatics, some other mechanisms that promote airway inflammation in specific subsets of patients are also activated.

Viral or bacterial infections can contribute to the development of asthma by activating cells of the innate immunity such as macrophages or natural killer (NK) cells. Specific subtypes of T lymphocytes, namely Th1 and Th17 are increasingly recognized in chronic phase of asthma. Th17 cells are mainly involved in the defense against infectious agents but they are also acti-

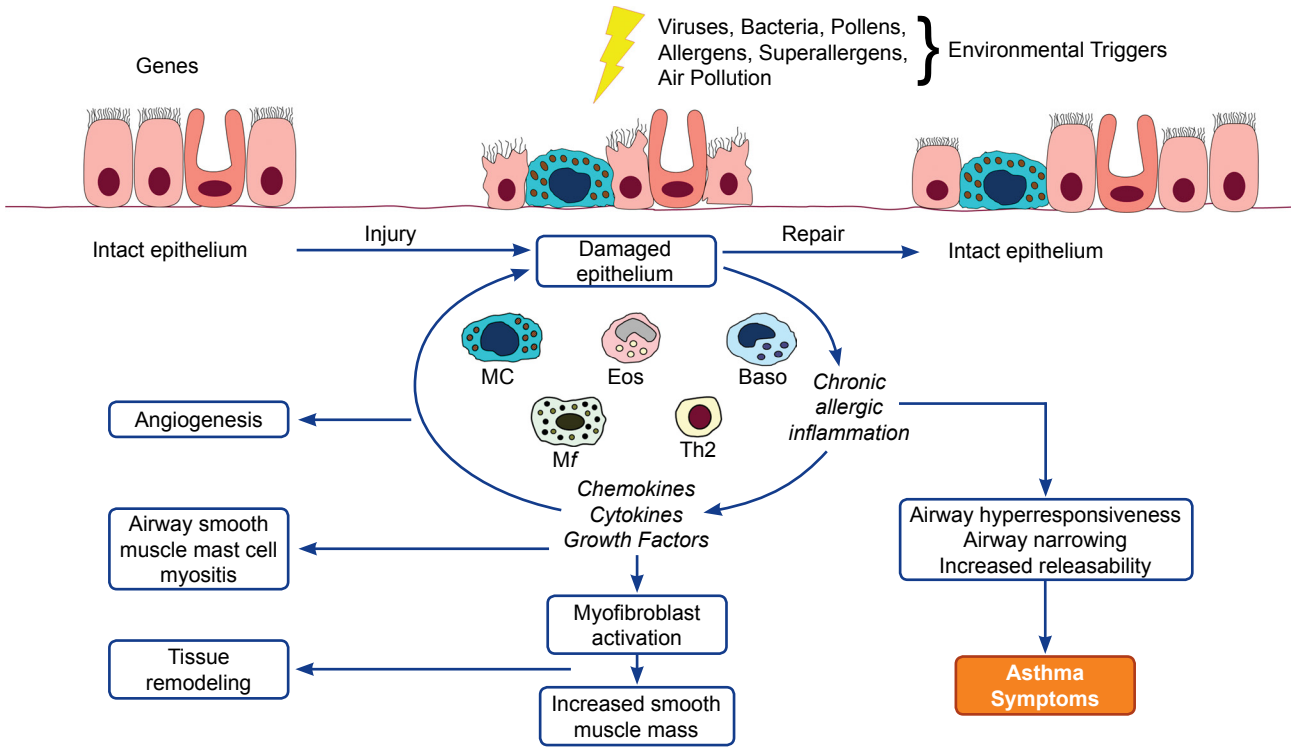

Figure 1 Pathogenic mechanisms of asthma. In genetically predisposed individuals environmental factors such as allergens, infections or irritants may induce epithelial damage that leads to a dysregulated immune response. Several cells including T lymphocytes (Th2 cells), mast cells (MC), eosinophils (Eos), basophils (Baso) and macrophages (Mf) are activated in the airways of asthmatics and secrete mediators responsible for persisting inflammation, bronchoconstriction and airway remodeling.

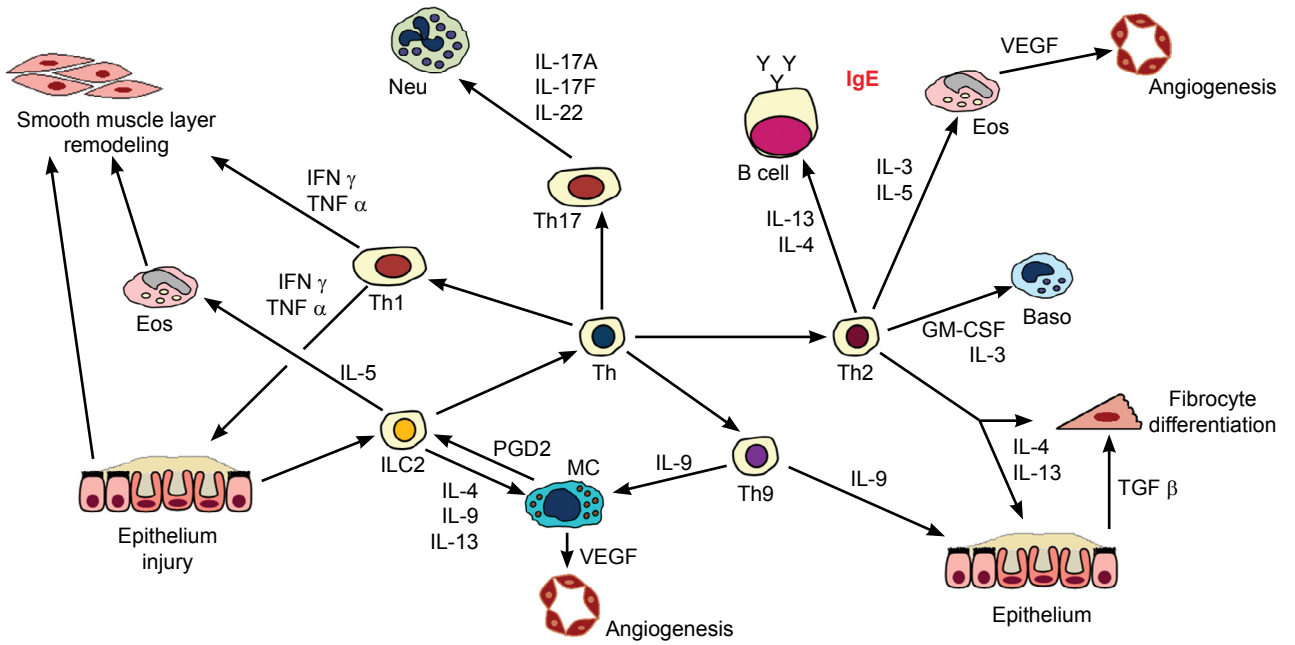

Figure 2 The complex network of immune response in asthma. T lymphocytes are the key players in asthmatic inflammation, orchestrating adaptive and innate immunity and triggering airway structural remodelling. ILC2: innate lymphoid cells type 2. *(Adapted from Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. J Allergy Clin Immunol 2011;128:451-462).*

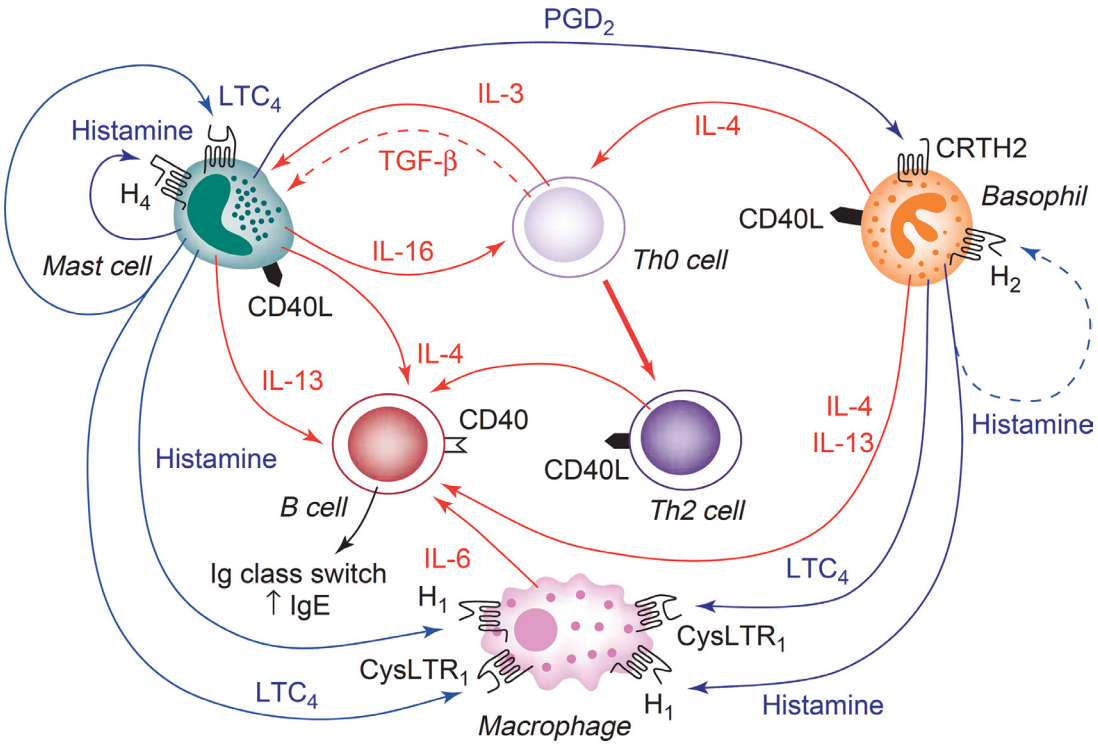

Figure 3 Central role of lung mast cells and basophils in bronchial asthma. *(Reprinted from Trends Immunol 26/1, Marone G, Triggiani M, de Paulis A, Mast cells and basophils: friends as well as foes in bronchial asthma?, 25-31, Copyright 2005, with permission from Elsevier.)*

vated in patients with asthma and produce specific cytokines that trigger the recruitment of neutrophils to the bronchial mucosa in severe forms of asthma.

In addition, the airway epithelium is not only important as a physical barrier, but can also respond to innate-type signals by releasing Th2-inducing cytokines, such as TSLP and potent pro-inflammatory cytokines such as TNFα. Chronic injury of the airway epithelium results in increased permeability of inhaled antigens, as well as induces reactivation of the epithelial–mesenchymal trophic unit (EMTU) formed by the epithelium and the underlying fibroblast sheath. The airway smooth muscle cells seem to be another important player by expressing numerous adhesion molecules, cytokine and chemokine receptors, as well as by releasing cytokines to the local environment.

Persistent inflammation in the airways and the ongoing structural remodeling of the airways is responsible for the bronchial hyperreactivity to both specific (allergen) and non-specific (irritants, histamine, metacholine) stimuli. The main features of remodeling in asthma are an increased thickness of the membrane below the surface epithelium of the bronchi, the growth in the size and number of mucous glands, an increase in the muscle layer of the bronchi and an abnormal formation of new blood vessels. All these changes determine further increase in the airway resistance and contribute to the worsening of lung function that can be observed in chronic asthma.

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11 PHENOTYPES & ENDOTYPES: EMERGING CONCEPTS ON ASTHMA HETEROGENEITY

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KEY MESSAGES

- Asthma is a heterogeneous "disease" consisting of multiple different subgroups
- A phenotype is identified by the integration of characteristics arising from the interaction of the patient's genes with the environment
- Molecular phenotypes incorporate pathobiologic characteristics and biomarkers
- An endotype can only be fully defined when inhibition of a specific molecular pathway leads to improvement in clinical outcomes
- Th2-like molecular phenotypes are beginning to be identified which encompass both consistent clinical characteristics, biomarkers and even specific molecular pathways
- Non-Th2 associated phenotypes of asthma remain more poorly defined

Asthma is defined as reversible airflow limitation (or bronchial hyperresponsiveness) associated with a spectrum of related clinical symptoms. However, it is increasingly recognized that the underlying pathobiologic pathways leading to this integration of clinical and physiologic changes are diverse. While this concept of asthma heterogeneity has been around for years, increases in pathobiologic (particularly genomic) samples, the use of unbiased statistical clustering approaches and the emergence of targeted molecular-based therapies have rapidly advanced the concept. Inherent in these approaches is the recognition that phenotypes of asthma exist. A phenotype is defined as the characteristics of a patient which result from the interaction of genetic background with environmental influences (Figure 1). Examples include early onset allergic asthma and obesity-related asthma. However, efforts are now being made to identify asthma endotypes. An "endotype" is generally defined as the integration of a specific identifiable underlying pathobiologic process, the inhibition of which contributes critically to elemental clinical characteristics. While no widely agreed criteria upon endotypes are yet described, progress has been made.

Phenotyping began to move closer to endotyping with the observation that only a portion of "clinical asthma" was associated with an underlying Th2-like immuno-inflammatory process. This "Th2-like" (eosinophilic) molecular phenotype is present in about 50% of adult asthma, from mild to severe. This Th2 "molecular phenotype" encompasses some but not all patients with traditional "allergic asthma", as well as some patients with exercise-induced asthma. Importantly, it also includes a group with adult onset, highly eosinophilic asthma. Patients with a Th2-like molecular phenotype have a range of corticosteroid (CS) sensitivity, confirming the overall heterogeneity of even this molecularly defined phenotype. Biomarkers, including blood eosinophils, periostin and exhaled nitric oxide (NO) can be used to identify this Th2-like phenotype. In fact, using these Th2-like biomarkers improves the ability to identify responders to Th2 targeted therapies and improve outcomes. However, responses still vary, even in Th2-like patients. Thus, it is likely that some Th2-like

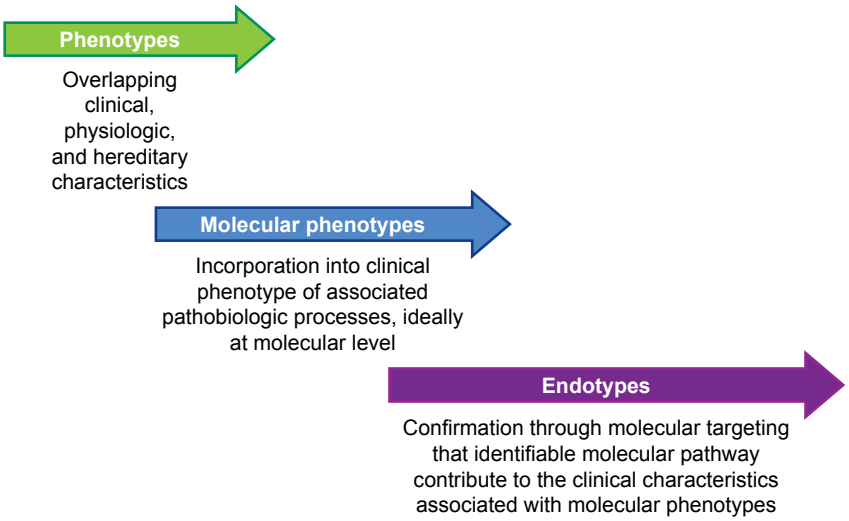

Figure 1 The progression of phenotypes to endotypes.

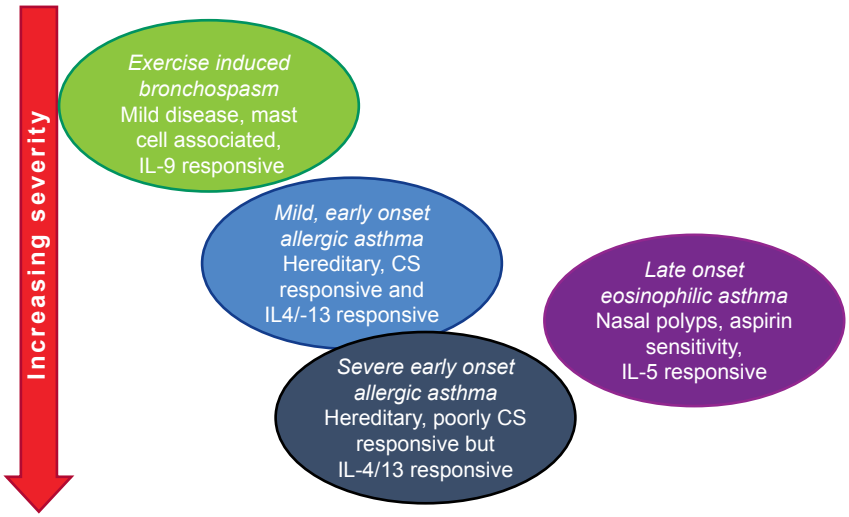

Figure 2 Potential Th2-associated endotypes.

molecular phenotypes (eventually endotypes) will respond better to interleukin-4/-13 directed therapy while another group will respond better to an interleukin-5 directed therapy (Figure 2). Studies that link these molecular targeted therapies to improvements in specific characteristics, pathobiology and biomarkers will ultimately identify asthma endotypes.

The other broad asthma phenotype includes patients who exhibit no evidence of Th2 inflammation. This "non-Th2" associated asthma generally is defined by the absence of biomarkers associated with Th2-like asthma and consists of a poorly defined mix of obesity associated asthma, neutrophilic asthma, paucigranulocytic asthma and smoking associated asthma, all of whom are generally poorly CS responsive. These patients may be less severe in general, with clinical trials suggesting Th2-like asthma is more likely to exacerbate. While there are few definitive studies of what is driving non-Th2 asthma, it is likely that neurogenic, oxidative stress and alternative innate or adaptive immune pathways are, playing a role. Interestingly recent studies strongly support the presence of a later onset, obese asthma phenotype, which lacks any Th2-like immune processes and which may be identified through alterations in the natural inhibitor of inducible NO synthase, asymmetric dimethylarginine in blood. Studies are ongoing to determine whether interventions in this pathway will improve clinical asthma outcomes. Future studies, which integrate clinical and molecular data, especially when done with a targeted intervention, in large numbers of patients will greatly refine our ability to define phenotypes and even endotypes of asthma.

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12 ENVIRONMENTAL RISK FACTORS FOR ASTHMA

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KEY MESSAGES

- Exposure to indoor and outdoor allergens contributes to asthma development, aggravations and exacerbations
- The irritant effects of environmental tobacco smoke and other indoor and outdoor air pollutants contribute significantly to asthma morbidity
- Climate change and extreme weather conditions impact on asthma directly and indirectly

ENVIRONMENTAL FACTORS AS TRIGGERS OF ASTHMA SYMPTOMS

Typical indoor air pollutants that can trigger asthma symptoms include biologic aeroallergens (house dust mites, cockroaches, animal dander, molds, etc.), environmental tobacco smoke (ETS), irritant chemicals and fumes and products from combustion devices (Figure 1), with severity of symptoms varying with the level of exposure. So far controlled data are still lacking on the effect of reduction of allergen exposure (house-dust mites) in the improvement of pulmonary function tests (PFTs) and reduction in airway inflammation and hyper-responsiveness. Successful allergen avoidance necessitates a comprehensive approach including education, regular cleaning and use of physical barriers, which poses a major problem for disadvantaged social classes.

Typical outdoor pollutants that can trigger and exacerbate asthma include pollen, mold spores and air pollutants (Figure 1). In the last decades, high levels of outdoor chemical air pollution have been associated with short-term increases in asthma morbidity and mortality. Other hazardous air pollutants, as well as industrial releases of volatile organic compounds metals, isocyanates, have been shown to cause and trigger asthma. Of note, most studies provide evidence that other precipitating factors, such as viruses, can increase the risk of asthma exacerbations via interactions with allergens. Overall, avoiding environmental allergens and irritants should be one of the primary goals of good asthma management. In addition, clinicians should be aware of the common air pollutants that may affect asthmatic patients.

Extreme weather conditions and changing climate may also be an asthma trigger in certain people. Extreme cold, hot, humidity, barometric pressure, thunderstorm or strong winds may trigger asthma symptoms in some people (Figure 1 and 2). Moreover, climate factors influence wind patterns, amount and intensity of precipitation and temperature and, thus, severity and frequency of air pollution episodes. Lastly, living in areas where forest fires are common during the summer months or where temperature inversion happens during the winter months may also trigger asthma symptoms as a consequence of poor air quality.

ENVIRONMENTAL FACTORS AND ASTHMA ONSET

Sensitization to indoor allergens and outdoor molds and pollen is a risk factor for the development of allergic asthma. Urban air pollution has been implicated as one of the factors responsible for the dramatic increase in asthma incidence in recent years. Regarding the onset of asthma, the evidence for causali-

Figure 1 Environmental triggers for asthma. *(From http://www.astmalergic.ro/images/triggers.jpg, accessed May 20, 2013.)*

ty has grown significantly, but it remains difficult to separate allergic from non-allergic asthma. Studies showed that children living near heavy traffick have significantly higher rates of wheezing and diagnosed asthma. Allergic individuals are at higher risk of the effects of the chemicals. The effect seems to be modified by co-exposures of allergens as well as genetic variants, particularly those moderating response to oxidative stress.

Climate change might affect asthma prevalence through an effect on aeroallergens and chemical air pollutants. Any longer-term change affects pollen and spore production and other phenological events and, at the same time, impacts various aerobiological processes (emission, dispersion and/or transport and deposition of aeroallergens). Moreover, climate change can affect anthropogenic emissions (e.g., increase in energy demand for

Figure 2 Thunderstorm (left) and microscope image of grass pollens (right). Moisture in the air in the initial phase of a thunderstorm causes the airborne pollen granules to rupture in to particles small enough to be breathed deep in to the smaller airways within the lungs. Here, they can irritate the lining to cause inflammation and mucus production which obstructs airflow leading to asthma attacks. *(Grass pollen reproduced with permission of NDT-Educational from http://www.ndt-educational.org/images/artefatti28.jpg, accessed May 20, 2013.)*

space cooling, heating) and induces an increase in secondary pollutants (i.e., ozone and particulate matter), thus increasing the risk of asthma development.

UNMET NEEDS

Except for aeroallergens, clearly involved in allergic asthma, the distinction between allergic and non-allergic asthma phenotypes has rarely been made when investigating environmental risk factors for asthma. This separation can be of importance for asthma management, treatment and prevention.

Educational programs for health care professionals and patients often fail to fully incorporate environmental and exposure history. For example, although over half of practicing pediatricians surveyed in the US see patients with health issues related to environmental exposures, fewer than 1/5 are trained in taking an environmental history.

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13 LIFE STYLE RISK AND PROTECTIVE FACTORS FOR ASTHMA

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KEY MESSAGES

- The occurrence of asthma is strongly influenced by environmental factors
- Exposure early in life to microbes from the environment can explain some of the protective effect on asthma and atopy
- Other significant risk factors for asthma are active and passive smoking, pollution, indoor moulds and dampness, weight gain or obesity
- Nutrition may also be a source of risk or protective factors

The occurrence of asthma is strongly influenced by environmental factors. It has been shown that populations with very similar genetic background differ in the prevalence of asthma depending on the area of residence. For example, childhood asthma is almost non-existing in rural areas in China, whereas in regions approximately 200 km away, in the capital of Bejing, the prevalence rises up to 5 percent. Such strong protection is also seen in Karelia which has been divided by the Iron Curtain after World War II into a Finnish and a Russian part. On the Russian side life style has been maintained as in former times, whereas people on the Finnish side have adopted a more westernized lifestyle. The prevalence of asthma in Russian Karelia is very low. In comparison asthma rates in Finnish Karelia are about 5.5 times higher (Figure 1). In Alpine regions protection is seen within rural areas, i.e. among children being raised on traditional dairy farms (Figure 2) as compared to their peers living in the same village but not living on a farm. Both in the Karelian studies and the farm studies microbial exposures in the environment have been found to explain some of this protective effect on asthma and atopy. The protection is not mediated by just one particularly potent protective microbe, but by a cocktail of microbial exposures, including exposures to certain Gram negative and Gram positive bacteria and fungi (Figure 3). It seems important that children get exposed early in life as this is the time when immune responses and lung tissues mature. The effect of exposures to traditional farms and Karelian environments is sustained until adulthood.

In turn, the use of antibiotics and antipyretics is still being debated. Some associations may be attributable to the indication. In other words asthmatics are more likely to use antibiotics and antipyretics because of their disease rather than these drugs causing the onset of disease. There is no indication that vaccinations may increase the risk for asthma.

There are however other significant risk factors for asthma. The most important is active smoking, particularly by the mother exposing her unborn child in utero or of adolescents and young adults. Not only does the risk of asthma increase, but also remission which occurs in a significant proportion of adolescent asthmatics is jeopardized by active smoking. Passive smoking also increases the asthma risk. The introduction of the smoking ban in Scotland has resulted in significantly reduced rates of asthma admissions to hospitals supporting such public health measures (Figure 4). Pollution by car and truck traffic exhausts has also been implicated as risk factor, particular-

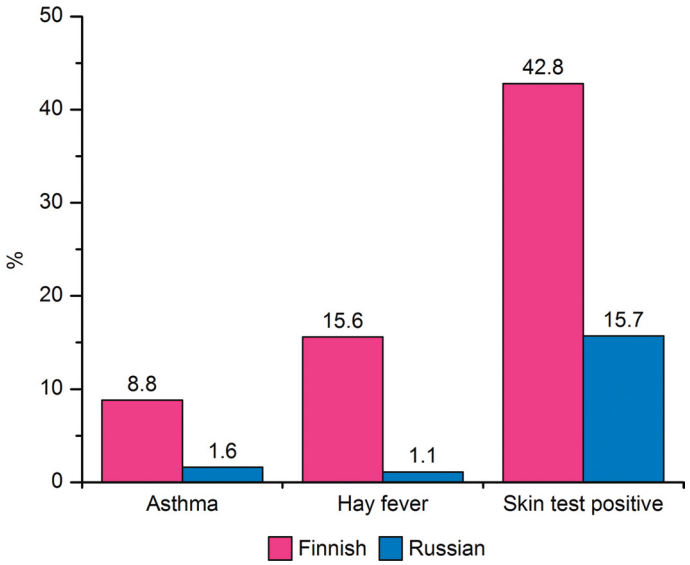

Figure 1 Prevalence of asthma and atopy in Karelian children. *(Data from von Hertzen L, Mäkelä MJ, Petäys T, et al. Growing disparities in atopy between the Finns and the Russians: a comparison of 2 generations. J Allergy Clin Immunol. 2006;117:151-157.)*

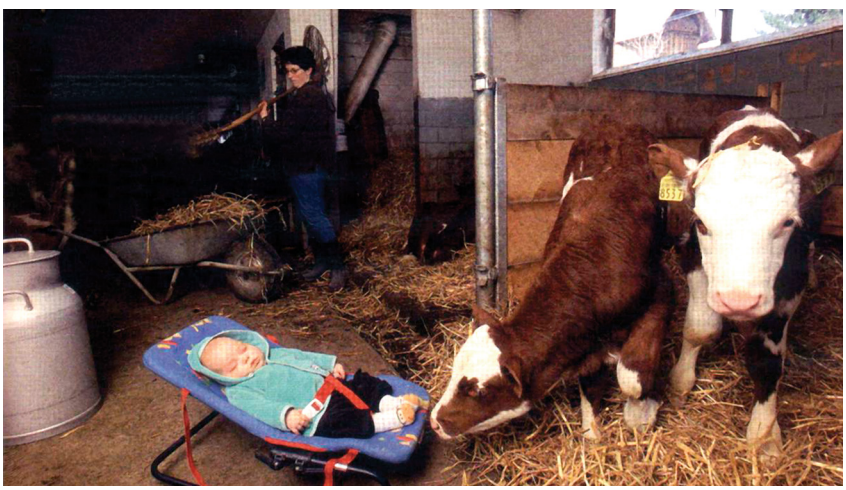

Figure 2 Protective environment in a traditional farm.

ly for highly exposed children, i.e. those living 100 – 500 m away from busy motorways. Indoor factors also play a role. Most consistently indoor moulds and dampness have been shown to increase the risk for asthma. It remains unknown which factors account for the risk associated with such moisture damage.

Lifestyle factors are furthermore important. Weight gain and obesity have been related to asthma like symptoms and weight loss has been shown to improve symptoms among asthmatic patients. Therefore, nutrition may also be a source of risk factors, but data collected so far have not identified certain foods as particularly asthmagenic.

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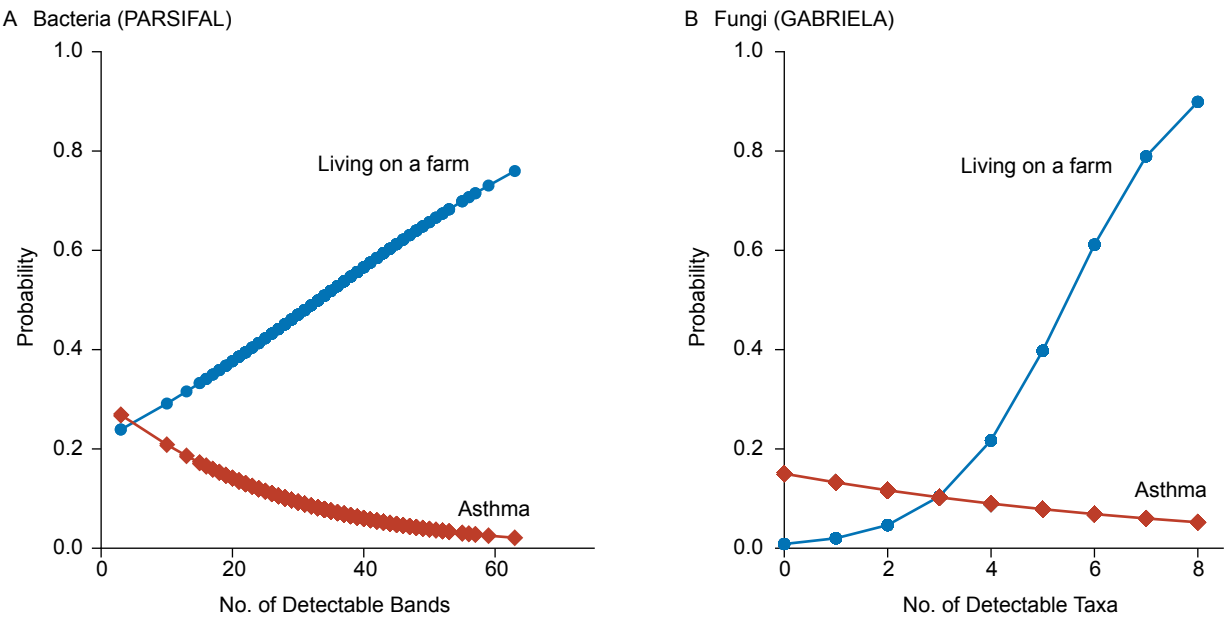

Figure 3 The diversity of microbial exposure is inversely related to asthma. *(From N Engl J Med, Ege MJ, Mayer M, Normand, et al. Exposure to environmental microorganisms and childhood asthma, 364, 701-709 Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)*

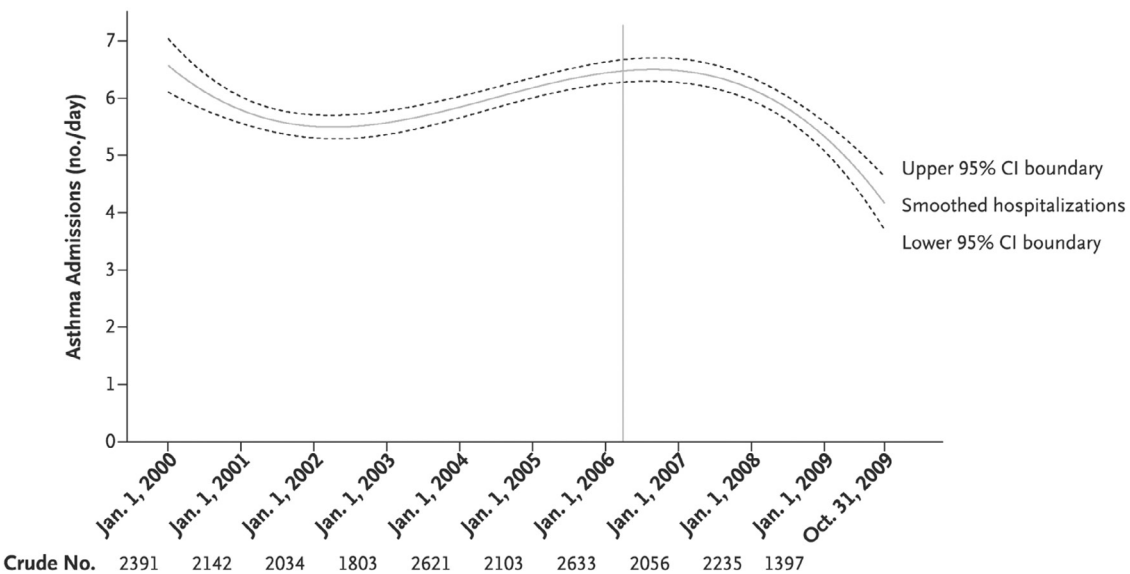

Figure 4 Decreased hospital admission for asthma after tobacco smoke ban in Scotland. *(From N Engl J Med, Mackay D, Haw S, Ayres JG, et al. Smoke-free legislation and hospitalizations for childhood asthma, 363, 1139-1145 Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)*

14 INFECTIONS AND ASTHMA

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Epidemiological, clinical, and mechanistic research demonstrates that viral, bacterial, and fungal infections, and commensal bacteria (microbiome), are strongly associated with asthma development and disease activity.

KEY MESSAGES

- Viral bronchiolitis in early childhood is associated with an increased risk of asthma development.
- Respiratory viruses, notably rhinoviruses, are the most important triggers of asthma exacerbations in both children and adults.
- Pathogenic bacteria, including atypical bacteria, and the composition of airway commensals (microbiome) can influence disease activity in asthma.
- Asthma increases the severity of respiratory viral infections and the risk of invasive pneumococcal infection.
- Fungal infection of the airways can provide high loads of allergens aggravating allergic asthma.
- Some infections, including helminth parasites, may protect against asthma.
- Understanding the mechanisms by which microbial components promote or inhibit asthma might provide the basis for prevention and curative treatment of asthma

ASTHMA DEVELOPMENT

Viral bronchiolitis in young children is associated with an increased risk of recurrent wheeze and childhood asthma. Respiratory syncytial virus (RSV) accounts for about 70% of bronchiolitis cases. In a Swedish longitudinal case/control study, severe RSV-bronchiolitis in infancy was the strongest risk factor for asthma development, independent of parental asthma or allergy, and remained associated with markedly elevated rates of asthma, allergic rhinitis and aero-allergen sensitisation at the age of 18 years. An even higher asthma risk follows rhinovirus (RV)-induced wheezing illness in infancy. In a birth cohort of children from atopic/asthmatic parents, allergic sensitisation preceded RV-wheezing illness and may have been required for its development. Whether early life bronchiolitis causes, contributes to and/or is a marker of asthma development still remains to be determined. The observation that premature infants who received passive immunisation against RSV (palivizumab), had less than half the risk of recurrent wheeze at 2-5 years of age, suggests that viral bronchiolitis does indeed contribute to asthma development. In addition to viruses, neonatal carriage of pathogenic bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moxarella catarrhalis*, has also been implicated in the development of childhood asthma.

ASTHMA SEVERITY AND EXACERBATIONS

In established asthma airway carriage of *Haemophilus influenzae* and *Streptococcus pneumoniae* is more frequent than in health and commensal bacteria of the *Phylum bacteroidetes* are lacking. The abundance of other airway commensals (*Comamonadaceae*, *Sphingomonadaceae*, *Oxalobacteraceae*) correlates with the degree of bronchial hyper-responsiveness, a marker of disease severity. Importantly, asthma increases the risk of invasive

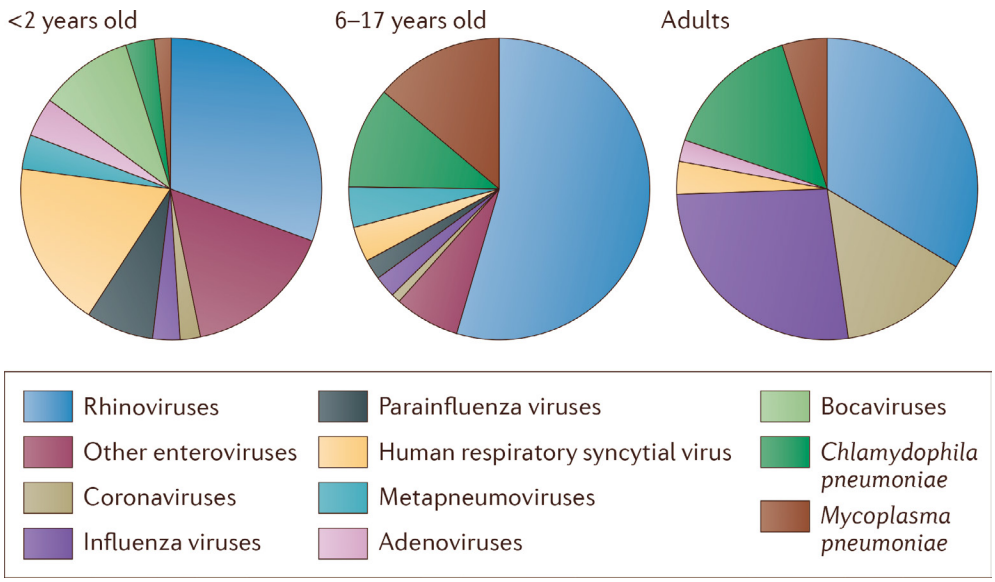

Figure 1 Viruses and bacteria associated with asthma exacerbations. The prevalence of viruses and bacteria in young children (<2 years old), older children (6–17 years old) and adults, presented as median percentages from several studies. Enterovirus estimations in adults and bocavirus estimations in 6–17 year olds and in adults may be under-represented since data is not available in published studies. *(Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Microbiol, Edwards MR, Bartlett NW, Hussell T, et al, The microbiology of asthma, 10, 459-471, copyright 2012.)*

pneumococcal infection.

Fungal allergens often drive allergic asthma and both fungal colonisation and infection, e.g. with *Aspergillus*, can aggravate allergic asthma through increased allergen exposure and infection induced inflammation.

Most acute asthma exacerbations (AAEs) are triggered by respiratory viral infections, with RVs being detected in up to 80% of AAEs in children and 65% in adults (Figure 1). Asthmatics develop more severe respiratory symptoms in RV-infection than non-asthmatic controls, possibly due to lower type-1 interferon responses of infected epithelial and resulting reduced viral control. Infections with the recently discovered species RV-C may result in particularly severe AAEs. Other viruses associated with AAEs include enteroviruses, RSV, influenza virus, coronavirus, metapneumovirus and parainfluenza viruses. Importantly, in allergic asthma AAEs are most severe if a viral infection coincides with exposure to an asthma-driving allergen (Figure 2).

The atypical bacteria *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are also frequently detected in asthma and may increase the risk and severity of AAEs. Treatment with macrolides can reduce the severity of AAEs, which may be due to their antimicrobial effects on atypical bacteria, but also to independent anti-inflammatory properties.

The mechanisms by which infections contribute to asthma development and disease activity are thought to include: damage to the mucosal airway barrier with increased infection risk and allergen up-take; heightened innate pro-inflammatory and pro-allergic responses from infected epithelial cells, fibroblasts and immune cells; enhanced adaptive immune responses to allergens; increased airway remodelling; delayed resolution of inflammation; hyperactivity and proliferation of airway nerves.

INFECTIONS PROTECTING FROM ASTHMA

Experimental models suggest that some infections, including with mycobacteria, *E. coli* and helminths can inhibit asthma. Endemic helminth infections have been associated with a low prevalence of atopy. In animal models, helminth infections can suppress the development of allergic airways disease.

Enhanced understanding of the microbial components and mechanisms that promote or inhibit asthma is necessary to provide the basis for prevention and curative treatment of asthma, both of which are currently lacking.

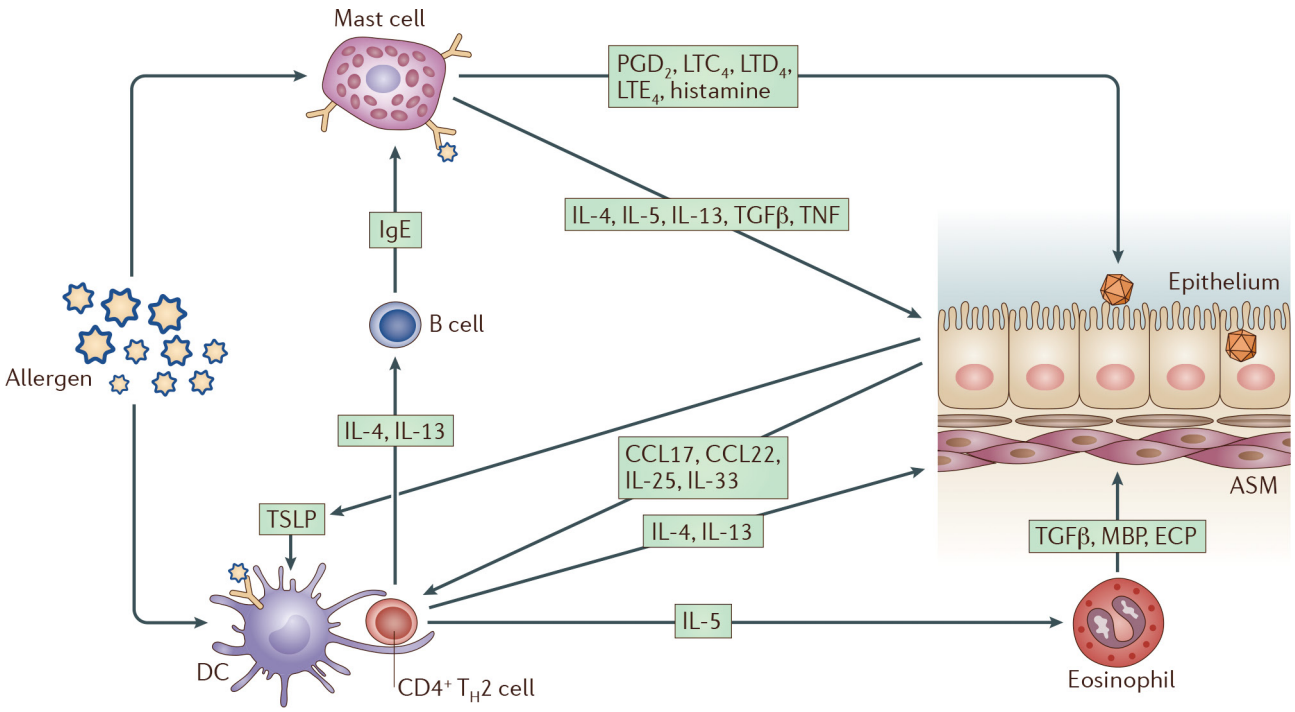

Figure 2 Respiratory viruses interact with allergens to promote asthma. Following sensitization, allergen presentation by airway dendritic cells (DCs) facilitates the promotion of T helper 2 (T_H2) cells. Viruses infect epithelial cells, stimulating the release of T_H2 cell-promoting chemokines CC-chemokine ligand 17 (CCL17) and CCL22, and cytokines thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and IL-33. The T_H2 type chemokines attract T_H2 cells into the airway, and these in turn secrete IL-4, IL-5 and IL-13. IL-5 promotes eosinophilia, and the resultant eosinophils release the inflammatory mediators major basic protein (MBP), eosinophil cationic protein (ECP) and transforming growth factor-β (TGF-β), inducing inflammation in the airway smooth muscle (ASM). IL-4 and IL-13 cause antibody class switching to immunoglobulin E in B cells, so that B cells secrete allergen-specific IgE. This antibody then binds mast cells, and crosslinking of the allergen on mast cell-bound IgE causes mast cell degranulation and release of preformed mediators, including histamine, prostaglandin (PGD_2) and leukotrienes (LTC_4, LTD_4 and LTE_4). These mediators cause bronchoconstriction and further airway inflammation. Mast cells also produce the T_H2 cytokines IL-4 and IL-13, as well as other cytokines, including TGFβ and tumour necrosis factor (TNF), promoting further T_H2 type immune responses and inflammation. *(Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Microbiol, Edwards MR, Bartlett NW, Hussell T, et al, The microbiology of asthma, 10, 459-471, copyright 2012.)*

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15 EMERGING RISK AND PROTECTIVE FACTORS FOR ASTHMA

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KEY MESSAGES

- Different factors are very likely to be important in promoting the development of different types of asthma
- Risk and protective factors may interact to modulate each others effects
- Large studies with well characterised populations need to be undertaken using a gene-environmental interaction approach
- A number of studies suggest that suboptimal fetal growth is associated with later asthma
- Deficient innate immune response might preceed the onset of asthma
- The relationship between low intake of specific micronutrients or a specific diet and the later onset of asthma remains to be proven

Despite considerable research over the last few decades, we still have an incomplete understanding of why and how asthma develops. As the previous chapters have described, a number of epidemiological factors and specific genotypic variants have been associated with asthma. None though massively increase the chances of an individual developing asthma in a manner that, for example, exposure to cigarette smoke dramatically increases your chance of developing lung cancer. So, we are still attempting to understand the full story. This is therefore a good time to take a step back, consider why this may be the case and think about how we can better understand the development of asthma in the future.

The factors that are seen to associate with asthma in studies are heavily influenced by the nature of the patients, who participate in the study. Usually asthma is defined as a doctor's diagnosis of asthma with or without the need for evidence of reversibility with a bronchodilator. Doctors diagnose asthma on the basis of a syndrome of clinical features, for example episodic wheeze or chest tightness in association with specific triggers. Many different pathological mechanisms can result in airway obstruction, which can give rise to the features of asthma. A clinician might recognise viral-associated asthma, exercise-induced asthma or allergic asthma while a histopathologist might recognise eosinophilic or neutrophilic asthma. The patient will be diagnosed as having asthma, despite different pathophysiology and precise clinical presentation. Different factors are very likely to be important in promoting the development of different type of asthma (Figure 1). For example, in the isle of Wight birth cohort maternal asthma and chest infections in early childhood were risk factors for non-atopic wheeze while co-existing allergic diseases and male gender were risk factors for atopic wheeze. Additionally, different factors may interact to modulate each other's effects. For example, in a study on farm living, specific alleles in the pattern-recognition receptor CD14 promoter region were associated with less risk of asthma, but only if farm milk was consumed.

So, we have a situation where we have subpopulations of individuals who have different genetic susceptibilities to different pathophysiological mechanisms that could give rise to asthma. Whether or not they develop asthma will depend

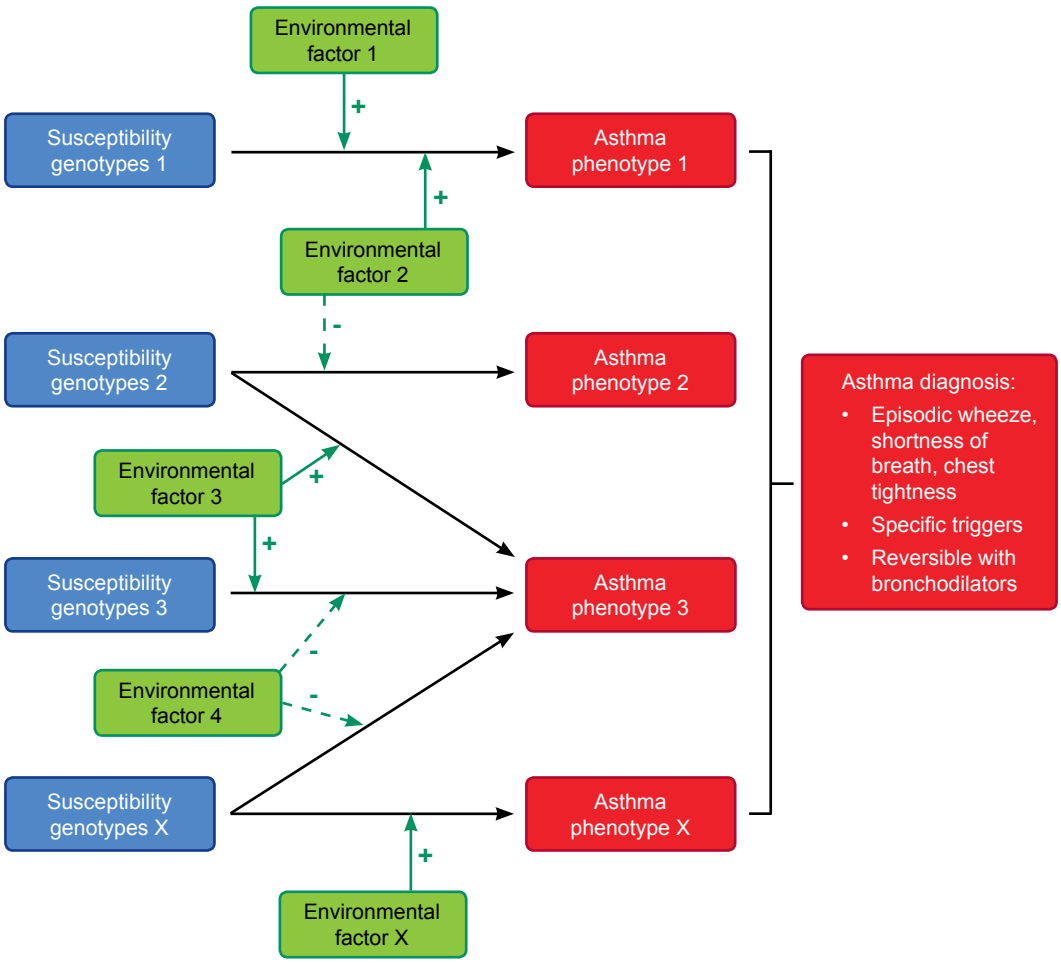

Figure 1 Impact of different environmental factors on individuals with differing genetic susceptibility to give rise to different asthma phenotypes. Exposure to specific environmental factors (green boxes) will give rise to specific asthma phenotypes (red boxes) in individuals with specific genotypic susceptibility profiles (blue boxes). One environmental factor may have very different impacts on individuals with different genotypic susceptibilities.

on what they are exposed to in their environment. That means an individual with a specific susceptibility may develop asthma in one environment, but not in another (Figure 1). A simple analysis within a genetically homogeneous population or with minimal variability in exposure to different environmental exposures will fail to uncover this complexity. Larger studies with well characterised populations need to be undertaken using a gene-environment interaction approach. We also need to better capture the heterogeneity in asthma phenotypes. Researchers are beginning to do this using unbiased approaches and systems medicine modelling for asthma and allergic disease.

What novel risk and protective factors (Figure 2) should these studies focus on? There are now a number of studies that suggest that suboptimal fetal growth is associated with later asthma. Larger birth cohort studies with fetal ultrasound assessments and infant lung function measures are needed to understand how suboptimal fetal growth impacts on childhood asthma, particularly in relationship with other factors such as atopy and innate immune response. The role of viruses in the pathogenesis of asthma has been actively discussed for many years. The missing factor in these discussions has been the innate immune response, for example, deficient anti-viral interferon response. We need to understand whether or not the deficient innate immune response pre-dates the onset of asthma. Finally, many studies have looked, with varying successful for relationships between low intake of

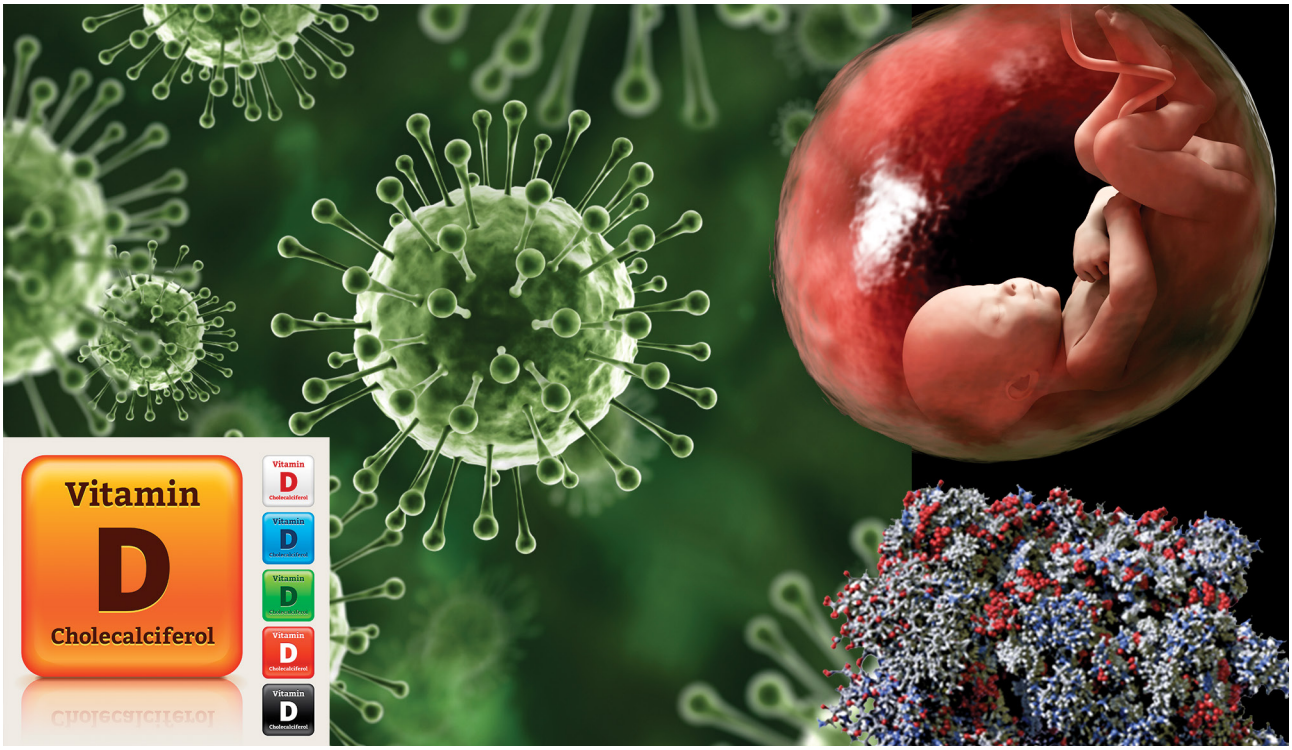

Figure 2 Novel risk and protective factors for asthma: fetal growth, anti-viral interferon response and diet.

specific micronutrients and the later onset of asthma. But evolutionally we have developed eating a diet that consists of a range of micronutrients and so it might be expected that dietary patterns are more likely to be related to the development of asthma than levels of individual micronutrients.

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16 PERINATAL AND EARLY LIFE INFLUENCES ON ASTHMA DEVELOPMENT

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KEY MESSAGES

- Two major sets of environmental influences, acting independently or synergising, are responsible for asthma induction: early postnatal sensitization to perennial aeroallergens and lower respiratory viral infections
- These effects are most profound in early childhood, but similar interactions underlie asthma exacerbations in older children
- Initial signals generated in the viral infected airway mucosa trigger a local Th2 cytokine "storm" that antagonizes Th1-associated viral clearance and boost a "tissue-to-tissue spread" of allergic inflammation
- Nasopharyngeal colonization during infancy with bacterial pathogens or low levels of bacteria in the conducting airways have been associated with asthma risk
- However, Th2 immunity to mucosal dwelling bacteria and prenatal bacterial exposure were associated with reduced risk for asthma

Over the last decade, there has been significant advances in our understanding of the mechanisms governing susceptibility to asthma development during childhood. Most notably, it has become clear that there are two major sets of environmental influences responsible for the airways inflammation that drives asthma induction. The first of these is early postnatal sensitization to perennial aeroallergens, and the second is lower respiratory viral infections. A wide body of epidemiological evidence suggests that both these environmental insults can act independently in driving asthma development, but risk is maximised if they occur concomitantly, inferring some form of synergistic interaction between the underlying inflammatory pathways they trigger. Thus, as illustrated in Figure 1, environmental exposures initiate inflammation-driven cycles responsible for transient airway symptoms, but the resulting repair/regeneration responses lead to persistent pathological changes associated with tissue remodelling, resulting in long term effects on respiratory function. These effects are most profound in relation to inflammatory cycles occurring during early childhood when lung growth and differentiation are progressing most rapidly.

It is clear that similar interactions underlie moderate-severe asthma exacerbations in older children, as the phenotypic features of these events reflect the same pattern of comorbidities in affected subjects (atopy plus respiratory infections). In this regard there has also been significant recent progress in elucidation of the nature the interactions between inflammatory pathways triggered by concomitant exposure to aeroallergens and viruses, employing virus-associated asthma exacerbations as windows into the underlying processes. Notably, initial interferon (IFN)-associated signals generated in the infected airway mucosa in the early stages of exacerbation events lead to upregulation of FcεR1-expression on resident dendritic cells (DC), facilitating markedly enhanced presentation of aeroallergen signals to transiting allergen-specific Th2-memory cells and an ensuing local Th2 cytokine "storm" that antagonizes Th1-associated viral clearance (Figure 2). Subsequent translocation of

both Th2 and IFN signals to bone marrow results in generation of lung-homing "alternatively activated" macrophages associated with tissue repair/remodeling, and also stimulates upregulation of FcεR1 on lung-homing DC precursors that further amplify subsequent expression of local Th2 immunity.

It is additionally clear that translocation of FcεR1-stimulatory signals from sites of allergic inflammation to bone marrow also occurs in the absence of virus infection. While these signals are less intense than those in Figure 2, they nevertheless also result in significant upregulation of FcεR1 in the circulating myeloid cell compartment. This population supplies precursors to replenish DC in all peripheral tissues, and this provides a potential mechanism for "tissue-to-tissue spread" of allergic inflammation (Figure 3).

While the major emphasis in relation to microbial risk factors in asthma development is currently on viruses, emerging evidence also points to an important additional role for bacteria. Notably, nasopharyngeal colonization during infancy with bacterial pathogens has been associated with risk for early onset asthma. Moreover, the presence of low levels of bacteria in the conducting airways has also been associated with asthma risk in older subjects. It is feasible that bacteria that broach the airway epithelium during virus-associated asthma exacerbations when local mucosal "barrier" functions are compromised, may amplify local tissue damaging inflammatory responses via interactions with local macrophages (Figure 2). In this context, it is noteworthy that recent findings indicate that underlying Th2 immunity to mucosal dwelling bacteria in children is associated with

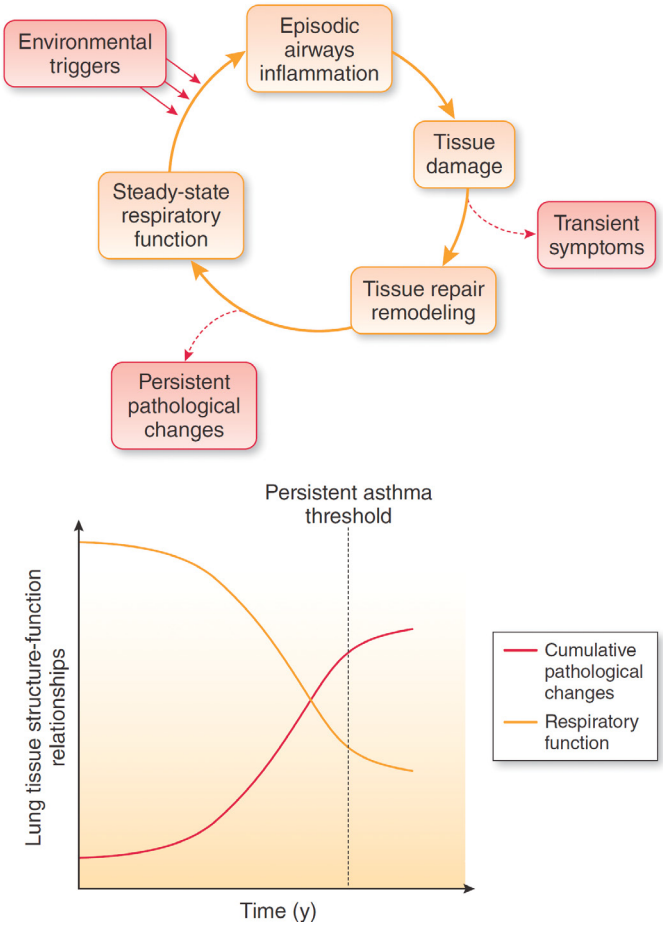

Figure 1 The inflammatory cycle in asthma pathogenesis. Asthma development is driven by repeated cycles of inflammation triggered by airborne irritant stimuli (top). Symptoms are initially intermittent and are associated with acute inflammation and edema and intermittent airway narrowing. Over time, the resolution of inflammation between clinically apparent episodes of asthma becomes less complete. Persistent inflammation leads to repeated cycles of tissue repair and regeneration, which may themselves be aberrant, and can lead to pathological changes that persist for long periods. As these changes accumulate, they lead to progressive deterioration in respiratory function (bottom). Once these changes exceed a critical threshold, they may not be reversible and may result in persistent asthma, with persistent symptoms that are not easily controlled by currently approved medications. *(Reprinted by permission from Macmillan Publishers Ltd: Nat Med, Holt PG, Sly PD, The microbiology of asthma, 18, 726-735, copyright 2012.)*

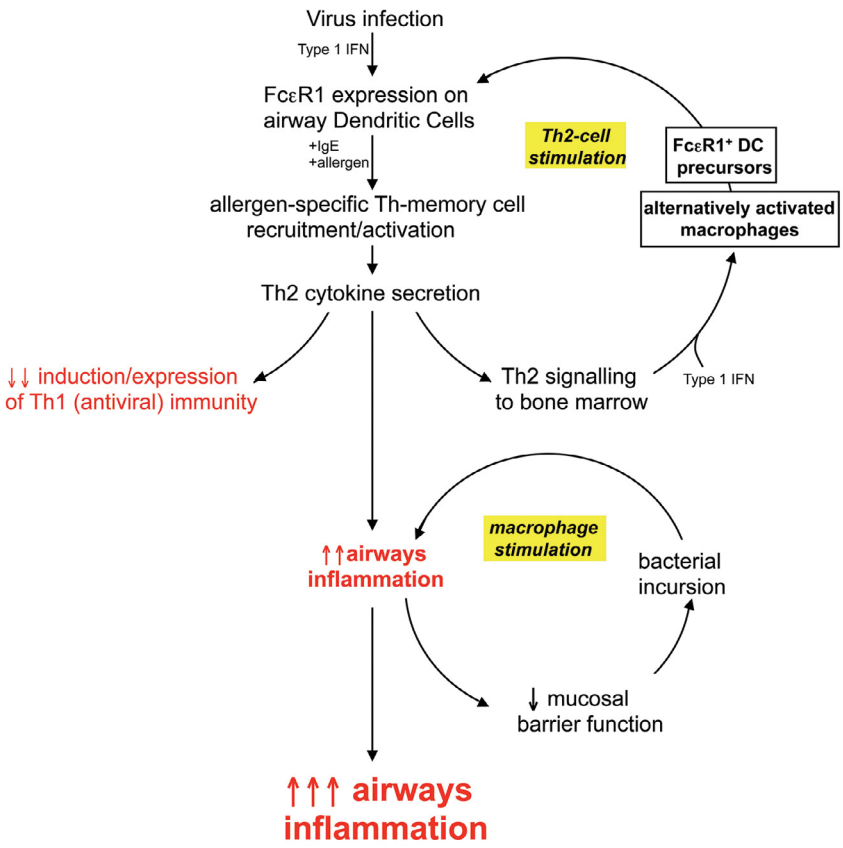

Figure 2 Virus associated atopic asthma exacerbations: harnessing aeroallergen specific IgE via FCεR1 on dendritic cells. Viral initiated production of Type 1 IFN in the airway mucosa of atopic asthmatics triggers a cascade including a bone marrow mediated amplification loop, through which Th2 immunity is recruited into the host defense response to the pathogen. Potential consequences include attenuation of sterilizing immunity and hence persistence of virus, and unmasking of susceptibility to the pro-inflammatory effects of airway mucosal dwelling bacteria. *(Reproduced with permission from the American College of Chest Physicians from Holt PG, Sly PD. Interaction between adaptive and innate immune pathways in the pathogenesis of atopic asthma: operation of a lung/bone marrow axis. Chest 2011;139:1165-1171.)*

reduced risk for asthma, likely via IL-4/IL-13-mediated attenuation of bacterial-induced macrophage activation in the airways following bacterial invasion.

It is pertinent also to note contradictory data associated with prenatal bacterial exposure. In particular, epidemiological evidence suggesting reduction in asthma risk in children of mothers who experience high exposure to airborne bacteria during pregnancy has recently been complimented by animal model studies confirming the phenomenon, and demonstrating a key role for the maternal TLR system in mediating these effects. The target for this mechanism appears to be the fetomaternal interface, possibly involving dampening of local inflammatory mechanisms which can interfere with placental function.

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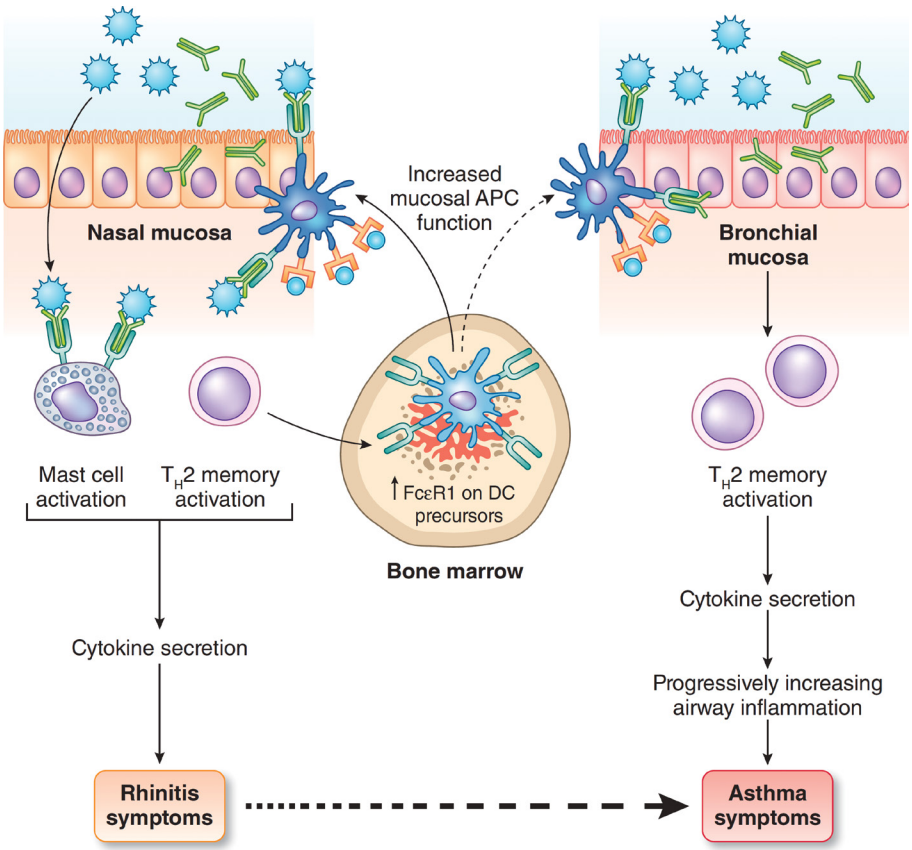

Figure 3 The "atopic march" – systemic spread of allergic reactivity between tissues. The bone marrow amplification loop depicted in Figure 2 also operates in allergic inflammatory responses in the absence of viral comorbidity, albeit at lower levels of intensity. Under such circumstances, chronic allergic diseases such as allergic rhinitis triggered by aeroallergens, initially in the absence of concomitant asthma exacerbations, has potential to increase the likelihood of the eventual development of asthmatic-like responses via enhancing the Th2-stimulatory functions of airway mucosal dwelling APC. *(Reprinted by permission from Macmillan Publishers Ltd: Nat Med, Holt PG, Sly PD, The microbiology of asthma, 18, 726-735, copyright 2012.)*

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17 PSYCHOLOGICAL FACTORS AND ASTHMA

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Since the beginning of the 20th century it has been recognised that asthma is a condition in which psychological factors have a major role. Clinicians recognise that emotional stress can precipitate or exacerbate asthma and that a patient's psychological status may affect their asthma control, by impacting on symptom presentation and treatment adherence (Figure 1). Thus, the relationship between asthma and psychological factors can be described as bi-directional.

KEY MESSAGES

- Asthma is associated with significant psychological burden and psychiatric co-morbidity
- Psychological distress may play a role in the perception of asthma symptoms and asthma treatment (e.g. adherence, health seeking behaviours), which in turn impacts on prognosis, morbidity and mortality
- There is global consistency in the relationship between asthma and mental disorders
- Adopting a bio-psychosocial approach when consulting with a patient with asthma ensures that the wider consequences of asthma and not just their physical symptoms are addressed
- Psychological interventions are used to augment pharmacological management of asthma but there is currently limited evidence of their effectiveness

PSYCHOLOGICAL STATUS AND PSYCHIATRIC CO-MORBIDITY IN PATIENTS WITH ASTHMA

Asthmatics tend to report high levels of negative emotions, and asthma exacerbations have been linked temporally to periods of heightened emotionality. The prevalence of depressive disorders is probably higher in people with asthma relative to the general population: a wide range of prevalence estimates have been reported, with some exceeding 40%. Interestingly, a relationship between depression and asthma is evident in families as well as in individuals; familial studies suggest that the prevalence of each disorder is higher in the family members of index cases with the other.

Patients with bipolar affective disorders also appear to have a higher risk than the general population of developing IgE-mediated allergic conditions, including asthma. Similarly, there is an increased prevalence of anxiety disorders in asthma, affecting as many as one third of asthmatic children and adolescents, and 24% of adults with asthma.

Unfortunately, the literature on the prevalence of psychological and psychiatric disorders in asthmatics is complicated by unclear disease definitions, differences in nomenclature, small samples and a focus on outpatient or inpatient populations rather than the community.

The World Mental Health Survey goes some way to address these methodological problems and provides standardised data for 17 countries worldwide (Table 1). The pooled estimates of age- and sex-adjusted odds of mental disorders among patients with asthma comparative to those without asthma were 1.6 (95% CI=1.4, 1.8) for depressive disorders and 1.5 (95% CI=1.4, 1.7) for anxiety disor-

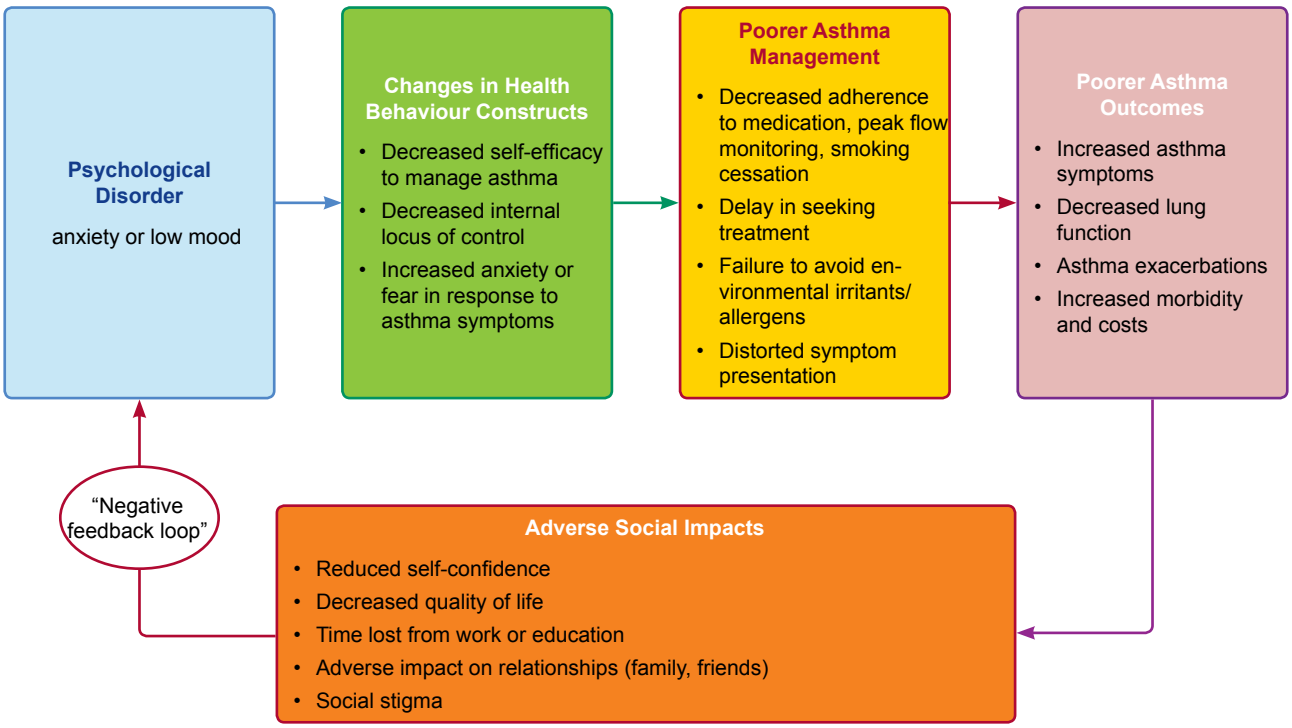

Figure 1 How might low mood or anxiety impact on asthma?

ders. This study also demonstrated a relationship between asthma and alcohol use disorders (OR 1.7 (95% CI=1.4, 2.1). Although the prevalence of mental disorders and asthma varies greatly between countries, the association of the two showed much less cross-sectional variability. This consistency is fascinating given that the countries included differ significantly in their culture, organisation of health services and stage of socioeconomic development. It indicates that wherever setting clinicians work, they need to be aware of the significant overlap of asthma with psychological and psychiatric disorders.

WHAT LINKS PSYCHOLOGICAL DISTRESS AND ASTHMA?

Early psychosomatic models supported a role for psychological distress in contributing to variable asthma morbidity among those with *existing disease*, but growing knowledge of patho-physiological pathways suggests a role for psychological factors also in the *genesis* of asthma. Asthma and major depressive disorders have similar patterns of dysregulation of key biological systems including the neuro-endocrine stress response, cytokines, and neuropeptides. Twin-pair studies provide additional evidence of a genetic link between atopic and depressive symptoms. Further work is needed to unravel these relationships.

PSYCHOLOGICAL INTERVENTIONS AND TREATMENTS FOR ASTHMA

Recognising the relationship between asthma and psychological factors psychological interventions are sometimes used to complement the pharmacological management of asthma. Many different therapies have been tried, including behavioural therapies, cognitive therapies, cognitive-behavioural therapy, relaxation techniques, psycho-dynamic psychotherapies and counselling (both for the individual and for the family). However, unlike pharmacological therapies for asthma, we still have very limited evidence of the effectiveness of these psychological interventions in children or adults.

This paucity of evidence arises because studies of psychological interventions for asthma have often not been randomised, and those studies that have used randomised controlled methodology have lacked power to confirm the utility of the intervention. Furthermore, combining studies in systematic reviews and meta-analyses is limited by the diversity of interventions used, and the variety of different outcomes measured. In a Cochrane review of psychological interven-

TABLE 1

Odds Ratio (age - sex adjusted) for mental disorders amongst adults with asthma versus without asthma

Country	Weighted asthma prevalance %	Major Depression OR	Dysthymia OR	General Anxiety OR	Panic Disorder OR	Social Phobia OR	Post traumatic stress disorder OR	Alcohol Use Disorder OR
Americas								
Colombia	3.0	3.8	7.5	0.6	2	1.1	-	8.9
Mexico	2.2	1.2	0.7	-	0.7	2.9	3.6	1.6
United States	11.6	1.4	1.7	1.7	1.3	1.0	1.3	1.8
Asia and South Pacific								
Japan	5.4	1.2	0.9	1.7	0.8	3.8	4.3	1.6
Beijing, PRC	2.3	2.5	2.8	2.9	-	5.0	-	0.9
Shanghai, PRC	5.1	1.4	-	-	-	-	-	0.8
New Zealand	17.2	1.5	1.5	1.7	1.5	1.1	1.8	1.5
Europe								
Belgium	5.8	1.2	0.2	4	-	0.9	0.5	0.9
France	7.5	1.5	2.6	2.8	0.8	2.1	3.3	0.6
Germany	4.5	2.1	5.4	-	4.1	1.0	-	1.8
Italy	4.6	2.2	1.6	-	0.4	3.2	2.8	-
The Netherlands	8.5	1.4	1.6	0.6	3.0	1.4	5.5	2
Spain	5.7	2.7	2.5	2.8	1.6	8.1	3.8	2.9
Ukraine	1.8	2.7	3.6	1.2	6.0	0.8	4.1	5.4
Middle East and Africa								
Lebanon	1.2	-	-	-	-	-	-	-
Nigeria	0.6	-	-	-	-	-	-	-
Israel	7.2	1.4	1.1	1.2	1.7	-	0.6	1.7
South Africa	5.8	2.1	-	2.7	2.6	3.1	0.8	1.4

Odds Ratio (OR) is not listed if fewer than 25 respondents have asthma or if the cross classification of mental disorder and asthma is null. PRC - People's Republic of China. (Data from Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 2007;29:123-133.)

tions for adults, meta-analysis identified the positive effect of cognitive behaviour therapy on quality of life, biofeedback on peak expiratory flow rate (PEFR), and relaxation therapy on medication use. In the equivalent review for children, relaxation therapy improved PEFR. Both reviews concluded that it was not possible to endorse psychological interventions on the basis of current literature.

Clinicians' observations of positive benefit for individuals from psychological interventions may challenge the formal review of the literature. In part this discrepancy may arise because in clinical practice psychological treatments are often reserved for distressed patients with severe or poorly controlled asthma whereas trials often recruit patients with milder and more controlled asthma, and have often failed to screen participants for psychological distress at inclusion, resulting in study populations that are less able to benefit (ceiling effect) from psychological intervention. Well designed trials are urgently needed.

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18 THE COMPLEX NETWORK OF ASTHMA RISK AND PROTECTIVE FACTORS

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KEY MESSAGES

- Environmental factors play a crucial role in asthma epidemics
- Higher risk of asthma is associated with markers of affluence
- Reduced exposure to infections in early life may favour allergic responses and asthma
- Asthma development is influenced by numerous environmental exposures
- The effect of specific environmental exposures is different amongst individuals with different genetic predispositions
- Only individuals with particular predisposition will benefit from a specific intervention aimed at asthma prevention; the same intervention amongst individuals with different susceptibility may cause harm
- "One size fits all" approach to asthma prevention and treatment has to be replaced by a personalised, stratified approach

A large variability in asthma rates across the world and a sharp rise in its prevalence in the last decades strongly suggest a crucial role of environmental factors in the causation of asthma. However, knowledge about the underlying cause(s) of asthma epidemics remains elusive. The answer is likely to lie in our environment and lifestyle, which have undergone profound changes in a relatively short period of time (including changes in housing design, exposure to pollutants, microbial exposure, family size and childcare arrangements, diet, sedentary life style and exercise).

A striking difference for incidence of asthma between urban and rural areas within one country has been consistently reported from many different parts of the world. Individuals who move from rural areas into cities are retaining this protection. Higher risk of asthma has been consistently associated with various markers of affluence (including decreasing family size and high socio-economic status), all of which may reflect eradication of infections (e.g. through vaccination programmes), increased cleanliness and modern diet. However, it is of note that in some areas of the world (e.g. South America and inner-city USA) poverty has been related to asthma.

The "hygiene hypothesis" suggests that reduced exposure to infections in early life may delay maturation of the immune system and favour allergic responses and asthma. For example, protective effect of contact with other children has been consistently reported using early life day-care entry as proxy of exposure. Similar protection has been observed in relation to contact with animals (in particular dogs and farm animals). Probably the most consistent protective effect against asthma has been reported for farming environments. Data from Europe indicate that the protective effect of farming on asthma is confined to traditional types of farms (e.g. with cows and cultivation).

All of these factors (crowding, day-care facilities, pet ownership and farming) may be markers of an increased exposure to various microbial compounds (including, but not confined to endotoxin). Infections with pathogens (such as *Salmonella*, *Toxoplasma gondii*, mycobacteria etc.) may also be protective, although the reported associations

Figure 1 Development of asthma may be influenced by a number of different environmental exposures.

may reflect unhygienic living conditions.

Some types of outdoor air pollution (in particular traffic exposure) may have adverse effects on asthma. Indoor pollutants, especially environmental tobacco smoke exposure, also contribute to asthma morbidity. Allergen exposure in homes has attracted considerable interest as a potential contributing factor. High allergen exposure amongst allergic asthmatic patients is associated with more severe disease; however, the relationship between allergen exposure and asthma development is more complex. For example, cockroach infestation is a strong risk for cockroach sensitisation and asthma morbidity (especially in the US inner-city homes), but it is unlikely that indoor allergen exposure has direct role of in asthma development.

A complex relationship between genetic predisposition and environmental exposures in the development of asthma has received increasing attention over the last decade. Development of asthma may be influenced by a number of different environmental exposures, but genetic predisposition of the individual plays a critically important role, in that the effect of specific environmental exposures is different amongst individuals with different genetic predispositions. Recent examples of gene-environment interactions include the observation of the opposite effect of day-care attendance in the first year of life on asthma development in children with different variants in the *TLR2* gene. Day-care appeared protective in the whole population, concealing the fact that in a subgroup of genetically susceptible individuals, attending day-care increased the risk of asthma.

Additional level of complexity is added by the increasing evidence that the effect of environmental exposures on asthma strongly depends on the timing of exposure. Throughout early life, children undergo a constant process of development and maturation. It seems likely that there are "windows of opportunity" during certain stages of development when individuals may be particularly vulnerable to extrinsic influences. Furthermore, prenatal factors (e.g. maternal exposures during pregnancy) may play an important role, either through direct effects acting *in utero*, or via epigenetic modifications.

Asthma arises as a consequence of environmental factors modulating the risk in genetically susceptible individuals through gene-environment interactions. As a consequence, only individuals with particular susceptibility will benefit from a specific intervention aimed at asthma prevention; the same intervention amongst individuals with different susceptibility may cause harm.

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19 ASTHMA IN CHILDHOOD

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KEY MESSAGES

- Important differences exist between pediatric and adult asthma, supporting the need for distinct management plans and guidelines
- Pediatric asthma phenotypes, including virus-induced, exercise-induced and allergen-induced asthma, highlight the complexity of the disease
- The diagnosis of asthma is difficult in early childhood
- Pediatric asthma treatment is multifaceted (including education, avoidance of triggers, pharmaceutical drugs and biological interventions) and dynamic (including monitoring, taking into account cost and geopolitical characteristics).
- Age and phenotype-specific characteristics of efficacy of different medications should be taken into account

Asthma is defined in the same way in children as in adults. However, there are many particularities that make childhood asthma a challenging condition, including the relative scarcity of evidence in this age group. Asthma starts early and persists, often for life, following a not completely defined pattern. Natural history studies have shown that many children, who wheeze early in life overcome this problem later on. However, some of these patients relapse, while others develop asthma at different times in their lives (Figure 1). Severity and atopy are the elements most strongly associated to wheeze/asthma persistence. Asthma symptoms coexist or follow other allergy-related conditions such as atopic dermatitis and/or rhinitis. In children, the "atopic march" has been used as a metaphor to characterize the longitudinal transformation of such conditions in the same patient. Frequent comorbidities, especially rhinitis, should always be taken into account, when evaluating patients.

The clinical presentation of asthma in childhood is dynamic, evolving in parallel to the development of both the respiratory and the immune systems. Symptoms are typical, including wheeze, cough, shortness of breath and chest tightness. Exacerbations are frequent in children, usually precipitated by a common cold. In many cases, such exacerbations are the only clinical expression of the disease. However, it is becoming increasingly clear that asthma includes several different disease patterns, with distinct triggers, response to treatment and prognosis. Such phenotypes, which reflect similar diversity of mechanisms (endotypes), can be useful in disease management. Phenotypes have been related to epidemiological outcome, severity, or triggers; among the latter, the distinction between virus-induced asthma, exercise-induced asthma and allergen-induced asthma, proposed by the Pediatric Asthma PRACTALL, may have practical implications (Figure 2). Age is also crucial, with major differences in clinical presentations, depending both on physiological development, but also social characteristics, cognitive capacity and compliance.

The pathology and pathophysiology of childhood asthma share key elements of inflammation and remodeling with adult asthma. However, inflammation may not always be eosinophilic; in milder cases, inflammation appears during exacerbations, in parallel to symptoms

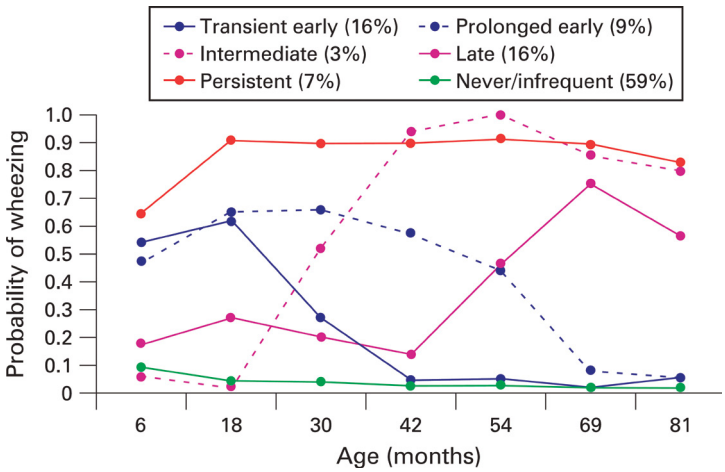

Figure 1 Patterns of wheezing persistence among 6265 children followed up longitudinally for 7 years (ALSPAC study). *(Reproduced from Thorax, Henderson J, Granell R, Heron J, et al, 63, 974-980, Copyright 2008, with permission from BMJ Publishing Group.)*

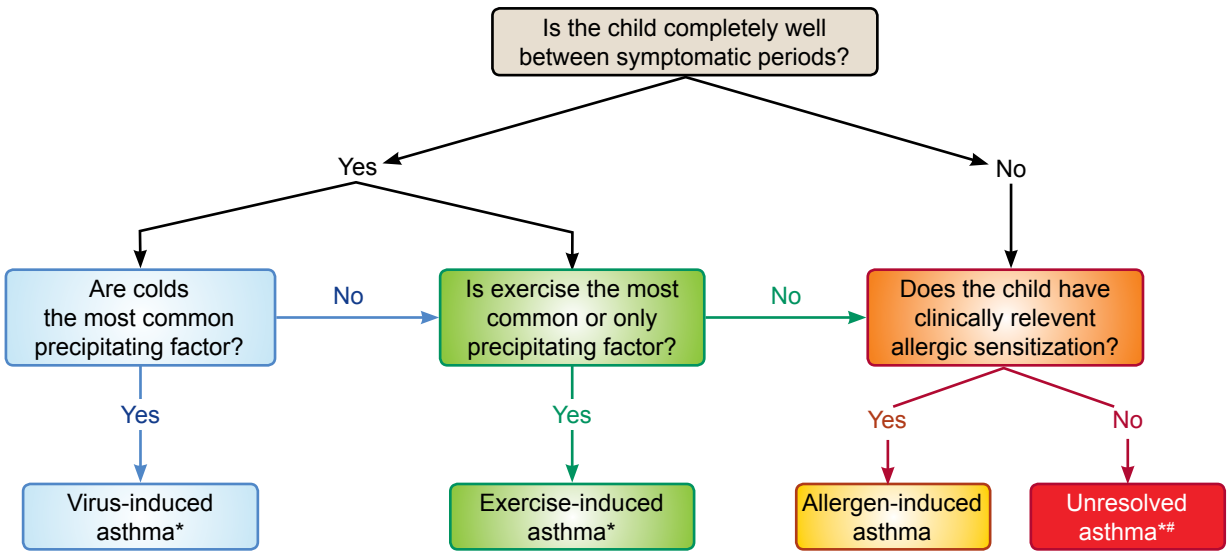

Figure 2 Asthma phenotypes in children aged >2 years of age. Phenotypes are a useful guide to the predominant problem and overlap between phenotypes is frequently present. *Children may also be atopic # Different etiologies, including irritant exposure and as-yet not evident allergies may be included here. *(Reproduced from Bacharier LB, Boner A, Carlsen KH, et al., Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008;63:5-34, with permission from Wiley-Blackwell.)*

and bronchoconstriction. Furthermore, outside exacerbations, lung function is very often within the normal range. Remodeling is present in preschool children (Figure 3) to the same extent as older children and adults, but not yet present in infants.

The diagnosis of asthma can be challenging, particularly in younger children. Asthma diagnosis is at best provisional in infants. In preschool children a detailed history and the exclusion of other wheezing disorders are mandatory and a well-designed therapeutic trial may help to establish the diagnosis. Lung function can be evaluated by impulse oscilometry. In school-age children and adolescents, evaluation of bronchial hyperresponsiveness and airway inflammation offer additional information. Atopic sensitization should always be assessed, as it offers information both about possible triggers and prognosis.

Patient education, identification and avoidance of triggers, pharmacotherapy, immunotherapy and close monitoring are the cornerstones of treatment. Each of these has age-related particularities. Educational programs should be age-tailored; school programs can be very helpful. In early childhood, respiratory viruses are by far the most common disease triggers. With increasing age, allergen triggers become more clinically relevant.

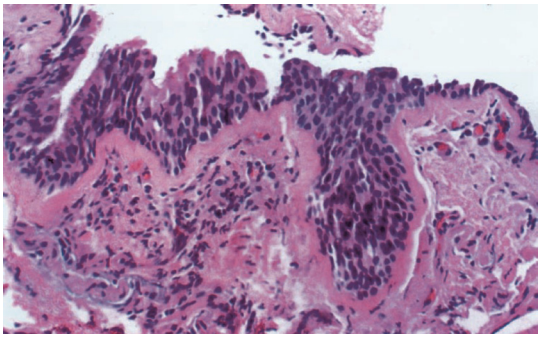

Figure 3 Bronchial biopsy from a 6-year old girl with severe persistent asthma. An intact but hyperplastic airway epithelium and markedly thickened basement membrane, with only minimal inflammation characterized by patchy lymphocytic infiltration immediately below the basement membrane can be seen. *(Reproduced with permission from the American College of Chest Physicians from Jenkins HA, Cool C, Szefler SJ, et al. Histopathology of severe childhood asthma: a case series. Chest 2003;124:32-41.)*

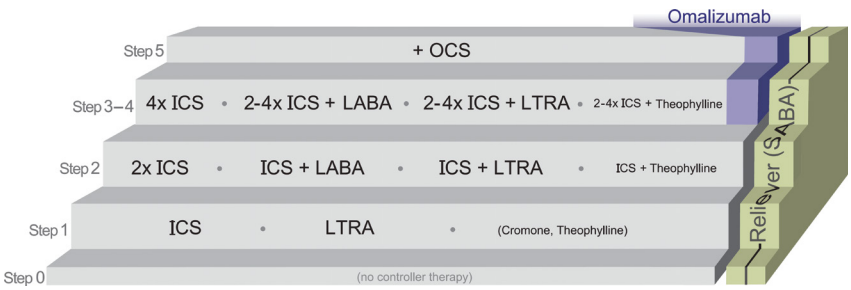

Figure 4 The stepwise approach to asthma treatment in childhood aims at disease control. An easy way to memorize this stepwise approach is that the number of each step suggests the number of medications, or ICS level, to be used. *(Reproduced from Papadopoulos NG, Arakawa H, Carlsen KH, et al. International consensus on (ICON) pediatric asthma. Allergy 2012;67: 976-997, with permission from Wiley-Blackwell.)*

Pharmacotherapy follows a stepwise approach, based on disease control (Figure 4). Unfortunately, the volume of evidence on drug effectiveness in children is inadequate, although it is clear that this differs from adults, or even between pediatric age groups. Inhaled corticosteroids remain the cornerstone of long-term anti-inflammatory treatment. Apparent differential responses to medications are those to leukotriene receptor antagonists and long-acting beta 2 agonists, the former being more and the latter less effective, as compared to adult studies.

Immunotherapy is currently the only treatment with disease-modifying potential, for patients with allergen-induced asthma. Intensive research is necessary to optimize this potential.

Close monitoring is essential. Increased difficulty in compliance and use of devices, rapid changes in disease development and the need to monitor growth, add complexity to the management and underline the importance on regular monitoring.

Strategies for primary prevention are still to be discovered, with the exception of smoking avoidance during pregnancy, which is strongly recommended.

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20 ASTHMA IN THE ELDERLY

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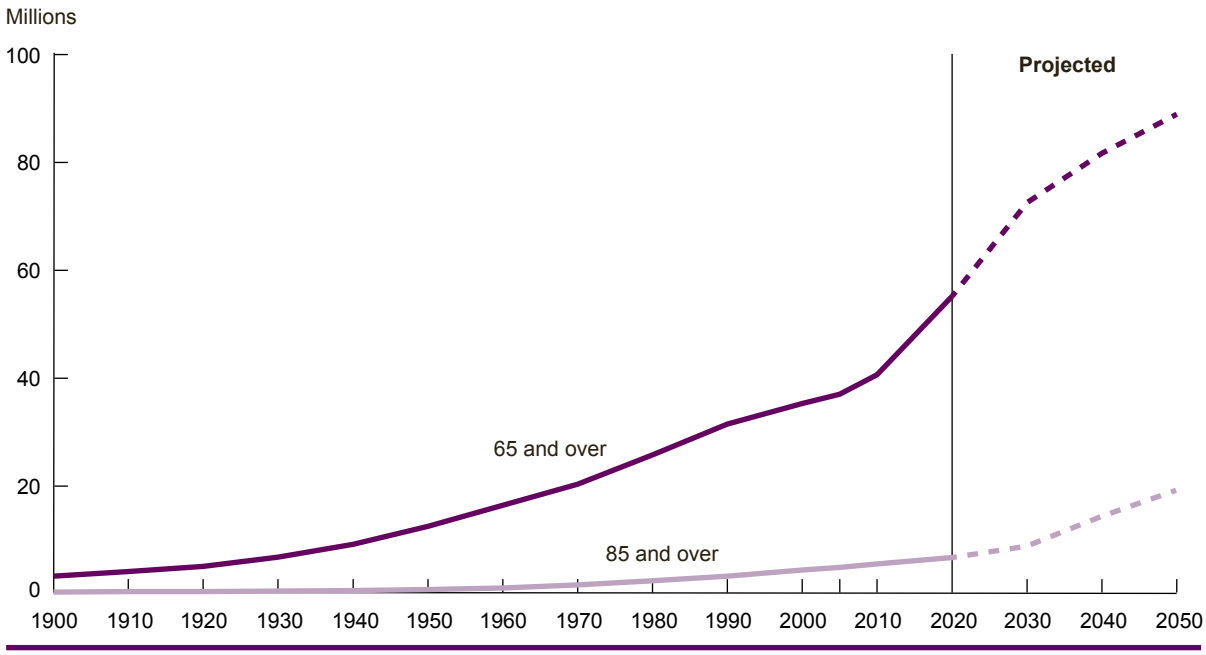
KEY MESSAGES

- Asthma in older adults is a result of both persistent disease and new onset disease
- Normal lung function in older subjects has features of airflow obstruction, complicating the diagnosis of asthma and challenging the distinction between chronic obstructive lung disease and asthma
- Allergens and allergic sensitivity are less important compared to younger populations but allergy remains relevant in the elderly
- Treatment of asthma is not fundamentally different. Imunotherapy and environmental control are generally less effective, tolerance to inhaled corticosteroids and beta agonists is decreased, anticholinergic therapy may be a consideration due to fixed obstructive changes of aging
- Infections are an important cause of severe exacerbations. Vaccination status should be verified in older subjects with asthma
- Medication side effects are a greater challenge in the elderly

The population of the world is aging, with the greatest increases occurring in those over 85 years of age. Twenty-five percent of the US population will be more than 65 years of age by 2050 (Figure 1). Asthma occurs in all adult age groups, both as a new diagnosis and as a condition that existed from a younger age. The prevalence of asthma in the elderly is 4 to 13%, similar to younger adult populations, and the incidence is approximately 1/1000/year. However, asthma is probably underdiagnosed due to the attribution of symptoms and signs to diseases other than asthma in older populations or acceptance of symptoms and limitations as the result of aging. Compared to asthma beginning at a younger age, new onset asthma in older adults tends to be more severe and progressive, more likely in women and less reversible. The mortality of asthma increases with aging (Figure 2).

Aging influences the symptoms of asthma as well as the mortality. This may be due to changes in airway physiology with aging and the decreased response to treatment. Lung function decreases with age due to increased stiffness of the chest wall, reduced respiratory muscle function and an increase in residual volume from the loss of elastic recoil. The decline in the elasticity of the airway with age is major contributor to the increase in fixed airflow obstruction and work of breathing. The result is a decrease in FEV1/FVC, such that normal elders have spirometric features suggestive of obstructive lung disease. Thus, the diagnosis of asthma in the elderly is challenging, and asthma in older adults is commonly misdiagnosed as chronic obstructive lung disease disease (COPD), resulting in under-diagnosis and under-treatment of asthma. Significant, irreversible airflow obstruction in older adults is usually due to COPD, asthma with remodeling or bronchiectasis with segmental fibrosis. Lung volume and diffusion capacity studies and high resolution tomographic imaging may be helpful in identifying diseases other than asthma in older adults with persistent dyspnea or FEV1 less than 60% of predicted.



NOTE: These projections are based on Census 2000 and are not consistent with the 2010 Census results. Projections based on the 2010 Census will be released in late 2012.

Reference population: These data refer to the resident population.

SOURCE: U.S. Census Bureau, 1900 to 1940, 1970, and 1980, U.S. Census Bureau, 1983, Table 42; 1950, U.S. Census Bureau, 1953, Table 38; 1960, U.S. Census Bureau, 1964, Table 155; 1990, U.S. Census Bureau, 1991, 1990 Summary Table File; 2000, U.S. Census Bureau, 2001, *Census 2000 Summary File 1;* U.S. Census Bureau, Table 1: Intercensal Estimates of the Resident Population by Sex and Age for the U.S.: April 1, 2000 to July 1, 2010 (US-EST00INT-01); U.S. Census Bureau, 2011. *2010 Census Summary File 1;* U.S. Census Bureau, Table 2: Projections of the population by selected age groups and sex for the United States: 2010–2050 (NP2008-t2).

Figure 1 Population of United States, age 65 and over and age 85 and over, selected years 1900-2010 and projected 2020-2050. *(From http://www.agingstats.gov/Main_Site/Data/2012_Documents/docs/Population.pdf, accessed May 20, 2013.)*

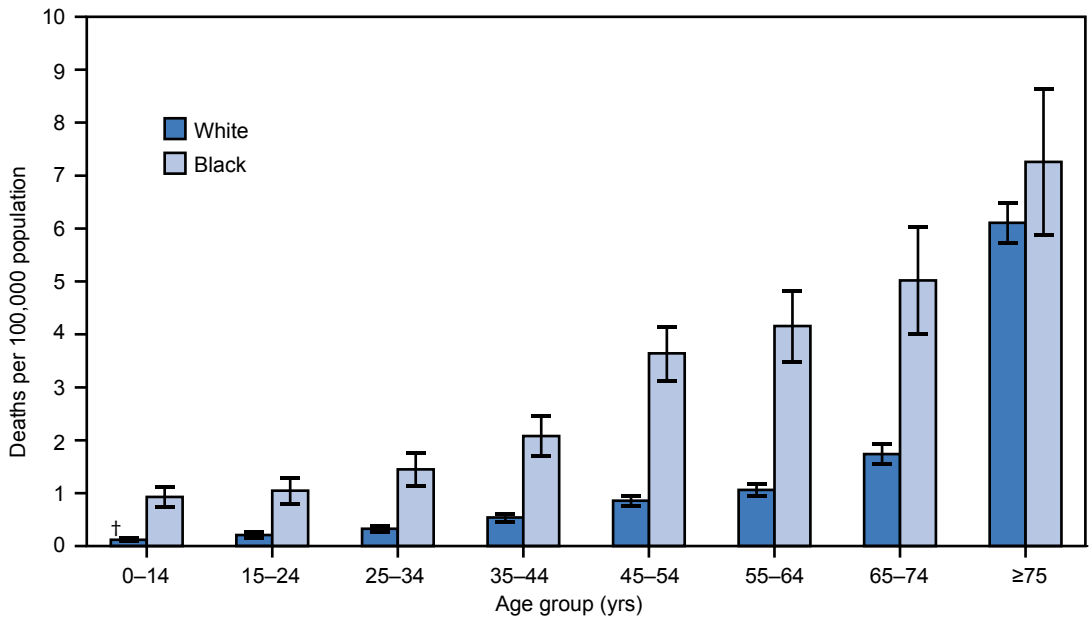


Figure 2 Asthma Death Rates by Race and Age, United States 2007-2009. *(From Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 2012;61:315.)*

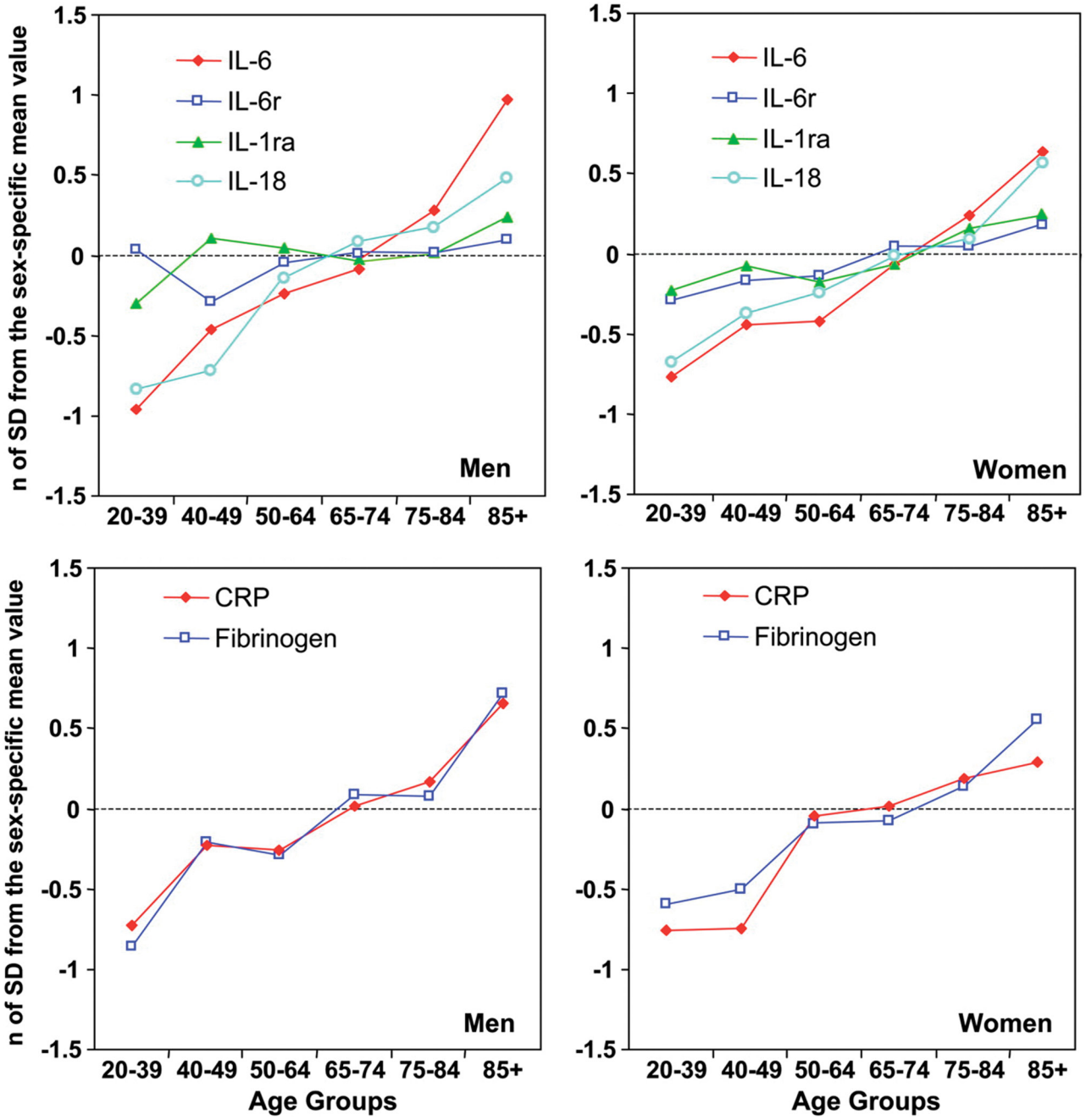


Figure 3 Effect of age on state of inflammation. Mean values of inflammatory markers according to age and sex group expressed as number of standard deviations from the population mean to make the values independent of different units of measure. *(Republished with permission of Blood, from The origins of age-related proinflammatory state, Ferrucci L, Corsi A, Lauretani F, et al, 105, 6, 2005; permission conveyed through Copyright Clearance Center, Inc.)*

Aging affects the immune system in various ways (Figures 3 and 4). Expected findings in the elderly are naïve T cells decrease with decline in ability to respond to new antigens, memory T cells increase, CD8 suppressor/cytotoxic cells increase, B-cell function decreases, innate immune function decreases, neutrophil number increases and eosinophil function is relatively unchanged. IgE production decreases with age, although some data do not support this point. However, wheal and flare skin test responses

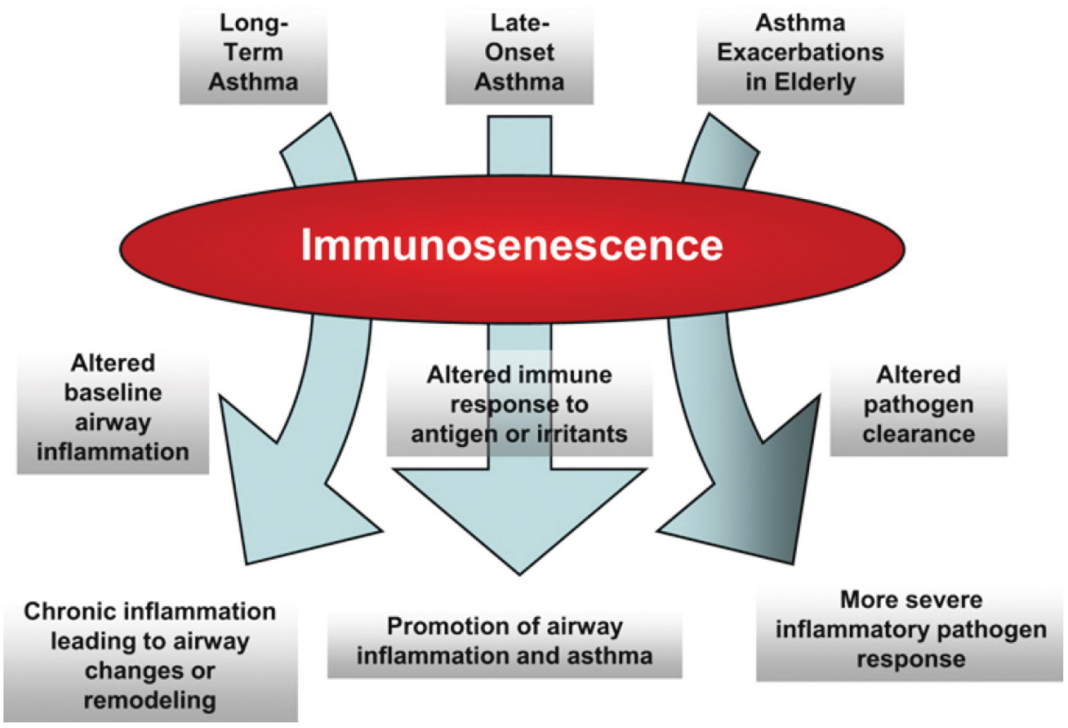


Figure 4 Immunosenescence and the potential effects on asthma. *(Reprinted from J Allergy Clin Immunol, 126/4, Busse PJ, Mathur SK, Age related changes in immune function: effect on airway inflammation, 690-696, Copyright 2010, with permission from Elsevier.)*

in older asthmatics are predictive of symptoms but are less reliable in predicting response to allergen inhalation challenge than in younger populations. Allergic sensitization is more common in older adults with asthma than in age-matched controls without asthma, with studies of Caucasian populations showing 28-74% of older asthmatics sensitive to at least one antigen. However, subjects who develop asthma later in life are much less likely to have specific-IgE than younger subjects. Aging of skin decreases the usefulness of skin testing in solar damaged skin. IL-6 increases with age and IL-6 inversely correlates with survival. IL-6 and associated noneosinophilic inflammation may affect the airway.

Asthma with onset after 40 years of age is rarely IgE mediated and has much less familial linkage. The greater duration of asthma, the less likely lung function will be normal (Figure 5). Lung function decreases with age from the maximum value at approximately 20 years of age. The average decrease in FEV1 is 25-30 ml/year, and this loss is accelerated in some by cigarette smoke exposure or chronic asthma.

Management of asthma in the elderly is no different than in younger populations, except the medications may be less effective and less tolerated. Inhaled medications require a sufficient airflow for powder devices or coordination for metered dose inhalers, possibly limiting effectiveness in the elderly. The dryness of oral and laryngeal mucosa in older subjects reduces the tolerance of inhaled corticosteroids, and older asthmatics may derive less benefit from inhaled corticosteroids. The tolerance to short or long acting beta agonists is another concern, and anticholinergic therapy, not approved in asthma but demonstrated to be effective, may be a consideration. Due to low flow rates and small airway disease, oral therapy may be desirable with consideration of short courses of oral corticosteroids, low dose theophylline or a trial of leukotriene modifiers. Infections are a frequent cause of exacerbations and may result in severe exacerbations requiring hospitalization. Therefore, vaccine recommendations include annual influenza vaccine, periodic pneumococcal vaccine and boosting of pertussis immunity once as an adult. Monitoring for side effects of therapy is very important in older subjects.

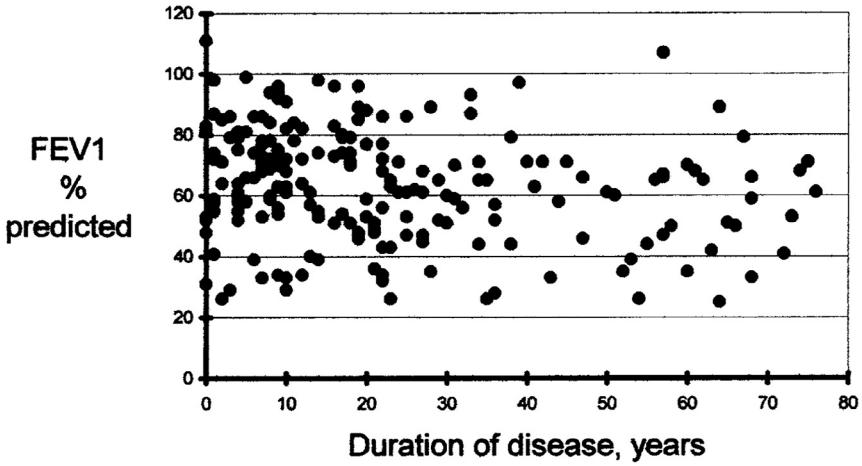


Figure 5 Lung function as measured by FEV1 in patients with diagnosis of asthma made after the age of 65 years at a single referral clinic. *(Reprinted from J Allergy Clin Immunol, 103/4, Reed CE, The natural history of asthma in adults: the problem of irreversibility, pp 539-547, Copyright 1999, with permission from Elsevier.)*

This monitoring includes serum potassium and glucose with inhaled beta agonists, particularly when combined with high dose inhaled corticosteroids or oral corticosteroids, bone density when regular inhaled corticosteroids or recurrent systemic corticosteroids are required, monitoring serum 25-hydroxyvitamin D with target concentrations of 40-50 ng/ml, and assessment of strength to detect myopathy.

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21 ASTHMA IN THE ELITE ATHLETE

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KEY MESSAGES

- The prevalence of asthma and airway hyperresponsiveness is increased in the athlete
- Asthma presents as a specific phenotype in the athlete, with a less eosinophilic airway inflammation, sometimes more difficult to control asthma and significant reversibility of changes in airway hyperresponsiveness (AHR) after cessation of training in subgroups such as swimmers
- Environmental factors such as repeated inhalation of chlorine derivatives (in swimmers), cold air (in winter sports), allergens and pollutants are considered to play a role in the development of asthma and AHR in the athlete
- Asthma should be diagnosed early in athletes and preventative measures suggested to protect the airways and optimize performance
- Medication use should comply with the requirements of the World Anti-Doping Agency

PREVALENCE OF ASTHMA IN THE ATHLETE

The prevalence of asthma, atopy, exercise-induced bronchoconstriction (EIB), and airway hyperresponsiveness (AHR) is increased in high-level athletes (Table 1). Asthma has been reported in 2.7 to 22.8% of summer sports athletes and from 2.8 to 54.8% of winter sports athletes, variations that may be related to the different athletes populations and diagnostic tests. The prevalence of AHR is even higher and varies from 25 to 79% in athletes performing endurance sports while it is around 20% in power and speed sports athletes.

MECHANISMS OF DEVELOPMENT OF ASTHMA AND RISK FACTORS

There are increasing evidences that high-intensity repeated exercise, particularly when the athlete is exposed to allergens, pollutants, chlorine derivatives or cold air during training, may promote the development of asthma and AHR (Figure 1). The mechanisms by which these agents could induce long-term changes in airway function in athletes are still to be determined but they seem to act through airways epithelial damage, inflammation - most often, neutrophilic or paucigranulocytic - and remodelling. Frequent/intense airway dehydration and mechanical airway stress from intense exercise may contribute to these changes.

CLINICAL FEATURES OF ASTHMA IN THE ATHLETE

Respiratory symptoms are unreliable to make the diagnosis of asthma in athletes and objective tests demonstrating variable airway obstruction and/or hyperresponsiveness such as methacholine or mannitol challenges, exercise tests (field or laboratory) or eucapnic voluntary hyperpnea test are needed.

MANAGEMENT

The optimal management of asthma in athletes includes general pharmacological and non-pharmacological measures suggested in current guidelines (Figure 2). Attention should be particularly paid to the prevention of EIB, the development of a tolerance to the bronchoprotective effects of inhaled β2-agonists and assessment

TABLE 1

Prevalence of physician-diagnosed asthma, exercise-induced bronchoconstriction and airway hyperresponsiveness in elite athletes

Type of sport	PDA	EIB	AHR
Winter athletes	14-28%	23-35%	23-52%
Swimmers	≅8%	---	36-79%
Other endurance sports	2-20%	15-19%	9-21%

Adapted from Langdeau et al. Sports Med 2001. (PDA = Physician-diagnosed asthma; EIB = Exercise-induced bronchoconstriction; AHR = Airway hyperresponsiveness as measured in assessing response to methacholine or other agents)

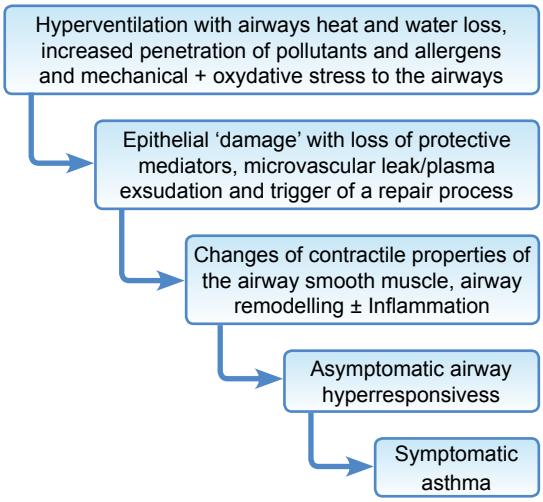

Figure 1 Possible mechanisms of development of asthma and airway hyperresponsiveness in athletes.

of the benefits from asthma medications, as these last seem often less effective in high-level athletes to relieve respiratory symptoms (Table 2). The sometimes observed poorer global treatment response may be due to the fact that some respiratory symptoms are not due to asthma, but are associated with other co-morbid conditions (rhinitis, gastro-esophageal reflux, vocal cord dysfunction) or to the intense exercise. It is also possible that athletes show a resistance to asthma drugs, possibly due to a predominant airway remodeling or more neutrophilic type of airway inflammation. Medication use should comply with the requirements of the World Anti-Doping Agency (http://www.wada-ama.org/en/, accessed May 20, 2013). Rhinitis is common in athletes and should be also treated according to current guidelines.

PREVENTATIVE MEASURES AND LONG-TERM OUTCOMES

Preventative measures include avoidance, whenever possible, of training during high-level exposure to allergens/ pollutants, extremely cold temperature and in improving measures to reduce chlorine by-products levels in pools (Table 3).

Interestingly, there are evidences that airway responsiveness can, at least partly, normalize after stopping training. Further research is needed on how to reduce the risk of developing asthma and/or AHR in the athlete, how these last influence athletes' performance and what is their outcome after cessation of training for various types of sports.

CONCLUSION

Asthma and AHR are common in the high-level athlete. Competitive endurance training may promote the development of asthma and AHR through various mechanisms. The diagnosis requires bronchoprovocation tests and although the management of asthma should be similar to other type of asthmatic patients, specific environmental preventative measures and prevention of tolerance to β2 agonist should be ensured. Airway function may partly or totally normalize after cessation of training but more research is needed on how to prevent the development of asthma and AHR in this population and what is their optimal pharmacological therapy.

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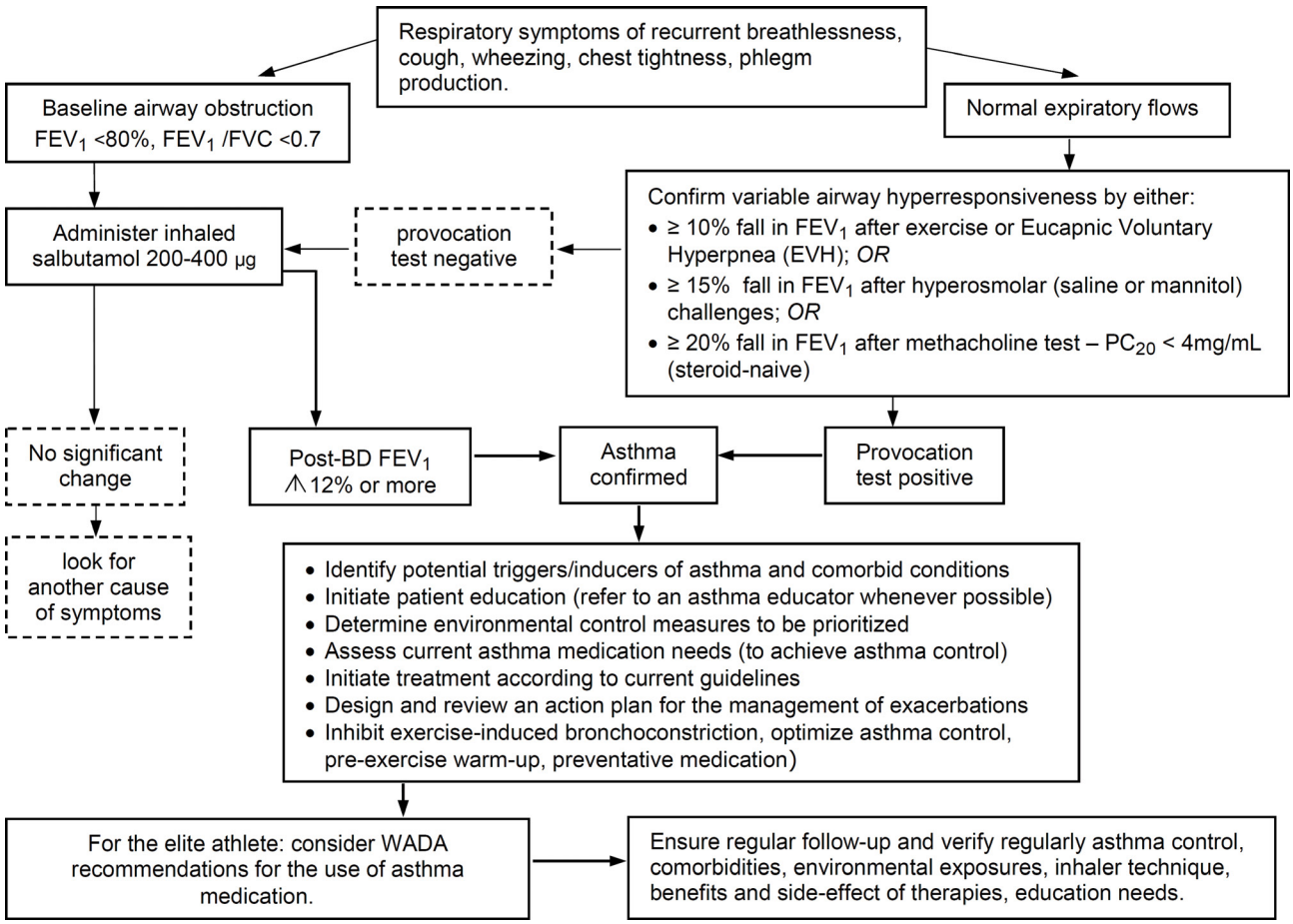

Figure 2 Asthma management for the athlete. BD - Bronchodilator; FVC - forced vital capacity; FEV1 - forced expiratory volume in the first second; WADA - World Anti Doping Agency. *(Adapted from J Allergy Clin Immunol, 122/2, Fitch KD, Sue-Chu M, Anderson SD, et al, Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008, 254-260, Copyright 2008, with permission from Elsevier.)*

TABLE 2

Specific considerations about the management of asthma in the high-level athlete
• Difficulties in assessing « asthma-like symptoms »
• Should we treat what is considered asymptomatic AHR ?
• Unrecognized alterations in lung function due to high baseline values
• High level of exposure to sensitizer/irritants
• Undertreatment/Overtreatment
• Presence of confounding conditions (VCD, over-training, etc.)
• Reduced response to therapy
• Requirements by sports authorities
• Assessment of long-term outcomes

TABLE 3

Examples of preventative measures for asthmatic athletes
Avoidance of training during:
• high-level exposure to relevant allergens
• days of intense air pollution
• extremely cold temperature
Reduce chlorine by-products levels in pools
• personal bathers hygiene
• control of chlorine levels
• Improved ventilation of pool environment
Ensure adequate asthma control
Warm-up before exercising

22 ASTHMA IN PREGNANCY

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KEY MESSAGES

- Pregnant asthmatics have a higher risk of adverse perinatal outcomes
- Adherence to treatment, specifically inhaled corticosteroids, has been a problem and is usually due to concerns regarding the safety of these medications during pregnancy
- Pregnant asthmatics should be monitored on a monthly basis so that any change in course can be matched with an appropriate change in therapy
- Patient education is an important part of managing the pregnant asthmatic, which includes explaining the relationship between asthma and pregnancy, identifying asthma triggers, providing training on correct use of inhalers and establishing an asthma action plan
- One of the most important needs for the future is the availability of further safety information for asthma medications used during pregnancy that can also account for asthma control

Asthma is the most common potentially serious chronic medical condition to affect pregnancy, with a prevalence of self-reported asthma in the United States between 8.4 and 8.8%. A meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women, (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse maternal and fetal outcomes (Table 1 and 2).

Mechanisms postulated to explain the increased perinatal risks in pregnant asthmatic women demonstrated in previous studies have included hypoxia and other physiologic consequences of poorly controlled asthma, medications used to treat asthma, and pathogenic or demographic factors associated with asthma but not actually caused by the disease or its treatment, such as abnormal placental function. There are data to show that suboptimal control of asthma or more severe asthma during pregnancy is associated with increased maternal or fetal risk.

Asthma may worsen, improve, or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequency. Asthma is likely to be more severe or to worsen during pregnancy in women with more severe asthma before becoming pregnant.

The mechanisms responsible for the altered asthma course during pregnancy are unknown. The myriad of pregnancy-associated changes in levels of sex hormones, cortisol and prostaglandins may contribute to changes in asthma course during pregnancy. In addition, exposure to fetal antigens, leading to alterations in immune function may predispose some pregnant asthmatics to worsening of asthma. Even fetal sex may play a role, with some data showing increased severity of symptoms in pregnancies with a female fetus.

Once the diagnosis of asthma is confirmed (Table 3), a decision regarding the need for controller medication versus rescue medica-

TABLE 1

Adverse maternal outcomes reported to be increased in pregnant asthmatic women

- Abortion
- Hyperemesis gravidarum
- Gestational diabetes
- Chorioamnionitis
- Pregnancy-induced hypertension or preeclampsia
- Antepartum hemorrhage
- Placental complications
- Preterm labor
- Complicated labor
- Cesarean section
- Preterm birth
- Post-partum hemorrhage

TABLE 2

Adverse fetal outcomes reported to be increased in infants of asthmatic women

- Low birth weight
- Preterm birth
- Small for gestational age
- Congenital anomalies
- Stillbirth
- Low APGAR scores at birth

TABLE 3

Differential diagnosis of dyspnea during pregnancy

- Asthma
- Dyspnea of pregnancy
- Reflux esophagitis
- Post nasal drainage
- Bronchitis
- Laryngeal dysfunction
- Hyperventilation
- Pulmonary edema
- Pulmonary embolism

tion can be made (Table 4). Inhaled corticosteroids are the mainstay of controller therapy during pregnancy. Because it has the most published human gestational safety data, budesonide is considered the preferred ICS for asthma during pregnancy. That is not to say that the other ICS preparations are unsafe. Therefore, ICS other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy, especially if it is thought that changing formulations may jeopardize asthma control. Controller therapy should be increased in steps (Table 5) until adequate control is achieved.

Adherence to therapy can change during pregnancy with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus. For example, one study found that less than 40% of women who classified themselves as "poorly controlled" reported use of a controller medication during pregnancy.

Patient education is an important part of the management of the pregnant asthmatic. Each patient should be provided basic information about asthma and the relationship between asthma and pregnancy. Monthly visits to assess asthma control and adherence are recommended for women who require controller therapy during pregnancy. Each patient should also receive a self-treatment action plan that includes how to recognize a severe exacerbation and when to seek urgent or emergency care (Table 6).

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TABLE 4

Safety of commonly used medications for the treatment of asthma during pregnancy *

Drug	FDA	Perinatal Outcome
Inhaled Bronchodilators Short-acting Bronchodilators	Albuterol(C)	Reassuring human data; some associations with specific malformations, but may be chance or confounding by severity
Long-acting bronchodilators	Formoterol(C) Salmeterol(C)	Minimal human data has been reassuring
Theophylline		No increase in congenital malformations ; toxicity may be an issue
Inhaled Corticosteroids	Budesonide (B) Beclomethasone (C) Fluticasone (C) Mometasone (C) Triamcinolone (C)	Substantial reassuring data. Risk of increased malformations with high dose, but may be confounding by severity. Most data for budesonide.
Leukotriene Receptor Antagonists	Montelukast (B) Zafirlukast (B)	Moderate amount of reassuring data
5-LO Inhibitors	Zileuton (C)	Animal studies not reassuring
Anti-IgE	Xolair (B)	Risk of low birth weight and preterm birth, but may be confounding by severity

** Adapted from Schatz M, Zeiger RS, Falkoff R, et al. Asthma and allergic diseases during pregnancy. In: Adkinson, NF, Yunginger, JW, Busse, WW, et al, editors. Middleton' s Allergy: Principles and Practice, 8 th edition. St. Louis, MO: Mosby, 2013 with permission from Elsevier.*

TABLE 5

Steps of asthma therapy during pregnancy *

Step	Preferred Controller Medication	Alternative Controller Medication
1	None	-
2	Low dose ICS	LTRA, theophylline
3	Medium dose ICS	Low dose ICS + either LABA, LTRA or theophylline
4	Medium dose ICS + LABA	Medium dose ICS + LTRA or theophylline
5	High dose ICS + LABA	-
6	High dose ICS + LABA + oral prednisone	-

ICS = inhaled corticosteroids; LTRA – leukotriene-receptor antagonists; LABA = long-acting beta agonists

**From N Engl J Med, Schatz M, Dombrowski MP, Clinical practice. Asthma in pregnancy, 360, 1862-1869 Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*

TABLE 6

Patient education for self-management of asthma during pregnancy *

Subject	Recommendation
General Information	Provide basic information about asthma and relationship between asthma and pregnancy
Use of inhaler device	Demonstrate proper technique for specific device and ask patient to perform the technique; demonstrate use of spacer device for metered-dose inhaler if patient's technique is suboptimal
Adherence to treatment	Discuss self-reported adherence to treatment with controller medication and, if needed, address barriers to optimal adherence (e.g. cost, convenience, concern about side effects)
Self-treatment action plan	Provide schedule for maintenance medication and doses of rescue therapy for increased symptoms; explain when and how to increase controller medication and when and how to use prednisone(for patients with previous prednisone use or poorly controlled asthma); explain how to recognize a severe exacerbation and when and how to seek urgent or emergency care

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23 WORK-RELATED ASTHMA

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KEY MESSAGES

- Occupational exposures are a significant contributor to the burden of asthma
- Work-related asthma can be classified into occupational asthma (OA) and work-exacerbated asthma
- OA is usually due to an allergic response to high or low-molecular weight agents. Less commonly OA can result from high-level irritant exposures at work
- The cornerstone for the diagnosis of OA is evidence of a causal relationship between exposure to the offending agent, clinical symptoms and changes in lung function
- In the evaluation of OA appropriate clinical, immunological and environmental investigations should be carried out in a stepwise fashion
- The appropriate management remains early removal from exposure with preservation of income

DEFINITIONS AND EPIDEMIOLOGY

Work-related asthma comprises two major entities (Figure 1): occupational asthma (OA), defined as a type of asthma caused by the workplace and work-exacerbated asthma (WEA), which refers to the worsening of asthma triggered by various work-related factors (e.g., irritants, aeroallergens, or exercise) in workers who are known to have pre-existing or concurrent asthma.

There are two major forms of OA:

- Allergic OA characterised by a latency period required for developing sensitisation prior to the development of symptoms.
- Non-allergic irritant-induced OA characterised by the onset of asthma following single (i.e. reactive airways dysfunction syndrome, RADS) or multiple exposures to high concentrations of irritant agents.

A significant excess asthma risk has been observed after exposure to substances known to cause OA. OA is the most common occupational lung disease in industrialised countries and the second most common work-related lung disease reported after pneumoconioses in developing countries. In a large longitudinal study, the population-attributable risk for adult asthma due to occupational exposures ranged from 10% to 25%, equivalent to an incidence of new-onset asthma of 250–300 cases per million people per year.

ETIOLOGY

More than 400 agents encountered at work have been reported to induce OA. These agents are categorized into high-molecular weight (HMW) compounds, which are proteins acting through an IgE-mediated mechanism, and low-molecular weight (LMW) compounds (<1000 Da), which are chemical sensitizers that, with few exceptions, are not associated with an IgE-dependent mechanism. Table 1 shows common causal agents of allergic OA. A more comprehensive list of etiologic agents can be found at: http://www.eaaci.org/sections-a-igs/ig-on-occupational-allergy/allergen-list.html and http://www.asthme.csst.qc.ca/document/Info_Gen/AgenProf/Bernstein/BernsteinAng.htm (accessed May 20, 2013).

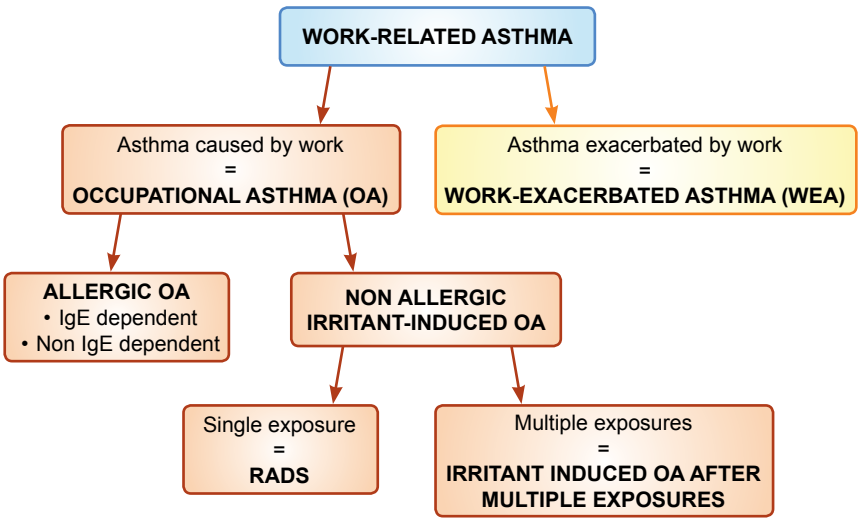

Figure 1 Classification of work-related asthma. RADS - Reactive Airways Disfunction Syndrome. *(Reproduced from Moscato G, Pala G, Barnig C, et al. European Academy of Allergy and Clinical Immunology. EAACI consensus statement for investigation of work-related asthma in non-specialized centres. Allergy 2012;67:491-501, with permission from Wiley-Blackwell.)*

TABLE 1

Common specific agents and jobs associated with allergic occupational asthma

Causal agents	Selected jobs or industries
High-molecular weight compounds	
Cereals and flour	Bakers and pastry makers, grain handlers
Animal epithelia, hairs, secretions	Farmers, livestock workers, veterinaries
Seafood and other food-derived proteins	Food processors, cooks, butchers
Latex proteins	Healthcare and social workers
Enzymes (from bacterial, fungal and plant origin)	Detergent industry workers, researchers, bakers, food technology
Vegetal gums	Printing, food industry, carpet manufacture
Insects, mites	Farmers, greenhouse workers, researchers
Low-molecular weight compounds	
Isocyanates	Spray painters, lacquerers, foam workers
Metals (e.g. platinum, nickel sulfate)	Alloy and refinery workers, electroplating
Persulfate salts	Hairdressers
Acrylates (methacrylate, cyanoacrylate)	Glue handlers, dentists, artificial nail workers
Aldehydes (e.g. glutaraldehyde)	Hospital and laboratory workers
Acid anhydrides (e.g. trymellitic anh.)	Plastics industry, eposy resins workers
Amines (e.g. ethanolamine)	Metal workers (cutting fluids), various
Soldering flux (colophony)	Welders
Mixed or uncertain relevant compounds	
Wood dust (red cedar, iroko, obeche, etc)	Woodworkers, carpenters, sawmill workers

Bakers and pastry makers, spray painters, cleaners and healthcare workers are the occupations consistently associated with a higher incidence of OA. The main causes of OA include isocyanates, cereal flour/grain dust, welding fumes and wood dust.

NATURAL HISTORY AND RISK FACTORS

OA is the result of an interaction between multiple genetic, environmental, and behavioral influences. Rhinoconjunctivitis often precedes the onset of IgE-mediated OA and it should be considered an important risk factor for OA.

Although many factors influence the host response after exposure to workplace agents, four determinants have received particular attention: level of exposure (the higher the exposure, the greater

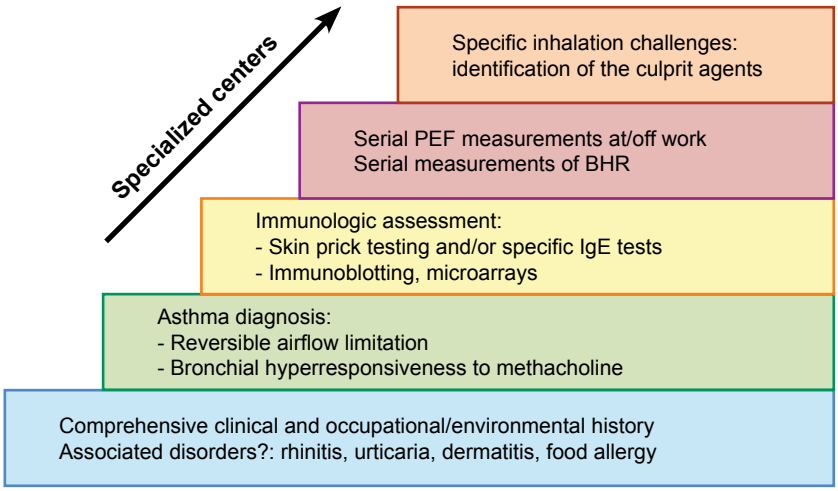

Figure 2 Stepwise approach for the clinical investigation of suspected work-related asthma. (PEF - peak expiratory flow; BHR - bronchial hyperresponsiveness to methacholine/histamine).

the risk); atopy, which is considered a risk factor for IgE-mediated sensitization to HMW agents, although atopy itself is a weak predictor of development of OA; cigarette smoking (shown to be a risk factor for the development of specific IgE antibodies against occupational agents, although not necessarily for asthma); and genetic predisposition.

DIAGNOSIS

The primary goal for diagnosing OA is to demonstrate a causal relation between exposure to a specific agent encountered at work and asthmatic responses. Facts that reinforce the suspicion of work-relatedness of asthma are summarized in Table 2. A stepwise approach is often used (Figure 2). The advantages and disavantages of the different diagnostic methods are shown in Table 3.

Specific inhalation challenge tests have been proposed as the gold standard in the diagnosis of OA. Evaluation of airway inflammation using non-invasive methods such as exhaled nitric oxide and induced sputum to assess inflammatory cells and soluble markers of cell activation can be used as an adjunct to making the diagnosis of OA.

MANAGEMENT AND PROGNOSIS

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causal agent, in workers who have relatively normal lung function at the time of diagnosis, and in workers who have shorter duration of symptoms prior to diagnosis or prior to avoidance of exposure. Thus, early diagnosis and early avoidance of further exposure are the cornerstones of patient management for patients with allergic OA (Table 4). Whenever feasible the patient should be relocated to a job category without exposure. For patients with irritant-induced asthma, however, they usually may keep working in the same job, provided measures are taken to prevent further exposures to high concentrations of irritant agents.

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TABLE 2

Facts that reinforce the suspicion of work-relatedness of asthma *

- Recognition of high-risk jobs and/or exposure to known sensitizers
- Co-existence of allergic symptoms on other organs: rhinitis, conjunctivitis, contact urticaria
- Other coworkers affected
- Special events related with symptoms onset (new products used, new tasks, change in work practices, accidental exposures)
- Absence of response to conventional asthma therapy
- Personal risk factors (atopy, rhinitis, genetic background)

** Reproduced from Quirce S. Occupational asthma. In: Polosa R, Papale G, Holgate ST, editoris. Advances in Asthma Management. London: Future Medicine Ltd, 2012; 88-102.*

TABLE 3

Advantages and disadvantages of diagnostic methods for occupational asthma *

Method	Advantages	Disadvantages
Clinical history	Simple, sensitive	Low specificity
Immunologic testing	Simple, sensitive	Valid only for some agents; identifies sensitization not disease; lack of standardized extracts
Bronchial responsiveness to methacholine	Simple, sensitive	Not specific for asthma or OA; OA not ruled our by a negative test
Serial PEF monitoring at work and off work	Relatively simple, affordable	Depends on patients' cooperation; no standardized interpretation
Specific inhalation challenge in the laboratory	If positive, confirmatory	If negative, diagnosis not ruled out; few specialized centers; sophisticated equipment
Workplace challenge	If negative under usual work conditions rules out diagnosis	A positive test may be due to irritation; requires collaboration (worker and employer)
Biomarkers of airway inflammation	Assess inflammation, specificity of reaction	Different types of inflammation; research tool, not validated

** Reproduced from Quirce S. Occupational asthma. In: Polosa R, Papale G, Holgate ST, editoris. Advances in Asthma Management. London: Future Medicine Ltd, 2012; 88-102.*

TABLE 4

Management of occupational asthma

1. Work exposure
   - For sensitizer-induced occupational asthma, avoid any further exposure to causative agents. If this is not possible, then reduce exposure as low as possible
   - For irritant-induced occupational asthma avoid further high level exposure
2. Asthma treatment according to asthma guidelines
   - Assessment of asthma control and severity
   - Optimal pharmacotherapy, consider allergen immunotherapy
   - Avoidance of asthma triggers, environmental control
   - Patient's education
3. Assist patient with relevant compensation claim and rehabilitation
4. Consider other co-workers affected and notify public health and company

24 ASTHMA MANAGEMENT

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KEY MESSAGES

- The goal of asthma management is to achieve clinical control of the disease and of its risks
- Management of asthma requires a close partnership between patients and healthcare professionals
- Educational plans are important for self-management of asthma
- Prevention and avoidance of risk factors that may precipitate asthma are key elements of asthma management
- Regular treatment is recommended
- Asthma management should be adapted to every patient to maintain asthma control with the minimum dose of medication
- Asthma control should be assessed at regular intervals and treatment level should be adjusted accordingly

Asthma is a chronic inflammatory disease of the airways characterized by recurrent episodes of symptoms such as dyspnea, wheezing, chest tightness and/or cough. According to international guidelines the ultimate goal of asthma management is to achieve control of the disease in terms of symptoms, pulmonary function, prevention of asthma exacerbations while avoiding adverse effects from asthma medications. Although effective medications are available, asthma remains substantially poorly controlled in real life. The reasons are diverse, partially related to inadequate diagnosis or treatments or to low adherence to the prescribed inhalation treatment.

Solid partnership between patients and physicians/health care professionals is crucial to attain efficacious asthma management. Educational plans for patients play a major role in this partnership (Figure 1). Patients must be informed about the disease, how to prevent, treat and keep asthma under control. Tools for guided self-management such as written action plans developed with the health care professional should be provided, asthma control regularly assessed and treatment reviewed at regular intervals (Figure 2).

Asthma exacerbations are crucial events in the natural history of the disease. They are defined as a sudden and/or progressive worsening of asthmatic symptoms and may occur even in patients under regular treatment. Preventing risk factors could improve asthma control, reduce asthma exacerbations and treatment requirements. Thus, asthmatic patients should not smoke, avoid exposure to second hand smoke and reduce where possible, exposure to domestic allergens and occupational sensitizers. Foods, additives and drugs known to worsen asthma symptoms should be avoided. Since viral infections are the most frequent cause of asthma exacerbations, patients should be advised to receive influenza vaccination every year. Rhinitis, polyposis and sinusitis are comorbidities favoring poor asthma control; thus they should be adequately treated. Since pregnancy can undermine the control of the disease, pregnant women must be educated on the importance of adequate treatment during pregnancy for their own safety and for the safety for their babies. Asthma in obese asthmatics is often difficult to control. Weight loss should be pursued to improve asthma control (Figure 3).

Medications for asthma are classified as controllers (to be taken on regular basis) and relievers (they provide rapid relief of asthma symptoms). They are administered by inhalation: this is an effective way to reach the airways and to limit systemic side effects. The main controller medications are inhaled corticosteroids that switch-off the inflammation of asthmatic airways; long acting bronchodilators (β2 agonists) can be added when asthma is not adequately controlled. Other secondary controller medications include antileukotriens, theophylline or anti-IgE monoclonal antibodies in selected patients with severe allergic asthma (Figure 4).

Reliever medications (β2 fast acting agonists) are prescribed in every step of asthma severity. They have the ability to obtain a rapid bronchodilation in a very short time. A frequent use of reliever medication is a marker of poor controlled asthma.

Asthma is "controlled" when patients have no clinical symptoms such as day time symptoms (or less than twice/week) and/or nocturnal symptoms/ awakening for asthma, no limitation of their daily activities, no need use for the reliever medication (or less than twice/week) and have a normal lung function (in terms of FEV1 or PEF) for over 4 weeks (Figure 5). Asthma treatment should be adjusted according to the level of asthma control and stepped-up until good control is achieved. Treatment should be stepped down when asthma control is stable and maintained for more than 3 months. Step-up and step-down should be adapted to every patient in order to maintain asthma control with the minimum dose of medication (Figure 6).

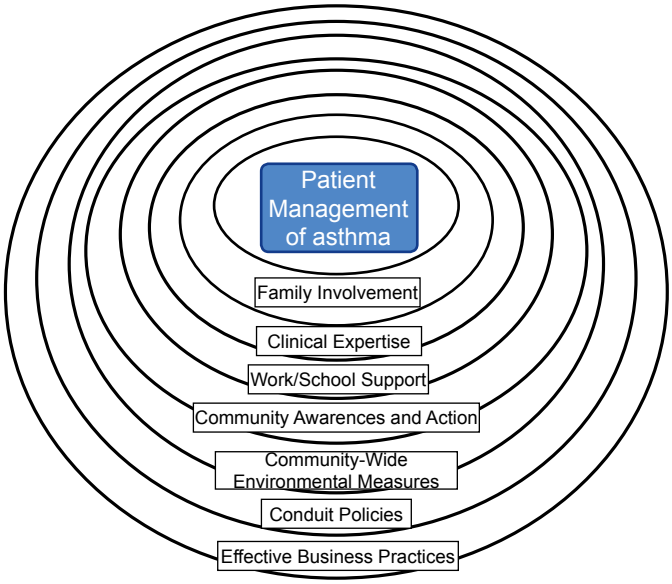

Figure 1 The circle of influence on management of asthma. Each ring represents people from family involvement, school or work, organizations, business practices and programs that turn around the patient represented at the center of the circle. *(Reproduced with permission from the American College of Chest Physicians from Clark NM, Partridge MR. Strengthening asthma education to enhance disease control. Chest 2002;121:1661-1669.)*

Asthma exacerbations should be treated by increasing the use of reliever medication and may require administration of systemic corticosteroids until improvement of symptoms is obtained. Less frequently severe exacerbations may lead to hospital admission, oxygen supplementation and mechanical ventilation.

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Your Regular Treatment:
1. Each day take _____
2. Before exercise, take _____

WHEN TO INCREASE TREATMENT
Assess your level of Asthma Control
In the past week have you had:

Daytime asthma symptoms more than 2 times ?	No	Yes
Activity or exercise limited by asthma?	No	Yes
Waking at night because of asthma?	No	Yes
The need to use your [rescue medication] more than 2 times?	No	Yes
If you are monitoring peak flow, peak flow less than_____?	No	Yes

If you answered YES to three or more of these questions, your asthma is uncontrolled and you may need to step up your treatment.

HOW TO INCREASE TREATMENT
STEP-UP your treatment as follows and assess improvement every day:
_____ [Write in next treatment step here]
Maintain this treatment for _____ days [specify number]

WHEN TO CALL THE DOCTOR/CLINIC.
Call your doctor/clinic: _____ [provide phone numbers]
If you don't respond in _____ days [specify number]
_____ [optional lines for additional instruction]

EMERGENCY/SEVERE LOSS OF CONTROL
✓If you have severe shortness of breath, and can only speak in short sentences,
✓If you are having a severe attack of asthma and are frightened,
✓If you need your reliever medication more than every 4 hours and are not improving.
1. Take 2 to 4 puffs _____ [reliever medication]
2. Take ____mg of _____ [oral glucocorticosteroid]
3. Seek medical help: Go to _____; Address_____
   Phone: _____
4. Continue to use your _____[reliever medication] until you are able to get medical help.

Figure 2 Example of an written action plan developed with the health care professional for self-management of asthma by the patient. (*Reproduced from the Global Strategy for Asthma Management and Prevention, 2012 with permission of Global Initiative for Asthma (GINA)).*

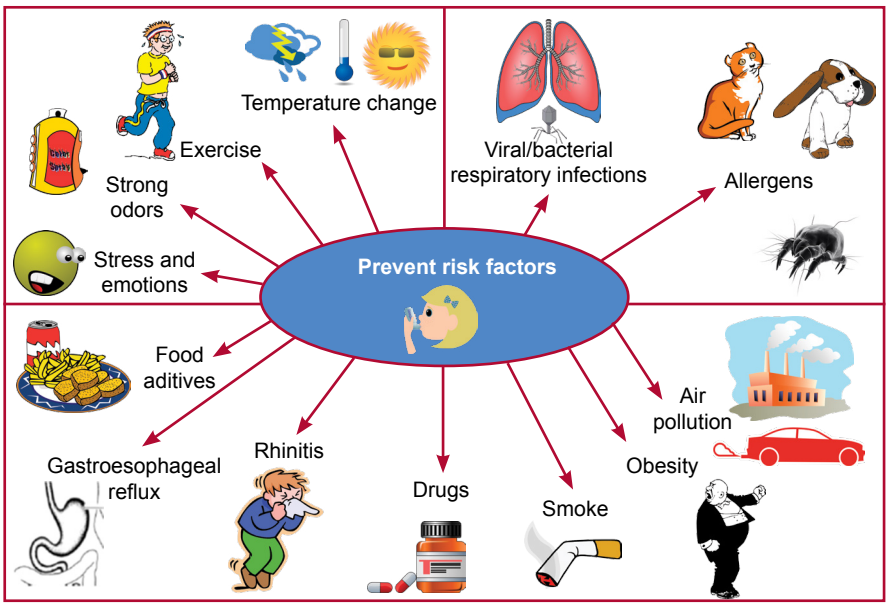

Figure 3 Risk factors for asthma exacerbations and/or poor control.

Treatment Steps

Reduce ← → Increase

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education. Environmental control. (If step-up treatment is being considered for poor symptom control, first check inhaler technique, check adherence, and confirm symptoms are due to asthma.)				
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options***	Select one	Select one	To Step 3 treatment, select one or more	To Step 4 treatment, add either
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2-agonist	Medium-or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium-or high-dose ICS Low-dose ICS plus leukotriene modifier	Leukotriene modifier Sustained release theophylline	Anti-IgE treatment
		Low-dose ICS plus sustained release theophylline		

* ICS = inhaled glucocorticosteroids
**= Receptor antagonist or synthesis inhibitors
*** = Recommended treatment (shaded boxes) based on group mean data. Individual patient needs, preferences, and circumstances (including costs) should be consic

Figure 4 Treatment steps on asthma. Asthma medications are divided in relievers and controllers. The reliever medications must be prescribed in each step. The main controller medications are inhaled corticosteroids; long acting bronchodilators (β2 agonists) can be added when asthma is not adequately controlled. When patients are not controlled with optimal doses of inhaled glucocorticoids in combination with long acting β2 agonists other adjunctive secondary controller medications might be considered. (*Reproduced from the Global Strategy for Asthma Management and Prevention, 2012 with permission of Global Initiative for Asthma (GINA)).*

A. Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	**Controlled (All of the following)**	**Partly Controlled (Any measure present)**	**Uncontrolled**
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/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 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.

Figure 5 Levels of asthma control evaluating daytime and nocturnal symptoms, limitation of activities, needs for reliever medication, lung function and exacerbation. (*Reproduced from the Global Strategy for Asthma Management and Prevention, 2012 with permission of Global Initiative for Asthma (GINA)).*

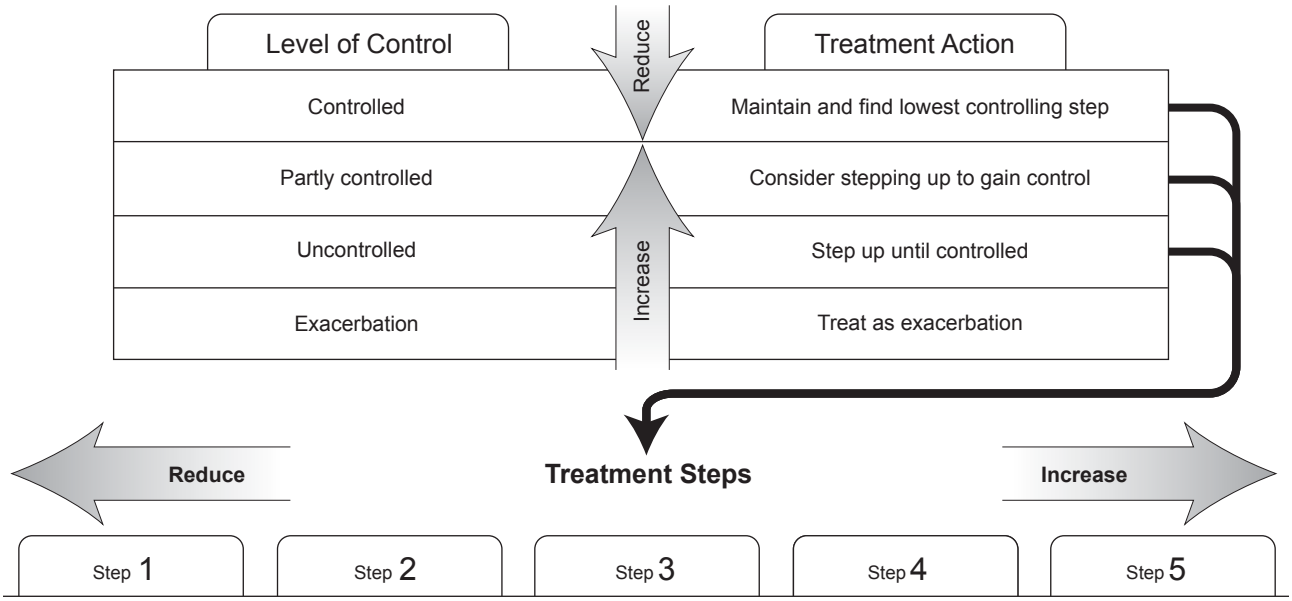

Figure 6 Step up and step down of treatment should be adapted to every patient in order to maintain asthma control with the minimum dose of medication. (*Reproduced from the Global Strategy for Asthma Management and Prevention, 2012 with permission of Global Initiative for Asthma (GINA)).*

25 ASTHMA MONITORING

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KEY MESSAGES

- Asthma monitoring is a collaboration between the patient and the medical team
- Successful monitoring helps to achieve good control and reduces hospitalisation
- Monitoring is only useful if the results are acted upon
- Asthma monitoring should be incorporated with a pre-specified written asthma management plan
- For most people with asthma, self-monitoring through recognition of key symptoms is sufficient
- People with more severe asthma, or those who have difficulty recognising changes in severity, may benefit from more detailed monitoring
- Monitoring may also be helpful in specific situations such as assessing response to a trial of treatment or diagnosis of occupational airways disease
- Emerging technologies (electronic monitors, telemonitoring) and biomarkers have great potential but more research is needed

The variable nature of asthma means that active monitoring is required to optimise treatment. The aim of monitoring is to assess disease control and allow proactive changes in management. When successful, this approach leads to reduced symptoms, improved quality of life and fewer serious events such as hospitalisation. Proactive monitoring also permits prompt reduction in medication, where appropriate, minimising side-effects.

There are many forms of monitoring, both community and clinic based (Figure 1), but to succeed, all rely on a collaboration between the patient and medical team. Monitoring is not a therapeutic end in itself, to be useful results must be acted upon. Monitoring options include relying on symptoms, reliever use, measures of airflow obstruction and biomarkers (Table 1).

SYMPTOMS AND MEDICATION USE

The simplest and most commonly used form of monitoring is based on recognition of key symptoms. For the majority of people with asthma, their symptoms and need for reliever inhalers are accurate guides to disease activity. When patients are provided with an agreed written asthma management plan (Figure 2), they are able to respond to changes in symptoms with appropriate changes in medication and to seek help promptly where appropriate.

Patients with moderate to severe disease, and those who are poor perceivers of changes in asthma control, may benefit from the addition of peak flow measurements at home.

In the clinic setting, patient's controller adherence, exacerbation history and asthma control should be reviewed. Short questionnaires such as the Asthma Control Test (ACT) may improve consistency of assessment over time.

MEASURES OF AIRFLOW OBSTRUCTION / AIRWAY RESPONSIVENESS

The degree of airway narrowing in asthma varies over time and is usually assessed with tests of lung function such as spirometry or peak flow monitoring. Spirometry

Figure 1 Different forms of asthma monitoring.

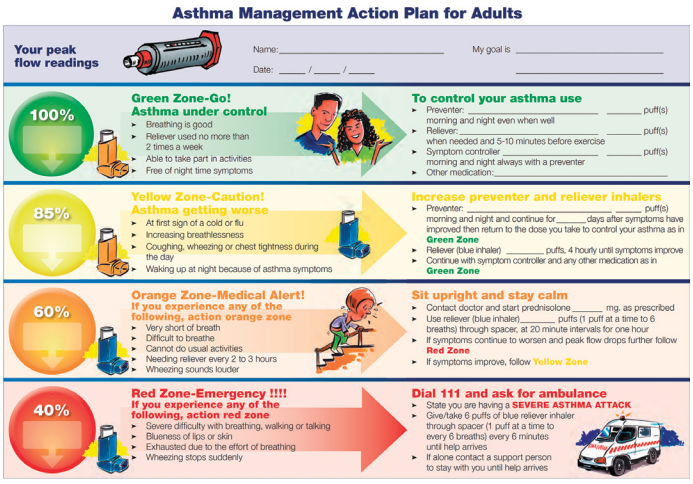

Figure 2 Example of an Asthma Management Plan. (Asthma New Zealand)

TABLE 1

Patient education for self-management of asthma during pregnancy

Causal agents	Selected jobs or industries
Symptoms and medication use	• Symptoms and limitation of activity • Reliever use • Controller adherence • Symptom questionnaires, e.g. ACT • Electronic symptom monitoring
Exacerbation history in past year	• Number of exacerbations • Number of courses of oral steroids
Measures of Airflow obstruction / responsiveness	• Peak Flow Meter • Spirometry • Airways responsiveness
Biomarkers / Inflammometry	• Induced sputum • Exhaled nitric oxide • Blood biomarkers

First line techniques which can be used in any setting, including the home

Techniques suitable for primary and secondary care

Techniques best suited to specialist care

Emerging techniques not yet proven to be clinically beneficial for long term monitoring

requires more expensive equipment and staff training and is mainly used in primary care or hospital settings, whereas peak flow meters can be used anywhere, including the home.

All airflow measurements show some natural variation over time but large variations in peak flow suggest poorly controlled asthma. Patients with asthma and significant variability in their peak flow show an improvement in peak flow and a reduction in variability once treated with inhaled corticosteroids (Figure 3).

Peak flow monitoring is simple, relatively inexpensive, and widely available, and therefore features prominently in current asthma guidelines. However, values are effort dependent, a single reading provides limited information, and diaries are reviewed only in retrospect. There is accordingly interest in methods of electronic PEF monitoring which may provide a more accurate and contemporaneous assessment.

EMERGING TECHNOLOGIES / ELECTRONIC MONITORING

The simplest forms of electronic monitoring are electronic diaries, which prompt the patient to take a peak flow reading and then enter it into the diary. These may improve adherence to treatment and monitoring and are widely used in clinical trials, however as yet they have not been shown to improve patient outcomes.

Telemonitoring, where information on symptoms and peak flow is collected regularly and reviewed remotely, has the potential to improve outcomes if it aids recognition of worsening control and treatment is changed appropriately. Trials have suggested that patients like telemonitoring systems, but have not consistently shown an improvement in control or reduction in exacerbations. Potential alternatives could include inhalers with built-in monitoring devices which recognise increasing reliever use and prompt the patient to seek early medical review, as patient symptoms, peak flow readings and rescue inhaler use increase up to 10 days before an exacerbation is recognised and treated (Figure 4).

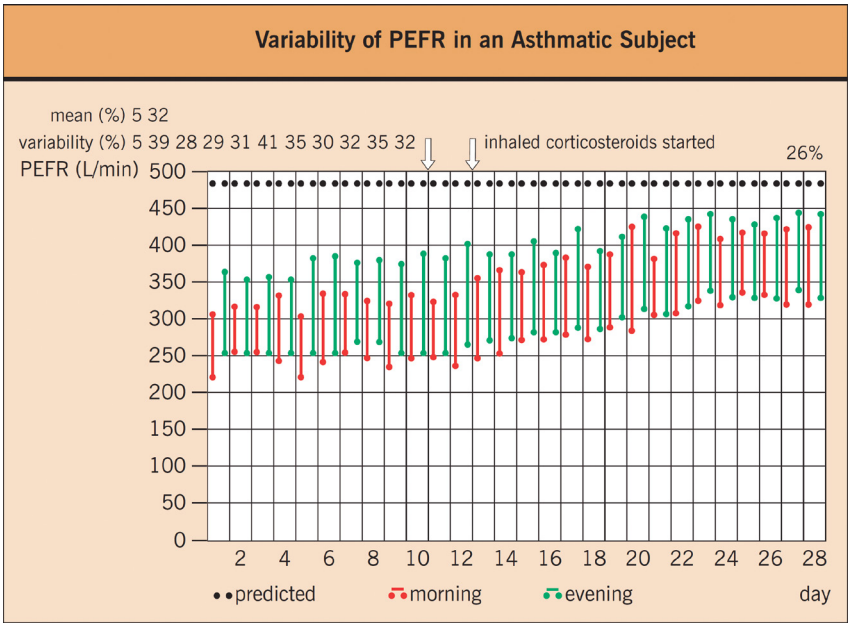

Figure 3 Example of a peak flow diary showing improved peak flow and reduced variability in response to starting a steroid inhaler. (Reprinted from Allergy, 3rd edition, Platts-Mills T AE, Adachi M, Pauwels RA, et al, Asthma, 26, Copyright 2006, with permission from Elsevier.)

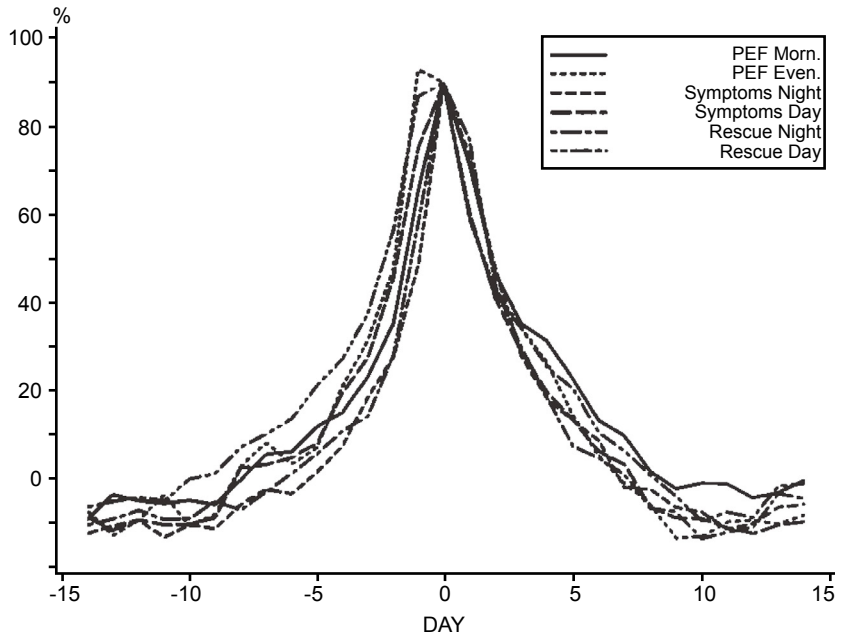

Figure 4 Change in peak flow, symptoms and rescue inhaler use around an exacerbation. Day 0 is the day an exacerbation was diagnosed. (*Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Crit Care Med 1999;160:594-599. Official journal of the American Thoracic Society.)*

BIOMARKERS / INFLAMMOMETRY

As some people with asthma are recognised to be "poor perceivers" of worsening control, and measures of airflow obstruction are effort dependent, there is considerable interest in identifying biomarkers that can effectively identify patients at high risk of future exacerbation or who may benefit from a change in treatment. As yet there are no biomarkers which are suitable for widespread use in guiding treatment, but research is ongoing into different techniques including induced sputum examination and exhaled nitric oxide measurement, as well as possible blood biomarkers which may guide doctors about the type and severity of inflammation in the lung and the type of treatment a patient may respond to. As our knowledge of biomarkers improves, the prospect of true personalised medicine, where proactive monitoring leads to the right medication for an individual at the right time, should become a reality.

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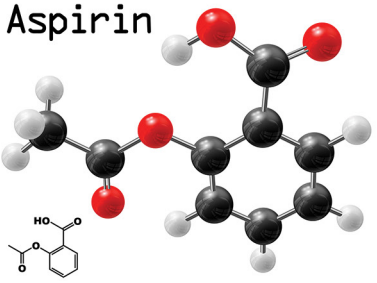
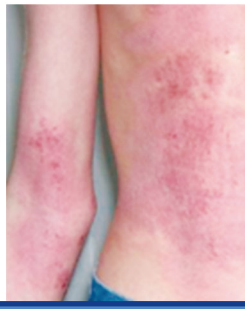
Section B





DISEASES ASSOCIATED WITH ASTHMA

* Atopy and asthma
* Upper airway diseases and asthma
* Asthma and obesity, the twin epidemics
* Aspirin exacerbated respiratory disease
* Gastro-esophageal reflux disease and asthma
* Cardiovascular diseases and asthma
* Food allergy and asthma
* Skin and lung: atopic dermatitis, urticaria and asthma

1 ATOPY AND ASTHMA

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KEY MESSAGES

- Asthma and atopy are closely linked
- Atopy is a risk factor for asthma, especially in children
- Asthma and rhinitis commonly co-exist
- The epidemiology suggests the causes of asthma and allergic sensitisation are probably different
- Treating rhinitis may improve asthma symptoms, especially cough
- Allergic triggers are important in asthma, but allergen avoidance has been disappointing as a means of controlling asthma

The association between atopy and asthma has long been recognised: asthma and other allergic conditions often run in families, and many patients are aware of allergic triggers for their asthma. Atopic eczema is often the first sign that a child has the atopic phenotype, and may go on to develop rhinitis and asthma as they grow up. About 75% of adults with asthma have allergic rhinitis and 50% of people with allergic rhinitis have asthma, although this is not always clinically recognised. Genetic studies have identified several candidate genes, some of which are linked to regulation of Th2-pattern cytokines or epidermal barrier function. However, the variability of the clinical phenotype suggests that the development of clinically apparent atopic disease involves complex gene-environment interactions (Figure 1).

Both asthma and childhood wheezing illness have increased steadily over the past 50 years, in parallel with increasing rates of other atopic conditions such as rhinitis, eczema and food allergy. Studies of the natural history of asthma showed that wheeze in the first 3 years of life often resolves, whereas persistent asthma often starts after the age of three years. Wheezing up to the age of 18 months is unrelated to the risk of developing atopy by age seven years, but being atopic is linked to wheeze that persists into later childhood. In other words, early wheeze is likely to be driven by infection but atopy is a key risk factor for persistent asthma.

How allergy and other inflammatory processes interact to produce the acute and chronic features of asthma should be envisaged in a complex framework (Figure 2). Having an atopic parent increases the risk of developing asthma, but this risk interacts with risks conferred by maternal smoking: children with one atopic parent are seven times more likely to develop allergic sensitisation and 5.7 times more likely to wheeze if their mother smokes during or after pregnancy, as compared to having a non-smoking mother.

However, the general increase in rates of asthma cannot be blamed solely on allergic sensitisation. We have done many things to improve our living conditions which have made our houses more friendly to house dust mites, and the allergen concentrations in European houses have increased dramatically over the past 50 years, but the overall rate of house dust mites (HDM) sensitisation has not changed anything like as much as the rate of asthma.

Asthma and rhinitis commonly co-exist. The nasal and airway mucosa are similar and show similar patterns of cellular inflammation after exposure to allergens. Rhinitis

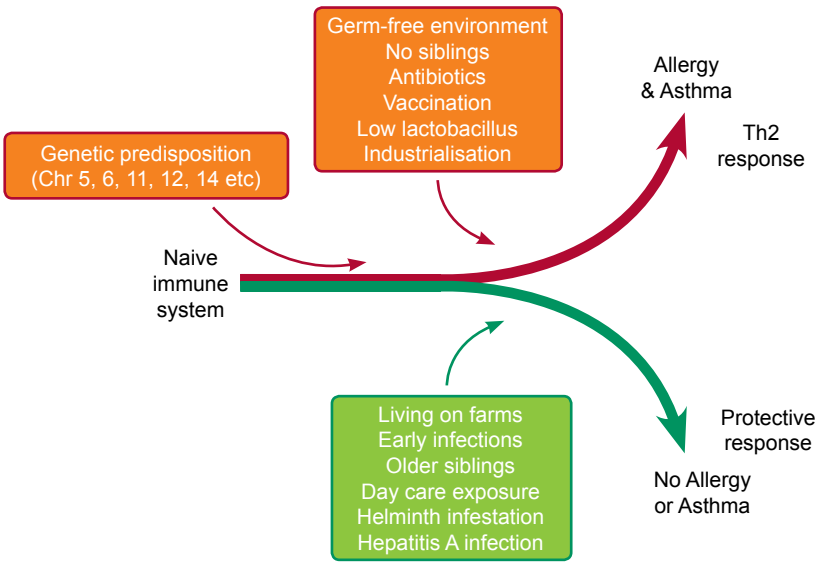

Figure 1 Risk factors for the development of atopy and asthma.

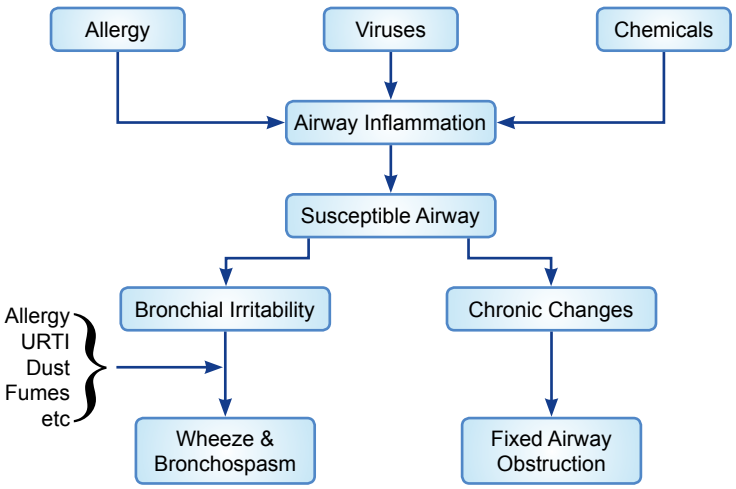

Figure 2 Conceptual framework showing how allergy and other inflammatory processes interact to produce the acute and chronic features of asthma. URTI - upper respiratory tract infection.

is present in about 75% of people with asthma; conversely asthma is present in about 50% of people with allergic rhinitis. Treating rhinitis improves asthma control. This may be through damping down the systemic effects of eosinophilic inflammation in the nose, or it may be simply due to reduction in nasal secretions dripping down onto the larynx. Either way it is important to recognise rhinitis in patients with asthma and treat it appropriately.

The link between atopic eczema and asthma is less clear-cut. Being atopic is a risk factor for developing asthma, so eczema and asthma are linked, but there is no evidence that treating eczema alters the natural history of asthma.

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2 UPPER AIRWAY DISEASES AND ASTHMA

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KEY MESSAGES

- Global airway disease should be evaluated in patients presenting with chronic upper or lower airway symptoms
- Both allergic and non-allergic rhinitis represent risk factors for the development of asthma
- Chronic rhinosinusitis with/without nasal polyps often occur together with asthma
- The interaction between chronic upper and lower airway inflammation has primarily been studied in allergic individuals
- The presence of asthma is a negative predictor of outcome after endoscopic sinus surgery for chronic rhinosinusitis with/without nasal polyps

Due to its' strategic position at the entry of the airways, the nose plays a crucial role in airway homeostasis. By warming up, humidifying and filtering the inspired air, the nose is essential in the protection and homeostasis of the lower airways. The nose and bronchi are linked anatomically, and both are lined with a pseudo-stratified respiratory epithelium and equipped with an arsenal of innate and acquired immune defense mechanisms. It is not hard to imagine that nasal pathology bypassing the function of the nose may become a trigger for lower airway pathology in susceptible individuals. It is however evident that the nasobronchial interaction is not restricted to bronchial repercussions of hampered nasal function. The nose and bronchi seem to communicate via mechanisms such as neural reflexes and systemic pathways (Figure 1). Bronchoconstriction following exposure of the nose to cold air suggests that neural reflexes connect nose and lung. The neural interaction linking the release of inflammatory mediators in the bronchi following a nasal inflammatory stimulus has recently been shown by bronchial release of neural mediators after selective nasal allergen provocation. The systemic nature of the interaction between nose and bronchi involves the blood stream and bone marrow (Figure 2). In addition, genetic factors may as well play a role in the manifestation of nasal and/or bronchial disease.

In the context of global airway disease, it is important to recognize the epidemiologic and pathophysiologic link between upper and lower airways (Figure 3). Both allergic as well as non-allergic rhinitis are major risk factors for the development of asthma. Therefore, it is not a surprise to find that most patients with asthma present with symptomatic or even asymptomatic upper airway inflammation. Beside rhinitis, asthma patients are more susceptible to develop recurrent acute or chronic rhinosinusitis (CRS). Interestingly, most patients with CRS who do not report to have asthma show bronchial hyperresponsiveness when given a metacholine challenge test. Histopathologic and immunologic features of CRS and asthma largely overlap. Recently, the nasal application of *Staphylococcus aureus* enterotoxin B has been shown to aggravate the allergen-induced bronchial eosinophilia in a mouse model. Medical treatment for CRS has been shown to be beneficial for asthma, as well as endoscopic sinus surgery (ESS). Interestingly, the presence of lower airway disease may have a negative impact on the

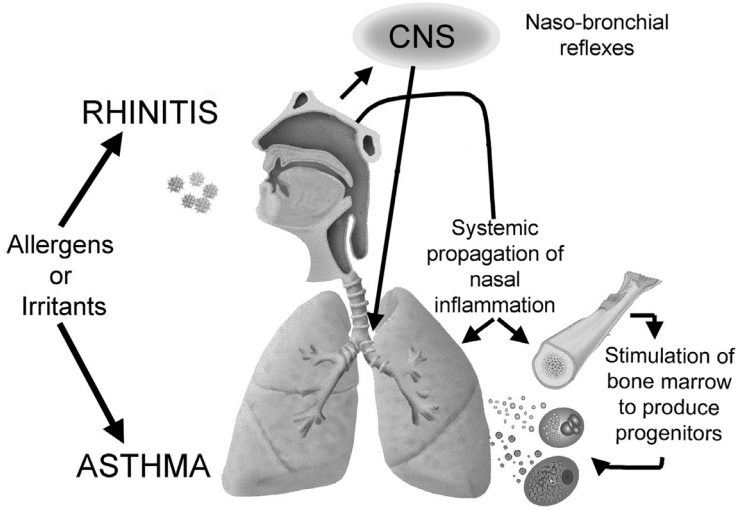

Figure 1 Mechanisms explaining the naso-bronchial interaction. *(Modified from Bergeron C, Hamid Q. Relationship between Asthma and Rhinitis: Epidemiologic, Pathophysiologic, and Therapeutic Aspects. Allergy Asthma Clin Immunol 2005;1:81-87. Reprinted with permission under the Creative Commons Attribution License or equivalent.)*

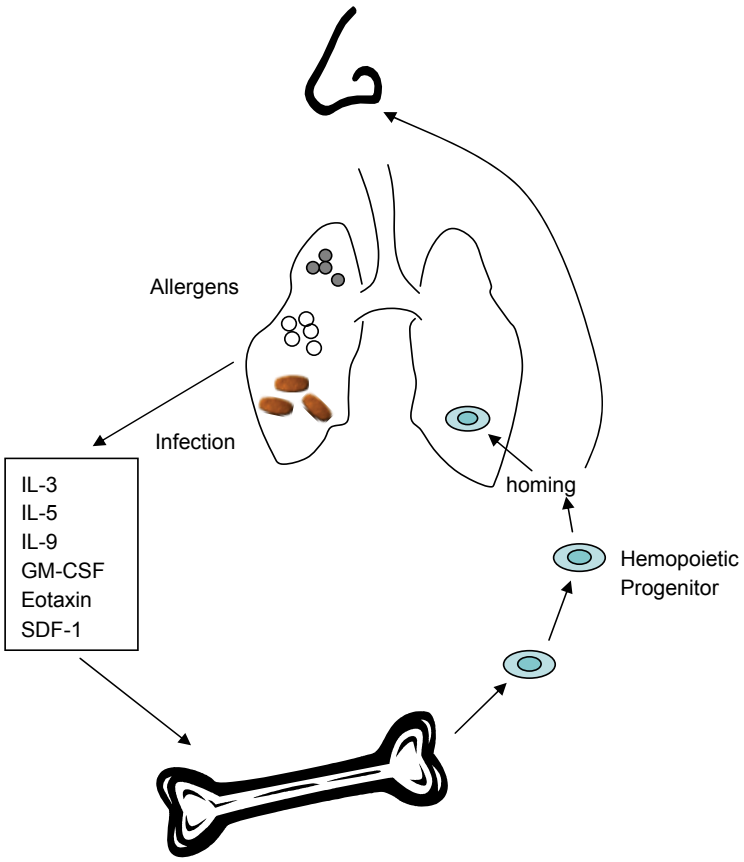

Figure 2 Systemic inflammation in asthma and rhinitis. *(Reproduced with permission from the American College of Chest Physicians from Denburg JA, Keith PK. Eosinophil progenitors in airway diseases: clinical implications. Chest 2008;134:1037-1043.)*

outcome after ESS. Poor outcomes after ESS have also been reported in patients with aspirin-intolerant asthma. Aspirin-intolerant asthma is a distinct clinical syndrome characterized by the triad aspirin sensitivity, asthma and nasal polyps (NP) and has an estimated prevalence of one percent in the general population and ten percent among asthmatics. Increased nasal colonization by *Staphylococcus aureus* and presence of specific IgE directed against *Staphylococcus aureus* enterotoxins were found in NP patients. Interestingly, rates of colonization and IgE presence in NP tissue were increased in subjects with NP and co-morbid asthma or aspirin sensitivity. By their superantigenic activity, enterotoxins may activate inflammatory cells in an antigen-unspecific way.

No well-conducted trials on the effects of medical therapy for NP on asthma have been performed so far. After ESS for NP in patients with concomitant asthma, a significant improvement in lung function and a reduction of systemic steroid use was noted, whereas this was

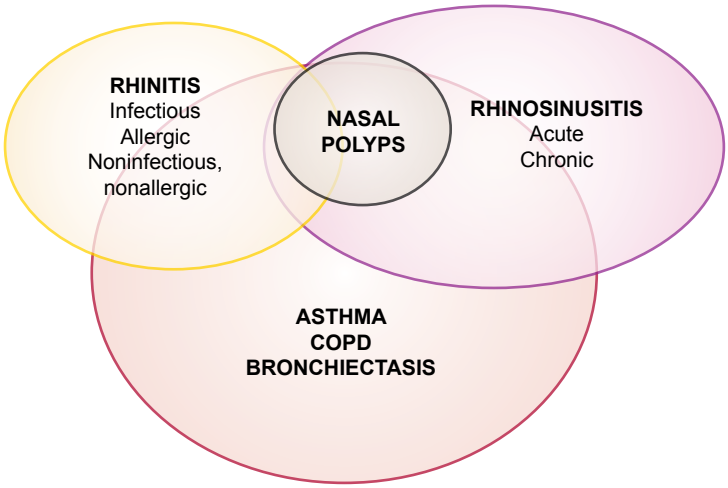

Figure 3 Global Airway Disease. *(Reproduced from Hellings PW, Prokopakis EP. Global airway disease beyond allergy. Curr Allergy Asthma Rep. 2010;10:143-149 with kind permission of Springer Science + Business Media.)*

not the case in aspirin-intolerant asthma patients. Data on effects of surgery for NP on asthma mostly point towards a beneficial effects of surgery on different parameters of asthma.

The upper airways of chronic obstructive lung disease (COPD) patients remain less studied than in asthma in spite of the fact that a majority of COPD patients presenting at an academic unit of respiratory disease do experience sinonasal symptoms (Figure 1). Several pro-inflammatory mediators have been found in nasal lavages of COPD patients and nasal symptoms corresponded with the overall impairment of the quality of life. A high number of patients with bronchiectasis have shown to present with rhinosinusitis symptoms, radiologic abnormalities on CT scans and have a reduced smell capacity. The impact of upper airway treatment in patients with COPD and bronchiectasis still needs to be properly investigated.

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3 ASTHMA AND OBESITY, THE TWIN EPIDEMICS

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KEY MESSAGES

- Asthma and obesity are related chronic disease epidemics
- Obesity modifies asthma, resulting in the obese-asthma phenotype
- The physiological changes in obese asthma include reduced expiratory reserve volume and airway closure during tidal breathing
- Adipose tissue is inflamed leading to proinflammatory cytokine and adipokine production
- Airway inflammation is altered to a non-eosinophilic pattern
- These changes may contribute to treatment resistance in obese asthma
- Management of asthma in obese patients requires intervention at both the individual and societal levels
- Effective public health interventions are urgently required

Asthma and obesity are linked global chronic disease epidemics. The prevalence of both diseases is high and shows considerable geographic variation (Figure 1). Obesity can potentiate the development and clinical severity of asthma. Like all chronic disease epidemics, asthma and obesity often begin in childhood and several different chronic different diseases may occur in the same person. The approach to prevention and treatment of the asthma and obesity epidemics needs to be long-term and systematic.

Obesity modifies the clinical expression of asthma, resulting in the obese-asthma phenotype (Table 1). Deposition of adipose tissue in the thoracic and abdominal regions leads to lung restriction and physiological changes such as reduced expiratory reserve volume (the earliest change in static lung volumes) and airway closure during tidal breathing. This results in loss of the 'physiological breathing space', the gap between tidal and maximal expiratory airflow (Figure 2). In obesity, asthma symptoms are worse, and response to asthma treatment is impaired. Adipose tissue is inflamed with an infiltration of macrophages and mast cells, leading to proinflammatory cytokine and adipokine production (Figure 3). This results in chronic low-grade systemic inflammation with elevated C-reactive protein levels and increased cardiovascular risk. In obese asthma, the changes in adipokines such as leptin are enhanced (Figure 4), and the pattern of airway inflammation is altered to a non-eosinophilic pattern, with elevated neutrophils in women with obese asthma. These changes may contribute to treatment resistance in obese asthma.

Obesity results from an imbalance between caloric intake and energy expenditure. This includes eating excessive amounts of food that is high in saturated fat and reducing physical activity levels. Both of these changes are increasingly prevalent in modern urbanized societies, and identify the important social and political dimensions to obesity and its management. Consumption of a meal that is high in saturated fat leads to systemic inflammation with elevated C-reactive protein in obese asthma. There are, in addition, changes to the asthmatic airway indicating activation of innate immune responses with elevated gene expression for

Toll-like receptor 4 and elevated neutrophils, and activation of the pathways as depicted in Figure 3. The associated functional consequences include reduced bronchodilator responsiveness.

Management of obese asthma requires intervention at both the individual and societal levels. Weight loss leads to improved asthma and can even lead to resolution of asthma in some individuals. Weight loss can be achieved by caloric restriction and bariatic surgery. Increasing physical activity during weight loss can minimize the loss of lean body mass (skeletal muscle). The goals of weight reduction need to be clearly defined for individuals, and can be to reverse obesity or to improve the asthma. Large amounts of weight loss are required to reverse obesity, however only a modest weight loss of 10% body weight is sufficient to improve the medical complications of obesity, including asthma.

Effective public health interventions are urgently required at a societal level to manage the obesity epidemic, and its adverse impact on asthma.

TABLE 1

Characteristics of the obese asthma phenotype *
Worse asthma control
Decreased response to controller medication
Presence of comorbidities related to obesity
Presence of metabolic/immune derangements related to obesity

** Reproduced from Lugogo NL, Kraft M, Dixon AE, Does obesity produce a distinct asthma phenotype? J Appl Physiol 2010;108:729-734 with permission of The American Physiological Society.*

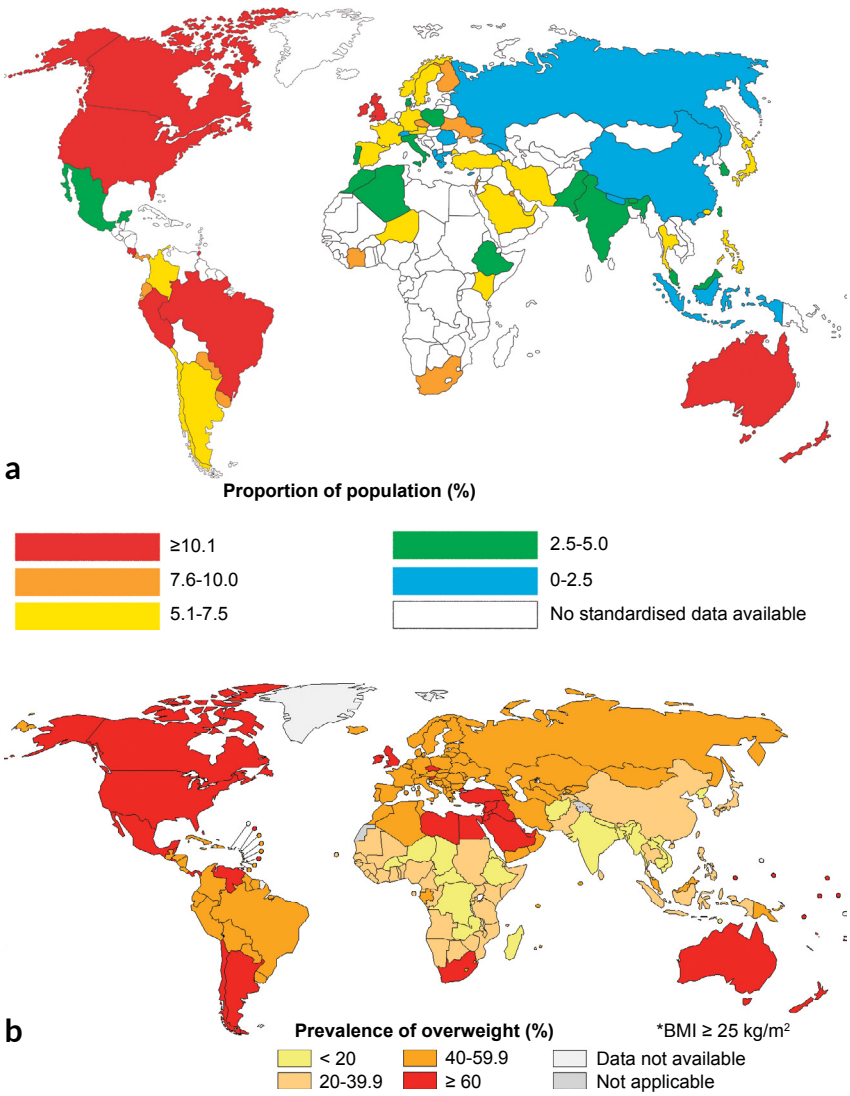

Figure 1 World map of the prevalence of asthma (panel a) and obesity (panel b). *(Panel a reproduced from Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-8 with permission from Wiley-Blackwell. Panel b reproduced from World Health Organisation, Global Health Observatory.)*

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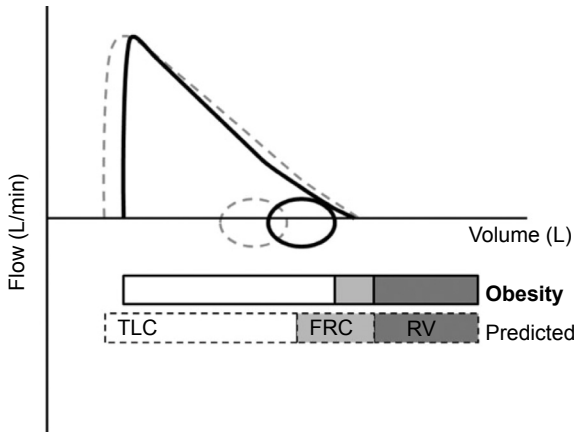

Figure 2 Effects of obesity (solid lines) on airway physiology. Compared to normal (dotted lines), obesity leads to reduced static lung volumes (bars) and airflow limitation during tidal breathing in the expiratory flow volume curve, resulting in loss of the 'breathing space', the gap between tidal flow and maximal expiratory flow. TLC - total lung volume; FRC - forced residual capacity; RV - residual volume *(Reproduced from Farah CS, Salome CM. Asthma and obesity: a known association but unknown mechanism. Respirology 2012;17:412-421 with permission from John Wiley and Sons, Inc.)*

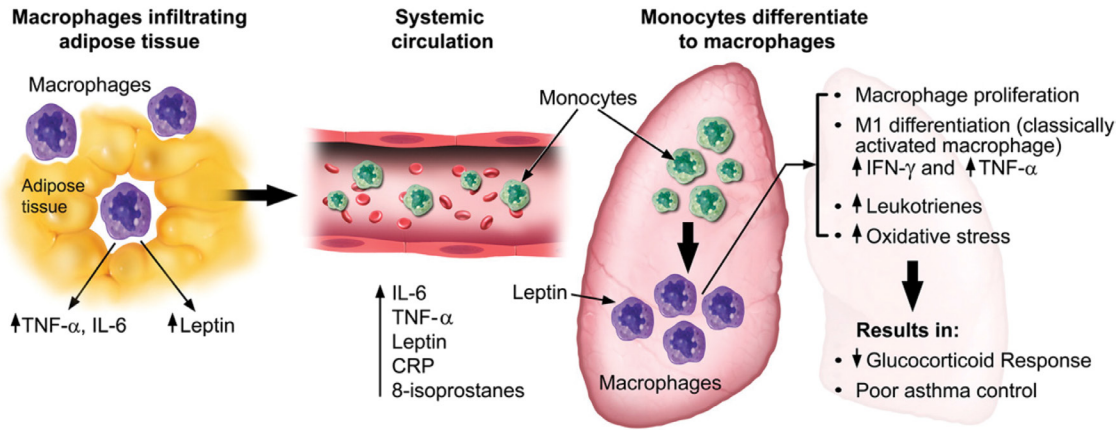

Figure 3 Inflammatory pathways in obesity leading to altered systemic and pulmonary inflammatory responses in asthma. *(Reprinted from Biochem Biophys Acta, 1810/11, Lugogo N, Bappanad, Kraft M. Obesity, metabolic dysregulation, and oxidative stress in asthma, 1120-1126, Copyright 2011, with permission from Elsevier.)*

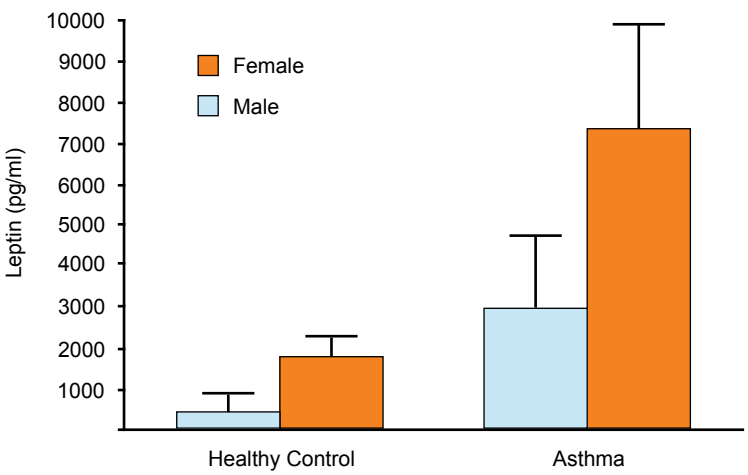

Figure 4 Elevated leptin in obesity and asthma, and effects of gender. *(Reproduced from Berthon BS, Macdonald-Wicks LK, Gibson PG, et al. An investigation of the association between dietary intake, disease severity and airway inflammation in asthma. Respirology 2013;18:447-454 with permission from John Wiley and Sons, Inc.)*

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4 ASPIRIN EXACERBATED RESPIRATORY DISEASE

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Sevim Bavbek
Ankara University
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KEY MESSAGES

- Aspirin Exacerbated Respiratory Disease (AERD) is a distinct phenotype of asthma with coexisting chronic rhinosinusitis, nasal polyps and hypersensitivity to aspirin and to other non-steroidal anti-inflammatory drugs
- AERD is characterized by an increased risk for uncontrolled upper and lower airway disease
- Patients with AERD require comprehensive and multidisciplinary diagnostic approach
- Management of asthma and rhinosinusitis in a patient with AERD is similar to other forms of asthma and rhinosinusitis
- Aspirin desensitization may be an effective treatment option for some AERD patients

DEFINITION AND CLINICAL CHARACTERISTICS OF AERD

Aspirin Exacerbated Respiratory Disease (AERD) is a distinct clinical syndrome observed in 5-10% of patients with asthma and characterized by history of acute dyspnea usually accompanied by nasal symptoms (rhinorrhoea and/or nasal congestion) within two hours after ingestion of acetylsalisilic acid (ASA) (Figure 1). These patients suffer from chronic, usually severe rhinosinusitis with recurrent nasal polyps and do not tolerate other non-steroidal anti-inflammatory drugs (NSAIDs), which are strong cyclooxygenase-1 (COX-1) inhibitors. The syndrome has been previously called "Aspirin-triad" or "Aspirin-Sensitive Asthma". Patients with AERD are quite heterogeneous with respect to asthma severity, presence of atopic sensitization (up to 70% may be atopic) and general responsiveness to treatment. However, on average AERD is associated with increased risk for severe asthma, frequent exacerbations and sudden death.

PATHOGENESIS OF AERD AND HYPERSENSITIVITY TO NSAIDS

The mechanism of hypersensitivity to ASA and NSAIDs in asthmatic patients is not immunological, but is related to inhibition of COX-1, an enzyme that converts arachidonic acid into prostaglandins, thromboxanes and prostacyclin. According to the " prostaglandin/cyclooxygenase theory" proposed by Andrew Szczeklik inhibition of COX-1 by ASA or other NSAID, by depriving the system from prostaglandin E2 (PGE2) triggers activation of inflammatory cells (mast cells, eosinophils and platelets) with subsequent release of inflammatory mediators, including cysteinyl leukotrienes (Figure 2). Baseline abnormalities of arachidonic acid metabolism (e.g. PGE2 deficiency and overproduction of leukotrienes), persistent viral infections, *Staphylococcus aureus* enterotoxins and underlying genetic predisposition may have important role in the pathogenesis of chronic eosinophilic inflammation typically present in the upper and lower airway mucosa of AERD patients.

DIAGNOSIS OF NSAID HYPERSENSITIVITY

In the majority of patients the diagnosis of ASA/NSAID hypersensitivity can be based on a history of respiratory symptoms induced by the ingestion of aspirin or other NSAIDs. Confirmation by controlled aspirin challenge may be necessary in some patients. Oral aspirin provocation (Figure 3) is

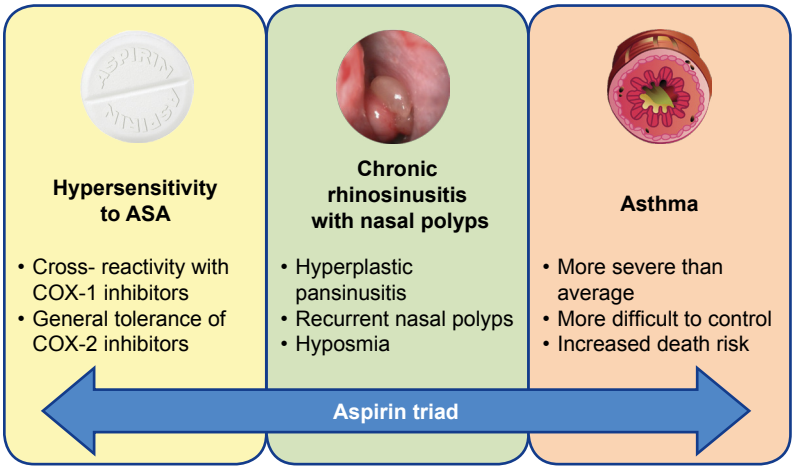

Figure 1 Clinical characteristics of Aspirin Exacerbated Respiratory Disease.

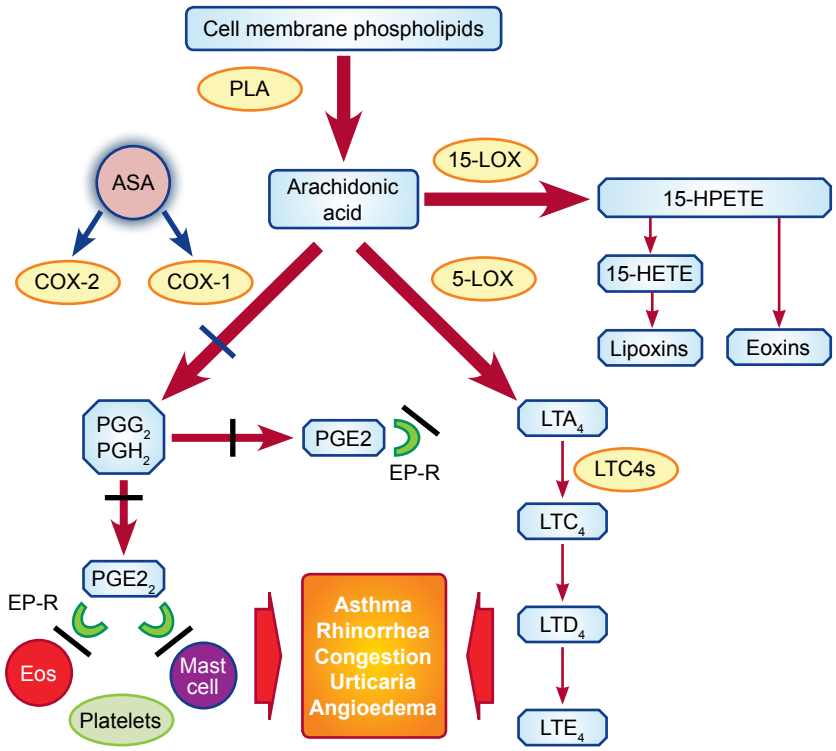

Figure 2 Pathomechanism of aspirin induced hypersensitivity reactions in AERD patients. *(Reproduced and modified from Kowalski ML. Diagnosis of aspirin sensitivity in aspirin exacerbated respiratory disease. In: Pawankar R, Holgate ST, Rosenwasser LJ, editors. Allergy frontiers: diagnosis and health economics. New York: Springer, 2009; 349-372, with kind permission of Springer Science + Business Media.)*

the gold standard for the diagnosis, but bronchial or nasal provocation with lysine-ASA may be valuable alternative diagnostic tools. Several *in vitro* cell activation tests have been evaluated, but none of them can be recommended for routine diagnosis.

MANAGEMENT OF AERD

Careful avoidance of ASA and other NSAIDs, which are strong COX-1 inhibitors, is necessary to prevent severe asthma attacks. As alternative to NSAIDs acetaminophen or preferential/selective COX-2 inhibitors, are recommended (Table 1). Management of asthma and rhinosinusitis in AERD is similar to other forms of asthma and rhinosinusitis and international treatment guidelines should be followed. Inhaled glucocorticosteroids in appropriate doses, often in combination with long acting beta-2 agonists are effective in controlling asthmatic inflammation and symptoms, but in some patients chronic treatment with oral prednisone may be necessary.

Addition of a leukotriene receptor antagonist such as montelukast to standard anti-inflammatory therapy may be effective in relieving symptoms and improving respiratory function in some patients with AERD, but the degree of improvement is similar to ASA tolerant asthmatics. Topical nasal steroids are preferred for controlling symptoms of rhinosinusitis and may slow down recurrence of nasal polyps. Surgical procedures (polypectomy, functional endoscopic sinus surgery or ethmoidectomy) are usually needed at certain stage of the disease.

The special approach for these patients is ASA desensitization. The alleviation of chronic upper and lower airway symptoms, reduction in hospitalization and emergency room visits, and decreased need for nasal/sinus surgery is observed in desensitized patients. However, only a fraction of patients with AERD will benefit from aspirin desensitization and at present it is not possible to predict the responders.

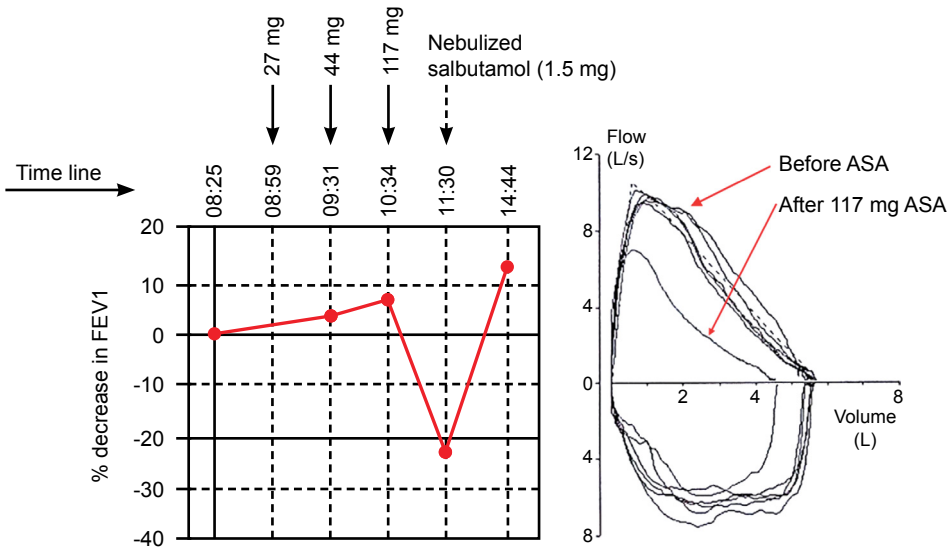

Figure 3 Oral aspirin challenge test report in a patient with AERD. The significant drop in FEV1 (>20% baseline) supports the diagnosis of aspirin intolerance.

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TABLE 1

NSAIDs tolerance in patients with AERD *	
Group A: NSAIDs cross-reacting in the majority of hypersensitive patients (60–100%)	
Diclofenac	Etololac
Fenoprofen	Flurbiprofen
Ibuprofen	Indomethacin
Ketoprofen	Ketorolac
Meclofenamate	Mefenamic acid
Nabumetone	Naproxen
Piroxicam	Sulindac
Group B: NSAIDs cross-reacting in a minority of hypersensitive patients (2–10%)	
Rhinitis/asthma type	
acetaminophen (doses below 1000 mg)	
meloxicam	
nimesulide	
Urticaria/angioedema type	
acetaminophen	
meloxicam	
nimesulide	
selective COX-2 inhibitors (celecoxib, rofecoxib)	
Group C: NSAIDs well tolerated by all hypersensitive patients **	
Rhinitis/asthma type	
selective cyclooxygenase inhibitors (celecoxib, parvocoxib)	
trisalicylate, salsalate	
Urticaria/angioedema type	
new selective COX-2 inhibitors (etoricoxib, pavocoxib)	

* *Reproduced from Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy 2011;66:818-829.*
** *Single cases of hypersensitivity have been reported*

5 GASTRO-ESOPHAGEAL REFLUX DISEASE AND ASTHMA

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KEY MESSAGES

- Gastro-esophageal reflux disease (GERD) is an increase of retrograde movement of gastric content into the esophagus
- Laryngopharyngeal reflux is reflux which reaches the larynx
- Ten to 20% of the general adult population in western countries and 5% of subjects in the Asia Pacific region suffer from GERD
- Asthma and/or upper airway complaints or problems are associated with GERD
- Double-blind controlled studies demonstrate that treatment of asymptomatic GERD in adults and children does not improve asthma
- Just as GERD may aggravate asthma, so too, could asthma or asthma therapy aggravate GERD
- Diagnosis of GERD in both adults and children is primarily suspected and made by a detailed history
- Treatment includes lifestyle changes and where necessary H2 blockers, proton pump inhibitors and prokinetics

Gastroesophageal reflux disease (GERD) is an increase of retrograde movement of gastric content into the esophagus. Laryngopharyngeal reflux is reflux which reaches the larynx. GERD is present when the frequency and duration of acid reflux exceeds defined parameters, as quantified by a pH probe placed in the esophagus. Regardless of its more formal definition, it is a disease in and of itself, often associated with esophageal complications such as esophageal erosion and stricture and Barrett's esophagus, the latter of which can lead to adenocarcinoma of the esophagus. Factors which contribute to or cause GERD are illustrated in Figure 1.

Ten to 20% of the general adult population in western countries and 5% in the Asia Pacific region suffer from symptoms of GERD. The presence of GERD in some pediatric studies is between 2-8%. Typical symptoms particularly in adults, include esophageal burning and discomfort (heartburn) as well as regurgitation of gastric content into the posterior pharynx (water brash) (Table 1). Other symptoms include belching, indigestion, nausea, vomiting, odynophagia, dysphagia, and halitosis. Throat tightness, throat clearing, cough, chest tightness, postnasal drip, and hoarseness are all potential symptoms of GERD, particularly with laryngeal pharyngeal reflux. Cough, associated with laryngopharyngeal GERD, is usually described as originating in the laryngopharynx, whereas cough associated with asthma usually originates in the chest; however, this distinction is subjective as can be differentiating the symptoms of cough from throat clearing. The same symptoms can occur in children, however, recurrent regurgitation, with or without vomiting, weight loss or poor weight gain, irritability, and behavioral problems may occur.

Asthma and/or upper airway complaints or problems are associated with GERD. Epidemiologic studies demonstrate a variable prevalence in subjects with asthma of between 12 to 85%. The variability is largely dependent on the method used to define GERD. Conversely, asthma also appears to be more common in individuals with GERD. Two hy-

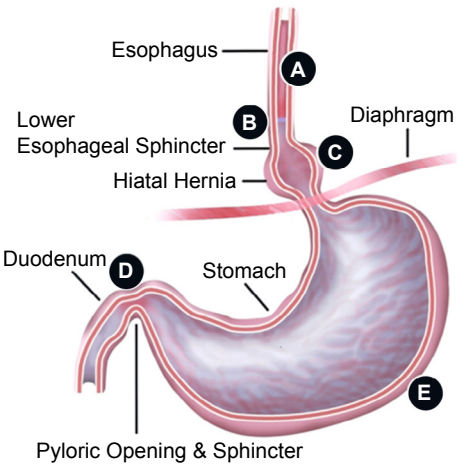

Figure 1 Factors which contribute to or cause GERD.

A. Defective clearance of esophageal contents secondary to reduced salivary and esophageal submucosal gland secretion and ineffective peristalsis

B. Lower esophageal dysfunction with prolonged and inappropriate relaxations of the sphincter with reduction in basal lower esophageal sphincter pressure and tone

C. A hiatal hernia may compromise lower esophageal function causing gastric contents to be trapped above the diaphragm exacerbating reflux

D. Delay of gastric emptying may increase gastric contents available for reflux into the esophagus

E. Various illnesses, such as asthma, which are associated with chronic cough and expiratory straining during breathing, can increase intra-abdominal pressure, pushing gastric contents into the esophagus

TABLE 1

GERD Symptoms and Signs *	
Gastroesophageal	Heartburn, chest/epigastric/cervical pain, water brash, belching, indigestion, nausea/vomiting/hematemesis
Respiratory	Cough, wheeze, dyspnea, hemoptysis
Laryngeal	Hoarseness, throat clearing, sighing dyspnea, irritation, globus, voice changes, soreness
Nasal	Congestion, itching, sneezing, soreness
Sinuses	Headache, pressure, purulent discharge
Ears	Otalgia
Teeth	Loss of dental enamel

** Reproduced from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.*

potheses are proposed to explain this association; asthma bronchospasm is attributed to aspiration or reflux of gastric contents into the trachea, whereas the second implicates vagal reflexes mediated through stimulation of esophageal mucosal receptors by a low pH and distention. Both mechanisms probably contribute to asthma in varying degrees.

Double-blind controlled studies demonstrate that treatment of asymptomatic GERD does not improve asthma in adults or children; however, other controlled studies show that GERD-treated subjects with asthma and symptomatic GERD experience improved asthma quality-of-life and have a reduced number of asthma exacerbations, while there are questionable effects on asthma symptoms, albuterol use, and pulmonary function. A Cochrane review of controlled studies in both adults and children with asthma indicates that treating GERD does not increase asthma control but does decrease the use of albuterol; it benefited a subset of affected patients.

Just as GERD may aggravate asthma, so too, could asthma or asthma therapy aggravate GERD or GERD-associated symptoms. Beta agonists and theophylline reduce esophageal sphincter tone, systemic glucocorticosteroids increase gastric acid production, and inhaled corticosteroids induce cough and cause chronic laryngeal irritation and hoarseness, the latter of which are also associated with GERD. Asthma also is associated with chronic cough and wheezing, both of which increase intra-abdominal pressure, which can theoretically result in pushing gastric contents up through the lower esophageal sphincter into the esophagus aggravating GERD.

Diagnosis of GERD is primarily based on a detailed history since it is impossible to confirm the diagnosis with a pH probe and/or endoscopy in all individuals with this disease (Figure 2). When complications are suspected, a gastroenterologist consultation is indicated.

Treatment (Figure 3) includes lifestyle changes, i.e., avoiding large meals, maintaining ideal weight, not eating meals three hours before retiring, not lying down within two hours after meals, elevating the head of the bed with 6-inch blocks or using a foam wedge to elevate the trunk and head. Avoiding acid-containing foods, carbonated beverages and fatty foods also may be beneficial. Medications include H2 blockers, proton pump inhibitors and prokinetic agents, the latter for individuals with delayed gastric emptying. GERD common-

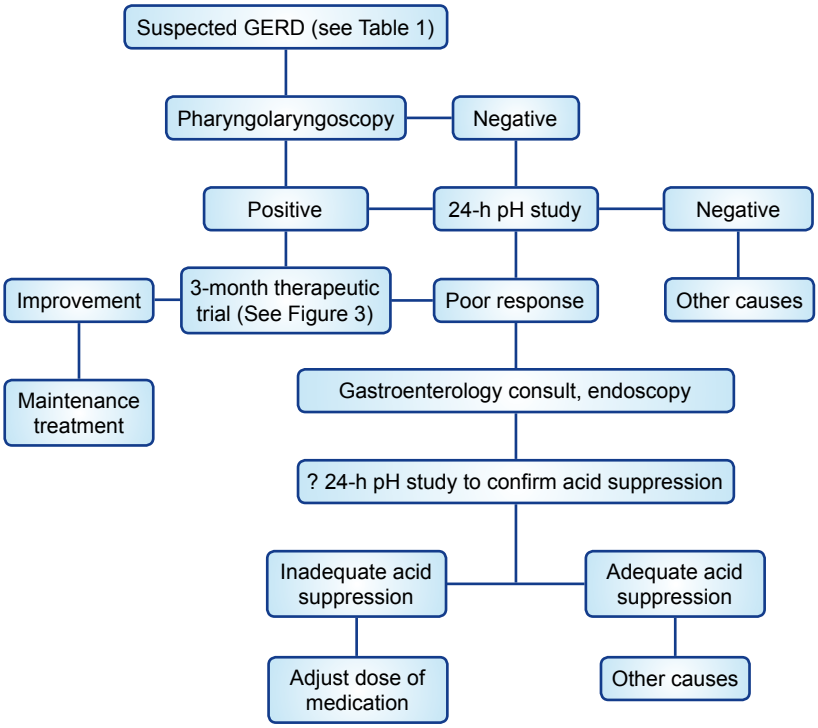

Figure 2 Diagnosis of GERD. *(Modified from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.)*

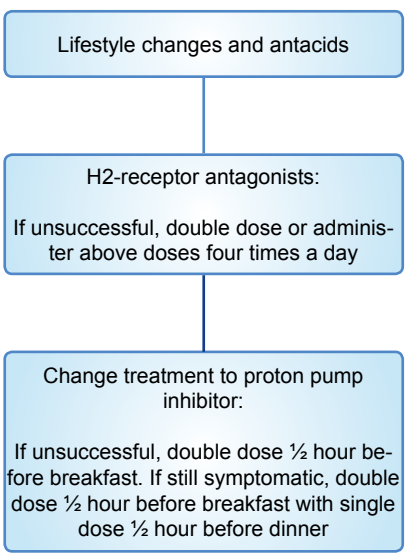

Figure 3 Maintenance treatment for GERD. *(Modified from Theodoropoulos DS, Lockey RF, Boyce HW Jr. Gastroesophageal reflux and asthma: a review of pathogenesis, diagnosis, and therapy. Allergy. 1999;54:651-661, with permission from Wiley-Blackwell.)*

ly resolves by age 4 years in most children. When such resolution does not occur, treatment is similar to adults. Rarely, anti-reflux surgery is indicated.

Another problem, laryngopharyngeal reflux, believed to be secondary to the regurgitation of gastric content into the laryngeal pharynx, can result in laryngopharyngeal and upper airway symptoms. Laryngopharyngeal reflux is also a co-morbid condition for asthma, if for no other reason, for the cough associated with such reflux. Also, upper airway disease is commonly associated with asthma, and documented GERD is associated with a variety of different laryngeal and upper airway symptoms.

In summary, regardless of whether there is a true association with GERD, i.e., that GERD can exacerbate asthma, or the converse, that asthma can exacerbate GERD, both seem reasonable because of the close association of the esophagus with the trachea and lungs and the similar embryologic derivation of the nervous system shared by both. Regardless, treating symptomatic GERD in any patient, particularly those with asthma, is essential to prevent complications from GERD, as well as to increase the quality-of-life of the patient with or without asthma.

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6 CARDIOVASCULAR DISEASES AND ASTHMA

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Some studies report a significant association of asthma with cardiovascular disease, but there is a conflict in the literature surrounding the asthma-related risk of cardiovascular disease identified in large, longitudinal epidemiologic studies.

Adult-onset asthma is associated with increased carotid atherosclerosis in women, and patients with bronchial hyperresponsiveness to methacholine demonstrated increased carotid intima–media thickness. Relationships between asthma and cardiovascular disease in women seem to be stronger than those observed in men (Figure 1). In general, allergic disease is more common in women after adolescence and it is thought that sex hormones modulate immune response. Estrogen is considered to increase humoral immunity. Being female slightly increases the association of all cardiovascular diseases, mainly heart failure, but not angina, coronary disease and acute or old myocardial infarction, with asthma. In contrast to females, males present with a positive association between asthma and angina and coronary disease, but a negative association with acute or old myocardial infarction. An increase in age results in a progressive increase in the prevalence of the diagnosis of cardiovascular disease and hypertensive disease. Apparently, the smoking habit does not modify the prevalence of cardiovascular disease, compared to the general population.

KEY MESSAGES

- There is a conflict in the literature surrounding the asthma-related risk of cardiovascular disease identified in large, longitudinal epidemiologic studies
- Relationships of asthma and cardiovascular disease seem to be stronger in women
- A common mechanism may contribute to allergies and atherosclerosis and systemic inflammation associated with asthma may adversely affect cardiovascular function
- Decreased pulmonary function, increased airway infection, and use of β2-agonists may increase the risk of cardiovascular disease
- Patterns of risks of myocardial infarction are similar between inhaled short-acting β2-agonists, long-acting β2-agonists and inhaled corticosteroids

A common mechanism may contribute to allergies and atherosclerosis. IgE is itself potentially proatherogenic through actions on mast cells and platelets, although epidemiological studies indicate that atopy may be an independent protective factor against myocardial infarction. In any case, asthma and atherosclerosis occur on a background of inflammation. Animal studies have shown increased myocardial vulnerability in rabbits with systemic allergy and asthma. It has been suggested that airway allergen exposure results in impaired vasodilatory response of the aorta in a murine model of pulmonary allergic response. This finding suggests that systemic inflammation associated with asthma may adversely affect cardiovascular function. Actually, systemic inflammation occurs in asthma, with an increase in circulating proinflammatory cytokines, such as interleukin IL-6 and tumor necrosis factor-α and also in high-sensibility

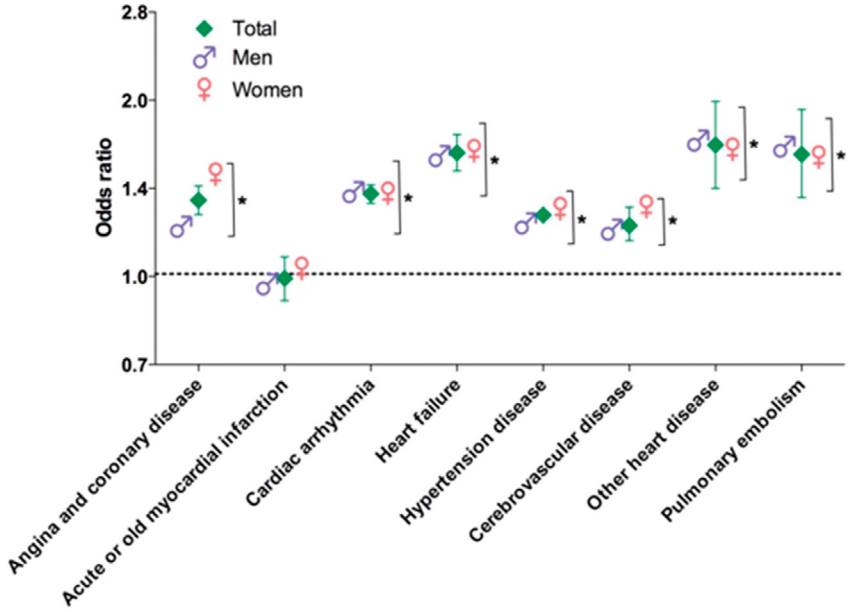

Figure 1 The association between asthma and cardiovascular comorbidities in Italy. *(This article was published in Respir Med, 106, Cazzola M, Calzetta L, Bettoncelli G, et al, Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study, 249-56, Copyright Elsevier 2012.)*

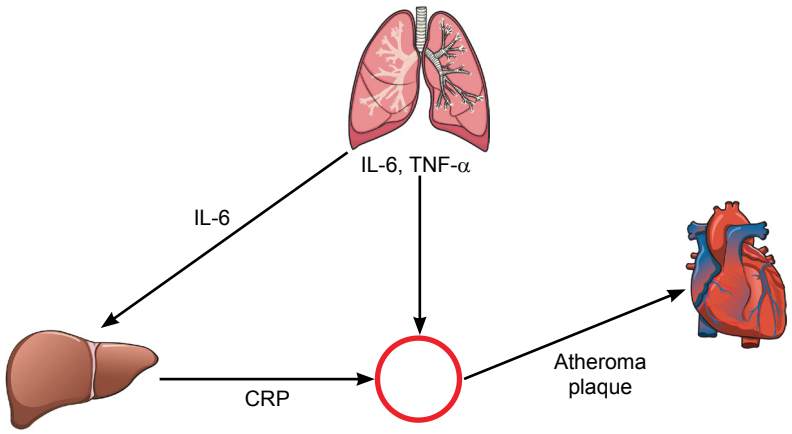

Figure 2 The inflammation in the lung 'spills over' into the systemic circulation to produce systemic effects, such as cardiovascular complications.

C-reactive protein, likely because of the systemic dissemination of local lung inflammation leading to an overspill effect (Figure 2). This systemic component could feed back into and perpetuate the original local reaction and lead to the development of distant local reactions.

However, the role of systemic inflammation in asthmatic patients is still unclear and, consequently, debated. Asthma is a long-term inflammatory status complicated by decreased pulmonary function, increased airway infection, and use of β2-agonists. These factors may increase the risk of cardiovascular disease. Patterns of risks of myocardial infarction are similar between inhaled short-acting β2-agonists, long-acting β2-agonists and inhaled corticosteroids. It is likely that the initial presentation with symptoms evoking asthma (dyspnoea presumably) is, in a large proportion of cases, the appearance of ischaemic heart disease. Nonetheless, it is noteworthy that some epidemiological studies have been unable to register concrete association of asthma with acute or previous myocardial infarction.

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7 FOOD ALLERGY AND ASTHMA

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Food allergy (FA) is an adverse reaction to food caused by an overreaction of the immune system that occurs each time a food is consumed. These reactions can be immune responses mediated by IgE antibodies, by immune cells, or by a combination of both. Food allergies are however most commonly caused by IgE antibodies, and are characterized by acute onset of symptoms (usually within minutes to a few hours) following the ingestion of an implicated allergenic food. Symptoms can involve the skin, the gastrointestinal tract, the cardiovascular system including life-threatening anaphylactic shock, and of relevance at this place, the respiratory tract including asthmatic symptoms. FA is estimated to affect 3-8% of children and 1-5% of adults, but considerable geographic differences exist also with respect to the type of foods involved. FA is often seen together with asthma, especially in infancy.

KEY MESSAGES

- Foods can induce asthmatic reactions in patients with food allergy
- Patients with both asthma and food allergy are at risk of food-induced anaphylaxis
- Food allergy often precedes asthma and is a risk factor for its development
- Both being chronic allergic disorders, asthma and food allergy often go together
- Cross-reactive IgE of asthmatic patients with seasonal allergic rhinitis can cause subsequent food allergy

THE LINK BETWEEN FOOD ALLERGY AND ASTHMA

Firstly, asthma can be one of the manifestations of an allergic reaction to food (Figure 1). Also, food additives, especially sulphites and monosodium glutamate, have been reported to trigger asthma. Besides consumption of food, inhalation of cooking vapours of especially fish, shellfish and eggs, is known to potentially cause asthmatic symptoms, and inhalation of wheat flour may cause occupational asthma in bakers.

Secondly, patients that have both asthma and food allergy have a higher risk to develop severe anaphylactic reactions when exposed to the food they are allergic to (Figure 2). Therefore, these patients need to be particularly cautious in avoiding the culprit foods.

Thirdly, sensitization (IgE) to food and clinical FA often precede the development of asthma (Figure 3). This sequence of appearance, often referred to as the "atopic march", points towards a common genetic predisposition for both diseases. A whole spectrum of gene polymorphisms has been implicated in the development of asthma, illustrating the complex multi-factorial nature of the genetic predisposition of this disease. Far less is known about gene polymorphisms with relevance for FA. Recently a polymorphism in a gene coding for a protein involved in the integrity of the skin barrier was reported to be a risk factor for FA in patients that also have asthma.

Fourthly, food allergy not only precedes asthma but both chronic allergic disorders often also stick together (Figure 3). Although some food allergies like to milk and egg are outgrown by the majority of

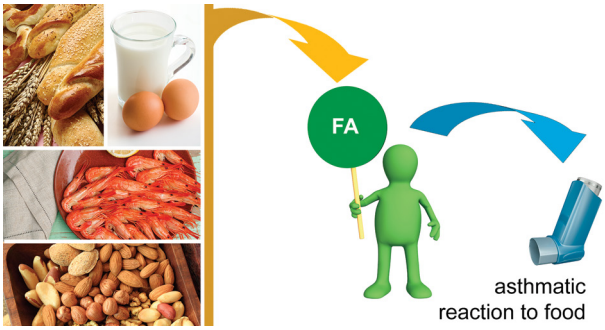

Figure 1 Asthma can be one of the manifestations of an allergic reaction to food. FA - food allergy.

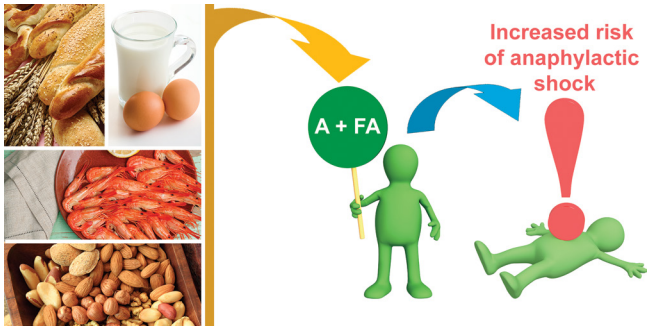

Figure 2 Patients that have both asthma (A) and food allergy have a higher risk to develop severe anaphylactic reactions when exposed to the food they are allergic to.

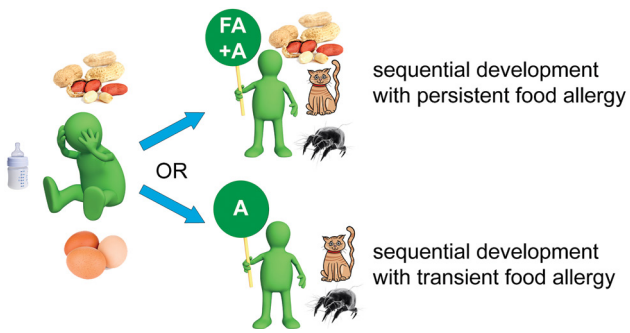

Figure 3 Sensitization (IgE) to food and clinical FA often precede the development of asthma (the "atopic march").

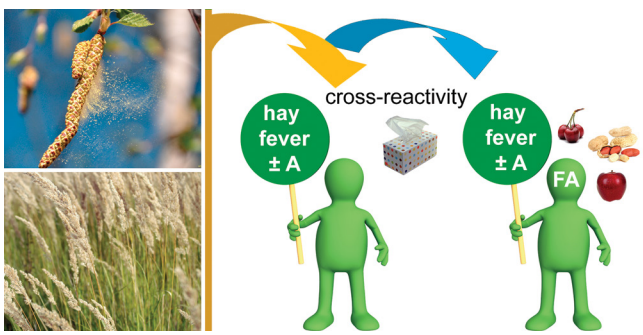

Figure 4 Asthma induced by tree and/or grass pollen can precede the development of FA (oral allergy syndrome).

children before the age of five, most other common food allergies such as to peanut and tree nuts are usually persistent and are still present when asthma develops.

Lastly, asthma with seasonal allergic rhinitis (hay fever) induced by tree and/or grass pollen can also precede instead of follow the development of FA (Figure 4). Although most pollen allergies present as hay fever, some patients develop asthma as well. In many of those patients some years after the onset of their pollen allergy, also symptoms of FA start developing. This phenomenon can be explained by pollen-induced IgE antibodies cross-reacting to foods. The most well-known example of such cross-reactivity is observed in patients with birch pollen allergy. Their IgE antibodies cross-react with fruits like apple and cherry, with tree nuts like hazelnut and with some vegetables like carrot and celeriac. Symptoms of FA in such patients are almost always mild and limited to the oral cavity.

In conclusion, asthma is often accompanied by FA but the basis of this co-morbidity is diverse.

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8 SKIN AND LUNG: ATOPIC DERMATITIS, URTICARIA AND ASTHMA

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Atopic dermatitis (AD) is a common inflammatory skin disorder, characterized by pruritus, a chronic relapsing course, a distinctive distribution of eczematous skin lesions (Figure 1) and a personal or family history of atopic diseases including asthma. It results from the complex interplay between defects in skin barrier function, environmental and infectious agents, and immune abnormalities.

During the last decades a marked increase in the frequency of AD has been observed and it is now the most frequent inflammatory skin disease, with a childhood prevalence of more than 10% in most European countries. The manifestation of AD in childhood is greater in families with a higher income and a more privileged lifestyle. This may be due to reduced incidence of infections in early childhood and reduced contact with agents that elicit Th1 associated cellular immune responses. Of note, differences in prevalence of respiratory allergic diseases often do not parallel prevalence of AD in larger epidemiologic studies, which points to independent risk and manifestation factors being critical for both atopic diseases.

AD often begins in early infancy. Severe AD beginning before 6 months of age is a high-risk phenotype for the development of asthma, especially in boys. Furthermore, AD is linked to food allergy and children with multiple severe food allergies are also at a higher

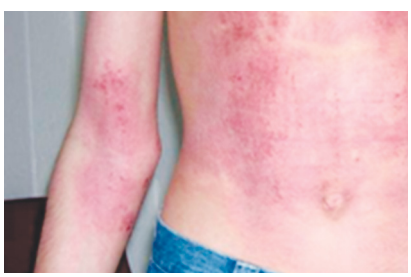

Figure 1 Flexural dermatitis on the right arm and disseminated eczema on the trunk in a male adolescent patient with atopic dermatitis.

KEY MESSAGES

- Atopic dermatitis (AD) is the most frequent inflammatory skin disease and results from the complex interplay between defects in skin barrier function, environmental and infectious agents, and immune abnormalities
- Severe AD beginning early in life is a high-risk phenotype for the development of asthma
- Specific IgE is associated with food or environmental allergens, which may be relevant trigger factors for both AD and asthma
- The disturbed expression of the skin barrier protein filaggrin is linked to childhood AD and the subsequent development of asthma
- Urticaria is often a presenting feature of anaphylaxis, involving respiratory difficulty due to inspiratory stridor, expiratory wheeze or both. Acute urticaria by definition does not involve respiratory distress
- Bronchial hyperreactivity has been reported in some patients with chronic spontaneous and inducible patterns of urticaria
- Kinin-induced angioedema involving the airways in hereditary or acquired angioedema and angiotensin converting enzyme inhibitor-induced angioedema requires emergency treatment and may be fatal

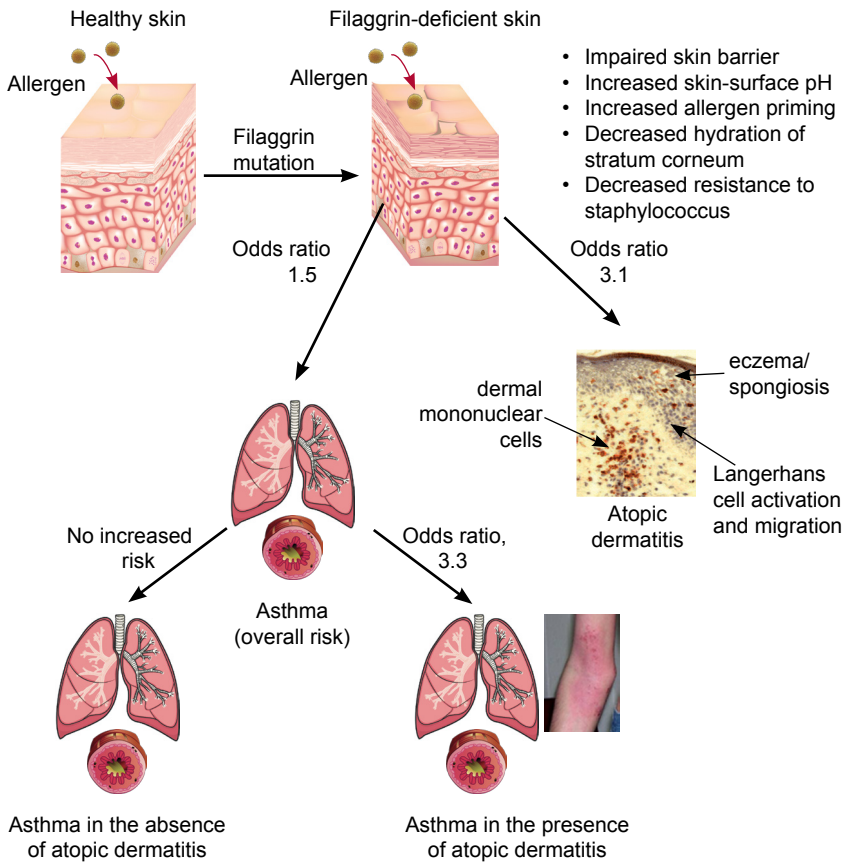

Figure 2 Filaggrin mutations and atopic dermatitis and asthma. *(Adapted from Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011;365:1315-1327.)*

risk of developing asthma.

Like in allergic asthma, there is an overexpression of Th2 cytokines in lymphatic organs, circulating T-cells and the acute phase of cutaneous inflammation in many patients with AD. This is closely linked to the regulation of IgE, which is higher than normal in 80% of all patients. Specific IgE is commonly associated with food or environmental allergens, which may be relevant trigger factors both for AD, rhinitis and / or asthma in individual patients.

Studies of the gene of encoding the skin barrier protein filaggrin have shown the link between early childhood eczema and the subsequent development of asthma which may, in part, be due to defective epidermal barrier function leading to increased allergen sensitization (Figure 2).

It appears that different disease mechanisms are important for different subgroups of patients suffering from AD. Described genetic polymorphisms in AD involve mediators of atopic inflammation on different chromosomes. Some, but not all of these may also play a role in respiratory atopy.

Besides the "allergic" variant of AD there is a non-allergic form which is found in 20% of diseases with the typical clinical appearance of the disease. In this respect, AD resembles asthma, which also has allergic and non-allergic variants.

Management of AD exacerbations is a therapeutic challenge, as it requires efficient short-term control of acute symptoms, without compromising the overall management plan, which is aimed at long-term stabilization, flare prevention, and avoidance of side effects. Exacerbation may sometimes uncover relevant provocation factors, for example food or inhalant allergy, or infection, which in turn may also lead to worsening of asthma (Figure 3).

The prognosis for patients with AD is generally favourable, but patients with severe, widespread disease and concomitant asthma are likely to experience poorer outcomes.

Urticaria does not characteristically involve the respiratory tract, but there are a few situations where there is overlap. The first is anaphylaxis where urticaria involving wheals, angioedema or both may be the initial presentation of an acute systemic illness defined by respiratory difficulty, hypotension or both, with or without gastrointestinal symptoms. Anaphylaxis is often due to an immediate hypersensitivity response to a food, drug or sting, but may be non-allergic. The boundaries between anaphylaxis and acute urticaria may not be clear at the time, particularly when food allergy presents with generalized urticaria. By definition, acute urticaria does not present with systemic symptoms, is continuous (daily or almost daily eruptions itchy skin or mucosal swellings) and lasts for up to 6 weeks, but usually resolves over 10 to 14 days.

Chronic urticaria is not associated with asthma and is hardly ever due to IgE-mediated allergies (except perhaps in very young children with undetected food allergies)

although it may occur as an apparently independent illness in atopic patients. Around 30% of patients with chronic spontaneous urticaria have functional autoantibodies that release histamine from skin mast cells and basophils, so it is surprising that the respiratory tract is not overtly affected. One study concluded that bronchial hyperresponsiveness is a common feature in patients with active chronic urticaria. Twenty six adults with chronic spontaneous urticaria were assessed with respiratory function tests and methacholine provocation. Two had asthma on baseline pulmonary function tests and twenty others (77%) showed bronchial hyperresponsiveness on methacholine challenge. Bronchial hyperresponsiveness has also been demonstrated in patients with cholinergic urticaria and symptomatic dermographism.

Spontaneous and inducible urticarias are believed to be caused by mast cell and basophil mediator release (primarily histamine). By contrast, there is a small, but very important group of patients who present with angioedema without wheals due to kinin generation. These include hereditary angioedema, acquired angioedema associated with lymphoproliferative disease or autoantibodies against C1 esterase inhibitor, and angiotensin converting enzyme inhibitor (ACEI)-induced angioedema. The pathways involved with ACEI-induced angioedema are complicated (Figure 4). Kinin-induced angioedema often affects the respiratory tract from the lips to the larynx and may be fatal. The specific bradykinin 2 receptor receptor antagonist, icatibant, offers a specific treatment for these patients presenting acutely with respiratory tract involvement.

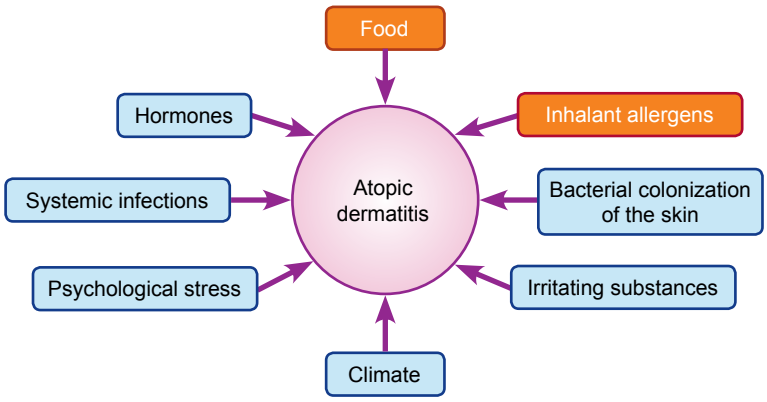

Figure 3 Trigger factors of atopic dermatitis.

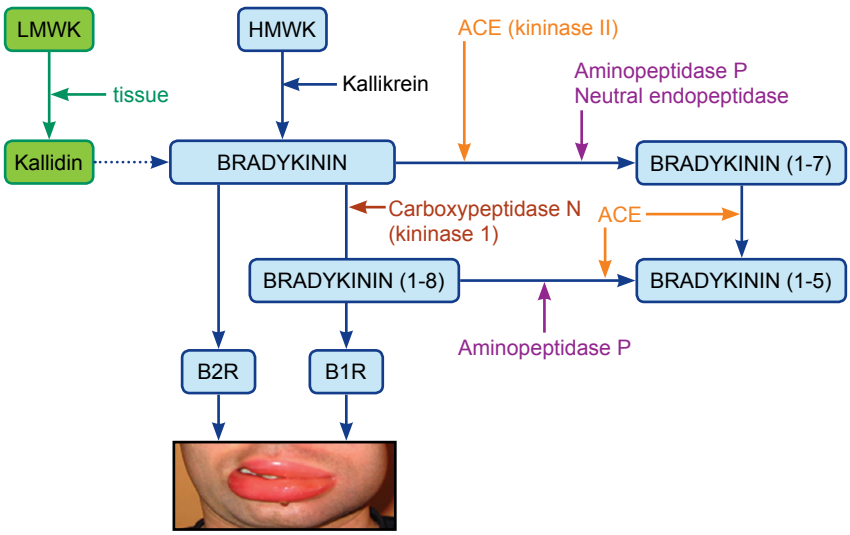

Figure 4 Kinin formation and breakdown relevant in urticaria. LMWK, low molecular weight kininogen; HMWK, high molecular weight kininogen; kallidin, Lys-bradykinin; B2R, bradykinin receptor 2 – receptor for bradykinin; B1R, bradykinin receptor 1 – receptor for the active metabolite of bradykinin (bradykinin 1-8 or des arginine bradykinin); ACE-angiotensin converting enzyme

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Section C

MAJOR CURRENT PROBLEMS IN ASTHMA

* Unmet needs in asthma
* Asthma exacerbations
* Severe asthma
* Adherence to asthma treatment
* Social determinants of asthma
* Inequities and asthma

1 UNMET NEEDS IN ASTHMA

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KEY MESSAGES

- Pathomechanisms of asthma are still not fully known
- There is a global burden of limited access to drugs and good patient care in underdeveloped regions
- There is no established way towards a prevention of asthma
- There is no established curative treatment
- Biomarkers to subgroup patients, predict outcomes and follow therapy response are needed
- Vaccine development against viruses that trigger exacerbations should be supported
- Patient-tailored treatment should be implemented
- Next generation global guidelines that consider individual needs, regional differences and disease subgroups are needed
- A worldwide registry and regional biobanks for asthma are needed

Unmet needs in asthma cover almost every aspect of the disease. They can be classified as unmet needs due to missing scientific knowledge, related to patient care and chronic nature of the disease, and related to socioeconomic factors.

Knowledge on pathomechanisms of asthma has several essential gaps (Table 1). One main historical reason was disregarding its complexity and consideration of asthma as a single disease entity. It is now becoming clear that the complex interplay between the environment and the immune system in combination with the response of the tissue cells ultimately determines the development and expression of asthma with different phenotypes and endotypes. Particularly, the intrauterine and lifelong exposure to every facet of the environment, the so called exposome and its role in activation and tolerance thresholds of the tissues and the immune system represent major targets for research.

Asthma prevention includes primary prevention to prevent the development of the disease and secondary prevention to prevent asthma development in subjects with atopy. There is no established way of primary prevention of asthma and a series of questions in the public remain unanswered such as, if parents have asthma, will the child also develop asthma? Is there any way to avoid this? If asthma develops, will it be possible to outgrow asthma?

A global unmet need is the **international and regional burden of access to drugs and good patient care**. Asthma prevalence is globally increasing in parallel to urbanization and economic development, however individuals with low socio-economic status, minorities and urban populations are deeply affected. Low socio-economic status individuals are highly exposed to triggers such as environmental pollutants, poor housing, indoor allergens, and psychosocial stressors. It is essential to develop global approaches to fight with inequities, educational deficits and delivery of high quality asthma care in the whole World to improve individual patient care.

The possibility of cure in asthma is a fundemental issue for research, because the currently used medications only temporarily relieve

TABLE 1

Major research gaps for asthma

- Immunological basis of asthma epidemic
- Innate immune response and tissue response to exposome such as molecules that are coexposed with allergens, microbes, pollutants
- Role of novel subsets of T cells, B cells and innate lymphoid cells in asthma development
- Indepth analysis of individuals who outgrow from asthma
- Epithelial barrier function and its role in asthma development and chronicity
- Mechanisms of development of immune tolerance to allergens and novel ways to induce this
- Understanding epigenetic regulation of the asthmatic inflammation
- Development of novel biologicals for treatment
- Identification of novel biomarkers for endotyping patients for the prediction of treatment response and prognosis
- Development of immunological registries and disease-specific biobanks

TABLE 2

Unmet needs in patient care

- Patient adherence
- Inequities in asthma care in the whole World
- Education of patients and careers
- Self management of patients
- Prevention of asthma exacerbations
- Severe asthma patients
- Side effects of medications
- Better drug delivery systems
- Patient tailored therapies

TABLE 3

Next steps in diagnosis of asthma endotypes

- Improvement of molecular diagnostics methods
- Discovery of surrogate biomarkers
- Easy and standardized tests for cellular diagnosis from peripheral blood
- Easy and standardized analysis of exhaled breath condensate and sputum
- Development of point of care assays and devices
- Development of tests for prediction of exacerbations and treatment response
- Development of tests for the analysis of immune response to respiratory viruses

symptoms by suppressing inflammation. A long-term cure for allergic asthmatic patients can be achieved through the use of allergen immunotherapy, which has a disease-modifying effect and might also lead to decreased requirements for anti-inflammatory and symptomatic medications. However, only a fraction of asthma patients respond successfully to allergen-immunotherapy and there is no established clinical criteria or a predictive biomarker for the selection of these patients.

Unmet needs in **patient care in asthma** remain essential problems similar to many chronic diseases (Table 2). It is expected that patient-tailored therapies will improve and become a standard in patient care one day. Accordingly, problems in adherence to treatment, self management, prevention of exacerbations, development of severe asthma, side effects of medications are expected to diminish in time.

Biomarkers to diagnose, subgroup and follow patients represent an important need in most of the chronic diseases. We have no biological indicators that accurately predict the development of asthma, identify high risk children and the disease course of an asthmatic patient. In addition, there is very few indicators for the selection of a certain therapy responsive patients, such as allergen-immunotherapy or a treatment with a biological immune response modifier (Table 3). Apparently, novel biologicals should be developed together with their biomarker for the selection of responsive patients.

Asthma exacerbations are linked with high morbidity, significant mortality and represent an outstanding problem in the clinical management of asthma. They constitute the biggest immediate risk and anxiety to patients and their families, linked to continuous decline in lung function over time and generate a huge financial burden in health care systems. Targeting respiratory viruses with vaccines will be one of the most efficient ways to prevent exacerbations.

Severe asthma represents one of the most significant burdens of all diseases from all perspectives of affected patients and health care system. These individuals use a large proportion of public health resources devoted to the treat-

TABLE 4

Problems in drug development for asthma

- There is a huge amount of missing knowledge in the complexity of the whole disease spectrum with highly complex molecular mechanisms and multiple subgroups
- Almost no biomarkers exist for patients' selection, therapy response, and for prediction of disease development
- There is limited space to improve the patients response over existing therapies, because currently used inhaled steroid and β-adrenergic agonist combination therapy is effective and relatively inexpensive
- Most drugs that are effective in mouse models have failed in clinical trials, because currently available animal models do not represent human asthma
- Individual outcomes are different due to molecular complexity and cannot be distinguished using a bulk approach
- Most novel biologicals are unlikely to be effective, when used alone and it is not possible to study the combination of two new biologicals that may potentiate each other until one of them is approved

ment of asthma and more effective therapies are urgently required. Novel drugs are needed for severe asthma. Unfortunately, drug development programs have failed in the last several decades due to multiple reasons summarized in Table 4.

Guidelines developed for asthma have grouped all asthma phenotypes and endotypes together as if they are a single uniform disease. The heterogeneity of asthma, defining of asthma subgroups and their particular needs have not been taken into account. Regional needs and differences have not been deeply considered and input of patients themselves have been neglected. An advance for currently existing guidelines was the implementation of evidence-based medicine as a movement toward a more structured assessment of clinical knowledge and was providing a method of evaluating health effects and economic impact. Next generation global guidelines will have to appreciate the needs of individuals, consider regional differences, different disease subgroups with a scientific approach.

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2 ASTHMA EXACERBATIONS

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KEY MESSAGES

- Acute exacerbations of asthma require urgent treatment to prevent a serious outcome and generate the greatest financial burden for health care systems
- Asthma exacerbations rate reported in clinical trials ranges from 0.3 - 0.9 /patient /year; surveys of 'real life' asthma patients indicate a higher incidence, particularly in poorly-controlled asthmatics
- Factors reported to be associated with frequent exacerbations include poor asthma control, respiratory infections, female sex, obesity, psychopathology, chronic sinusitis, gastro-oesophageal reflux and obstructive sleep apnoea
- Viral infection and allergy interact to increase the risk of an exacerbation
- Patient education, self-management plans and most of the anti-asthmatic drugs have been convincingly shown to reduce exacerbations requiring hospitalisation
- Vaccination against respiratory viruses remains an attractive and potentially effective strategy

The Global Initiative for Asthma (GINA), defines acute exacerbations of asthma as "*episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow that can be quantified by measurement of lung function.*" They are a marker of severe loss of control and require urgent treatment to prevent a serious outcome. Exacerbations constitute the greatest immediate risk to patients, are associated with accelerated decline in lung function over time, significant anxiety to patients and family members alike, and generate the greatest financial burden for health care systems.

Airflow obstruction during exacerbations stems from a combination of concentric smooth muscle contraction, airway wall oedema, airway inflammatory cell infiltration and luminal obstruction with mucus and cellular debris (Figure 1). Exacerbations vary greatly in speed of onset, intensity and in time to resolution both between patients and for individual patients.

EPIDEMIOLOGY OF ASTHMA EXACERBATIONS

The frequency with which asthma exacerbations are reported in the clinical trial literature ranges from 0.3 - 0.9 /patient /year and varies according to the definition of exacerbation used and the severity and/or level of disease control of the asthmatic population being studied. However surveys of 'real life' asthma patients indicate that the incidence of exacerbations is much higher, particularly in poorly controlled asthmatics.

Additional factors reported to be associated with frequent exacerbations include female sex, obesity, psychopathology, chronic sinusitis, gastro-oesophageal reflux, respiratory infections and obstructive sleep apnoea.

AETIOLOGY OF ASTHMA EXACERBATIONS

Since the early 1960s, viral respiratory tract infections have been reported as triggers for asthma exacerbations. Following the intro-

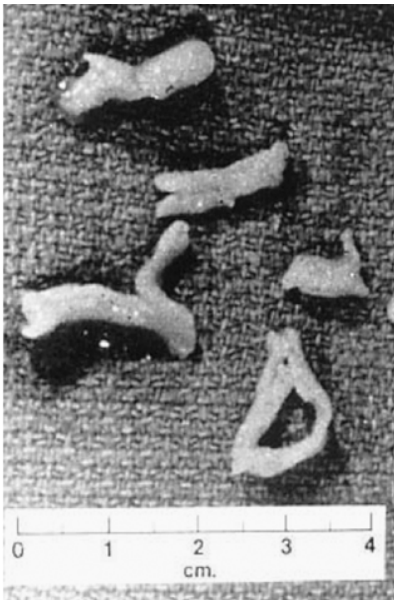

Figure 1 Airway casts recovered from an asthmatic subject during an acute exacerbation. *(This article was published in Ann Allergy, 67, Lang DM, Simon RA, Mathison DA, et al, Safety and possible efficacy of fiberoptic bronchoscopy with lavage in the management of refractory asthma with mucous impaction, 324-330, Copyright Elsevier 1991.)*

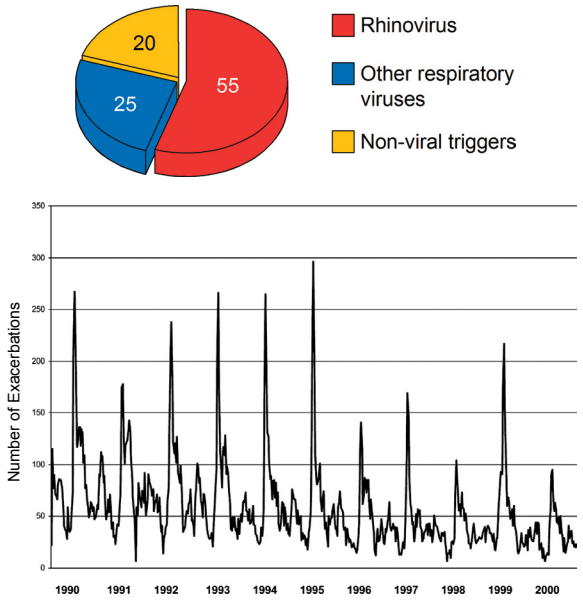

Figure 2 Respiratory viruses are the most common trigger for asthma exacerbations in both adults and children with rhinoviruses identified as the most frequently identified trigger (A). The September epidemic of asthma hospitalisation appears to reflect school children acting as disease vectors spreading viral infections following the return to school after the summer holiday (B). *(Reprinted from J Allergy Clin Immunol, 115/1, Johnston NW, Johnston SL, Duncan JM, et al, The September epidemic of asthma exacerbations in children: a search for etiology, 132-128, Copyright 2005, with permission from Elsevier.)*

duction of polymerase chain reaction (PCR) technology in the 1990s a clear demonstration of this important link has been repeatedly observed with rhinoviruses consistently highlighted as the most frequently detected pathogens (Figure 2). Influenza viruses and respiratory syncitial virus (RSV) as well as other respiratory viruses are less common, but well recognised precipitants.

A growing body of evidence supports the view that viral infection and allergy interact to increase the risk of an exacerbation with the virus acting as a cofactor along with environmental allergens to initiate an exacerbation to an extent that neither alone can achieve. The apparent synergy between respiratory viruses and exposure to sensitising allergens has been reported in both children and adults and suggests atopic asthma is associated with more severe illness following virus infection than asthma in the absence of allergic sensitisation (Figure 3).

Bacteria (in particular the atypical organisms *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*) have also been reported as contributors to exacerbations however differences in sampling/diagnostic methodologies have led to inconsistent results. Standard bacterial infection has recently been reported as important as viral in children under 3 years of age. Further studies are required to confirm this and to investigate other ages. Other important but less common triggers include pollutants, smoking, and psychological factors.

PREVENTION OF EXACERBATIONS

Non-pharmacologic approaches emphasised in recent years include the role of patient education and self-management plans, which have been convincingly shown to reduce exacerbations requiring hospitalisation. A large number of clinical trials have also shown the benefit of drug therapies in reducing exacerbations including inhaled corticosteroid (ICS) treatment (with a combination of ICS and long-acting bronchodilators being more effective than ICS alone) as well as leukotriene receptor antagonists. In addition, monoclonal antibodies directed against IgE and the Th2 cytokines IL-5 & IL-13 have shown promise in selected asthmatics.

Finally, vaccination against respira-

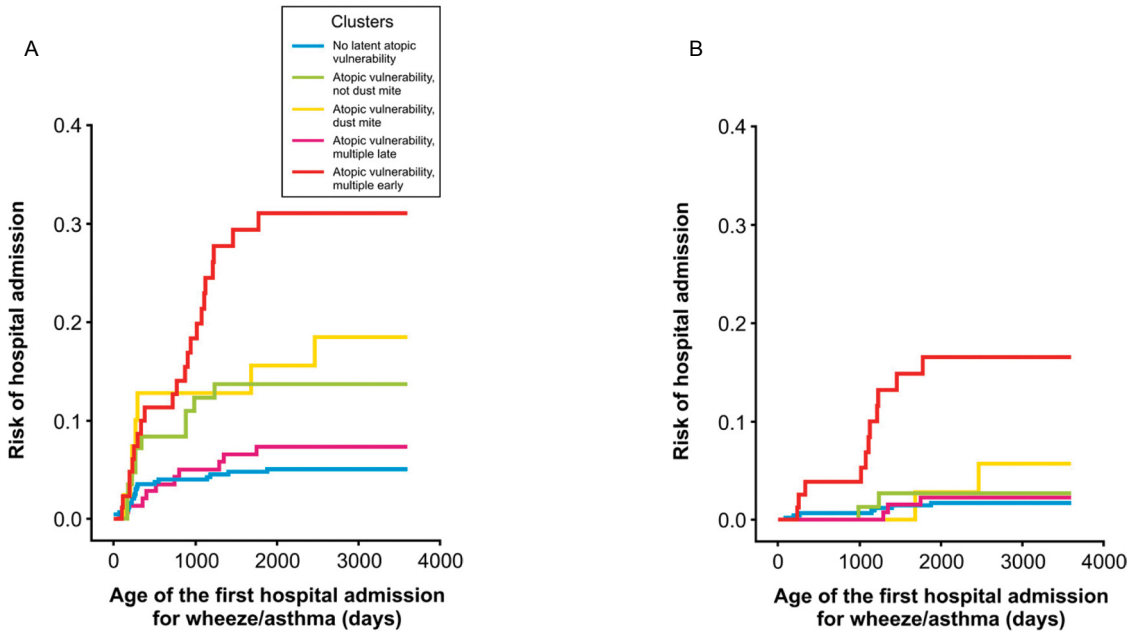

Figure 3 Kaplan-Meier estimates of cumulative risk of hospital admission with wheeze or asthma during the first 8 years of life stratified on 5-class model. A - Age at first hospital admission for children who had a hospital admission with wheeze or asthma at any age. B - Age at first hospital admission among children who had a hospital admission after age 3 years. A significant increase in the risk of hospital admission with acute asthma is seen only among children in the multiple early class, but not among those in any of the other atopy classes. *(Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Simpson A, Tan VY, Winn J, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. Am J Respir Crit Care Med 2010;181:1200-1206. Official journal of the American Thoracic Society.)*

tory viruses remains an attractive and potentially effective strategy. However, whilst influenza vaccination in asthmatic patients is recommended, an effective vaccine for rhinovirus infection remains a long way off at present.

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3 SEVERE ASTHMA

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KEY MESSAGES

- Severe asthma is a major public health problem.
- It is comprised of 3 groups, each carrying different public health messages and challenges:
  - Untreated severe asthma
  - Difficult to treat asthma
  - Treatment resistant severe asthma:
    - Controlled on high dose medication
    - Not controlled on high dose medication
- Asthma severity is determined by the intensity and phenotype of the underlying disease.
- Risk factors for the development of severe asthma include factors associated with low pre-bronchodilator FEV1% predicted.
- All patients with severe asthma should be on age-appropriate high doses of inhaled corticosteroids and other controllers.

EPIDEMIOLOGY AND SCOPE OF THE PROBLEM

Asthma is a global health problem resulting in approximately 250,000 deaths/ year, many of which result from severe asthma. Severe asthmatics (5 to 10% of all patients) impose a significant burden on healthcare utilization through unscheduled primary care visits, emergency room visits, hospitalizations, days off work / school and a requirement for multiple asthma medications. In comparison with mild or moderate asthma, severe asthmatics are 15 times more likely to use emergency services and 20 times more likely to be admitted to hospital. Severe asthma is generally associated with poor asthma control (defined by daily symptoms, poor quality of life and deteriorated lung functions) and increased risk of frequent severe exacerbations (or death) and/or chronic morbidity (including impaired lung function or reduced lung growth in children) despite intensive treatment and/or adverse reactions to medications.

SEVERE ASTHMA DEFINED

There are many definitions of severe asthma, but perhaps one of the best came about as a result of a World Health Organization (WHO) meeting convened in 2009. The WHO panel stated that severe asthma includes 3 groups, each carrying different public health messages and challenges: (1) Untreated severe asthma: untreated either because of failure to make the diagnosis or because basic access to care or to medications are not available or affordable. (2) Difficult-to-treat severe asthma: asthma not adequately responding to prescribed treatment due to adherence issues, inappropriate or incorrect use of medications or other reasons. (3) Treatment-resistant severe asthma (also known as severe, therapy-resistant asthma, or treatment refractory asthma). The last group includes asthma for which control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment which may result in untoward adverse effects from the therapeutic regimen.

Asthma severity is determined by the intensity and phenotype of the underlying disease, both of which may be characterized by pathological and physiological markers.

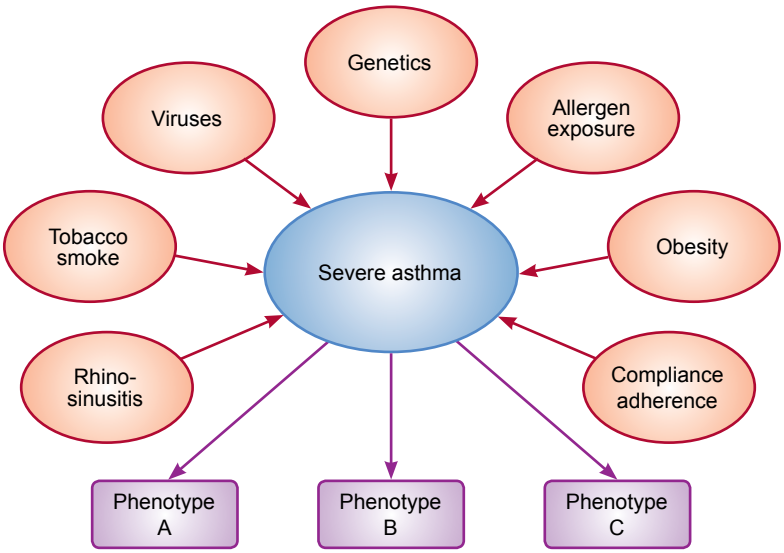

Figure 1 Factors influencing severe asthma, development and persistence. *(Reproduced from Kupczyk M, Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? J Intern Med 2012;272:121-132 with permission from John Wiley and Sons, Inc.)*

However, it is important to recognize there are no current biomarkers or even distinct physiological parameters that define severe asthma or its phenotypes. It is postulated that the effectiveness of a given pharmacotherapy may be dependent on asthma phenotype and genetics with this heterogeneity likely impacting the variable responses to medications observed in severe asthma.

RISK FACTORS FOR SEVERE ASTHMA

Although largely unknown, there are many factors known to influence severe asthma development and persistence (Figure 1). Low pre-bronchodilator FEV1% of predicted increases the risk of being classified as severe asthma. Thus, abnormalities in genes related to poorer lung functions, racial background, male sex, sputum eosinophilia and personal smoking are likely to play a role. Other identified risk factors include a history of pneumonia and secondhand tobacco smoke exposure.

THERAPY OF SEVERE ASTHMA

Improved care of severe asthma is a major unmet medical need. Optimal therapy includes appropriate environmental modifications, management of comorbidities and pharmacotherapy, assuring adherence (Figure 2). According to the Innovative Medicine Initiative, all patients with severe asthma should be on high intensity asthma treatment defined as:

- 1000 mcg/day fluticasone equivalent combined with long acting beta-2- agonists or other controllers (adults)
- 500 mcg/day fluticasone equivalent (school-aged children)
- 400 mcg/day budesonide equivalent and oral leukotriene receptor antagonists (pre-school children).

In patients unresponsive to this regimen and having a significant allergic component, the anti-IgE monoclonal antibody, omalizumab, may be added.

There are many therapies in development for severe asthma. However several unanswered questions surround these novel treatments including:

- Will therapies be phenotype/endotype/biomarker driven?
- Which treatments will decrease symptoms and exacerbations and improve quality of life with a favorable risk/benefit ratio?
- Will any of the novel therapies truly be immunomodulators capable of preventing the onset or reversing asthma pathophysiologic changes?

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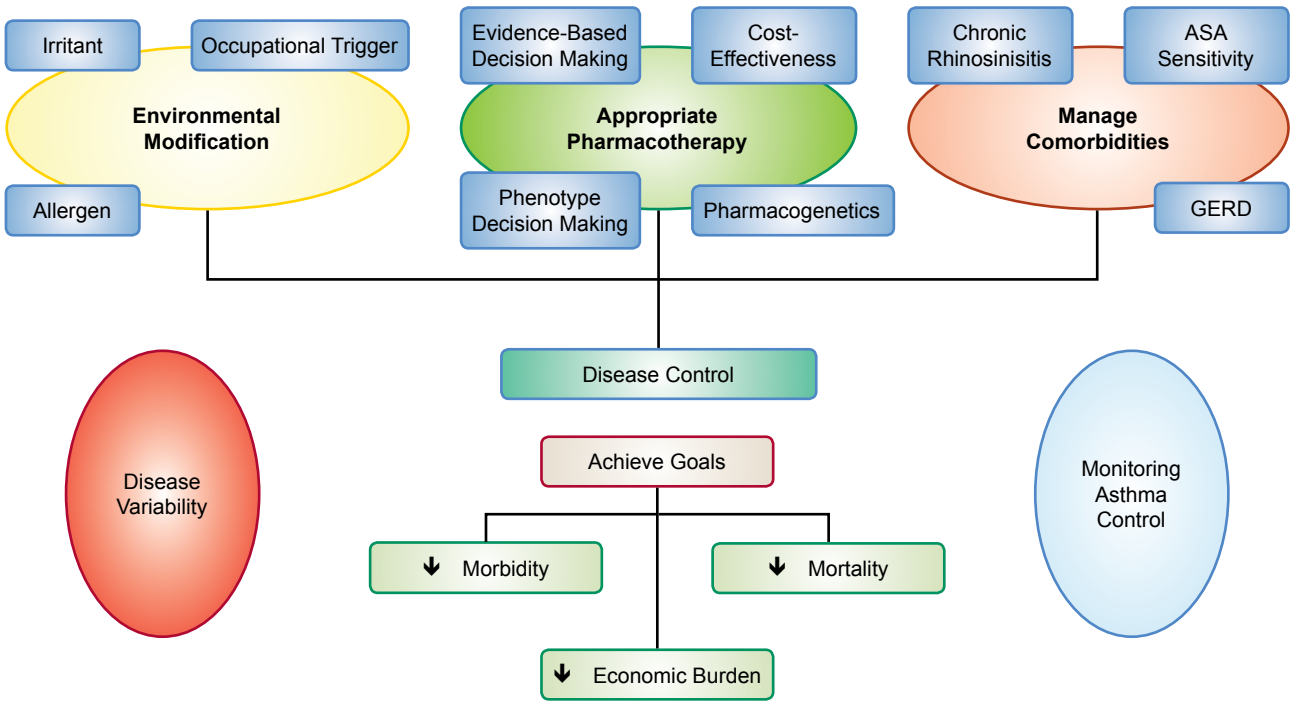

Figure 2 Severe asthma management paradigm.

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4 ADHERENCE TO ASTHMA TREATMENT

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KEY MESSAGES

- Adherence to asthma treatment has been found to be globally poor
- Low adherence leads to increased morbidity and costs
- Factors involved in poor adherence to treatment can be classified as drug and non-drug related factors
- Most of the non-drug related factors can be overcome by an improved doctor - patient communication and educational interventions

Adherence to medical recommendations is defined by the extent to which the patient's behavior matches agreed recommendations from the prescriber. The patient is free to decide whether to adhere to the doctor's recommendations or not and failure to do so should not be a reason to blame the patient. Concordance describes the patient / prescriber relationship and the degree to which the prescription represents a shared decision, in which the beliefs and preferences of the patient have been taken into consideration.

Two types of non-adherence are described: intentional, usually due to lack of motivation, and non-intentional, which occurs when patients/caregivers do not properly understand the prescription or the use of the medication, as well as when they forget or are unable to administer the inhaled medication. Usually, the attending physician measures the adherence to treatment, while lifestyle changes receive less attention.

Several methods were used to measure adherence to treatment in asthma: patient or family reports, clinical judgment, weighing/dispensing of medication, electronic medication monitoring and biochemical analysis.

Adherence to asthma treatment has been found to be poor globally. True adherence rates are lower than those reported by patients, and this should be considered first in cases of poor control of asthma. The outcome of non-adherence is loss of opportunities for patients to improve their health, loss of medication by health-care systems, loss of working and school days. The financial perspective of non-adherence in asthma is impressive: approximately £230 million of medicines are returned to pharmacies in the UK each year, with a great deal more disposed of by patients themselves, while in the US non-adherence to medical regimens has been estimated to cost the US healthcare system $100 billion per year.

An epidemiological study called Asthma Insights and Reality in Japan in 2011 (AIRJ 2011) collected data representative for real life Japanese asthmatics using a computer assisted telephone interview. The study included 400 adult asthmatics (27% males, mean age 46.4 years old), with mild intermittent asthma (65 %), mild persistent asthma (17%), moderate persistent asthma (8%) and severe persistent asthma (11%). In the last month thirty-four percent of adult asthmatics received inhaled corticosteroids (ICS) or ICS and long acting β2-agonists (LABA) combination (ICS/LABA). Only 41% of 304 asthmatics used regularly the drugs for 10 months or longer and 14% did not use any drug in the last year (Figure 1). The reasons for stopping the medication were:

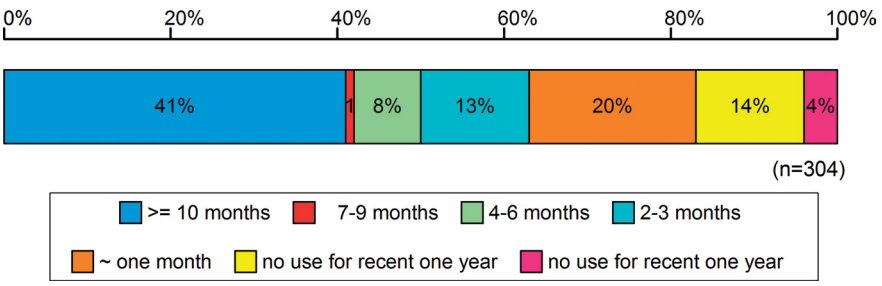

Figure 1 Adherence to ICS or ICS/LABA in the AIRJ study. Data from adult asthmatics who had used ICS or ICS/LABA at least once in the past. Adherence was assessed by duration of use of ICS or ICS/LABA in the recent one year.

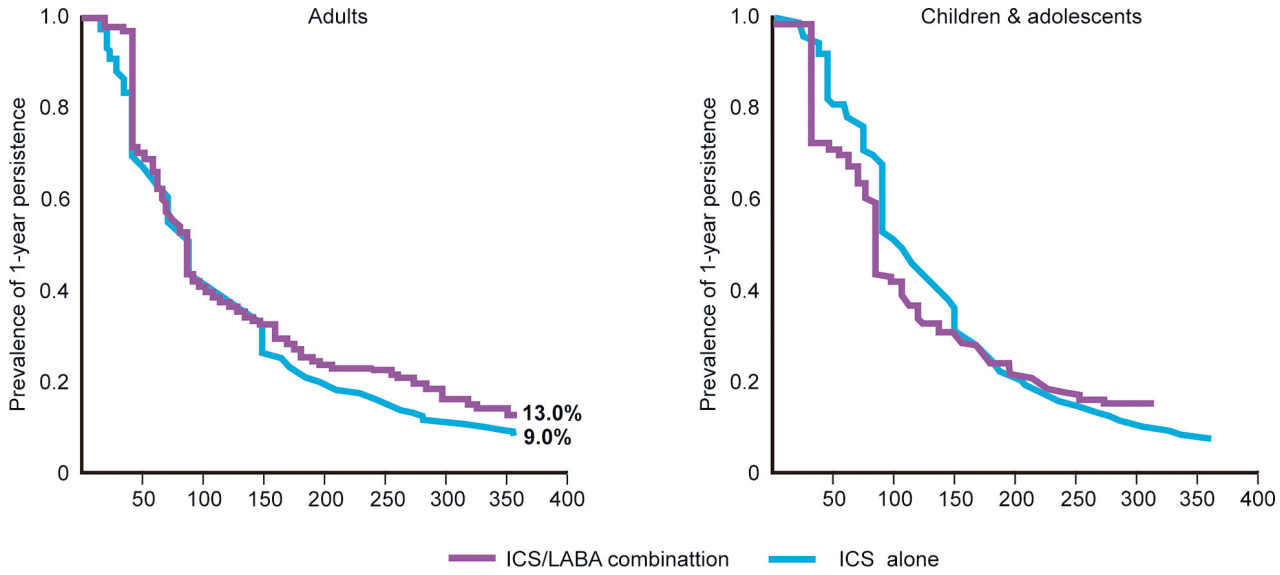

Figure 2 Overall adherence to ICS and fixed drug combinations in new users with asthma. *(Reproduced from Breekveldt-Postma NS, Koerselman J, Erkens JA, et al. Treatment with inhaled corticosteroids in asthma is too often discontinued. Pharmacoepidemiol Drug Saf 2008;17:411-22 with permission from John Wiley and Sons, Inc.)*

disappearance of asthma symptoms (61%), relief from the asthma attack (39%) and unexpectedly, doctor's suggestion (17%). As a result of poor adherence, 62% of the patients were symptomatic in the last month. Eighty-five percent of the asthmatics did not receive any information on the existence of guidelines for the management of asthma.

A cohort study evaluating 5563 new users of ICS and 297 new users of ICS/LABA (age<35 years) in The Netherlands also showed poor adherence to maintenance treatment with ICS regular use by less than 10% of patients and ICS/LABA use by less than 15%. Similar rates were observed when stratified for age (Figure 2). This study concluded that adherence to regular treatment in asthma is influenced by patient factors, such as asthma severity, and treatment-related factors, such as once-daily dosing frequency.

In the 2012 the updated Global Strategy for Asthma Management and Prevention (GINA) classified factors involved in poor adherence to treatment as drug factors (Table 1) and non-drug factors (Table 2). Most of the non-drug factors can be overcome by an improved doctor - patient communication. GINA 2012 recommends for the usual care level short questionnaires to identify poor adherence instead of prescription monitoring and pill counting. The approach is dependent on the level of trust subsidized in the doctor-patient relationship. An example question offered by GINA is "So that we may plan therapy, do you mind telling me how often you actually take medicine?"

Improving the reliability of clinical

TABLE 1

Drug factors involved in poor adherence *

- Difficulties with inhaler devices
- Awkward regimens (e.g. four times daily or multiple drugs
- Side effects
- Cost of medication
- Distant pharmacies

** Reproduced from the Global Strategy for Asthma Management and Prevention 2012 with permission of Global Initiative for Asthma (GINA).*

TABLE 2

Non-drug factors involved in poor adherence *

- Misunderstanding or lack of instruction
- Fears about side-effects
- Dissatisfaction with health care professionals
- Unexpressed/undiscussed fears or concerns
- Inappropriate expectations
- Poor supervision, training, or follow-up
- Anger about condition or its treatment
- Underestimation of severity
- Cultural issues
- Stigmatization
- Forgetfulness or complacency
- Attitudes toward ill health
- Religious issues

** Reproduced from the Global Strategy for Asthma Management and Prevention 2012 with permission of Global Initiative for Asthma (GINA).*

judgment implies a correct evaluation of the patient's expectations from the drug and for the course of the disease (the necessity-concern construct) and of the potential impediments (financial, psycho-social and cultural, such a steroid phobia). Clear instructions provided by health professionals, social support and discussion groups for a better understanding of the disease and active measures of maintaining contact with patients are recommended.

Figure 3 Adherence patterns in asthmatic children.

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5 SOCIAL DETERMINANTS OF ASTHMA

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KEY MESSAGES

- Asthma rates and severity are rising globally, but disproportionately impact low socio-economic status (SES), minority, and urban populations
- Social stratification can significantly influence asthma outcomes through mediation of exposure to risk and protective factors
- Low-SES individuals are more likely to be exposed to environmental pollutants, indoor allergens, and other respiratory irritants that adversely affect asthma
- Low-SES individuals are also more likely to be exposed to psychosocial stressors such as community and domestic violence as well as poor housing
- Efforts to eliminate asthma disparities must address both environmental and psychosocial determinants of asthma, which will require reducing exposure, especially among low-SES groups

Asthma is a complex developmental condition, the impact of which is highly socially patterned. Though asthma prevalence and morbidity are on the rise globally, this increase is not uniformly distributed, with a disproportionate asthma burden falling on low socio-economic status (SES) and/or minority populations residing in urban areas. Moreover, in the United States this burden has been found to be highly clustered within urban communities particularly marked by social adversity and deprivation, most notably those containing a high percentage of African-American or Puerto Rican residents. This community-level inequality is mirrored by worldwide trends in asthma prevalence and severity published in the most recent Global Asthma Report of the International Study of Asthma and Allergies in Childhood (ISAAC). Time trends analyses contained within this 2011 report found that rising global prevalence estimates are being driven primarily by rapid increases in low and middle-income countries with large populations, while prevalence in many high-income countries reached a plateau or even began to decrease. Similarly, phase three of ISAAC found that asthma is more severe in low and middle-income countries.

A social determinants of health approach acknowledges that social stratification can significantly influence health outcomes through mediation of exposure to risk and protective factors at both the household and community levels. For instance, individuals living in poverty are more likely to be exposed to environmental pollutants (e.g. particles related to the combustion of diesel and cooking fuels), indoor allergens (e.g. mold and dust containing mouse or cockroach excrement), and other respiratory irritants (e.g. tobacco smoke). However, these differences in environmental exposures alone do not fully explain the significantly increased asthma risk found in certain socially disadvantaged populations. Though the etiology of this excess asthma burden remains unclear, exposure to violent crime was recently implicated as an environmental factor impacting pediatric asthma prevalence in a large urban cohort, with exposure to community violence conceptualized as a source of psychosocial stress. Indeed, community, family and individual-level

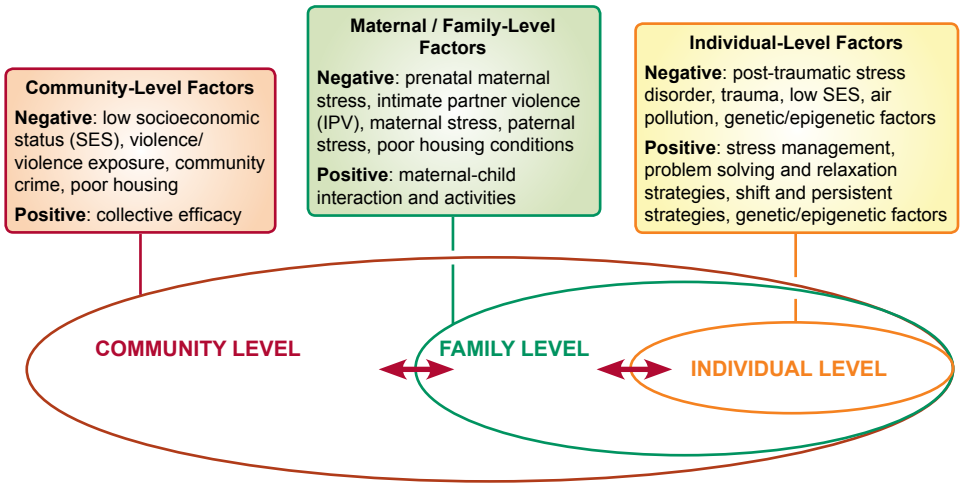

Figure 1 Ecological framework of the relation between psychosocial stressors and asthma morbidity. *(Reproduced from Yonas MA, Lange NE, Celedón JC. Psychosocial stress and asthma morbidity. Curr Opin Allergy Clin Immunol. 2012;12:202-210.)*

exposure to psychosocial stressors (Figure 1) increasingly characterized as "social pollutants", has been shown to predict some of this additional variation in asthma risk. Beyond exposure to community and domestic violence, these stressors can include food, housing, and financial insecurity as well as social marginalization. Conversely, there is evidence that community vitality/collective efficacy, increased maternal-child interaction, and effective utilization of psychological coping strategies (e.g. "shift-and-persist") may positively impact asthma outcomes at the community, family and individual levels.

Much as environmental pollutants like diesel exhaust enter the body and disrupt biological systems via pro-inflammatory processes, the "social pollutant" model of psychosocial stress hypothesizes that it also "gets under the skin" leading to the dysregulation of inflammatory processes. In general, low-SES individuals are more likely to encounter both psychosocial stressors and physical environmental toxins that may each independently contribute to the increased asthma burden levied upon these populations (Figure 2). Moreover, given that these psychosocial and physical stressors often co-occur in disadvantaged environments and may influence common physiological pathways, it is possible that the aforementioned psychosocial stressors may potentiate an individual's susceptibility to environmental exposures, thus giving rise to further asthma disparities.

Given the considerable evidence linking social inequality to population-level asthma disparities, it is clear that health equity cannot be achieved without taking concrete steps to address societal inequality more broadly. Efforts to eliminate asthma disparities must include direct acknowledgement of social determinants of health such as poverty, racism, lack of economic opportunity and community deprivation. Furthermore, structural and policy interventions must address these root causes of asthma disparities at the community and broader societal level, and accompany efforts to ensure effective disease self-management at the family and individual levels.

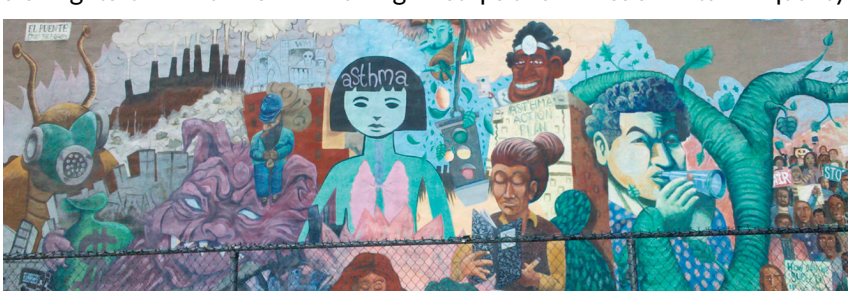

Figure 2 Asthma mural depicting psychological and environmental stressors. *(From http://aceandson.com/blog/?p=948, accessed May 20, 2013)*

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6 INEQUITIES AND ASTHMA

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KEY MESSAGES

- Asthma patients do not have access to basic asthma medications or medical care in many areas of the world
- The solution to the problem in developing countries will not be achieved only by improving access to medication
- National Health Ministries must consider asthma as a public health priority
- National programmes need to be implemented to improve diagnosis, management, and reduce direct and indirect costs
- Evidence from well-established national asthma management programmes proves a substantial improvement of asthma burden

The International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 study has demonstrated that the prevalence of asthma in African and Latin American children, assessed by a self-reported questionnaire, is higher than the global average. In addition, children with asthma in low and middle-income countries, have more severe symptoms than those in high-income settings, possibly due to lack of diagnosis, poor access to care, lack of affordability of therapy, environmental irritants, genetic susceptibility to more severe disease or a combination of these.

Despite access to appropriate healthcare resources, several studies have demonstrated that asthma is often underdiagnosed and undertreated in many parts of the world.

The multinational Asthma Insights and Reality (AIR) surveys show the rate of exacerbation, including hospitalizations, emergency room visits and unscheduled visits to physician office, are higher in Asia Pacific and Latin America compared to Europe and USA. The same observation was made for the indirect cost of asthma evaluated by the level of school and work absenticism.

Close to 50% of medical expenditures for asthma are a consequence of exacerbations. There are only a few pharmacoeconomic studies in developing countries. In Latin America, unscheduled health care resource use was particularly high among patients with uncontrolled asthma. For both adults and children, scheduled health care costs were approximately 3-fold higher in those with severe persistent symptoms than in those with mild intermittent symptoms. Regardless of symptom severity, almost threequarters of expenditure was due to unscheduled health care.

One succesfull program (ProAR) was developed in 2003 in Salvador, Brazil, prioritising the control of severe asthma. By facilitating referrals from the public health system and providing proper multidisciplinary, but simple, management including education and medication for free, ProAR enrolled >4,000 patients with severe asthma. The patients were offered regular follow-up and were referred back to primary healthcare only when asthma control could be maintained without requirement of a combination therapy. This intervention was associated with a steep decline in health resource utilisation and remarkably reduced the rate of hospital admissions due to asthma by 74% in 3 yrs in the entire 2.8 million city habitants. Cost analysis demonstrated that this intervention was very cost-effective and provided a financial relief to the families and the government.

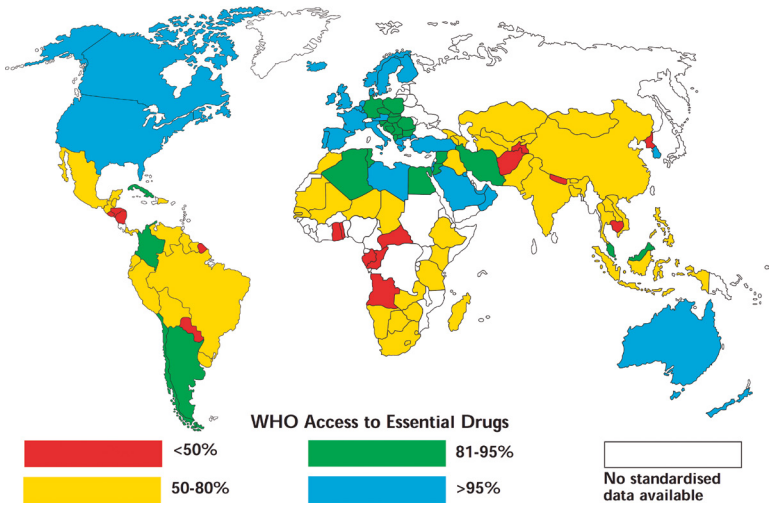

Figure 1 World Map of the Proportion of the Population with Access to Essential Drugs. *(Reproduced from Masoli M, Fabian D, Holt S, et al. Global Burden of Asthma. 2004, Global Initiative for Asthma (GINA).)*

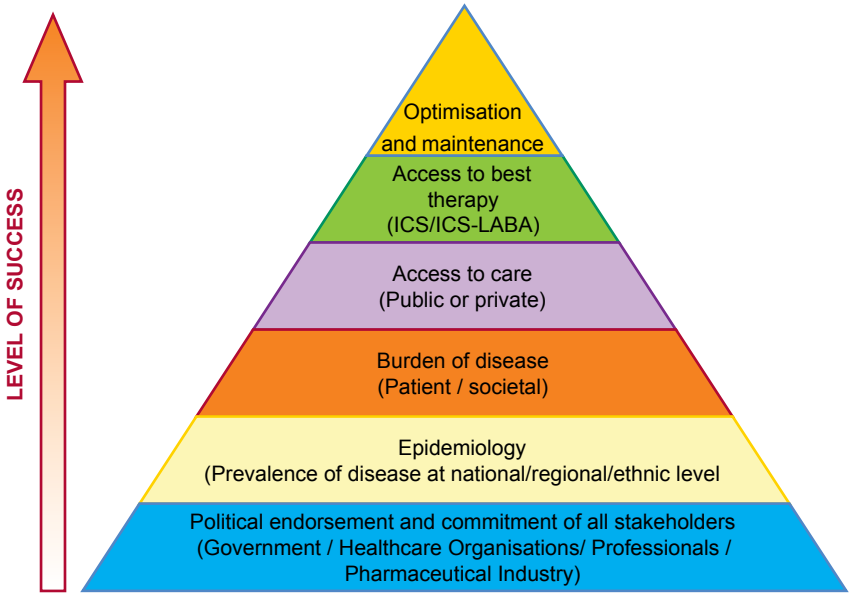

Figure 2 Essential steps for a successful asthma management program. *(Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union. Lalloo UG, Walters RD, Adachi M, et al. Asthma programmes in diverse regions of the world: challenges, successes and lessons learnt. Int J Tuberc Lung Dis 2011;15:1574-1587.)*

In many areas of the World, persons with asthma do not have access to basic asthma medications or medical care (Figure 1).

The solution to the problem in developing countries will not be achieved only by improving access to medication; National Health Ministries must consider asthma as a public health priority, and national programmes need to be implemented in order to improve diagnosis, management, and reduce direct and indirect related costs.

Evidence from the studies conducted in countries with well-established or developing national asthma management programmes suggests that establishment of an overall successful programme requires a logical progression through specific stages, starting with epidemiological evaluation and leading up to optimisation and maintenance therapy for individual patients (Figure 2). Each development stage is likely to present a multitude of local and national challenges and specific implementation strategies, which will determine the overall success level of the asthma management programme.

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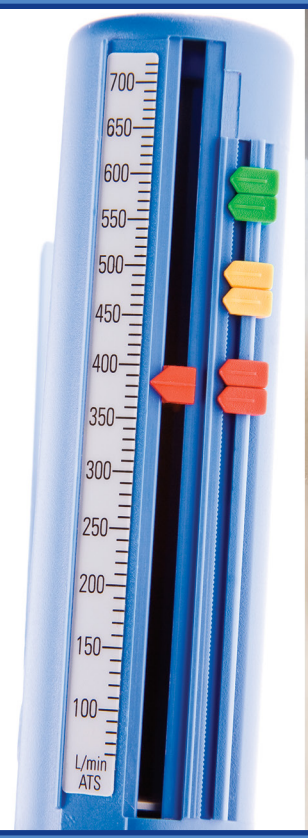
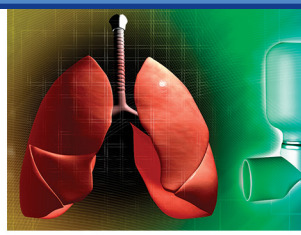
Section D





PREVENTION AND CONTROL OF ASTHMA

* Primary and secondary prevention of asthma
* Allergen immunotherapy in asthma
* Asthma control
* Best buys for asthma prevention and control
* Evidence for asthma control – zero tolerance to asthma with the Finnish programmes
* The need for integrated and complimentary strategies in the political agenda
* Policies and strategies to facilitate access to asthma diagnosis and treatment
* Policies and strategies to reduce risk factors for asthma
* Tobacco control and asthma
* Implementation of a healthy life style and asthma
* Individual interventions for asthma prevention and control
* The role of Primary Care in the prevention and control of asthma
* Role of patient organisations in the control and prevention of asthma
* Social mobilization for prevention and control of asthma
* Asthma in resource constrained settings
* Dealing with the implementation gap for asthma prevention and control
* Generating resources for prevention and control of asthma
* Asthma prevention and control: Why it should not be ignored any longer?
* Vision, roadmap and a land-marking event

1 PRIMARY AND SECONDARY PREVENTION OF ASTHMA

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Lifetime risk of asthma approximates 35%, most often starting early in life. Preventive measures reducing asthma prevalence and burden will have significant impact on healthy ageing, general population health and societal costs.

Primary prevention of asthma involves preventing disease development, whereas secondary prevention refers to preventing new asthma in subjects who have expressed other atopic diseases like atopic eczema or allergic rhinitis (Table 1, Figure 1). Prevention strategies should be well documented before implementation, ideally through randomised controlled intervention studies. Prospective observation studies may suggest potential benefits of the measures. Primary prevention should not be harmful, and should be applicable to the general population, since we are currently not able to predict asthma in early childhood. Recent studies have cast doubt on some previous primary prevention advice, possibly due to a change in causative factors for asthma development from "old" high-risk patients to the many "new" asthma cases of later years due to a change in our modern environment.

KEY MESSAGES

- Avoid smoking, including prenatal and second hand exposure
- Repair possible housing moisture damage
- Avoid traffic air pollution, if possible
- Participate in regular physical activity
- Include fruits and fish in food
- Pet avoidance reduce symptoms and exacerbations in patients with asthma, but does not prevent asthma development
- Breast milk is recommended, but does not protect against asthma

PREVENTABLE RISK FACTORS

Table 2 presents preventable risk factors for allergy and asthma.

Prenatal and second-hand tobacco smoke exposure increases risk of asthma and wheezing throughout childhood. Prenatal smoke exposure reduces lung function in the neonate. Low infant lung function tracks through childhood to adulthood. Smoke exposure is an important risk factor for severe adult lung disease, as for childhood asthma. Smoke induces methylation of genes protecting against smoke exposure. Intervention reduces morbidity as shown by the effect of smoke legislation on childhood asthma hospitalization. *Reduction of smoke exposure represents important primary and secondary asthma prevention.*

Moisture damage is a consistent finding in observational birth cohort and cross-sectional studies of housing conditions and childhood asthma. *Housing conditions should be improved when moisture damage is present.*

Air pollution, especially traffic and diesel vehicle pollution, increases risk of asthma development and asthma symptoms in children and reduces lung function, as shown in observational studies. Living close to heavy trafficked highways increases asthma risk and reduces lung growth through childhood. *Reducing traffic pollution, particularly from diesel exhaust, is a primary asthma preventive measure that should be implemented by politicians and community planners.*

TABLE 1

Definition of primary, secondary and tertiary prevention

Prevention - Level	Definition
Primary	Prevent occurrence of disease
Secondary	Prevent development of disease after first signs of disease have presented or predisposing factors are present
Tertiary	Prevent disease symptoms and progression including treatment, attempting to minimize the long-term effects of the disease.

TABLE 2

What advice can we give at present time for primary and secondary asthma prevention?

Prevention	Measure - Advice	Study designs
Primary prevention	Avoid primary and second hand smoke exposure	Observational and intervention studies
	Moisture damage should be repaired.	Observational birth cohort and cross-sectional studies
	Avoid traffic air pollution. Do not live close to highways. Kindergartens should not be positioned closed to highways.	Observational studies
	Humanised antibody against RS-virus reduces the risk of bronchiolitis which may reduce the risk of later asthma development	One interventional study
	Early pet keeping. No advice.	Observational studies
	Recommend regular intake of fish, Ω-3 fatty acids and antioxidant vitamins	Observational studies
	Recommend physical activity and training	Meta-analysis. Longitudinal and cross-sectional observational studies
Secondary prevention	Avoid primary and secondary smoke exposure	Observational and interventional studies
	Avoid traffic air pollution. Do not live close to highways. Kindergartens should not be positioned closed to highways.	Observational studies
	Pet avoidance will reduce symptoms in asthma patients with allergic sensitization to pets.	Observational studies
	Recommend physical activity and training (reduces airways inflammation and improves fitness and self perception).	Observational and interventional studies

Respiratory virus infections, as respiratory syncytial virus (RSV) bronchiolitis, increase the asthma risk. Rhinovirus infections induce acute asthma in asthma patients. Presently only humanised antibody against RSV virus reduces the risk of bronchiolitis, but the intervention is reserved for high-risk children. One observational study shows that RSV antibody given for the prevention of acute bronchiolitis reduces the risk of later asthma. *RSV vaccination represents a potential primary preventive measure.*

Early **allergen exposure** has been anticipated to increase the risk of allergic sensitization and asthma. Consequently, advising against pet keeping has been widely adopted. This advice was recently challenged, with a European study including 20000 children from several European birth cohort studies reporting no significant association between early pet keeping and asthma at school age. On the other hand, in case of asthma with allergic pet sensitization, pet avoidance will reduce symptoms. Mite sensi-

Figure 1 Primary and secondary asthma prevention.

tization increases asthma risk, but presently there is no convincing primary preventive effect on asthma by mite reduction measures. *Presently no advice should be given with regard to pet keeping for primary prevention of asthma.*

FACTORS PROTECTING AGAINST ASTHMA DEVELOPMENT

Several observational studies suggest that inclusion of certain **foods** in diet may protect against asthma development. This includes regular fish, Ω-3 fatty acids and fruit intake with respect to asthma and lung function development in healthy children.

Breast milk up to 6 months of age has been recommended to prevent asthma and allergy development. Several recent studies question this, and present evidence does not support that breast milk protect against asthma and allergy development. However, there are several other reasons for recommending breast milk feeding, both nutritional and protection against infection.

Physical activity is recommended to improve general health. A recent meta-analysis of studies in all ages found physical activity to protect against asthma development. Physical training was reported to reduce airways inflammation and improve fitness in asthma. However, no effect upon lung function and bronchial responsiveness was found.

Allergen immunotherapy as secondary prevention has been stated to prevent asthma in children with allergic rhinitis. However, with only one interventional multicentre study the evidence for this is presently too weak.

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2 ALLERGEN IMMUNOTHERAPY IN ASTHMA

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KEY MESSAGES

- Allergen immunotherapy is the only effective etiological treatment for respiratory allergy, which has the potential to change the course of the allergic disease
- The efficacy and safety of immunotherapy in allergic asthma have been demonstrated in controlled clinical trials
- Subcutaneous immunotherapy with some aero-allergens and good quality extracts has been shown to reduce significantly allergen specific bronchial hyperreactivity
- Sublingual immunotherapy is a good alternative for treating allergic asthma, but more evidence is needed to support its efficacy and safety

Allergen immunotherapy (AIT) is the only effective etiological treatment for respiratory allergy, which has the potential to change the course of the disease, thus improving quality of life, and reducing long-term costs and burden of allergies. Its immunological mechanisms of action have been demonstrated as induction of allergen-specific immune tolerance by regulatory T cells, specific antibody isotype change from IgE to IgG4 and decrease in the activity and mediators of eosinophils, mast cells and basophils.

However, unlike for allergic rhinitis, the role of immunotherapy in allergic asthma is still a matter of debate. Many controlled clinical trials have shown the efficacy and safety of AIT in allergic asthma. Some published meta-analyses (Table 1), have confirmed these findings, despite some methodological and clinical weaknesses. In a most recent meta-analysis on subcutaneous immunotherapy (SCIT) for allergic asthma, the authors have shown an overall significant reduction in asthma symptoms and medication use. It would have been necessary to treat three patients (95% CI 3 to 5) with SCIT to avoid one deterioration in asthma symptoms, and to treat four patients (95% CI 3 to 6) with AIT to avoid one requiring increased medication.

As for children, individual pediatric studies have shown moderate efficacy of SCIT in seasonal and perennial asthma and significant reduction in inhaled corticosteroid (ICS) doses in mite-induced asthma. This is of particular importance as allergic asthma is frequently associated with allergic rhinitis with the consequent need of simultaneous nasal steroid therapy. Furthermore, there is a concern of the possible adverse effects of long-term treatment with ICS in children. No children's sub-analysis was performed in the Abramson's Cochrane meta-analysis on SCIT and there is no clear consensus regarding the use of SLIT in asthmatic allergic children.

SCIT significantly reduced allergen specific bronchial hyperreactivity (Table 2), which was evaluated in the majority of the studies after one year of treatment. This is an important finding from a clinical point of view as the measurement of this parameter is the only accurate method of assessing the risk of an acute episode of asthma due to a sudden and increased level of an aeroallergen exposure, as in the case of mould allergic patients. Moreover SCIT is able to decrease not only early, but also late asth-

TABLE 1

Meta-analysis of studies of AIT in asthma

	Disease	Author	Studies (n)	Population	Participants		Effect Size SMD (95% CI)	Hetero-geneity I^2
					Active (n)	Placebo (n)		
Symptom Scores				SCIT				
	Asthma	Abramson MJ 2010	34	Adults and children	727	557	-0.59 (-0.83,-0.35)	73%
				SLIT				
	Asthma	Calamita Z 2006	9	Adults and children	150	153	-0.38 (-0.79, 0.03)	64%
	Asthma	Penagos M 2008	9	Children	232	209	-1.14 (-2.10, -0.18)	94%
Medication Scores				SCIT				
	Asthma	Abramson MJ 2010	20	Adults and children	485	384	-0.53 (-0.80, -0.27)	67%
				SLIT				
	Asthma	Calamita Z 2006	6	Adults and children	132	122	-0.91 (-1.94, 0.12)	92%
	Asthma	Penagos M 2008	7	Children	192	174	-1.63 (-2.83, -0.44)	95%

***Effect size (SMD - Standardized mean difference)**: poor <-0.20; medium = -0.50; high >-0.80*

***Heterogeneity (I^2)** = 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity*

TABLE 2

Injection allergen immunotherapy for asthma: summary of allergen-specific bronchial hyperreactivity indices *

Allergen-specific BHR index	Studies (participants)	SMD (95% CI)
Log PD_{20} mite	6 (148)	-0.98 (-1.39 to -0.58)
Log PD_{20} pollen	5 (202)	-0.55 (-0.84 to -0.27)
Log PD_{20} animal dander	6 (153)	-0.61 (-0.95 to -0.27)
Log PD_{20}/PC_{100} other allergens	2 (61)	-0.18 (-0.70 to 0.33)
Total	19 (564)	-0.61 (-0.79 to -0.43)

** Reproduced from Cox L, Calderón M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. Immunotherapy. 2012;4:601-16 with permission of Future Medicine Ltd.*

BHR: Bronchial hyperreactivity; PC_{100}: Concentration required to produce a 100% increase in lung resistance; PD_{20}: Provocative dose required to produce a 20% fall in forced expiratory volume in 1s; SMD: Standardized mean difference.

matic responses following allergen bronchial challenge, the presence of which is considered an experimental model resembling chronic bronchial allergic inflammation, thus confirming the anti-inflammatory effect of the AIT in the lung.

Evidences do exist for the efficacy of sublingual immunotherapy (SLIT), but SLIT meta-analyses are mostly questioned due to large methodological heterogeneity and inconsistencies (Table 1). SLIT is generally considered to have a better safety profile than SCIT both in children and adults. The risk of a systemic reaction to SCIT is greater in subjects with uncontrolled asthma and with accelerated dosing schedules. Systematic reviews have shown that SCIT is a safe therapeutic intervention when it is prescribed to well-selected patients, even in asthmatic children, and given in a specialist clinic with adequate facilities and by trained medical personnel.

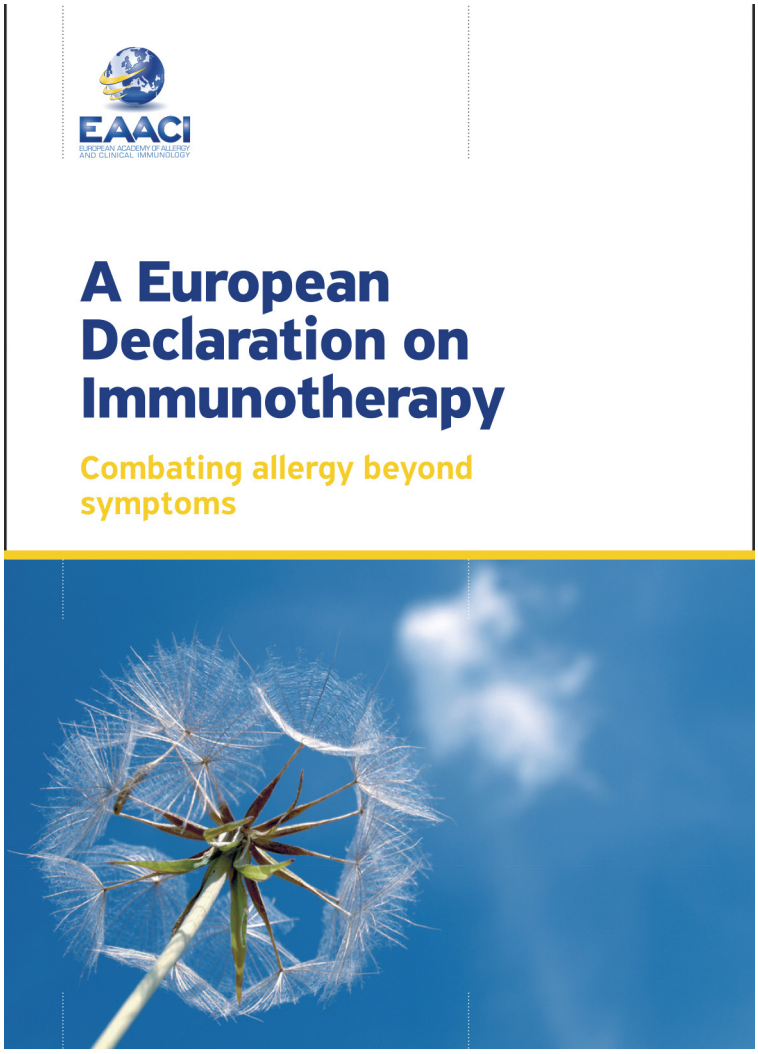

Figure 1 EAACI declaration on immunotherapy. *(http://www.eaaci.org/resources/immunotherapy-declaration.html, accessed May 20, 2013)*

UNMET NEEDS

- The main need is to perform separate clinical studies in adults and in children with allergic asthma, following standardized protocols, as recommended by international guidelines.
- Studies of AIT in allergic asthma should also focus more on the long term effect of the treatment (as well as on a long-term steroid-sparing effect) rather than considering only the immediate efficacy on allergic symptoms.
- Specific asthma features, like bronchial hyperreactivity, asthma control and exacerbations should be included among the study primary or secondary outcomes.
- Assessing the safety of SLIT in moderate to severe asthmatics is still an unmet need.
- The unmet needs of AIT have to be evaluated in an integrated multinational academic, research, industry and regulatory agencies effort in Europe.

In the recent European Declaration on Immunotherapy EAACI calls upon Europe's policy-makers to coordinate actions and improve individual and public health in allergy by promoting immunotherapy awareness, updating national healthcare policies to support allergen immunotherapy and prioritising funding for immunotherapy research (Figure 1).

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3 ASTHMA CONTROL

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KEY MESSAGES

- Optimal asthma control is the goal of asthma management
- Optimal asthma control consists of current (day to day) control and reduced future risk
- Asthma control and asthma severity are not synonymous
- Asthma control can be achieved in the majority of patients
- The most common reason for poor control is lack of adherence to medications
- There are several validated questionnaires to measure asthma control in research studies

National and international guidelines for asthma management have identified that the primary goal of management is to achieve asthma control. Asthma control consists of two domains. These are optimizing current (day-to-day) control, defined as the minimization of both daytime and night time symptoms, no limitation of activity, minimal rescue bronchodilator use and no airway narrowing; and minimizing future risk defined by long term decline in lung function, severe asthma exacerbations and unwanted effects from medications (Figure 1). The two domains which define asthma control are not independent. The more poorly controlled day-to-day asthma is, the greater the risk of a severe asthma exacerbation.

In the past, physicians were often confused by the terms ''asthma control" and "asthma severity". It was perceived that well-controlled asthma was synonymous with mild asthma and poorly controlled asthma was synonymous with severe asthma. This perception is incorrect. Severity is the intensity of the underlying disease process before treatment, and control is the adequacy of the response to treatment. Patients with severe asthma, if treated appropriately can be well controlled and patients with mild asthma, if they fail to follow treatment guidelines, will have inadequately controlled asthma, which may be perceived as severe (Figure 2). The goals of asthma management are the same for all degrees of asthma severity. Although patients with severe asthma will often be more difficult to control with an intervention, effective treatment can potentially fully control patients with severe asthma.

An American Thoracic Society and the European Respiratory Society joint Working Group have made recommendations about the important components of asthma control and their measurement. In addition, there are a range of questionnaires and diaries that have been developed to measure current asthma control and each one of which has strengths and weaknesses. Among the most commonly used are the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT), and the Asthma Therapy Assessment Questionnaire (ATAQ).

Despite the availability of effective and safe medications to treat asthma, the most important of which are inhaled corticosteroids, either alone or in combination with long-acting inhaled β2-agonists, many patients remain poorly controlled. The most important reason for this is poor adherence to treatment regimes. When patients are taking their asthma medications, many can achieve well controlled asthma; in some instances, how-

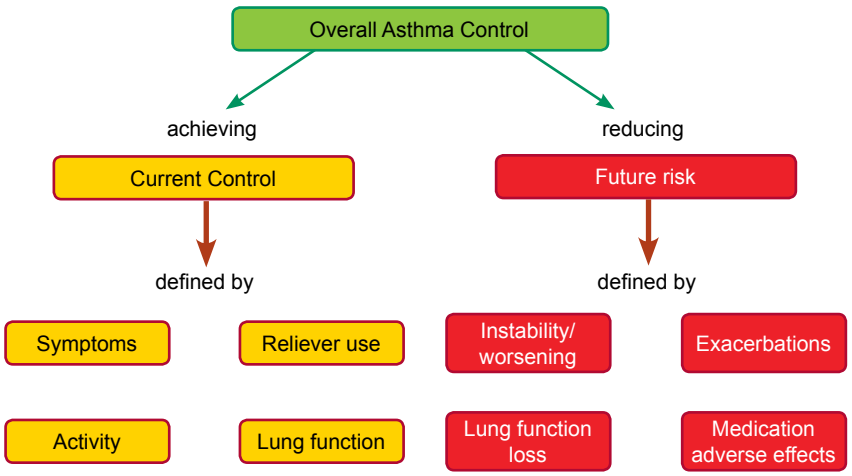

Figure 1 Overall asthma control. *(Reprinted from J Allergy Clin Immunol, 125/3, Bateman ED, Reddel HK, Eriksson G, et al, Overall asthma control: the relationship between current control and future risk, 600-608, Copyright 2010, with permission from Elsevier.)*

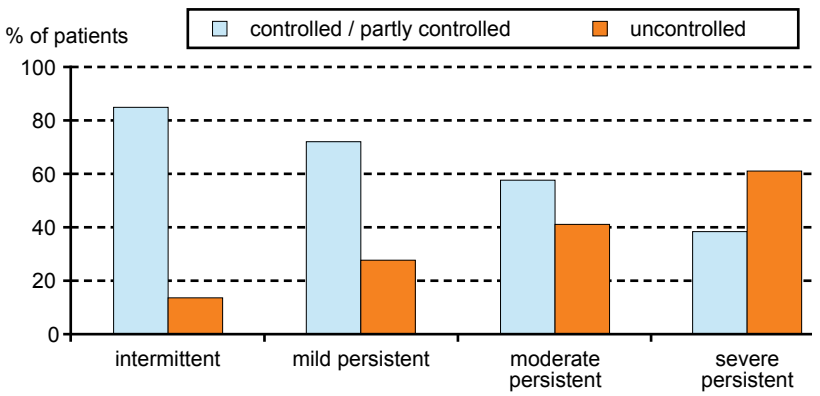

Figure 2 Percentage of patients with controlled/partly controlled or uncontrolled asthma (GINA classification) according to asthma severity *(Reprinted from Ann Allergy Asthma Immunol, 107/6, Korn S, Both J, Jung M, et al. Prospective evaluation of current asthma control using ACQ and ACT compared with GINA criteria, 474-479, Copyright 2011, with permission from Elsevier.)*

ever, asthma may be only partly controlled and a decision needs to be made by the patients and their managing health care professional whether to increase the treatment, or to accept partly controlled asthma. However, all guidelines indicate that if asthma is uncontrolled, treatment options should be carefully evaluated and additional treatment added.

There is a subset of asthmatic patients who, despite treatment with optimal doses of asthma medications, have uncontrolled asthma and are at risk for severe asthma exacerbations. These are considered severe refractory asthmatics, and are 5-10% of the asthma population and are the group of patients where phenotyping with relation to their atopic status, and the type of airway inflammation present, may provide additional useful information with regards to newer treatment options.

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4 BEST BUYS FOR ASTHMA PREVENTION AND CONTROL

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KEY MESSAGES

- A step-wise asthma management plan providing best-buy measures for asthma prevention and control is urgently needed
- Asthma should be recognised as a novel major public health problem
- Cost-efficient use of available resources, promotion of effective asthma management approaches and investment in innovative models and in asthma research are important steps forward
- Improving the distribution of resources between and within countries increases the accessibility to asthma diagnosis and to essential drugs
- Active involvement of all stakeholders is necessary to plan efficient management programs for asthma

With the projected increase in the proportion of the world's population that is urban in 2025, there may be an additional 100 million persons with asthma adding to the existing world asthma population of 300 million individuals. In addition, asthma morbidity and mortality account for 1% of all disability adjusted life years (DALYs), equivalent to 16 million DALYs lost per year worldwide. A step-wise asthma management plan providing cost-efficient measures for asthma prevention and control is urgently needed (Figure 1).

Identify and address barriers which limit the efficiency of interventions aiming to prevent and control asthma. Many economic and political factors impact the efficiency of asthma prevention and control strategies. Examples include poverty, poor education and infrastructure, low public health priority and the lack of good worldwide valid data on morbidity and mortality from asthma.

Position asthma as an important cause of morbidity, economic cost, and mortality worldwide. The burden of asthma around the world is of sufficient magnitude to warrant its recognition as a priority disorder in government health strategies. The low public health priority of asthma due to the importance of other illnesses and to insufficient awareness of the general public and policy makers negatively impacts efficient funding and implementation of asthma management plans.

Well-controlled epidemiological description and surveillance of asthma. National, regional and international asthma registries are urgently needed to continuously monitor the prevalence, morbidity and mortality of asthma at a global scale.

Cost-efficient use of available resources. Until asthma is recognised as a novel major public health problem and pharmacological measures become available to reduce the prevalence of asthma, resources need to be prioritised:

- to address asthma preventable risk factors, such as air pollution or tobacco smoke
- to improve the care of disadvantaged groups with high morbidity
- to ensure that cost-effective management approaches which have been proven to reduce morbidity and mortality are available to as many persons as possible with asthma world-

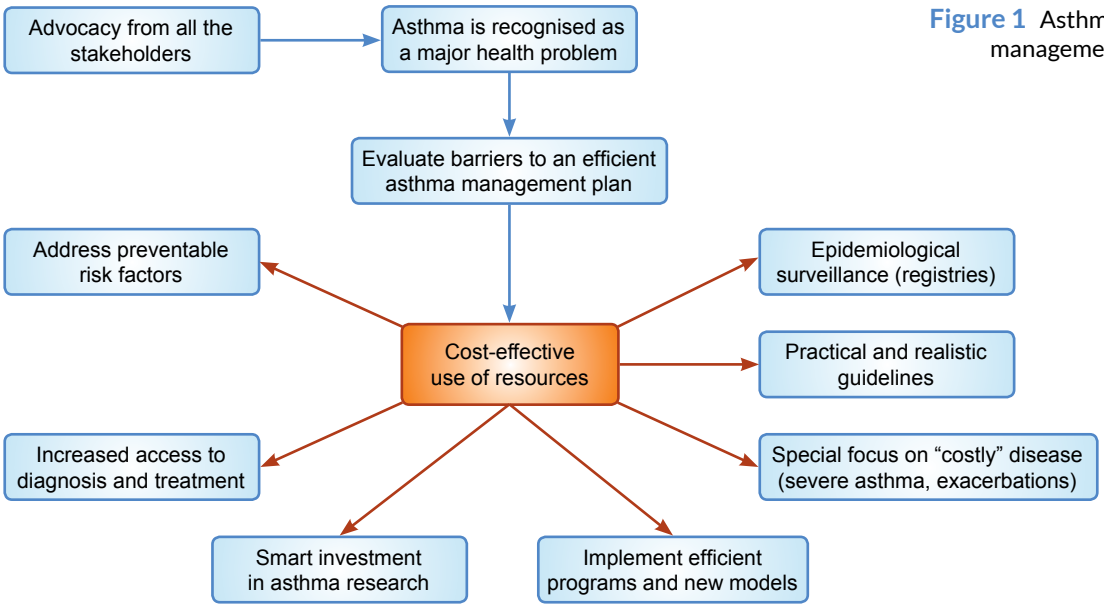

Figure 1 Asthma "best buys" management plan.

wide. Even if asthma control is not achieved, improvements in quality of life can still be obtained with appropriate treatment, thus lessening the asthma associated disability

- to support asthma research which should provide effective prevention, accurate and rapid diagnosis and a curative treatment of asthma

Improve accessibility to asthma diagnosis and to essential drugs in low- and middle-income countries and for hard-to-reach populations. Most of the lifestyle-related risk factors for asthma (poor hygiene or diet, obesity and psychosocial stress) are prevalent among the poor. In many areas of the world asthma sufferers do not have access to diagnosis or to basic asthma medications. Improving the distribution of resources between and within countries could enable better health care to be provided.

The "Yes We Can Urban Asthma Partnership" reaches out to high-risk children from underserved urban areas in different settings: urgent visits, the hospital, a specialty asthma clinic, and through an expanded community health worker programme. Significant increases in controller medications and action plans use and decrease in asthma symptoms were demonstrated. Additional changes occurred within the local system of asthma care to support ongoing efforts to improve asthma management.

The La Red intervention in the selected Puerto Rican communities experiencing a disproportionately high level of asthma burden combined the key components from the "Yes We Can" and the "Inner-City Asthma Study" interventions. The program significantly reduced asthma symptoms, asthma-related hospitalizations and emergency department use, and their associated high costs.

Control the preventable environmental factors by using standardised decision support tools. Decision support tools (DSTs) are used at various levels and by various stakeholders. A recent survey showed that DSTs address only one pollution source or environmental stressor, are only applied to one chronic disease or one decision making area and are used only by national authority and/or municipality/urban level administration or only by environmental professionals and researchers. There is a need to develop standardised DSTs covering an increasing number of pollution sources, environmental stressors and health end points.

Adapt international asthma guidelines to low- and middle-income countries and use realistic dissemination and implementation strategies. Guidelines used to prevent and control asthma should be practical and realistic in terms of differences across cultures and health care systems and between high- and low and middle-income countries. Crowd-sourcing provides an additional opportunity to increase the sustainability of the guidelines.

Promote cost-effective asthma management approaches and invest in innovative models. The Finnish experience proved that asthma prevention and control is achievable in a cost-efficient way.

Telemanagement of asthma in-

cludes key components of asthma management, and is tailored to the individual patient needs. The approach is effective in improving quality of life and clinical outcomes, especially in adult patients with moderate to severe asthma. More research is needed on the long-term effectiveness and cost-effectiveness under real-world conditions.

The Healthy Living Pharmacy or the Chronic Care Model are new concepts designed to meet public health needs through community pharmacy, tailored to local requirements for tackling health inequalities, or through multi-component remodelling of chronic disease services. Their applicability to asthma care was recently demonstrated.

Smart investment in asthma research. The "asthma epidemic" cannot be fully explained by the current knowledge of the causation of asthma. In addition, very few intervention strategies to prevent and control asthma were fully successful.

Key priority areas in the field of asthma research are:

- unveiling the risk factors and mechanisms that cause asthma, including detailed phenotyping/endotyping
- novel biotechnological innovations and patient-oriented diagnostic and treatment protocols
- well designed intervention strategies for asthma prevention and control, fully applicable in low and middle-income countries

Special focus on difficult-to-manage and costly severe disease forms and/or exacerbations of asthma. Severe asthma consumes ~50% of the global asthma budget. A key challenge is to recognize and treat factors that make asthma difficult to manage and to predict differences in response between groups of patients. A multidisciplinary approach within specialist centers with experience and wider access to national and international severe asthma networks was suggested.

Patients at risk of severe exacerbations contribute disproportionally to asthma mortality, morbidity and costs. Using asthma risk registers in primary care reduced hospitalisations and increased prescriptions of preventative therapies without increasing costs. Monitoring induced sputum eosinophil cell counts is helpful in preventing exacerbations in some patients with severe asthma. Future developments include better biomarkers to predict exacerbations or the cause of exacerbations, augmentation of the immunological response to viruses, the use of telemonitoring in patients with severe asthma and the development of improved therapies targeted at reducing exacerbations.

Involve all stakeholders. Active involvement of all stakeholders, including asthma educators, the primary care network, patient organizations and policy makers are necessary to plan efficient management programs for asthma.

Decisions by policy makers that are granting access to asthma diagnosis and treatment are summoning action from patients, physicians, and their organizations. One of the strongest advocacy to date is from patient organizations, which strive to educate stakeholders on key issues that determine patient access to appropriate asthma diagnosis management. Advocacy by physicians at the local level is needed, as are national and international efforts by organizations such as the European Academy of Allergy and Clinical Immunology.

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5 EVIDENCE FOR ASTHMA CONTROL – ZERO TOLERANCE TO ASTHMA WITH THE FINNISH PROGRAMMES

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KEY MESSAGES

- Asthma is a public health problem. A community problem needs community solutions
- Most of asthma suffering is unnecessary. Every asthma death is an accident and potentially avoidable
- Asthma is a quite treatable disease, but much too often the diagnosis is severely delayed causing poor disease control
- To take asthma into control, "hit early and hit hard". Keep up the control with individualized maintenance treatment and follow-up
- National and local action plans with defined goals, tools and outcome measurements are effective and reduce asthma burden with relatively simple means
- Networking of specialists, family physicians, nurses and pharmacists is the key to implement the best practices in health care
- Guided self-management is the key for patients to proactively stop asthma attacks and exacerbations

In Finland, a comprehensive and nationwide Asthma Programme was undertaken from 1994 to 2004 to improve asthma care and prevent the predicted increase in costs. The main goal was to lessen the burden of asthma on individuals and society. "The Finnish Programme" has been followed in other countries with equally good outcomes. The implementation strategy has been adopted by the GINA Asthma Control Challenge (Figure 1).

GOALS OF THE "ASTHMA PROGRAMME"

Five specific goals were set, for example, decreasing the number of days hospitalised patients by 50% and reducing annual costs per patient by 50%. The programme comprised both evidence-based management guidelines, which have been available to general practitioners and nurses via the Internet since 2000, and an action plan with defined tools to achieve the goals. The action plan focused on implementation of new knowledge, especially for primary care. At that time the new medical knowledge was: "Asthma is an inflammatory disease and should be treated as such from the very beginning." The key to implementation was an effective network of asthma-responsible professionals and development of an evaluation strategy. In 1997 *Finnish pharmacies* were included in the Pharmacy Programme, and in 2002 a *Childhood Asthma Mini-Programme* was launched.

RESULTS: THE BURDEN OF ASTHMA HAS DECREASED

As a result of this programme, the burden of asthma in Finland has decreased considerably. Key indicators have fallen significantly: number of hospital days with 86% from 110 000 (1993) to 15 000 (2010) and disability with 76% from 1993 to 2003 (Figure 2). In recent years, only a few asthma deaths/year under the age of 65 have been recorded in Finland (total population 5.4 million). In young age groups there is virtually no asthma mortality. In 1993 the number of patients needing regular medication for persistent asthma (entitled to 75% reimbursement of medicine costs) was around 135 000. By 2011 this number was around 239 000,

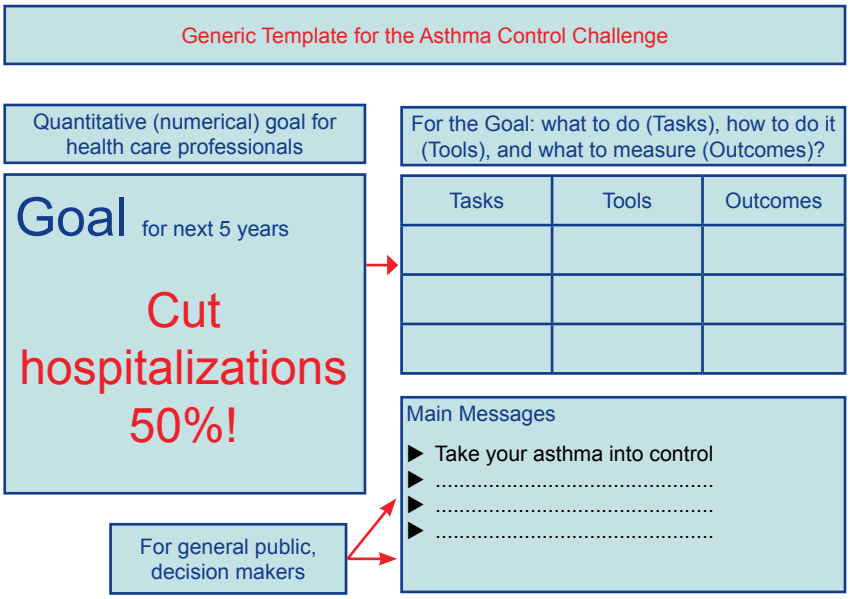

Figure 1 Simple outline for a local or national asthma implementation programme. Set a goal, decide the activities, tools and outcome measurements. "Advertise" to patients and general public with attractive and straight forward messages: "You control asthma, asthma does not control you!"

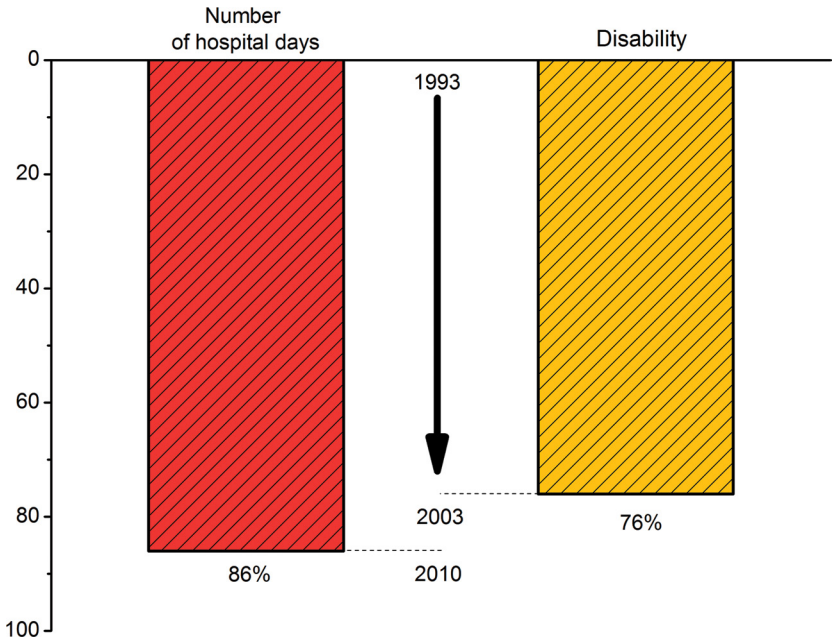

Figure 2 Decrease in the number of hospital days and disability.

indicating a 77% increase and reflecting earlier and more effective detection and intervention (Figure 3). The most remarkable increase was in the use of first-line inhaled corticosteroid treatment during the early years of the programme (1994–1999).

PREVALENCE IS UP; COSTS ARE DOWN

In spite of increasing prevalence, the overall costs related to asthma (compensation for disability, medicines, hospital care and outpatient doctor visits) leveled off and then continued to decrease. This has been in stark contrast to what was predicted. The overall costs of asthma in 1993 were around €330 million, including loss of productivity. By 2010, this figure had dropped to €195 million (Figure 4). Based on the 1993 asthma prevalence trends, the 2010 costs would have been at least €500 million (min scenario). An estimate of the theoretical cost savings for the year 2010 alone was around €300 million. Annual costs per patient attributable to asthma were reduced by more than 50%. The extra costs of planning and implementing the programme were small, primarily because most of the activities were carried out as part of the routine work of the clinicians and administrators.

PATIENT BENEFITS: EARLY DETECTION, TIMELY TREATMENT

For the patients with asthma, the main improvement was early detection of the disease and its timely treatment: "Hit early and hit hard!" Patients with chronic asthma have been educated to employ guided self-management, an approach that encourages them to be proactive in preventing asthma attacks and exacerbations. Effective net-

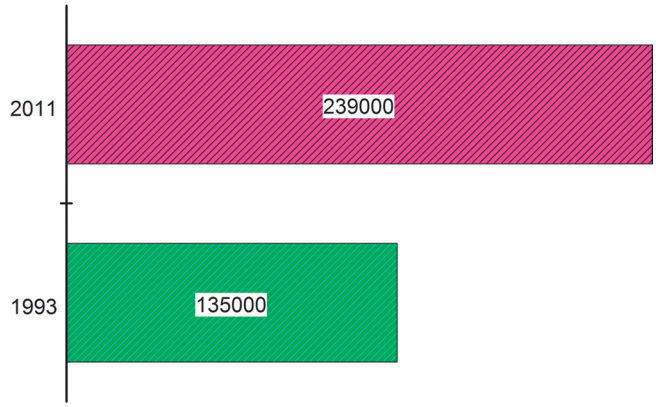

Figure 3 Significant increase in use of asthma controller medication.

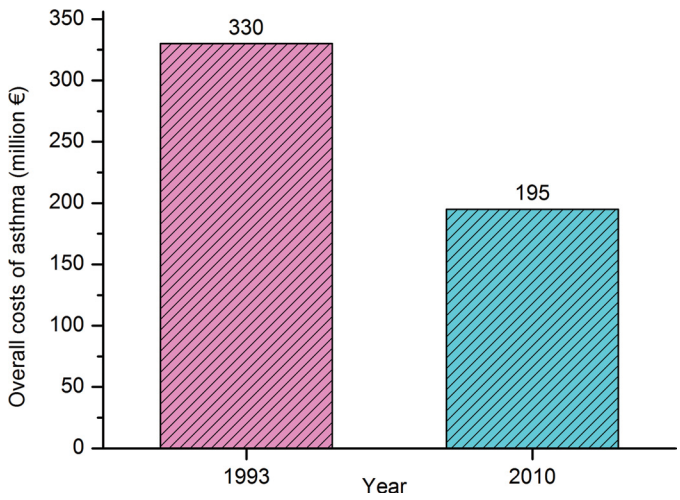

Figure 4 Decrease in asthma related costs.

working of specialists with "local asthma champions", such as general practitioners (n=200), asthma nurses (n=700) and pharmacists (n=700) has also considerably improved the overall asthma care in Finland.

EXPANDING THE PROGRAMME'S SCOPE

The Finnish experience shows that it is possible to considerably reduce the morbidity of asthma and its impact on individuals, as well as on society. Worrying trends continue to be the still slightly increasing prevalence of asthma and growing drug costs. A new *Allergy Programme* 2008–2018, has been launched in Finland to expand the good asthma results to all allergic diseases and to take a step forward from treatment to prevention. Asthma is included with the specific goal to reduce emergency visits by 40% in 10 years. For children with mild persistent asthma (the majority!), a strategy of intermittent (periodic) treatment has been developed. The long-term aim is to have an impact on the incidence of both asthma and allergies.

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6 THE NEED FOR INTEGRATED AND COMPLIMENTARY STRATEGIES IN THE POLITICAL AGENDA

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KEY MESSAGES

- The Integrated Care Pathways (ICPs) are structured multidisciplinary care plans that promote the translation of guidelines into local protocols and their subsequent application to clinical practice
- ICPs differ from practice guidelines as they are utilized by a multidisciplinary team and have a focus on the quality and co-ordination of care
- Multisectorial ICPs for rhinitis and asthma co-morbidity need to be developed and implemented combining preventive and disease control strategies, and placing a special emphasis on elderly patients and/or underserved patient populations, and on cultural and societal aspects of the diseases in a project centred around the patient

The Integrated Care Pathway (ICP) concept was initiated in 1985 by Zander and Bower. ICPs are structured multidisciplinary care plans, which detail essential steps in the care of patients with a specific clinical problem. They promote the translation of guidelines into local protocols and their subsequent application to clinical practice. An ICP forms all or part of the clinical record, documents the care given, and facilitates the evaluation of outcomes for continuous quality improvement. ICPs empower patients and their carers (health and social). ICPs differ from practice guidelines as they are utilized by a multidisciplinary team and have a focus on the quality and co-ordination of care.

Asthma and allergic diseases are major chronic respiratory diseases and occur along the life time. People with low socioeconomic status and women bear a disproportionate burden. Two debates at the European Union Parliament have been organized during Presidencies of the EU Council (Poland: 2011, Cyprus: 2012) and stressed the importance of prevention, early diagnosis and management of chronic respiratory diseases in children. The Cyprus Presidency debate focused on the management of chronic respiratory diseases in children for the promotion of active and healthy ageing.

Effectives strategies are needed to reduce asthma and allergy burden. (Figure 1). The Finnish Asthma Programme is cost-effective in different countries. However, it is insufficiently implemented and an ICP combining rhinitis and asthma comorbidity deployed in EU regions is a priority, as indicated by the Council of the European Union (2011). ARIA (Rhinitis and Asthma co-morbidity) is a co-morbidity guideline initiated in 1999 in collaboration with the World Health Organisation (WHO). It has been developed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) and variance analysis and is available in many countries.

Integrated Care Pathways for rhinitis and asthma need to be developed and implemented. The objectives of AIRWAYS-ICP are (i) to develop multisectoral ICPs which can be used across Europe and other countries, (ii) to allow the practical use of a combined asthma and allergy programme by European countries and regions, (iii) to com-

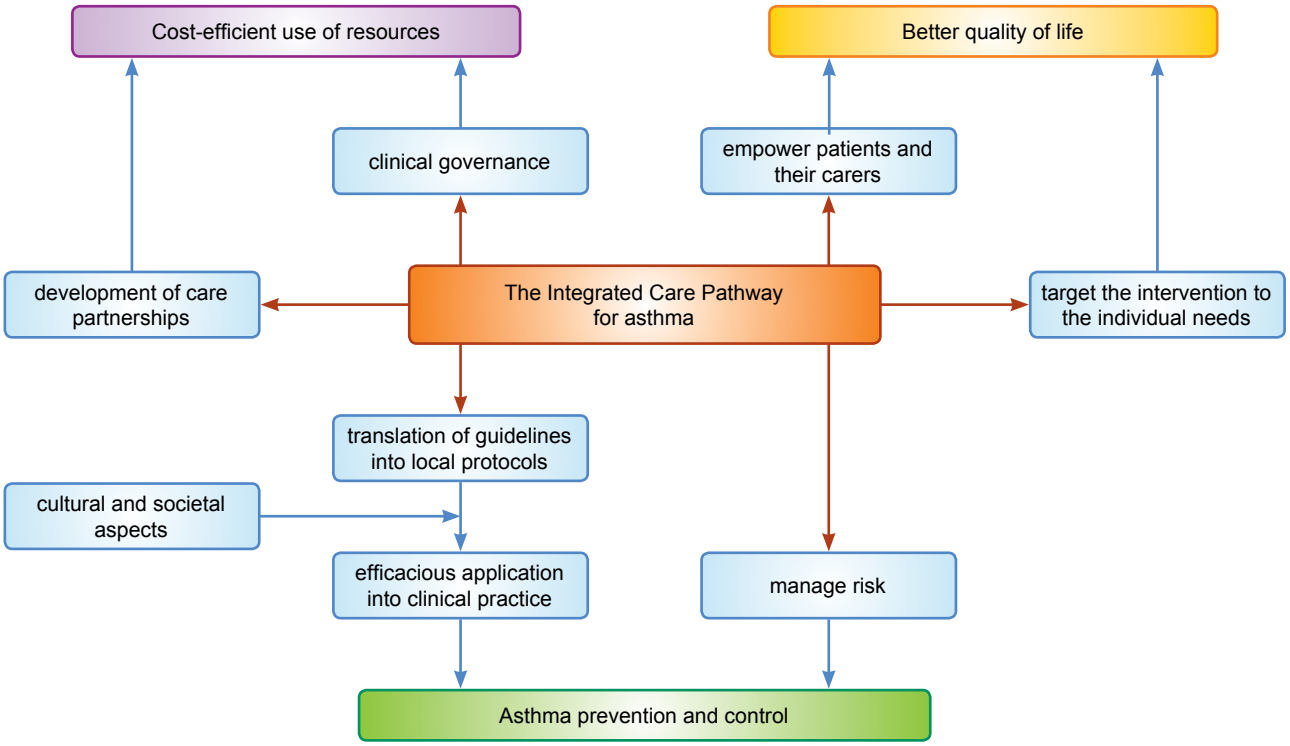

Figure 1 The Integrated Care Pathway for Asthma.

bine preventive and disease control strategies, (iv) to place a special emphasis on elderly patients and/or underserved patient populations, (v) to implement cost-effective policies on prevention of asthma and allergy and (vi) to have an impact on active and healthy ageing. AIRWAYS-ICP places a particular interest in cultural and societal aspects of the diseases in a project centred around the patient.

Patient's organisations and major European scientific societies are partners of the WHO Collaborative Center for Asthma and Rhinitis for this initiative.

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7 POLICIES AND STRATEGIES TO FACILITATE ACCESS TO ASTHMA DIAGNOSIS AND TREATMENT

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Asthma ranks amongst the commonest diseases globally. Its prevalence is increasing, but at the same time access to asthma diagnosis and treatment lacks behind the burden of disease. It is a major disease in low and middle income countries, and unfortunately still remains under-recognised, under-diagnosed and therefore, under-treated, or sometimes even over-treated.

Effective policies and strategies are needed to fill this gap and facilitate access to the diagnosis and treatment of asthma. These are necessary at the global, regional, national and local level. These must be dispersed widely and proper implementation must be ensured to be effective.

KEY MESSAGES

- Create awareness for early recognition of asthma
- Provide easily accessible facilities for asthma diagnosis and treatment
- Create awareness for early recognition of asthma triggers and their prevention
- Develop workable strategies for facilitating access to asthma diagnosis and treatment
- Develop global, regional, national and local policies to improve asthma diagnosis and treatment
- Develop, promote and ensure the use of evidence based guidelines for asthma diagnosis and treatment
- Empower people with asthma to participate and make choices about asthma care and to lobby for better treatment and prevention health policies

GLOBAL AND REGIONAL POLICIES AND PROGRAMMES FOR ASTHMA

1. The United Nations – Non Communicable Diseases Agenda

The United Nations (UN) recognized the global importance of Non Communicable Diseases (NCDs) and the place of Chronic Respiratory Diseases (CRD), including asthma, as being responsible for more deaths than all other causes combined.

2. The WHO NCD Action Plan 2008-2013

The World Health Organisation (WHO) recommended a 5 year NCD Action Plan in 2008 (Table 1).

3. Global Alliance against Chronic Respiratory Diseases (GARD)

GARD is a voluntary alliance of national and international organizations, institutions and agencies from many countries working towards the common goal of reducing the global burden of CRDs, including asthma. Its vision is a world where all people breathe freely (Figure 1).

4. The International Union against Tuberculosis and Lung Disease (The Union)

The Union's approach to asthma management is adapted from international asthma guidelines and uses a framework based on The Union's model for tuberculosis services. This framework advocates for standard case management, use of simple tools for the diagnosis and classification of the asthma severity, careful monitoring and evaluation of asthma care, and provision of essential medicines through it's Asthma Drug Facility, as a practical solution to this problem.

TABLE 1

Global action plans and barriers to improving asthma care

NCD Action Plan

Action points

1. Raise the priority accorded to non-communicable disease (NCDs) at global and national levels
2. Establish and strengthen national policies and plans for the prevention and control of NCDs
3. Promote interventions to reduce the main shared modifiable risk factors: tobacco use, unhealthy diets, physical inactivity and harmful use of alcohol
4. Promote research for the prevention and control of NCDs
5. Promote partnerships for the prevention and control of NCDs
6. Monitor NCDs and their determinants and evaluate progress at the national, regional and global levels

Global Initiative for Asthma (GINA)

Action points

1. Evidence-based guidelines must be effectively implemented and disseminated at the national and local levels
2. Implementation of asthma guidelines should involve a wide variety of professional groups and other stakeholders, including patient groups and organizations, policy makers and planners, and others.
3. Asthma guidelines should take into account local cultural and economic conditions
4. Evaluate the effectiveness and quality of care
5. Adaptation and implementation of asthma guidelines require an understanding of the cost and cost effectiveness of various management recommendations in asthma care.
6. Access to available and affordable medication, especially in LMIC; cost should not be a barrier to achieve asthma control.

Brussels Declaration from the European Summit for Change in Asthma Management

Action points

1. Make asthma a political priority
2. Understand that, in addition to local mechanisms, asthma is a respiratory manifestation of systemic inflammation
3. Ensure rapid responses to the most current scientific understanding of asthma
4. Update the European Medicines Agency (EMA) regulatory guidance on asthma
5. Include evidence from real-world studies in treatment guidelines
6. Provide funding for real-world studies
7. Explore variations in asthma care across Europe
8. Enable people with asthma to participate and make choices about their care
9. Understand and reduce the impact of environmental factors
10. Set targets to assess improvements

Barriers to Improving Asthma Care

Action points

The Union

- lack of political commitment to fund non-communicable diseases
- lack of structure or organization for following up patients with chronic disease
- high cost of equipment and essential medicines
- lack of personnel trained to manage asthma
- health services oriented for acute care are unable to organize the long-term management needed for asthma care

GINA: Evidence based guidelines can become ineffective, if there is:

- Poor infrastructure to use recommended medications
- Suboptimal use of medications
- Lack of physicians use of guidelines

5. The International Primary Care Respiratory Group (IPCRG)

Primary care is the cornerstone of a health system being pivotal in prevention, diagnosis, patient engagement and supported self-management, and treatment of asthma. Integration between primary and secondary care is essential for facilitating access to asthma diagnosis and treatment.

6. Global Asthma Network (GAN)

This new network, launched in November 2012, aims to improve care for people with asthma around the world. A world without asthma is the ultimate goal of the GAN.

7. The Global Initiative for Asthma (GINA)

Patient care following evidence-based asthma guidelines leads to improved outcomes. Implementation of asthma guidelines should include setting of goals and development of strategies through collaboration amongst diverse professional groups including both primary and secondary health care professionals, public health officials, patients, asthma advocacy groups, and the general public (Table 1).

Goals and implementation strategies vary from country to country and within countries for reasons of economics, culture, and environment. The priority ranking of asthma amongst other diseases, especially in low- and middle income countries (LMIC), must be increased (Figures 2-4).

8. Allergic Rhinitis and its Impact on Asthma (ARIA)

Rhinitis is the most common NCD among children. Asthma and rhinitis often co-exist, and it is important to recognize, diagnose and treat rhinitis to prevent the devel-

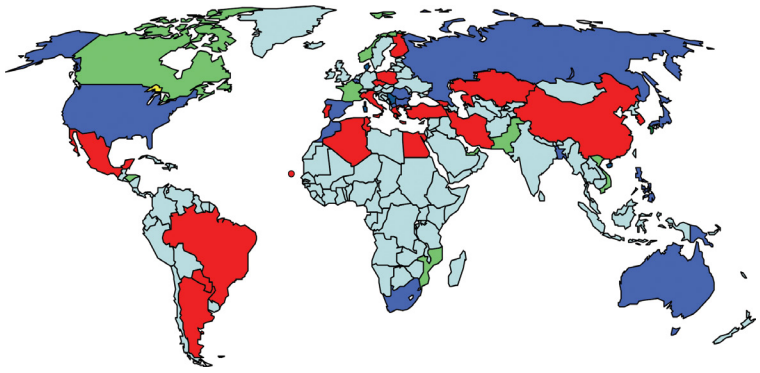

Figure 1 Countries with Global Alliance for Respiratory Diseases (GARD) programmes and activities. *(Reproduced from Bousquet J, GARD General Meeting, Istanbul, 30-31 May 2008)*

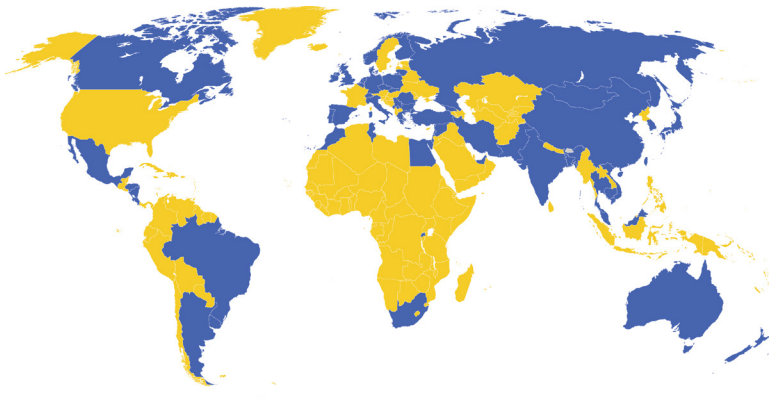

Figure 2 GINA Member countries

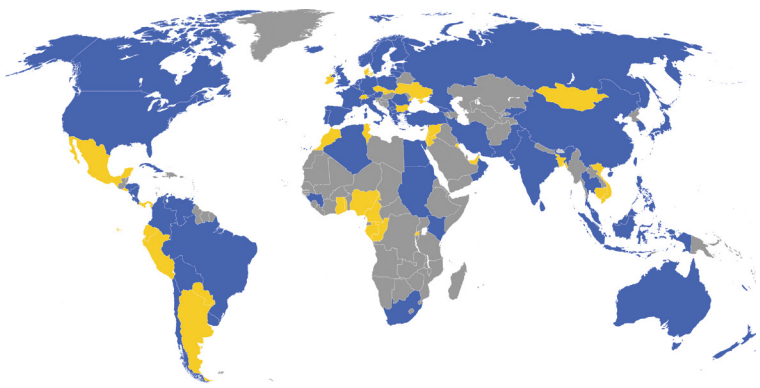

Figure 3 Countries having asthma guidelines for adults

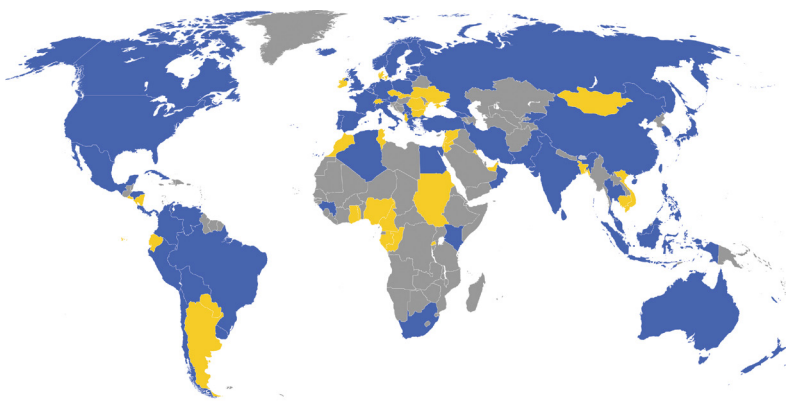

Figure 4 Countries having asthma guidelines for children.

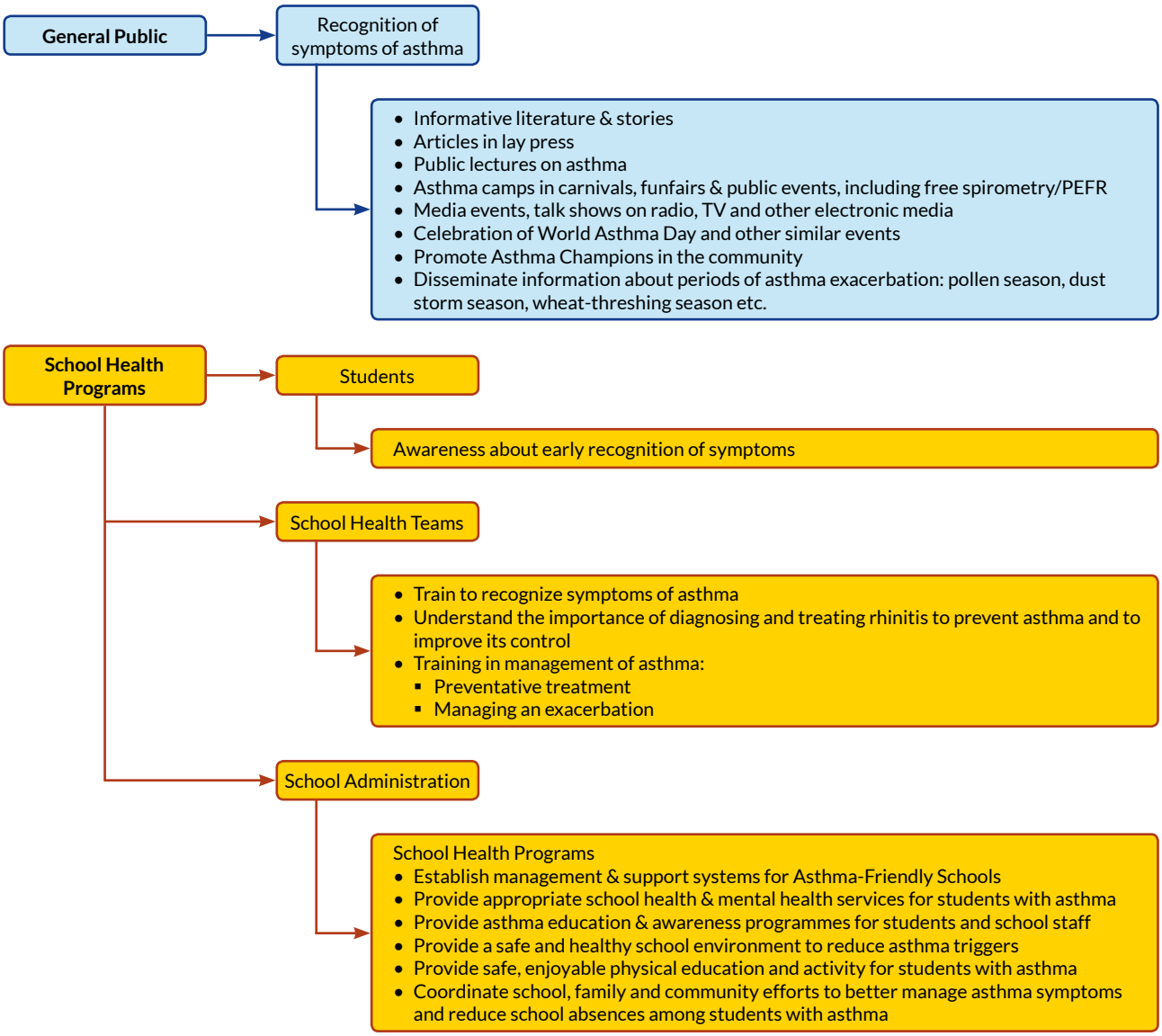

Figure 5 Strategies to facilitate access to asthma diagnosis and treatment. *(Continued on next page)*

opment to asthma or to improve asthma control.

9. The Brussels Declaration

The Brussels Declaration on Asthma was developed to call attention to the shortfalls in asthma management and to urge European policy makers to recognise that asthma is a public health problem that should be a political priority (Table 1).

The diagnosis of asthma is difficult. It is important to understand that the diagnosis and treatment of asthma of children is different from adults. There should be adequate access to the diagnosis and treatment of comorbidities as well.

STRATEGIES

Strategies for facilitating access to diagnosis must focus on creating awareness and recognition of asthma at all levels of society, including the general public, students, patients and other stake-holders. Physicians and health care workers must be trained for early and accurate diagnosis, taking the correct history, and managing treatment according to the availability of therapies and their affordability by the patient. They have to be tailor-made according to the specific requirements of each and every patient.

Strategies for facilitating access to asthma diagnosis and treatment are highlighted in Figure 5.

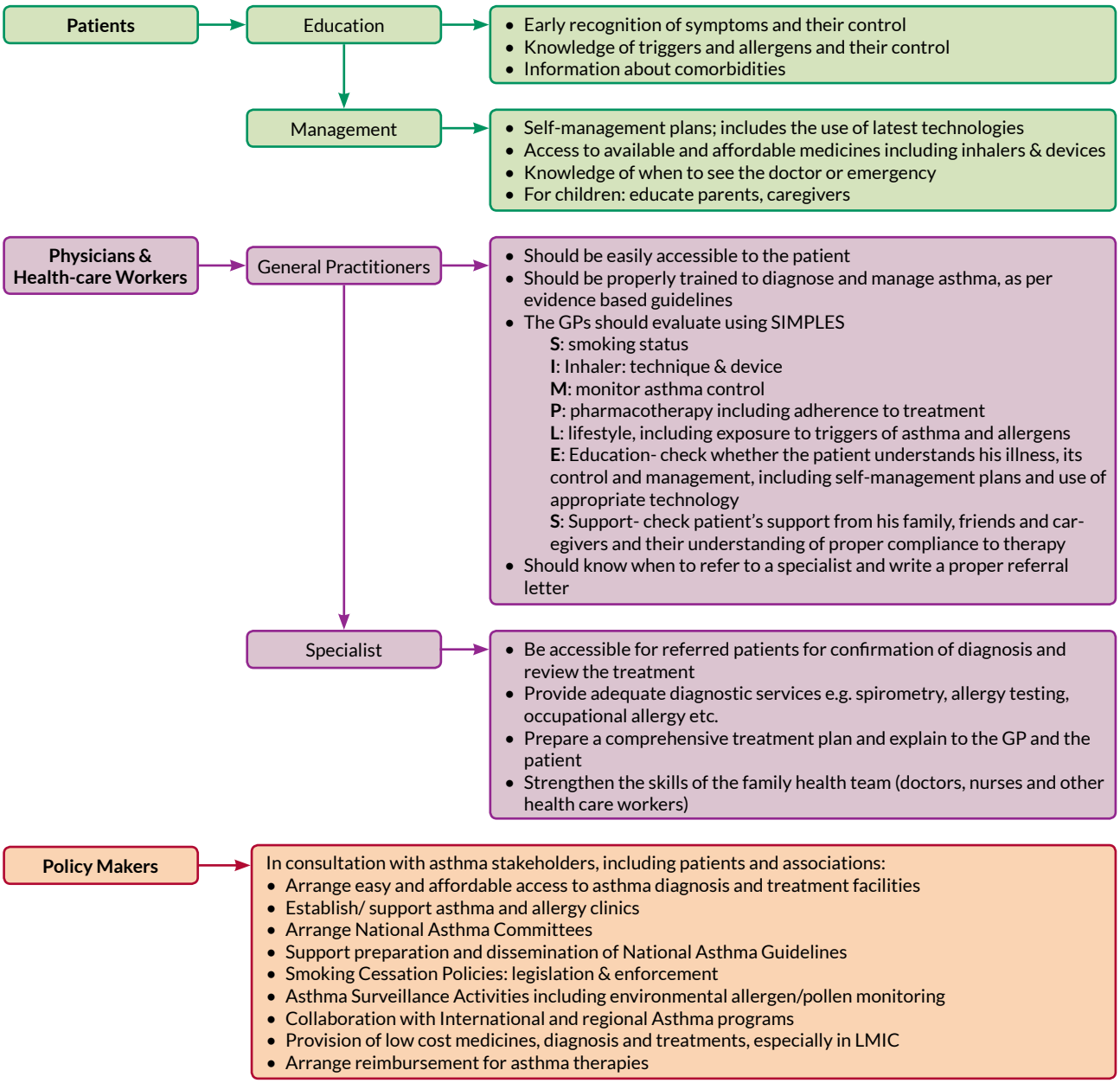

Figure 5 Strategies to facilitate access to asthma diagnosis and treatment. *(Continued from previous page)*

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8 POLICIES AND STRATEGIES TO REDUCE RISK FACTORS FOR ASTHMA

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Many factors are known to be triggers of asthma exacerbations in patients with asthma. Much less is known regarding the factors that may cause asthma. Although genetic factors are likely to be important in the development of asthma, the rapid increase of asthma with urbanization clearly points to the importance of environmental factors in the pathogenesis of asthma. Indoor and outdoor air pollution, tobacco smoke exposure, school environment, potential toxic exposure are all factors which may contribute to asthma morbidity. Effective implementation of related public policies may help to reduce the morbidity and to minimize the societal cost of asthma control.

KEY MESSAGES

- A wide variety of factors are known to precipitate attacks of asthma in affected individuals and many of these factors can be controlled by implementation of effective public policies
- Public policies in controlling outdoor and indoor air pollution can reduce asthma morbidity and even mortality
- Burning of biomass is an important contributing factor to respiratory health and asthma morbidity especially in developing countries
- Public policies in controlling environmental tobacco smoke exposure reduce asthma morbidity

OUTDOOR AIR POLLUTION AND ASTHMA

Outdoor air pollution is mostly generated from burning of biomass fuels and exhausts of motor vehicles. Increase in the levels of different air pollutants are known to induce inflammation within the asthmatic airways resulting in narrowing of the airways, deterioration of lung function, asthma attacks, hospitalization, and even death. As there is no threshold level of so called safe levels, efforts should try to reduce the levels to the lowest possible (Table 1). Traffic pollution (Figure 1) is becoming increasing important in both developing and developed countries. Research studies have shown that children who live close to a freeway are at higher risk of developing asthma. As children spend most of their time at schools during the day in California, schools are not allowed to be built within 500 feet from a freeway. Public policies to reduce emissions from power plant and control of diesel powered vehicles can reduce significantly outdoor air pollution. Establishment and adoption of air quality guidelines are important in helping to set national goals for reducing levels of air pollutants for the benefits of patients with asthma and other respiratory diseases.

Figure 1 Traffic pollution affects all ages

INDOOR AIR POLLUTION

Environmental tobacco smoke (ETS) exposure and emissions from burning of biomass fuels in poorly ventilated homes are the most important causes of indoor air pollution (Figure 2). Exposure to pollution related to use of biomass fuels have been associated with lower respiratory tract infections in children, asthma symptoms in children and adults, as well as lower lung function in exposed adults. Research has also shown that improvement of the design of biomass stove can reduce indoor air pollution leading to improvement of lung function of people living in such households. With regards to the adverse effects of ETS exposure, children and the fetus are at higher risk of the effects. Public policies in reducing second hand tobacco smoke both in public areas as well as areas where there are children would be important in reducing the detrimental influences especially on asthmatics subjects. Poor ventilation and sanitation in households or school can result in excessively high level of allergens (such as indoor molds) which can precipitate asthma attacks in susceptible individuals. Public policies governing building codes and levels of sanitation are important in protecting susceptible individuals.

WORK-RELATED ASTHMA

Workers in a wide range of occupations or industries are at higher risk of development of asthma. These include bakers, forestry, textiles, rubber, chemical and electrical production workers. Due to the job nature, exposure to different irritants, allergens, or chemicals results in inflammation of the airways and asthma. Public policies in setting standards in reducing exposure for related occupations or industries are of paramount importance in the primary and secondary prevention of work related asthma.

TABLE 1

European Ambient Air Quality Standards *		
Pollutant	**Concentration (µg/m³)**	**Averaging period**
Fine articles (PM2.5)	25	1 year
Sulphur dioxide (SO_2)	350	1 hour
	125	24 hours
Nitrogen dioxide (NO_2)	200	1 hour
	40	1 year
PM10	50	24 hours
	40	1 year
Carbon monoxide (CO)	10	Maximum daily 8 hour mean
Ozone	120	Maximum daily 8 hour mean

** From European Commission Ambient Air Quality Standards. http://ec.europa.eu/environment/air/quality/standards.htm, accessed May 20, 2013.*

Figure 2 Sources of indoor pollution.

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9 TOBACCO CONTROL AND ASTHMA

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KEY MESSAGES

- Prevalence rates for active cigarette smoking in adolescents and adults with asthma are similar to the general population
- Active cigarette smoking and exposure to second-hand smoke are risk factors for the development of asthma and are associated with poor asthma control, exacerbations and hospital admissions and an accelerated decline in lung function
- Tobacco control offers a major opportunity to prevent and improve health care outcomes in asthma
- Smoking cessation is an important goal in the management of smokers with asthma and in the parents of children with asthma
- Legislation to control cigarette smoking in public places improves asthma control in both children and adults

ASTHMA AND THE ADVERSE EFFECTS OF SMOKING

Prevalence rates for active cigarette smoking in adolescents and adults with asthma are similar to those in the general population (Figure 1).

Exposure to second-hand smoke and active smoking has a major adverse health impact in asthma. Maternal smoking, both during and after pregnancy, increases the risk of asthma among children. In adolescents and adults exposure to second-hand smoke is also associated with the development of asthma. In both children and adults with asthma, exposure to second-hand smoke is associated with worse clinical outcomes (Table 1) and higher health care costs.

Smokers with asthma have worse asthma control, poorer quality of life, more frequent exacerbations and hospital admissions, as well as an accelerated decline in lung function compared to never-smokers with asthma (Figure 2). In addition, active cigarette smoking is associated with a reduced therapeutic response to corticosteroids, which may contribute to the adverse effects of cigarette smoking in asthma.

TOBACCO CONTROL

The World Health Organization's (WHO) Framework Convention on Tobacco Control is being implemented worldwide to improve health outcomes in the general population. Tobacco control in society offers a major opportunity to prevent asthma and improve symptom control in people with asthma through reduction in exposure to tobacco smoke, both direct and second-hand. A key component of the WHO initiative involves the implementation of the 'MPOWER' policy on tobacco control (Table 2), and some of these measures have been shown to impact positively on health outcomes in asthma.

PROTECT PEOPLE WITH ASTHMA FROM TOBACCO SMOKE

Stopping parental smoking is an essential component to reducing the risk of developing of asthma. Preventing exposure to second-hand smoke should begin before child birth and throughout childhood. Smoking cessation programmes in parents of children with asthma may reduce the burden of emergency events due to exposure to second-hand smoke, although the benefit of extensive interventions designed to reduce smoking rates on asthma outcomes has not been established. Reducing maternal smoking before conception or

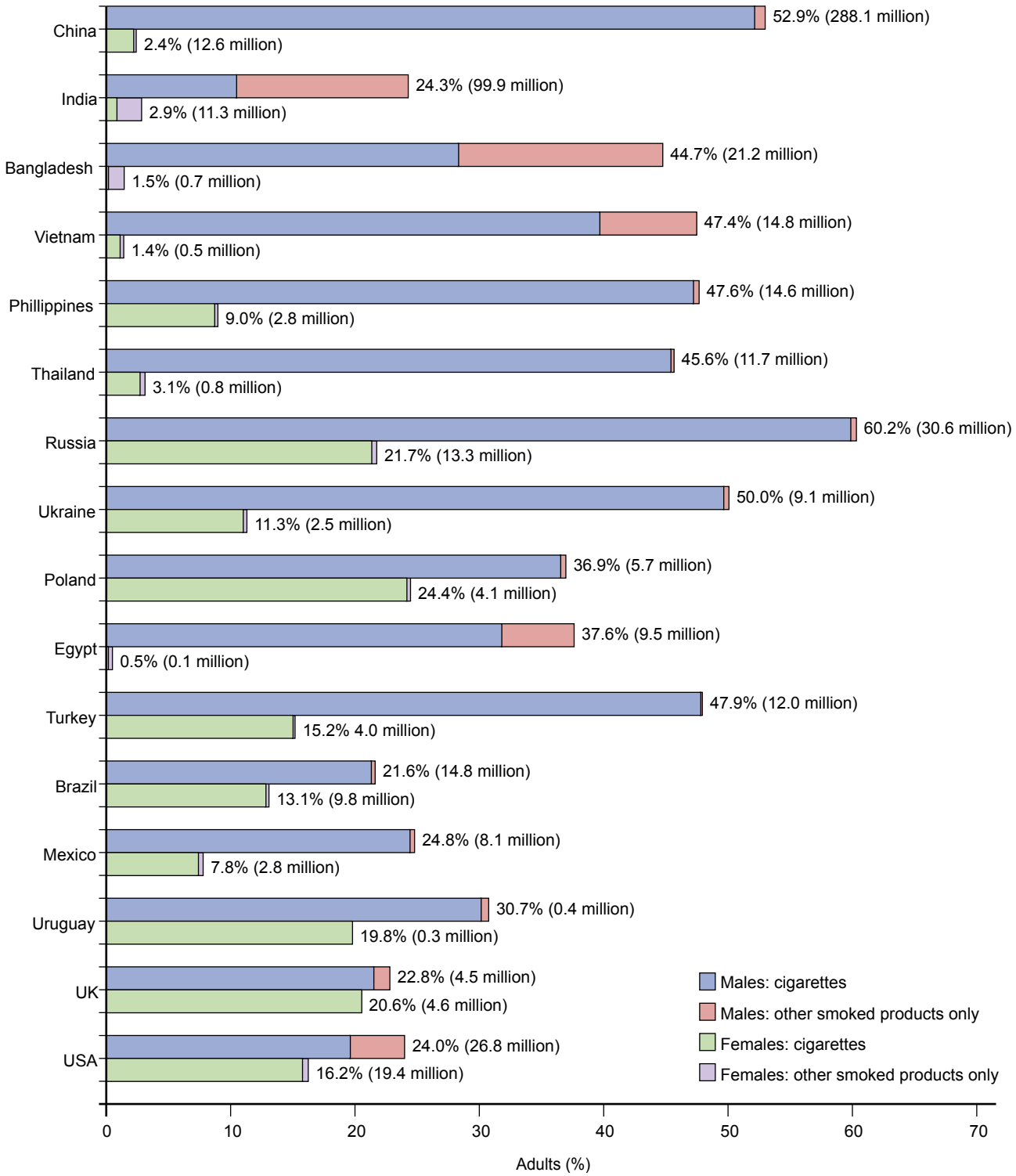

Figure 1 Proportion of adults ages 15 years or older who currently smoke cigarettes and other tobacco products and number of current tobacco smokers (in millions), by sex, for the UK, USA, and 14 GATS countries GATS-Global Adult Tobacco Survey. *(Reprinted from The Lancet, 380, Giovino GA, Mirza SA, Samet JM, et al, Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys, 668-679, Copyright 2012, with permission from Elsevier.)*

TABLE 1

Exposure to second-hand smoke is associated with increased health care utilisation in adults with non-severe asthma *				
	No exposure to second-hand smoke (n=252)	Exposure to second-hand smoke (n=108)	Odd Ratio (95% CI)	p value
Intensive Care Unit Admission	11 (4.4%)	19 (17.6%)	4.7 (2.2 to 10.5)	<0.001
Night in hospital	69 (27.1%)	(40 (37.7%)	1.6 (1.0 to 2.6)	0.04
Urgent Care visit due to asthma	51 (20.0%)	32 (30.2%)	1.8 (1.0 to 2.9)	0.03
Assisted Ventilation	5 (2.0%)	11 (10.4%)	5.8 (2.1 to 18.9)	<0.001
Emergency Room visit for breathing problem	31 (12.2%)	26 (23.9%)	2.3 (1.3 to 4.0)	0.006

** Reproduced from Comhair SA, Gaston BM, Ricci KS, et al. Detrimental Effects of Environmental Tobacco Smoke in Relation to Asthma Severity. PLoS ONE 2011;6:e18574.*

All data are presented in No (%).

in early pregnancy may have the greatest effect on preventing the development of asthma. Legislation to control cigarette smoking in public places results in improvements in symptom control for adults with asthma and in rate of hospital admission with acute asthma in children (Figure 3).

OFFER HELP TO QUIT TOBACCO USE IN ASTHMA

Smoking cessation is an important goal in the management of smokers with asthma. A small number of studies have examined the role of smoking cessation on asthma outcomes and reported improvements in symptoms and lung function in those people who quit smoking successfully. In addition, former smokers with asthma have better asthma control than ex-smokers with asthma. Despite the known adverse effects of active smoking in asthma, this group are no more likely to receive physician counselling regarding smoking cessation, nor smoking cessation pharmacotherapy compared to the general smoking population.

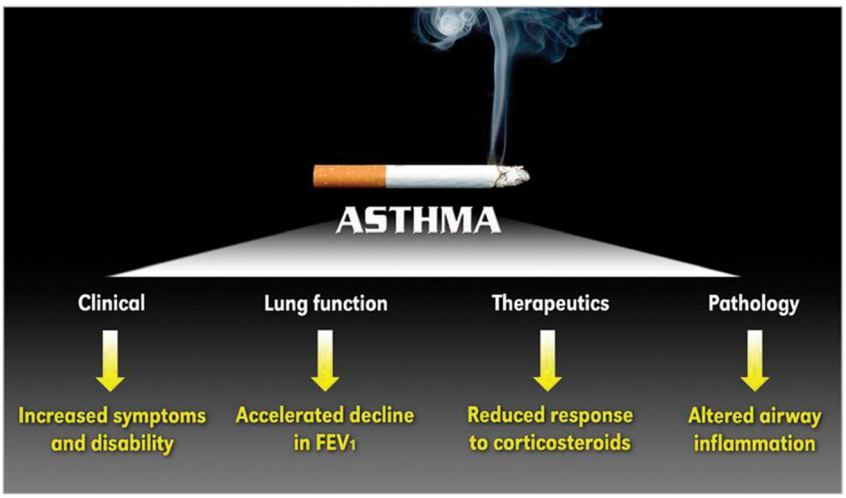

Figure 2 Interaction of active cigarette smoking and asthma. *(Reproduced from Thomson N, Chaudhuri R, Livingston E. Active cigarette smoking and asthma. Clin Exp Allergy 2003;33:1471-1475 with permission from John Wiley and Sons, Inc.)*

TABLE 2

WHO MPOWER policy on tobacco control
• **M**onitor tobacco use and prevention policies
• **P**rotect people from tobacco smoke
• **O**ffer help to quit tobacco use
• **W**arn about the dangers of tobacco
• **E**nforce bans on tobacco advertising, promotion and sponsorship
• **R**aise taxes on tobacco

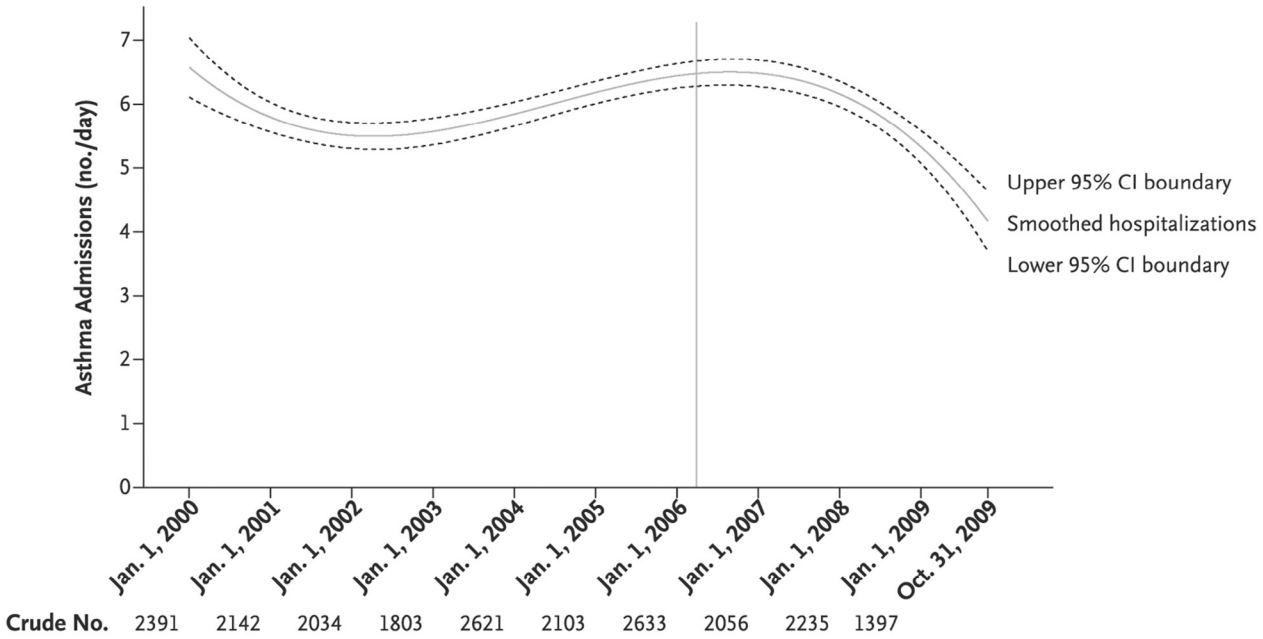

Figure 3 Daily hospital admissions for asthma among children between January 2000 and October 2009. Ban on smoking in public places in Scotland was initiated in 2006 *(From N Engl J Med, Mackay D, Haw S, Ayres JG, et al. Smoke-free legislation and hospitalizations for childhood asthma, 363, 1139-45 Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)*

EXAMPLE OF WHO MPOWER POLICY ON TOBACCO CONTROL IN PRACTICE

A comprehensive tobacco-control campaign in a low-income to middle-income country (Uruguay) that included actions such as the banning of tobacco advertising, the banning of smoking in all enclosed public spaces, tax increases, and legislation requiring health warnings on cigarette packets resulted in a substantial reduction in tobacco use. Implementation of similar policies should result in improved health for the general population as well as for people with asthma, or those who are at risk of developing asthma.

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10 IMPLEMENTATION OF A HEALTHY LIFE STYLE AND ASTHMA

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KEY MESSAGES

- The increased incidence and prevalence of asthma is multifactorial and includes epigenetic mechanisms and lifestyle factors: changes in the traditional diet, physical inactivity and stress
- Asthma has been associated with reduced physical activity, but also with high-intensity long-term exercise, as seen in athletes. As the benefits of regular, moderately intense aerobic exercise have been demonstrated in allergic asthma, there is no reason to discourage asthmatics with controlled disease from regular exercise
- The increase in obesity, a known risk factor for metabolic and cardiovascular diseases, also increases the risk of incident asthma and of a difficult-to-control asthma phenotype
- Adherence to a Mediterranean diet associates better asthma control in adults and, during pregnancy, decreased risk of asthma symptoms in the offsprings. Achieving a balanced healthy diet is recommended for weight management and overall health, and as part of a multidisciplinary asthma management plan

A consistent body of literature shows a positive association between the increased incidence and prevalence of atopic diseases, including asthma, and the westernized lifestyle. This seems to be more notorious after the Second World War and may have recently reached a plateau. Explanations for this association have been postulated and the most consistent ones include the decreased microbial exposure throughout life. With increased sanitation and hygiene, the progressive reduction or lack of exposure to a wide range of microbiota impairs immune regulatory mechanisms increasing the chance of immune dysfunction. This parallels with an increase in several chronic noncommunicable disorders - e.g. asthma and allergic diseases, diabetes and auto-immune disorders, metabolic (obesity and type 2 diabetes) and cardiovascular disease, cancer - all sharing underlying immune-regulatory dysfunction and low-grade, subclinical, chronic inflammation (Figure1).

However, it seems unlikely that the cause of the allergic epidemic rely in just one major factor. It should be multifactorial and include contributions from epigenetic mechanisms - the plastic interaction of a genetic background with changing environment factors (microbiota, nutrients, allergens, pollutants) - and lifestyle factors - changes in the traditional diet, physical inactivity and stress.

Diet and physical activity influence health both together and separately. Although the effects of diet and physical activity on health often interact, particularly in relation to obesity, there are additional health benefits to be gained from physical activity that are independent of nutrition and diet, and also significant nutritional factors that are unrelated to obesity.

PHYSICAL ACTIVITY AND ASTHMA

Physical activity is a fundamental way to improve the individual physical and mental health. The relationship between physical activity and asthma seems a paradox. Heavy physical activity has

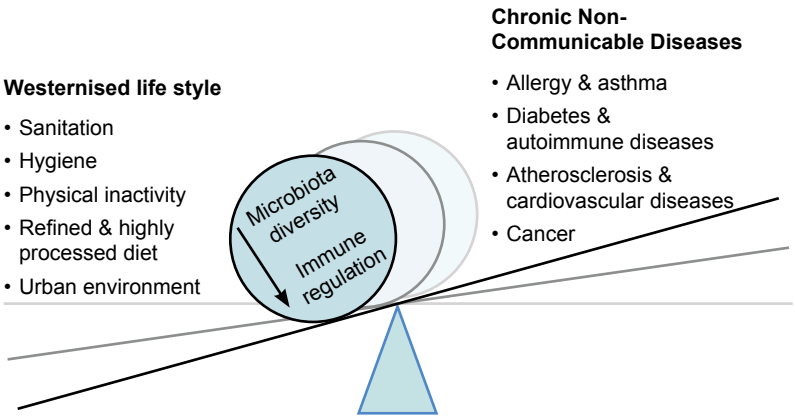

Figure 1 The increased prevalence of chronic noncommunicable disorders (including allergy and asthma) with westernized lifestyle. The reduced exposure to a diverse microbioma and physical inactivity may impair immune regulatory mechanisms increasing the chance of immune dysfunction.

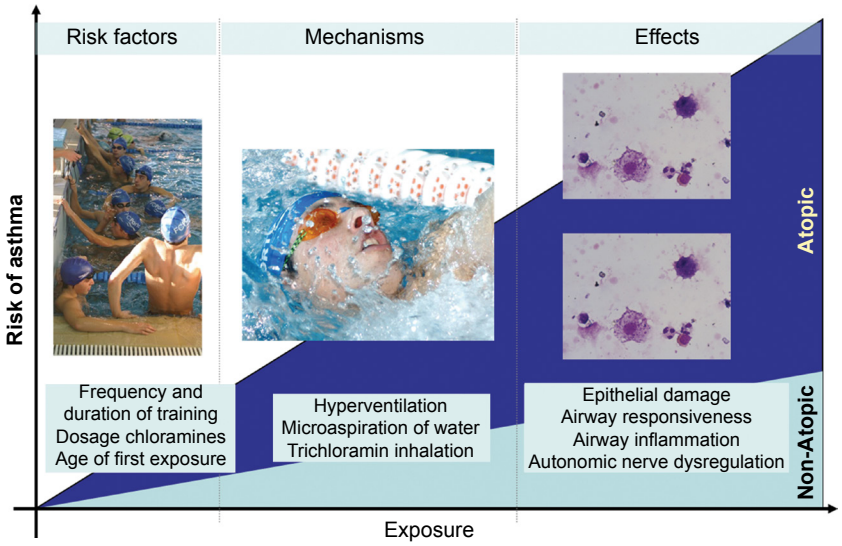

Figure 2 Exercise and asthma. The relationship between exercise and asthma seems a paradox. Asthma has been associated with reduced physical activity but also with high-intensity long-term exercise, as seen in elite athletes or competitive swimming. So, with exercise "less is more": the best way to increase activity levels is to spend more time on moderate-intensity exercise and less on high-intensity activity. *(Reproduced from Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes--practical implications. Allergy 2008;63:685-94, with permission from Wiley-Blackwell.)*

been related to asthma occurrence and exacerbation. In elite athletes asthma is diagnosed more frequently than in the general population. This has been attributed to airway inflammation and increased bronchial responsiveness induced by high-intensity long-term exercise, like long-distance running or competitive swimming (Figure 2). Exercise is also a powerful trigger of asthma symptoms and may result in asthmatic patients avoiding activity with detrimental consequences to their physical and social well-being. However, reduced physical activity has been associated with increased asthma prevalence, and moderate regular physical activity has been suggested to prevent disease progress.

Physical training may reduce breathlessness and asthma symptoms by strengthening respiratory muscles and decreasing ventilation rate during exercise. Although training programs in asthma have not improved lung function in controlled trials, positive effects on the allergic inflammation have been showed (Figure 3). The benefits of moderately intense aerobic exercise have also been shown in experimental models of allergic asthma, with attenuation of the Th2 mediated inflammatory responses in the lung.

THE OBESITY AND ASTHMA EPIDEMICS

Obesity prevalence is the easiest way to evaluate changes in diet and physical activity. According to most recent data obesity and overweight have reached epidemic proportions in westernized countries. In Europe prevalence of obesity has raised threefold or more since the 1980's, even in countries with traditionally low rates, and in the United States, obese or overweight subjects represent more than two thirds of the adults. The relevance of obesity as a risk factor for diseases, including type2 diabetes, hypertension, and atherosclerosis has been recognized for a long time. In the last decade, increasing evidence shows that obesity increases the risk of incident asthma and alters its course towards a more difficult-to-control phenotype.

Recent meta-analyses showed that overweight and obesity are associated with increase in the odds of incident asthma, in a dose-depend-

ent manner, and that weight gain, as much as required to become obese, almost doubles the odds of incident asthma. The relation between obesity and asthma has been traditionally explained by both inflammatory and mechanical pathways (Figure 4). Taken together, these observations support the recommendation of weight control and tackling obesity as part of an asthma management plan.

DIETARY PATTERNS AND ASTHMA

The remarkable variation in asthma prevalence between countries or geographically adjacent areas suggests that environmental factors play a determinant role both in asthma prevalence and severity. The marked changes in dietary patterns in recent decades – e.g. decreased intake of antioxidant micronutrients from fruits and vegetables and changes in fatty acids profile – may explain some of these variations.

Several epidemiological studies have reported beneficial associations for higher intake of nutrients that may be relevant in the redox mechanisms and immunomodulation, such as vitamins A, D, and E, selenium, magnesium, zinc and n-3 polyunsaturated fatty acids (PUFA), also observed for foods sources of these micronutrients, such as fresh fruits, vegetables, nuts, and fatty fish. However, interventions with supplementation of single nutrients in asthma have been disappointing, and currently there is no evidence to support its use. Dietary exposure should be considered as a whole to understand the possible synergistic effects between nutrients in foods and specific dietary patterns.

Mediterranean diet, a well-recognized cultural model for healthy

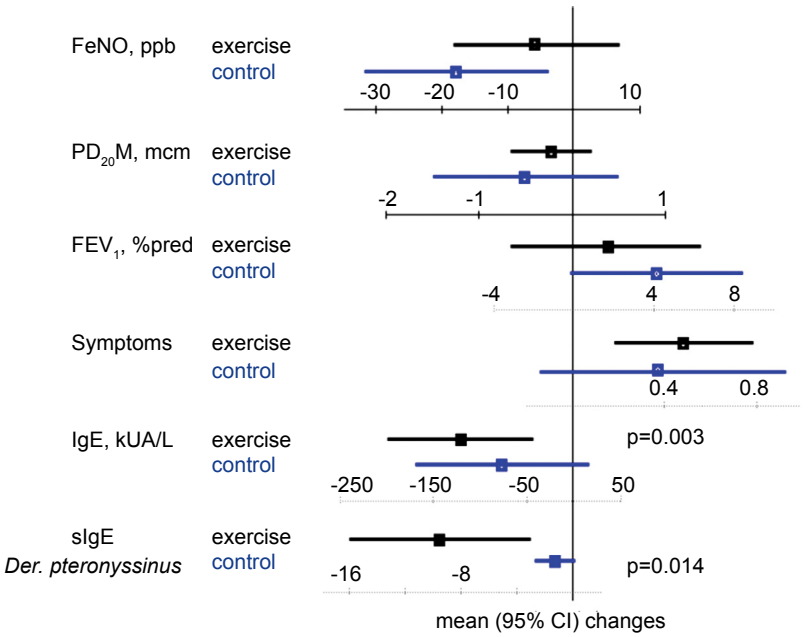

Figure 3 Physical activity and asthma. A randomized controlled study showed that engagement of asthmatic children in physical training does not worsen allergic inflammation or asthma outcomes and suggests a possible positive effect in IgE mediated allergy. *(Data from Moreira A, Delgado L, Haahtela T, et al. Physical training does not increase allergic inflammation in asthmatic children. Eur Respir J 2008;32:1570-5.)*

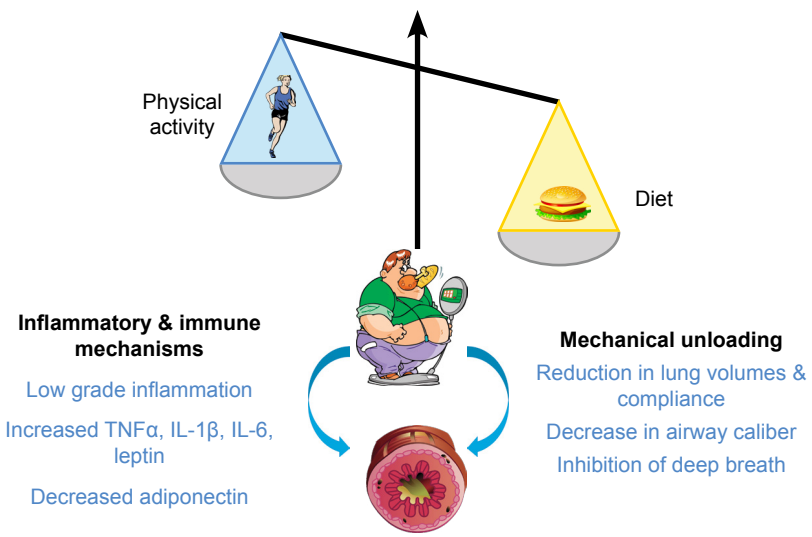

Figure 4 The obesity-asthma link. Obesity is the product of dietary and physical activity changes in lifestyle. Inflammatory mediators produced by adipose tissue modulate the immune responses in the lung, while chronic low-grade inflammation of the obese influence the susceptibility to airway obstruction. Animal experiments suggest that both the increases in serum leptin and the decreased serum adiponectine observed in obesity may exacerbate airway inflammation. Obesity also causes a reduction in lung volumes, compliance, and peripheral airway diameter, as well as an increase in airway responsiveness, changes in pulmonary blood volume, and a ventilation–perfusion mismatch.

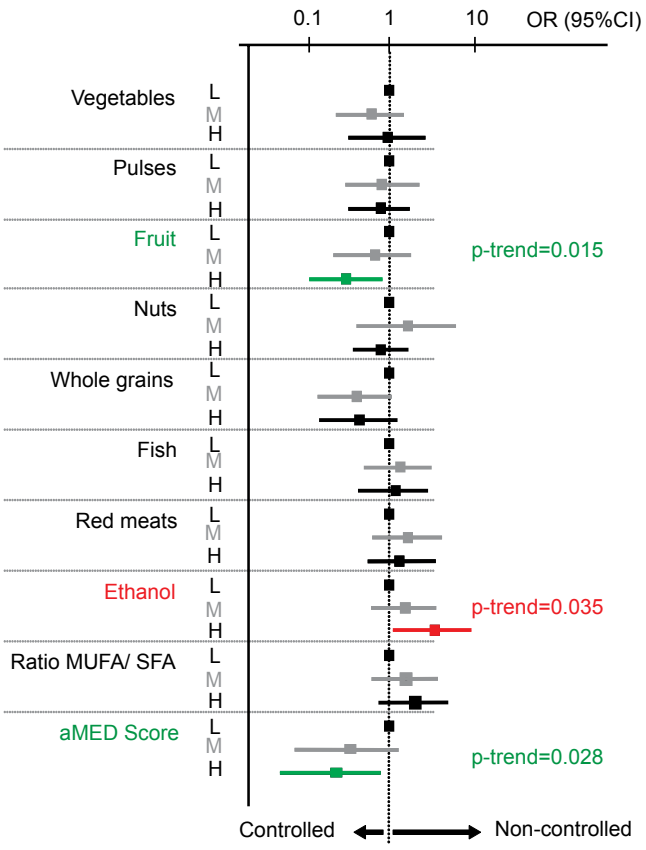

Figure 5 The beneficial link between the Mediterranean dietary pattern and adult asthma. MUFA - monounsaturated fatty acids; SFA - saturated fatty acids. Odds ratios between mediterranean diet and asthma control. The results suggest that high adherence (H) to Mediterranean diet (aMED Score) and of its typical foods, such as fresh fruits and nuts, reduces asthma severity in adults. *(Reproduced from Barros R, Moreira A, Fonseca J, Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. Allergy 2008;63:917-23, with permission from Wiley-Blackwell.)*

eating, has been associated with low incidence of mortality and morbidity by chronic diseases in Mediterranean populations, comparatively to the US or Northern Europe. A similar north-south gradient has been observed for asthma, with some countries such as Greece or Albania, presenting the lowest prevalence. Adherence to Mediterranean diet and fresh fruit intake has been shown to increase the likelihood of asthma being under control (defined by symptoms, lung function and airway inflammation), while higher intake of ethanol increased the risk of uncontrolled asthma (Figure 5). Higher intakes of nuts was associated with better lung function, and additionally dietary intake of n-3 PUFA, namely alpha linolenic acid, was also associated with good asthma control. Other factors of the traditional Mediterranean lifestyle, linked with small-scale farming of fruits, vegetables, and sun exposure, may also play a role. Reduced exposure to soil microbiota in urban environment was coined as a major facilitator of the "allergy epidemic" while the consumption of self-produced vegetables might protect against atopic conditions.

Adherence to Mediterranean diet may thus reflect greater exposure to immunomodulating soil saphrophytes giving protection against severe asthma.

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11 INDIVIDUAL INTERVENTIONS FOR ASTHMA PREVENTION AND CONTROL

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KEY MESSAGES

- Individual measures for prevention and control of asthma should be among the priorities of the health professionals
- Optimal management should involve a network of care in which a well instructed and implicated patient plays a key role
- Very few interventions proved effective for asthma prevention
- Individualised asthma control plans should be reinforced

Asthma is a chronic, sometimes lifelong condition, needing optimal adherence to best asthma care. In order to optimize the management of the asthmatic patient, individual prevention and control should be among the priorities of the health professionals (Figure 1).

Asthma prevention will mostly focus on nutritional and environmental interventions.

- **Primary prevention** addresses measures *preventing asthma to occur*, mostly in individuals with an increased susceptibility to develop the disease. Intervention trials have mostly focused on *diets avoiding allergenic foods* during pregnancy, breast-feeding, as well as on the delayed introduction of solid and/or allergenic foods into the child's diet. Overall, such measures have been proven to be ineffective in most groups of patients. Similarly, interventions leading to reduced allergen loads in the environment (e.g. dust mite avoidance measures) of children at risk for asthma have been proven mostly ineffective.
- **Secondary prevention** addresses measures *preventing the progression of the disease*. A few interventions have been successful in some studies. A large multicenter interventional trial testing 18 months treatment with oral anti-histamine (cetirizine) has shown a preventing effect on asthma development in children with atopic eczema already sensitized to dust mites or grass pollens. A smaller trial with oral chromoglycate has shown the same effect. Disease progression from grass-pollen allergic rhinitis to allergic asthma has been prevented in part in a group of children undergoing sub-cutaneous allergen specific immunotherapy. This effect has been lasting for up to 10 years after immunotherapy.
- **Tertiary prevention** focuses mostly on optimal therapeutic management of the disease and is addressed elsewhere in the Global Atlas.

Asthma control at the individual level is mostly related at translating the most recent therapeutic guidelines to the patient's daily life.

Asthma control in *children* is closely linked to the social environment of the child. Daycare and school caregivers need to be aware of the child's triggers for asthma (e.g. pet exposure), and adapt activities in order to avoid them. In addition to the parents, adults in charge of the child need to be instructed to recognize the first signs of asthma, and how to treat an asthma attack.

Asthma control in *adolescents and adults* is based on the individual's responsibility to avoid potential triggers and to self-treat first symptoms of asthma. Measuring peak flow expiratory rates may help to assess the degree of lung obstruction by the patient himself and to institute the initial "emer-

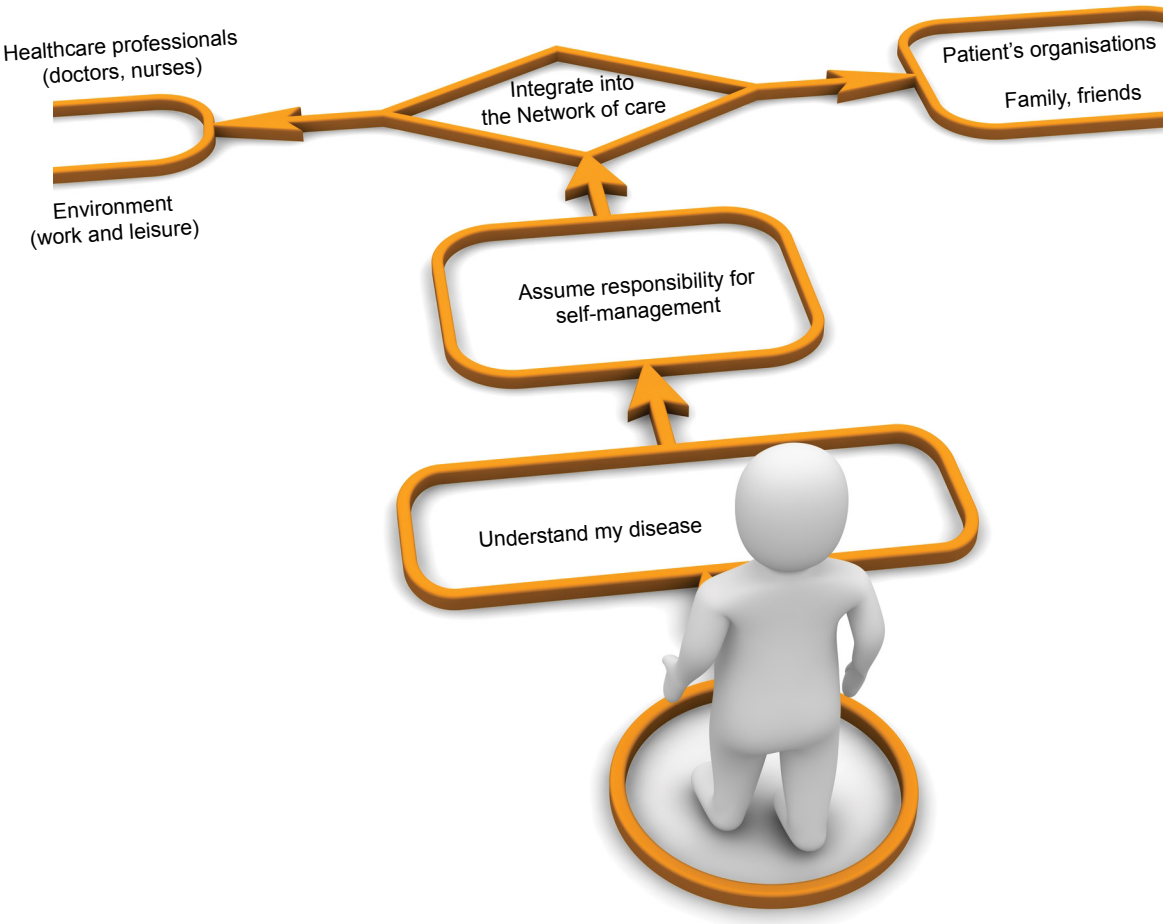

Figure 1 Essential steps towards an individualised asthma treatment plan.

gency treatment". Measuring nitric oxide at the doctor's office might provide guidance for assessing disease control.

In conclusion, asthma prevention will always need physician supervision, but optimal care will also need to involve a network of care, in which a well instructed and implicated patient plays a the key role.

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12 THE ROLE OF PRIMARY CARE IN THE PREVENTION AND CONTROL OF ASTHMA

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KEY MESSAGES

- Asthma is extremely common
- It is amenable to treatment
- Correct diagnosis is critical
- Appropriate treatment prevents morbidity and mortality
- Patient education and instruction on monitoring to aid self management are essential components of disease management
- Inhaler technique is of paramount importance
- Access to structured care and appropriate medication must become health care priorities
- If control cannot be achieved in the primary care setting onward referral for further evaluation is highly recommended

Asthma imposes a significant disease burden to individuals and health economies. Evidence suggests that a substantial number of patients are not controlled according to accepted parameters, although the level of control achieved is somewhat dependent on the instrument used to measure it. There is a pressing need to understand the level of control that could be achieved in primary care and a further need to understand the barriers to achieving this.

In many nations the first point of contact for many diseases is the general practitioner (GP) or family practitioner although this service may equally be provided by emergency rooms or specialists working in the primary care environment.

Although to date there is no effective primary preventative strategy to prevent the occurrence of asthma, we are fortunate to have many resources at our disposal to detect and make early interventions prior to significant lung damage occurring and to reduce the impact of the disease on quality of life by restoring lung function and reducing rates of complications (exacerbations, hospitalisations and death).

Although the incidence of asthma appears to have peaked and may be falling in higher prevalence countries it is very much on the increase in lower prevalence countries as life style and culture evolves (Figure 1).

The first role of Primary Care (PC) is to detect, in those presenting with symptoms, and make a diagnosis of asthma. The role of history taking is paramount but the use of simple diagnostic tests such as peak flow readings demonstrating variability or marked diurnal variation are helpful; spirometry with reversibility is the more favoured approach but is frequently not available; an elevated peripheral eosinophil count helps to support a diagnosis as does the presence of atopy. Bronchoprovocation testing has previously only been available in the hospital setting but new technologies such as mannitol challenge have the potential to allow this also to occur in the community setting. Guidelines may be helpful in determining the likelihood of a collection of signs and symptoms being representative of asthma (Table 1).

In terms of assessment of both severity and control, simple instruments such as the Royal College of Physicians Three questions, Asthma Control Test or Asthma Control Questionnaire are available. These give an indication of disease severity and are responsive to change

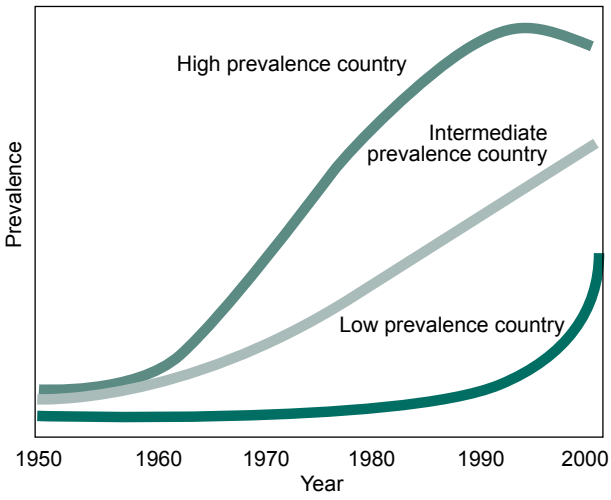

Figure 1 Incidence of asthma in high, intermediate in low prevalence countries. *(Reproduced from Bousquet J, Bousquet PJ, Godard P, et al. The public health implications of asthma. Bull World Health Organ 2005;83:548-54.)*

TABLE 1

The likelihood of signs and symptoms being representative of asthma *

Features increasing the likelihood of asthma
• More than one of the following clinical symptoms: wheeze, breathlessness, chest tightness and cough particularly: ▪ Worse at night or early morning ▪ Symptoms in response to exercise, allergen exposure, cold air ▪ Symptoms after taking aspirin or β blockers
• History of atopic disorder
• Family history of asthma/atopic disorder
• Widespread wheeze heard on auscultation of the chest
• Otherwise unexplained low FEV1 or PEF (historical or serial readings)
• Otherwise unexplained blood eosinophilia
Features that lower the probability of asthma
• Prominent dizziness, light headedness or peripheral tingling
• Chronic productive cough in the absence of wheeze or breathlessness
• Repeatedly normal examination of the chest when symptomatic
• Voice disturbance
• Symptoms with colds only
• Significant smoking history (i.e. > 20 pack years)
• Cardiac disease
• Normal PEF or spirometry when symptomatic. *A normal spirogram/spirometry when not symptomatic does not exclude the diagnosis of asthma. Repeated measurements of lung function are often more informative than a single assessment.*

* *Reproduced from British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma - A national clinical guideline, 2008, revised 2012*

as control is achieved. This assessment may be supplemented by evidence of peak flow variability, need for rescue inhalers or, potentially, exhaled nitric oxide, the role of which has yet to be clarified.

Once the diagnosis has been made the next task is to manage the disease in collaboration with the patient. A discussion with the patient as to what asthma is and what treatments and lifestyle modifications (such as smoking cessation) are necessary to help abolish symptoms and normalize life is of great importance.

A crucial factor in patient education is teaching patients how and when to use their inhaler (Figure 2). This is not as easy as it might first appear, as many clinicians, whether in the community or hospitals, do not themselves know how to use commonly used inhalers rendering them unable to teach or check inhaler technique. There is an urgent need to rectify this situation. Giraud eloquently demonstrated that the greater the number of errors in technique, the lower the likelihood of achieving asthma control. Molimard demonstrated that poor technique is encountered with virtually all inhaler devices, each of which have a number of critical success factors (Figure 3). Training of patients in inhaler technique can result in sustained benefit.

Figure 2 Which inhaler, how and when?
(© ruaidhri.ryan www.ruaidhri.co.uk)

Patients also need to know how to monitor their disease; recognizing and, if possible, avoiding identified triggers, having annual influenza vaccinations and attending for regular structured reviews. They need to be aware of what symptoms or change in lung function (peak flow monitoring) may indicate a need to step up treatment or seek urgent medical attention.

The clinician also needs to commence appropriate medication regimes, informed by their national guidelines. If failure to obtain control of symptoms occurs, rather than unquestioningly escalating treatment, the clinician must launch a comprehensive structured enquiry (Table 2) including the following items: smoking status; check inhaler technique; compliance with medication (checking against issues of prescriptions where possible); assess control using a validated instrument such as RCP three questions or Asthma Control Test evaluate the current treatment and assess whether it is adequate; enquire about co-morbidities in particular rhinitis, whether allergic or non allergic, lifestyle factors (diet, exercise, occupation, hobbies, house moves). The attending physician has to ensure that the patient has a clear understanding of asthma and the medications needed to manage it and to provide ongoing support by frequent reviews (until control is achieved) and refer to national asthma charities web sites for further information.

Finally, the GP has to reconsider whether the diagnosis of asthma is correct; failure to gain control after reiteration of the steps enumerated above suggests either an alternative diagnosis or the need for referral to a specialist in a refractory asthma clinic (Figure 4).

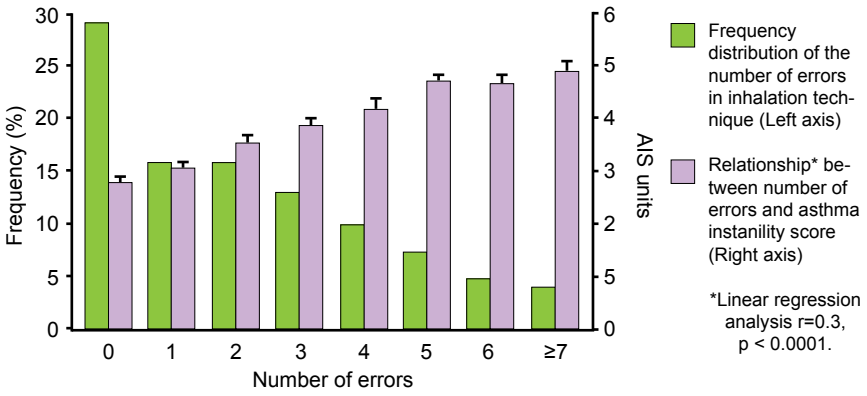

Figure 3 Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *(Reproduced with permission of the European Respiratory Society. Eur Respir J February 2002 19:246-251; doi:10.1183/09031936.02.00218402.)*

TABLE 2

Factors to be considered in a structured review	
Smoking cessation	psychological and pharmacological support
Inhaler technique	regular assessment with demonstration devices
Monitoring	symptom assessment (RCP3 questions, ACT, ACQ) lung function : peak flow, spirometry
Pharmacology	appropriate medications at appropriate doses
Life Style	exercise, diet, obesity, employment, hobby
Education	understanding asthma, medications used, self monitoring and self-management plan
Support	follow up arrangements; contacts with patient groups

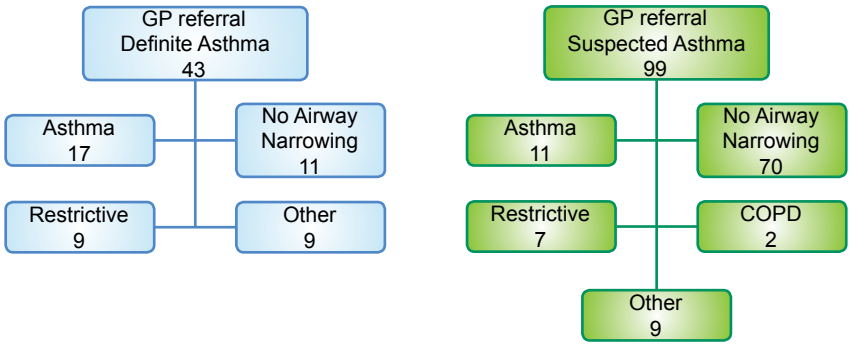

Figure 4 A centralised respiratory diagnostic service for primary care: a 4-year audit: 30% with a definite asthma and 11% with a suspected asthma. *(Adapted from Starren ES, Roberts NJ, Tahir M, et al. A centralised respiratory diagnostic service for primary care: a 4-year audit. Prim Care Respir J 2012;21:180-186.)*

There is increasing evidence that many of those with a diagnosis of asthma and are not well controlled may have alternative diagnoses, as demonstrated in a study carried out in London which demonstrated that only one third of those referred to a community respiratory assessment service with a definite diagnosis of asthma and only 11% of those with a diagnosis of probable asthma actually had asthma.

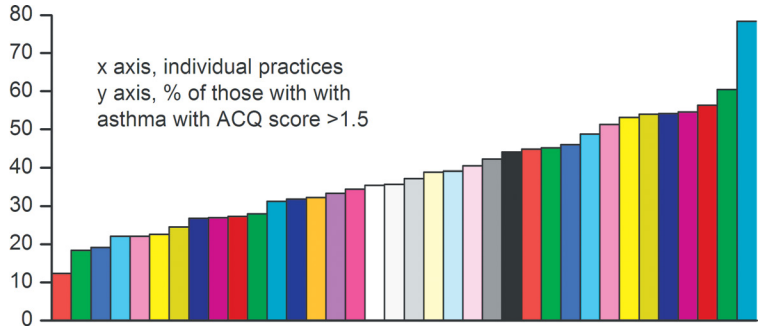

Figure 5 Significant variability between individual practices in achieving asthma control.

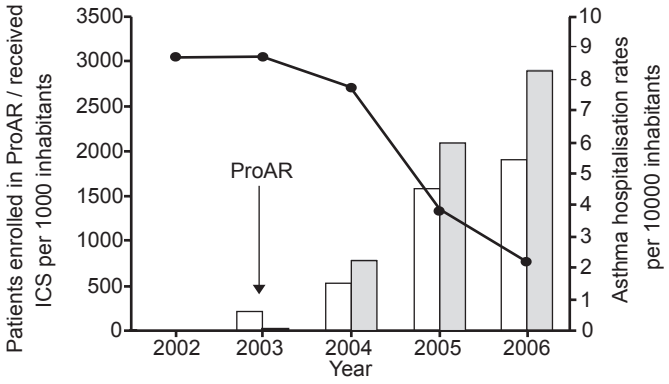

Figure 6 Reduction in hospitalisations after an intervention to manage severe asthma. *(Reproduced with permission of the European Respiratory Society. Eur Respir J March 2010 35:515-521; published ahead of print July 30, 2009, doi:10.1183/09031936.00101009.)*

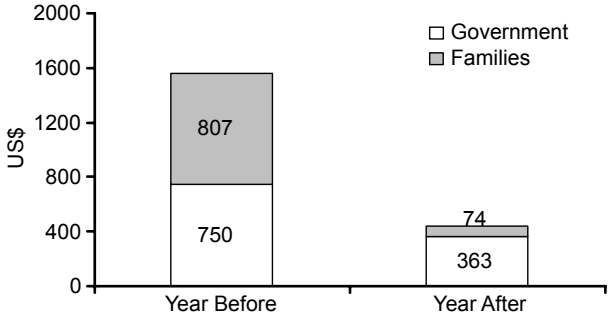

Figure 7 Cost-effectiveness analysis of a state funded programme for control of severe asthma. *(Reproduced from Franco R, Santos AC, do Nascimento HF, et al. Cost-effectiveness analysis of a state funded programme for control of severe asthma. BMC Public Health 2007;7:82. Reprinted with permission under the Creative Commons Attribution License or equivalent.)*

A further challenge facing primary care is the significant variability in the standard of care delivered from country to country, region to region and practice to practice as exemplified by the study illustrated below (Figure 5) which demonstrates that in some practices just above 12% of patients had an ACQ score of 1.5 or above suggesting poor control while in one practice just under 78% of patients had ACQ greater than 1.5%, with an average value of 36%. On the other hand this study gives an indication of what level of control it is possible to achieve and suggests that in the majority of patients achieving control is a real possibility.

A further barrier to achieving good outcomes for patients with asthma is the provision of a structured health service coupled with access to appropriate medications. Work in Brazil has demonstrated very clearly that such an approach significantly reduces both morbidity (Figure 6) and costs (Figure 7). Health care planners in different countries might wish to recognize this fact when allocating resources.

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13 ROLE OF PATIENT ORGANISATIONS IN THE CONTROL AND PREVENTION OF ASTHMA

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aha! Swiss Allergy Center
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KEY MESSAGES

- A strategic partnership for improving asthma care involves patient representatives, healthcare professionals and policymakers
- As multi-service advocacy organizations, asthma patient groups around the world coordinate action, awareness and research projects concerning asthma care, prevention and research and advocate patient centered healthcare through partaking in government asthma policy formulation
- Several initiatives like EFA's four year programme on allergy and pilot training for national programme development proved that patient groups can act as the key initiators for better priority, organization of care and collaboration in asthma

The role of asthma patient organizations is to support patients manage their everyday life and advocate patient centered healthcare, environment and research policies and practices. Most patients also have allergy on their agenda, which make activities comprehensive considering the link between several allergic diseases and asthma. Patient organizations are key partners for those working in asthma control and prevention. Asthma patient groups evolved from support groups into advocates for patient rights. The journey of patient groups globally has similar features; there is a need to meet other patients to share experiences and tips to manage with asthma in daily life, access information as well as education on asthma targeted and adjusted for patients, as for example, in the case of a family with a newly diagnosed asthmatic child. These are crucial traditional roles of patient organisations. The partnership between healthcare professionals and patient organisations is present from the beginning as there is a need for their medical expertise in their activities.

Development of asthma patient groups depends on the stage of a civil society's development in a particular country and the availabity of resources. Asthma patient groups around the world have developed or are on their way to develop into multi-service advocacy organisations. Apart from the traditional patient group activities, they coordinate action, awareness and research projects concerning asthma care, prevention, risk factors and research; advocate through partaking in government asthma policy formulation; support research or provide patient perspective in research projects; and develop tools for improved asthma management (Figure 1).

The European Federation of Allergy and Airways Diseases Patients' Associations (EFA) represents people with allergy, asthma and chronic obstructive pulmonary disease at the European level, supporting development of national plans on allergy/asthma, advocating at EU institutions, and influencing EU health, environment and research policies. For example, the framework for air pollution and tobacco control legislation occurs at the EU level, while EU funds research and the European Medicines Agency evaluates medicines and their information and coordinates Pharmacovigilance. EFA's job is to ensure patient's perspective in each of these. EFA's 4 year programme on allergy supports the development of and political priority for

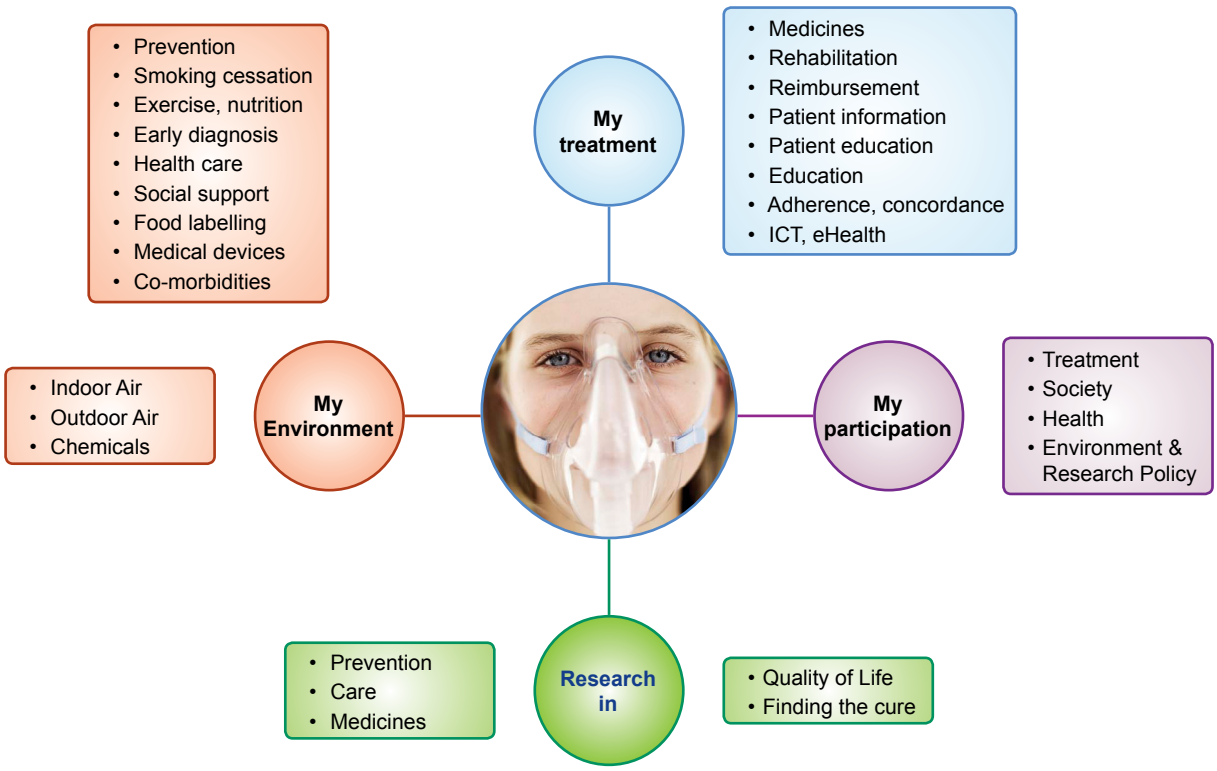

Figure 1 Issues for people with asthma.

Figure 2 Patients participation in the European Parliament.

national programmes on allergy/asthma, highlighting the current National Allergy Programme and a former on Asthma in Finland. EFA organized a pilot training for national programme development with delegations from three countries (Bulgaria, Norway, Italy). The delegations gathered key stakeholders: patient representatives, healthcare professionals and policymakers. Patient groups can act as the key initiators for higher priority, organization of care and collaboration in asthma. (Figure 2).

Asthma patient groups are organized from local to national level, from national to regional (like EFA) and now most recently at global level through Global Asthma and Allergy Patient Platform (GAAPP), founded in 2009. Like access to essential asthma control and prevention, disparities exist in the organization capacities of patient groups, and therefore their services and advocacy in the world. A global support for the development of such groups is in the interest of patients and all those interested and involved in asthma.

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EAACI PATIENT ORGANISATIONS COMMITTEE

aha! Center for Allergy Switzerland

Allergy India

Allergy New Zealand Inc

Anaphylaxis Australia Inc

Anaphylaxis Canada

Anaphylaxis Ireland

Anoiksi NGO

Asociacion espanola de alergicos a alimentos y latex

Association Francaise pour la Prevention des Allergie (AFPRAL)

Association québécoise des allergies alimentaires

Deutscher Allergie und Asthmabund eV

European Federation of Allergy & Airway Diseases Patients Association

Food Allergy Italia

Food Allergy Research & Education

Fundacion Creciendo con Alergias Alimenarias

Prevention des Allergies A.S.B.L.

S.O.S Alergia

Swedish Asthma and Allergy Association

The Allergy Society of South Africa

The Anaphylaxis Campaign UK

The European Anaphylaxis Taskforce CV

The Hong Kong Allergy Association

Yahel Food Allergy Network Israel

14 SOCIAL MOBILIZATION FOR PREVENTION AND CONTROL OF ASTHMA

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University of Turku
Finland

We need goal-orientation in the prevention and control of asthma. The only way to make changes happen is the social process, in which the attitudes of the population influence the decision making. Comprehensive social actions, activities and collaboration should be added to the concrete work for decreasing health risks.

The basis for an effective society input is to make changes in the whole society instead of only caring for patients or for those at high risk. When starting a national public health programme a practical plan for implementation is needed, in addition to clearly defined and measurable goals.

From the health care point of view it is important to allocate resources not only for the patients but also for public health actions, including preventative measures and life style changes. Good quality air, regular exercise, balanced diet, weight control and non-smoking are important for all chronic diseases.

KEY MESSAGES

- Asthma is a public health issue and needs a community-based solution. The first step is to involve all the key stakeholders
- Asthma exacerbations can be proactively prevented by improving disease control with the help of guided self-management
- With a nationwide multidisciplinary and comprehensive public health programme the burden of asthma and allergies on individuals and society can be decreased
- Networking of allergy experts with primary care and pharmacists is the key for effective implementation of a national public health programme
- Non-governmental organizations (patient associations) in collaboration with healthcare professionals are in a key position to inform and educate the general public
- The European Federation of Allergy and Airways Diseases Patients' Associations has started a 4-year Awareness Programme on Respiratory Allergies calling upon European policy makers to develop a strategic approach to asthma and respiratory allergies

ASTHMA AS A PUBLIC HEALTH PROBLEM

Asthma is a major global public health problem. The prevalence of asthma continues to rise in many countries: the current estimate of 300 million asthmatics worldwide is expected to increase with 33% by 2025. Every year 250 000 people die prematurely due to asthma. In Europe the prevalence of the doctor-diagnosed asthma in children is around 5% and slightly lower in adults. However, asthma symptoms in the general population occur at a three times higher rate, suggesting a considerable percentage of under diagnosis. Occupational asthma accounts for 15% of all occupational diagnoses. The annual costs of asthma in Europe are estimated at 18 billion Euro. The rising prevalence of asthma and of other respiratory allergies, the increased use of health services, emergency room visits, hospitalizations and medication costs poses a major socioeconomic burden on national and European budgets. Asthma leads to billions of days of lost productivity through absenteeism or presenteeism with costs estimated for Europe at approximately 10 billion Euro annu-

ally. In addition to the economic burden, physical, emotional, and social effects of asthma negatively impact the quality of life of patients and their families. Asthma is related to considerable absenteeism from school.

It is generally considered that the majority of patients with asthma can be sufficiently controlled using adequate treatments and a structured follow-up system. However, there are limitations in controlling patients with severe asthma who suffer from ongoing symptoms and have frequent exacerbations with emergency room visits and hospitalizations and reduced quality of life despite receiving the best available treatment. This group represents about 10% of all asthma patients and accounts for more than 75% of the overall asthma cost. In addition, even patients with mild to moderate asthma may have exacerbations adding to increased costs and to decreased quality of life.

SOCIAL MOBILIZATION FOR PREVENTION AND CONTROL OF ASTHMA

When asthma is controlled, most of the patients with mild and moderate asthma can live a normal life. Health care resources should be used more targeted and tailored to the patients with severe asthma or with frequent exacerbations. Asthma exacerbations can be prevented proactively by improving disease control using a guided self-management action plan.

National public health programmes decreasing the burden of asthma can be best exemplified by the Finnish Asthma Programme 1994-2004, the Czech Initiative for Asthma and the Finnish Allergy Programme 2008-2018.

In Finland, the burden of asthma was significantly reduced since early 90´s when the National Asthma Programme was initiated. The Finnish Asthma Programme focused on early treatment of bronchial inflammation ("hit early, hit hard"), networking and guided-self-management. The key tools were education of primary healthcare professionals, networking of primary and specialized care with pharmacies and patient organizations and the guided self-management plan to prevent and/or promptly treat asthma exacerbations. With these tools asthma patients have better control, less exacerbations, less school and work absenteeism, less retirement. And, less costs to the society and to the patient, even if at the same time the number of patients on regular asthma medication has increased.

The Czech Initiative for Asthma has also proven to be effective in improving the quality of life for patients and reducing costs despite the increasing number of asthma patients on regular treatment.

The Finnish National Allergy Programme 2008-2018 is focusing on prevention, tolerance induction, quality control of the diagnostic work-up and early treatment of exacerbations. New body of evidence for tolerance induction and national consensus gathering all relevant stakeholders are the foundation for this public health programme. The tools are far much the same as in the Asthma Programme, with education the key element. The knowledge accumulated from the asthma guided self-management in adults is being used in the Allergy Programme for children with asthma, allergic rhinoconjunctivitis, atopic dermatitis, food allergy and anaphylaxis. The key messages (Table 1) were taken very positively by the healthcare professionals and the general population. The Educational programme was a great success with quite limited man power. By the end of the year 2012 the Finnish Lung Health Association organized with one specialist, working half day in collaboration with local key opinion leaders and one full-time Project Nurse 175 multidisciplinary educational meetings with almost 11000 health care professionals participating: 25% physicians, 50% nurses, 10% pharmacists, 15% dieticians, students and others (Table 2). The topics of the meetings were targeted to the Goals of the Programme and tailored to local needs. Educational meetings were free of charge and organised during the working hours inside or nearby the healthcare unit (University/Central/Local Hospitals and Health Care Centres).

In 2011 three non-governmental organizations (Allergy and Asthma Federation, Pulmonary Association and Skin Federation), started a comprehensive information and communication campaign. This 4-year project implements the new recommendations among allergic people and general population. The main tools are the internet via

TABLE 1

The key messages of the Finnish Allergy Programme 2008-2018

- Endorse health, not allergy
- Strengthen tolerance
- Adopt a new attitude to allergy
  - Avoid allergens only if mandatory
- Recognize and treat severe allergies early
  - Prevent exacerbations and attacks
- Improve air quality. Stop smoking!

TABLE 2

Educational process of the implementation of the Finnish Allergy Programme to the health care

Themes	2008	2009	2010	2011	2012	Total
Programme Launch *Central Hospitals*	16	10	-	-		26 events 1585 participants
Food Allergy *Primary Care*	7	29	25	8	-	69 events 2253 participants
Allergy Health *Central Hospital districts*	-	3	10	11	-	24 events 2293 participants
Anaphylaxis *Primary Care*	-	-	1	16	14	31 events 2174 participants
Allergy-healthy Child *Central Hospital districts*	-	-	-	-	8	8 events 675 participants
More tolerance – less allergy *Central Hospital districts*	-	-	-	-	9	9 events 690 participants
Northern Lapland Military Forces etc	-	-	1	1	6	8 events 442 participants
All 26.11.2012	**23**	**42**	**37**	**36**	**37**	**175 events >10 000 participants**

the homepages of the project and seminars for media reporters. In addition other methods of modern media are used. Two half-time workers are managing the Project. They gave in 2011 and 2012 38 talks all over the country and 20 Radio and TV interviews. All three NGOs communicate on every day basis different topics of the Finnish Allergy Programme. The first results of the Finnish Allergy Programme indicate that allergy burden can be reduced with relatively simple means.

EUROPEAN AWARENESS PROJECT OF RESPIRATORY ALLERGIES

On European level, the European Federation of Allergy and Airways Diseases Patients' Associations (EFA) has started in 2011 a 4-year Awareness Programme on Respiratory Allergies – Raise Awareness, Relieve the Burden. The programme calls upon European policy makers, European Union and Member States to take the necessary steps to develop a strategic, comprehensive and integrated approach to asthma and respiratory allergies that brings all initiatives and actions under one umbrella, and to support the launch and implementation of national public health programmes.

EFA surveyed in 2011 its member associations in 18 European countries to gain information about national asthma and respiratory allergy policies. The survey showed that the quality of life of patients has improved considerably in countries with a robust national programme, but not in countries where national programme either fails to involve all stakeholders (e.g. involving only specialists) or has difficulties in being implemented or sustained.

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15 ASTHMA IN RESOURCE CONSTRAINED SETTINGS

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KEY MESSAGES

- Prevention and control of asthma need to be an integral part of the national strategy for prevention and control of noncommunicable diseases.
- Multisectorial public policies to reduce exposure to risk factors and address social determinants as well as health systems organized around the principle of universal health coverage are necessary for prevention and control of asthma.
- Scaling up efforts for prevention and control of asthma will contribute to the attainment of the voluntary global target of reducing premature mortality from noncommunicable diseases with 25% by 2025.

HEALTH AND ECONOMIC IMPACT OF ASTHMA

Chronic respiratory diseases, including asthma were responsible for 4.2 million deaths globally in 2008. Over the period 2011-2025, the cumulative lost output in low- and middle-income countries associated with chronic respiratory diseases including asthma, is projected to be US$ 1.59 trillion (Table 1). Social determinants significantly influence the prevalence of asthma (Table 2). There are substantial health and economic gains attached to prevention, early detection, adequate treatment and good control of asthma.

SUSTAINABLE SOLUTIONS

Prevention and control of asthma need to be an integral part of the national strategy for prevention and control of noncommunicable diseases (NCDs). Public health policies need to reduce the exposure of people to risk factors for asthma and mitigate social determinants that increase vulnerability to asthma. Tobacco smoke, allergens, air pollution including indoor air pollution from solid fuel combustion, poor housing, extreme weather conditions, all play a role in asthma and need to be addressed through multisectoral public policies.

In addition, effective control of asthma requires health system strengthening across all components: governance, health financing, information, human resources, service delivery and access to inexpensive good quality generic medicines and basic technologies. Health systems that have proven to be most effective in improving health and equity organize their services around the principle of universal health coverage and promote actions at the primary care level. An integrated primary care programme, delivered by trained health workers, which provides equitable coverage and access to basic diagnostics and essential medicines (e.g. at least salbutamol and inhaled beclometasone) is required. World Health Organization (WHO) guidelines and tools are available for this purpose.

The 66th World Health Assembly endorsed the Global Action Plan for prevention and control of noncommunicable disease and the global monitoring framework to track progress in its implementation. The monitoring framework includes nine voluntary global targets and 25 indicators. A 25% reduction in premature mortality from major NCDs by 2025 is one of the nine voluntary global targets. Scaling up efforts for prevention and control of asthma will contribute to the attainment of this volun-

TABLE 1

Economic burden of noncommunicable diseases, 2011-2025 (US$ trillion in 2008)

Country income group	Cardiovascular diseases	Cancer	Respiratory diseases	Diabetes	Total
Upper-middle	2.52	1.20	1.09	0.31	5.12
Lower-middle	1.07	0.26	0.44	0.09	1.85
Low-income	0.17	0.05	0.06	0.02	0.31
Total of low- and middle-income	3.76	1.51	1.59	0.42	7.28

TABLE 2

Economic burden of noncommunicable diseases, 2011-2025 (US$ trillion in 2008) *

	Middle income group		Low income group	
	Men	Women	Men	Women
No formal schooling	9.2 (7.7 - 10.8)	10.2 (9.0 - 11.4)	6.4 (5.7 - 7.1)	7.1 (6.5 - 7.7)
Less than primary school	6.8 (5.9 - 7.8)	9.7 (8.8 - 10.6)	5.7 (4.8 - 6.5)	5.7 (5.0 - 6.4)
Primary school completed	7.4 (6.5 - 8.2)	7.7 (6.7 - 8.6)	6.0 (5.0 - 6.9)	6.2 (5.2 - 7.2)
Secondary / high school completed	5.7 (5.1- 6.3)	6.2 (5.7 - 6.8)	4.6 (3.8 - 5.3)	5.5 (4.7 - 6.4)
College completed or above	4.2 (3.0 - 5.3)	3.9 (3.3 - 4.6)	3.7 (2.8 - 4.7)	3.1 (1.9 - 4.3)

** Data from Hosseinpoor AR, Bergen N, Mendis S, et al. Socioeconomic inequality in the prevalence of noncommunicable diseases in low- and middle-income countries: results from the World Health Survey. BMC Public Health, 2012;12:474*

tary global target for reducing premature mortality from NCDs.

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16 DEALING WITH THE IMPLEMENTATION GAP FOR ASTHMA PREVENTION AND CONTROL

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KEY MESSAGES

- Prevention, early diagnosis and treatment of allergy and asthma is recognized as a priority for the EU's public health policy and the United Nations
- Identifying the missing links in the process between setting-up a program for prevention and making it work is essential
- Focusing on pathomechanisms of asthma inflammation, identifying the factors increasing the risk of asthma exacerbations, the window of opportunity for a successful intervention and designing more effective anti-inflammatory drugs should go hand in hand with increasing networking with other specialists and healthcare professionals and patients organisations, educational programmes, increased social awareness and mobilisation of resources and a better definition of short, medium and long-term goals to impact morbidity in asthma and allergy

Asthma and allergic diseases start early in life and persist throughout life. They could also appear later, at any time for reasons we still do not understand. Many of the developing countries are facing a rapid increase in prevalence, disability and costs. In some countries the asthma and allergy epidemic may be leveling off, but the morbidity will stay high. They are indeed major chronic respiratory diseases, for which prevention, early diagnosis and treatment is recognized as a priority for the EU's public health policy and the United Nations (High Level meeting on Non-Communicable Diseases, 2011). Given that allergy triggers, including rapid urbanization, pollution and climate change, infections are not expected to change in the foreseeable future, it is imperative that steps are taken to develop, strengthen and optimize preventive and treatment strategies. However, we are still uncertain how to prevent children from developing asthma and allergic diseases.

Very few prevention programs have been successful so far: allergen avoidance, pharmacotherapy, allergen immunotherapy, food diet and pre/probiotics, education campaigns. The Finnish Asthma Programme (FAS-P: 1994-2004), extended to 7 countries (Brazil, Chile, China-Hong Kong, Ireland, Japan, Poland, Singapore), appears to have been the most effective, showing a cost-effective reduction of asthma burden but not asthma prevalence over time. The Finnish Allergy Programme (FAL-P, 2008-2018) is currently implemented in the country and a reduction of the allergy epidemic is expected. High oral dose of food allergens in early infancy may promote the development of immunological tolerance. Allergen immunotherapy is the only currently available medical intervention that has the potential to affect the natural course of the disease. What does work and not work should be listed and reanalyzed carefully. The missing links in the process between setting-up a program for prevention and making it work is labeled as "implementation gap".

In order to understand why some interventions and/or programs are working, while others have not met expectations, the common factors that stood out prior to successful implementations by examining the "implementation gap" are listed below:

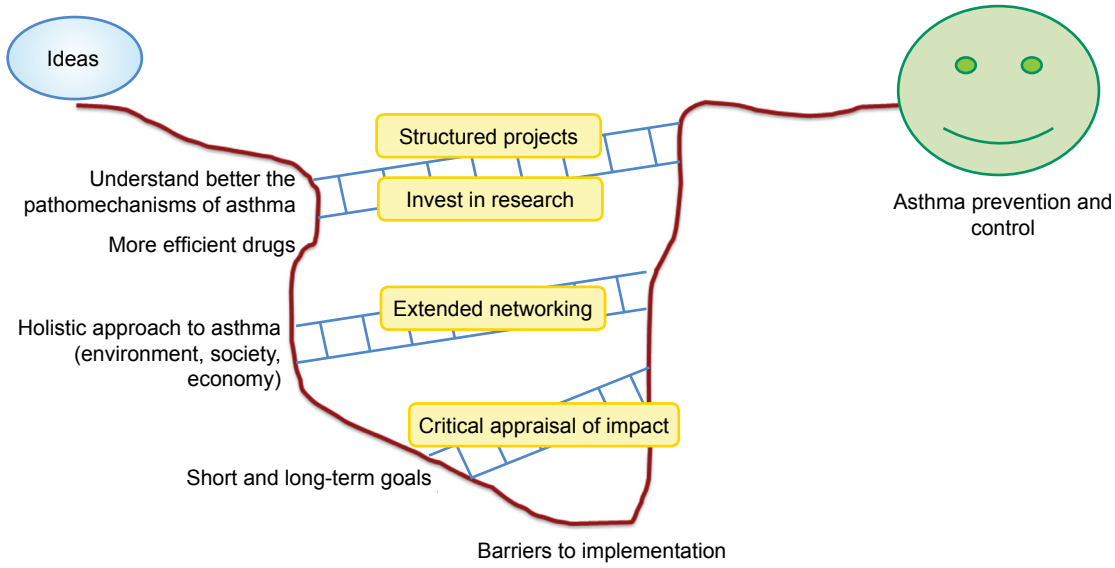

Figure 1 Dealing with the implementation gap for efficient asthma prevention and control.

- Understanding better the pathomechanisms of asthma inflammation; for example, important advances in our knowledge of genetic associations with allergic disease, have not clarified the underlying pathological pathways, probably because we have yet to understand their interactions with environmental exposures. We also lack knowledge on epigenetic mechanisms, now thought to be important in asthma and allergies
- Including scientists from other disciplines to better appraise the role of our environment in the epidemics
- Identifying the factors increasing the risk of asthma exacerbations (with a special focus on viruses, allergens and patient behaviors)
- Identifying the best window (age group) for intervention (depending on the aim: primary vs secondary/tertiary prevention)
- Having short-term goals to impact morbidity (emergency, hospitalization rate, mortality, disability) and long-term goals to decrease the incidence
- Designing more effective anti-inflammatory drugs / drug combinations and educational programs that maintain control of the diseases and novel treatments such as innovative immunological interventions that prevent asthma and allergies
- Combining both asthma and allergy plans

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17 GENERATING RESOURCES FOR PREVENTION AND CONTROL OF ASTHMA

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KEY MESSAGES

- Generating resources for prevention and control of asthma is a difficult issue requiring constant political work at national and international levels
- There are no asthma programs sponsored by the World Health Organisation
- In the European Union most of the basic funding for research and health programs comes from local financial commitments in individual EU countries
- The European Commission announces competitions: in science - DG RESEARCH, in public health - DG SANCO, in innovation and competitiveness - DG CNECT, and others

Information on best practices on measures for prevention and control of chronic diseases can be obtained through local or international sponsorship programs. In both cases, political decisions are fundamental. The global initiative highlights the key role of the World Health Organisation (WHO). The health policy is decided in the UN general assembly resolution which is preceded by a number of previous discussions and negotiations carried out at regional and global level in the WHO. The funds that the WHO receives from membership fees are not enough to conduct international programs. Usually the additional support comes from private sponsors such as the Bloomberg Foundation, which established programs dedicated to the fight against smoking. There are no programs sponsored by the WHO for asthma.

In the European Union (EU), according to article 168 of the Treaty on the Functioning of the European Union, a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities. In this context, the role of the promotion of human health by the European institutions is very important, particularly the Commission (EC) should also take into account the role of the National Contact Points during the consultations in the procedures for the elaboration of programmes. The subject should be promoted not only by interested stakeholders but also by national authorities. Actions at all levels of this complex network are needed to guarantee its translation into different European programmes and into the subsequent themes of calls for proposals. However, most of the basic funding for research and health programs comes from local financial commitments in individual EU countries. The internal politics of each country determines national priorities, resulting from the specific health status of the population. The transfer of these problems to the international forum is usually the result of an agreement between countries and is usually realized by the presidency of the council of the EU done by particular Member States (MS). The 27 EU Ministries of Health adopt conclusions on priorities on the basis of which the EC prepares specific programs and associated funding. For asthma, the Polish Presidency put forward the initiative “Conclusion of EU Council on chronic respiratory diseases in children” . Following this conclusion the Commission can includ this issue in different programs, ex. in science - DG RESEARCH, in

TABLE 1

EU resources for prevention and control of asthma

Institution	Programe	Website *
EC DG RESEARCH	*FP7 and from 2014 – Horizon 2020*	▪ http://cordis.europa.eu/fp7/dc/index.cfm ▪ http://ec.europa.eu/research/participants/portal/page/fp7_calls
EC DG SANCO,	*Public Health Programme*	▪ http://ec.europa.eu/health/programme/policy/index_en.htm ▪ http://ec.europa.eu/health/programme/how_does_it_work/call_for_proposals/index_en.htm
EC DG CNECT	*Competitiveness and innovation –ICT Policy Support Programme (ICT PSP)*	▪ http://ec.europa.eu/digital-agenda/en/ict-policy-support-programme ▪ https://ec.europa.eu/digital-agenda/sites/digital-agenda/files/cip_ict_psp_wp2013_publication.pdf
European Commission	*The European Innovation Partnership on Active and Healthy Ageing*	▪ http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing ▪ http://ec.europa.eu/social/main.jsp?langId=en&catId=89&newsId=1065&furtherNews=yes
Ambient Assisted Lining	*Ambient Assisted Lining Joint Programme -ICT for ageing well*	▪ http://www.aal-europe.eu

**accessed May 20, 2013*

public health - DG SANCO, in innovation and competitiveness – DG CNECT, and others, e.g. Ambient Assisted Lining (AAL). (Table 1). One of the distinguishing features of the conclusions adopted during the Polish Presidency was to support networks such as GA²LEN and GARD, which promote asthma policy based on scientific grounds. Thanks to the follow-on efforts of the Cyprus Presidency chronic respiratory diseases should be implemented into EU health policy as "the links between early life events and healthy ageing using inter alia longitudinal studies" as reflected in the conclusions section. Consequently, EU institutions gave rise to the support for further efforts to prevent and control asthma.

In conclusion, it should be noted that raising funds for prevention and control of asthma is a difficult issue requiring constant political work at all levels: national and international, including political lobbying, which aims to raise awareness among politicians and policymakers of the importance of the respiratory health of current and future generations.

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18 ASTHMA PREVENTION AND CONTROL: WHY IT SHOULD NOT BE IGNORED ANY LONGER?

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KEY MESSAGES

- Asthma treatment has improved with the development of guidelines
- The effectiveness of asthma treatment can be assessed by monitoring measures of disease control
- The next major advance to significantly reduce the burden of asthma is the development of approaches to prevent this disease

Over the past three decades, there have been amazing advances to more fully understand the mechanisms of asthma, risk factors associated in its development, and identification of safe and effective treatment approaches to control this disease. As a consequence, the significant morbidity associated with asthma has improved, but not disappeared.

To achieve goals of improved asthma care, guidelines for its diagnosis, treatment and management were developed. Asthma guidelines provide physicians, health care providers, and patients with an evidence-based approach to treatment and goals to measure the effectiveness of these undertakings. Central to the effective management of asthma is disease control. The effectiveness of asthma control can be defined by assessments made in two major domains: impairment and risks (Table 1). Impairment assesses the patient's symptoms, need for rescue treatment, interference with daily activities, and lung function. With treatment based upon the underlying severity of asthma, it is anticipated that markers of impairment can be reduced and sustained. Markers of impairment largely refer to the "here and now" aspects of asthma that patients experience on a day-to-day basis. In addition, effective control of asthma needs to include assessments of future risks. Future risks include exacerbations, progressive loss of lung function, and side-effects from medication. Therefore, effective and comprehensive management must include control of both components of asthma, impairment and risks. Guidelines for the care of asthma have helped us achieve success in the control of asthma and by this to reduce the burden of this disease.

TABLE 1

Assessment of asthma control
Impairment
• Symptoms (day and night) • Need for rescue treatment • Limitation of daily activities • Lung functions
Risks
• Exacerbations • Progressive loss of lung function • Side effects from medication

Despite these advances, asthma continues to impart a huge level of morbidity to patients with this disease, to families of the affected, and to society because of the associated costs. In the United States, for example, the burden of asthma is huge. Nearly 25 million patients in the United States have asthma. The prevalence of asthma is felt in patients of all ages with morbidity highly variable – mild disease with infrequent symptoms to patients who experience daily compromises to their lifestyle and have limited responses to treatment. In the United States, the economic

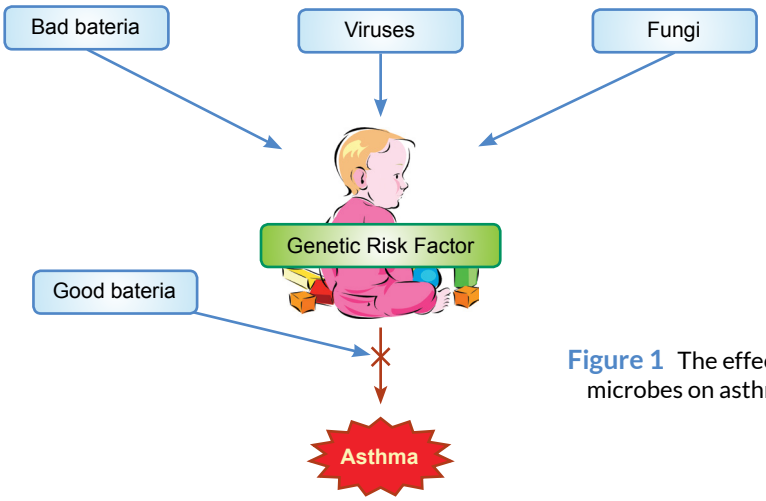

Figure 1 The effects of microbes on asthma.

burden of asthma is also high with annual costs in the range of $18 billion. These costs include direct expenses for care, medication, and, when necessary, hospitalizations. Indirect costs also contribute a significant portion of this burden and arise from loss of work, absence from school, and family expenses associated with the need to provide care for affected family members.

Treatments for asthma are continually improving and hold the promise for greater specificity towards the underlying disease; however, these are treatments for those already affected and afflicted with asthma. To truly have an impact on asthma and to reduce the burden of this disease, it is critical now to move forward and develop methods to prevent asthma. How close are we to this critical goal?

The development of asthma is influenced by many factors, many of which are interactive with one another. Asthma has its roots in the genetics of an individual patient as a family history for this disease is a major risk factor. For the disease to develop, however, other influences need to occur and by this create a 'gene-by-environment' interaction. In this regard, a number of key observations have been made. First, allergic sensitization appears, at least for children, to be a major risk factor in the development and expression of asthma. Allergic sensitization, however, by itself may not lead to asthma and other factors need to be considered. Evidence has shown that respiratory infections, primarily viral respiratory infections, are key to the development of asthma. Some bacterial infections early in life may also serve as similar risks.

The interaction of microbes and the host in the eventual development of various diseases, including asthma, is a delicate and intriguing interaction. Emerging and solid evidence indicates that children raised on farms have less asthma. Evidence has also shown that there may be distinct bacteria in these rural environments which can, perhaps, serve to protect from or prevent asthma. Thus, evidence is being accrued that microbes, or the environmental microbiome, may be a major determinant of the host's eventual immune system and, as a consequence, determine the individual patient's risk for a particular disease. This information is providing "clues" for new approaches to prevent the development of asthma (Figure 1).

We are now poised, I believe, to harness this information, and from it, develop novel strategies to move to "the next level" in asthma mechanisms and prevention of this disease. Although efforts will be ongoing to further develop of new treatments for existing asthma, our ultimate and hopefully achievable goal now needs to be on prevention of this disease. Until we make these necessary and appropriate inroads in prevention, the burden of asthma will continue to mount.

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19 VISION, ROADMAP AND A LAND-MARKING EVENT

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In less than half a century, asthma, originally a rare disease, showed an epidemic increase, and has become a major public health problem. Today, it is affecting the lives of more than 300 million people worldwide, and is expected to reach to 400 million in the next three decades. Its prevalence and impact are particularly on the rise in urbanizing regions and globalizing World associated with environmental and lifestyle changes. Apart from the individual suffering of patients, asthma presents a very high socioeconomic burden to health care systems and families. In addition, patient care and access to treatment is inadequate in many developing regions and countries. Effective policies and strategy development are needed to fill this gap at the global, regional, national level (Table 1).

KEY MESSAGES

- The asthma epidemic affects more than 300 million patients with a global rise in prevalence, as the most common chronic childhood disease with increasing health-care costs
- Effective policies and strategy development are needed to fill this gap at the global, regional and national level
- Efforts to overcome unmet needs should focus on 4 main directions:
  - Research and development
  - Better patient care at the global level
  - Increased public awareness
  - Asthma in the political agenda
- A "Global Fight Asthma Strategy" should be developed:
  - All stakeholders should be involved
  - A multidisciplinary and scientific approach should be used
  - "One Health" concept should be integrated
  - Next generation guidelines should be developed
  - A World Asthma Center and integrated asthma surveillance network should be established
  - Existing know-how from successful approaches in the past should be broadly implemented

EFFORTS TO OVERCOME UNMET NEEDS

The efforts to overcome high numbers of unmet needs described in Chapter C1 can be grouped in four directions:

A) **Research and development** should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, anti-viral vaccines, and novel drug development, particularly for the treatment of severe asthma. There are a number of barriers and obstacles in grant giving bodies to be solved in the short run (Table 2).

B) **Better patient care at the global level** requires a worldwide approach to identify barriers for prevention and cure; develop asthma registries; develop next generation guidelines (i.e. integrated care pathways); improve accessibility to diagnosis and essential drugs in low income countries; implement full environment control; realize psychological help directly and routinely without any need for consultation; implement every aspect of education of patients,

TABLE 1

Efforts for awareness in the political bodies for allergy and asthma

- Global Allergy and Asthma European Network (GA²LEN) was established with the efforts of EAACI in 2004 as an EU FP6 Network of Excellence.
- Allergy was listed in the food and agriculture group in the EU research grants until 2007, EU accepted allergy as an important health problem in 2007 with the efforts of the EAACI and GA²LEN
- The results of the Finnish Asthma Program demonstrated that asthma burden can be substantially decreased by relatively undemanding methods doable by every country (Chapter D5) is slowly being implemented by some national health-care systems
- Asthma is included in the EU Horizons 2020 programme. Allergy is still pending and efforts are needed to include allergy
- Many one day awareness meetings have been organized or attended by patient organizations, EAACI, GA²LEN and ERS leaderships and members of the EU Parliament in Brussels during the recent years

TABLE 2

Barriers in research grants and grant giving bodies

- Lack of political awareness and low understanding and priority setting for asthma and allergy epidemics
- Curative approaches and research for prevention has not been so far efficiently supported
- Small quantities of grants have been given to hypothesis-based research, although the real need is large scale, non hypothesis based, in dept research, which is now possible with the novel developments in next generation DNA and RNA sequencing, exposome analysis, and epigenetic analysis
- Human research is receiving relatively less funding in many grant giving bodies compared to animal models
- Many major grant giving bodies had to decrease their budgets during the last years
- Negative results that are not published will be repeated and repeated

primary care physicians and allied health personal.

C) To increase the public awareness, it is now essential to position asthma as one of the most important causes of chronic morbidity and health care burden. Asthma-focused patient organizations should be immediately established in all countries. There is a lot to learn from the fight with HIV/AIDS and utilize.

D) It is not possible for the politicians to remain silent at this stage, because the number of affected individuals and families are huge, and health care burden of asthma is forcing the budgets of health systems in all countries. A significant number of international alliances, societies, networks and academies are working on this (Table 3).

A WORLDWIDE STRATEGY TO FIGHT AND MANAGE ASTHMA SHOULD BE DEVELOPED

A) All stakeholders including specialists, primary care physicians, nurses, dieticians, psychologists, pharmacists, patient organizations, educators, industry, and policy makers should be involved.

B) Worldwide asthma management should be integrated with

TABLE 3

Global and transregional policies and programmes for asthma (Described in detail in Chapter D7)

- The United Nations recognized the importance of Chronic Non Communicable Diseases (NCD)
- The WHO established a 5 years NCD Action Plan 2008-2013
- GA²LEN was established as a European Network of Excellence in 2004
- Global Alliance against Chronic Respiratory Diseases (GARD)
- The International Primary Care Respiratory Group (IPCRG)
- Global Asthma Network (GAN)
- The Global Initiative for Asthma (GINA)
- Allergic Rhinitis and its Impact on Asthma (ARIA)
- The Brussels Declaration on asthma was developed in 2008
- Davos Declaration was developed in 2011
- EU Council Conclusion was developed after the prioritization of Childhood Chronic Respiratory Diseases by Polish Presidency in 2011

the "**One Health**" concept that acknowledges the systemic interconnections of human, animal and environmental health in close relationship with food safety and security. In the era of climate change, resource depletion, land degradation, food insecurity and development challenges, an integrative approach is needed to ensure sustainable health. This concept strongly applies to all chronic inflammatory diseases, because of a strong scientific basis of epigenetic regulation of the disease genes with the influence of changing environment. Human, animal and plant health, healthy air, water and earth, food safety & security are integrative components of the "**One Health**" concept.

C) Next generation guidelines, such as integrated care pathways (described in Chapter D6) should be implemented for asthma and its co-morbidities to provide structured, multidisciplinary, region and environment-oriented, individual patient-focused, considerate on differences across cultures and detailed patient care guidelines.

D) There is substantial experience of already established strategies and associations. We should avoid reinventing the wheel and utilize and implement the existing know-how. One of the most valuable experiences in our fight with asthma is the success of the **Finnish Programmes** (described in Chapter D5 and D14). Based on the accumulated knowledge it is now fundamental to disseminate the Finnish experience to whole world, collect feedback and further improve. A stepwise asthma management plan providing best-buy measures for asthma prevention and control is described in Chapter D4. Cost-efficient use of available resources, promotion of effective asthma management approaches and investment in innovative models and in asthma research are important steps forward.

E) A World Asthma Center should be established with a fully integrated network to all national and regional asthma centers and already established networks, alliances, societies and Academies, aiming at worldwide asthma surveillance, strategy development and education. Prioritization of asthma is going to take place more and more in United Nations, WHO and national political agendas, where chronic non-communicable diseases are being prioritized nowadays. Management of asthma together with other respiratory diseases and other chronic non-communicable diseases in these organizations may help to economize efforts in the early stage, however, **full and only focus to asthma** is inevitable for the success in the long run. A **worldwide and integrated asthma surveillance network**, using disease registries, pharmacoeconomic evaluation, as well as large biobanks should be developed.

F) Health economics studies in asthma and other life-long lasting chronic diseases demonstrate a huge financial benefit of prevention and curative treatments. Particularly, prevention

TABLE 4

Davos Declaration

Research Needs

- The causes of the epidemic increase in allergic diseases are unknown. Environmental exposures that appear to be critical factors include factors as diverse as air quality, diet and nutrition, climate, UV radiation, and direct skin contact as well as psycho-social interactions. Moreover, when genetic predisposition is taken into account, environment can provide either risk or protection.
- The effects of changes in climate, urbanization, etc. have to be anticipated. Better ways to assess spatial and temporal environmental exposure at population and individual levels are much needed and should be related to the assessment of individual genetic susceptibility.
- The interactions between microbes, pollutants, and the immune system are marginally understood.
- There is inadequate understanding of the natural mechanisms that limit acute vs. chronic disease or spontaneous resolution.
- There is a need for better subclassification of allergic disorders based on pathobiology.
- There is a need for new agents acting on specific pathways in pathogenesis with regard to new therapeutic approaches.
- There is a need for better preclinical models for translational research.
- There is a need to develop better tools for complex data analysis.
- There is a need for efficient strategies for primary and secondary allergy prevention.
- There is a need for better approaches in diagnosis and prediction of treatment responses and the monitoring of therapeutic effectiveness.

Needs for Education and Awareness

- Apart from true lack of information, there is a tremendous gap between actual existing knowledge and its effective application for the millions of people in need.
- There is a shortage of well-trained specialists in most countries.
- Education and training efforts should also be directed toward medical students at the curricular level and extended to primary care physicians, who have to be involved in a strategy for diagnosing and managing allergic diseases with such high prevalence rates of 20% of the population.
- Awareness campaigns for targeted public groups should be performed. Allied health professionals, such as nurses, school teachers, etc., should be included. Better and more effective tools to spread the available information should be developed.
- Close cooperation with patient organizations is highly recommended.
- Decision makers involved in developing and approving health policies and administration must be made more aware of the problem.

of severe asthma development and exacerbations has an immense effect on healthcare costs. It is now very appropriate that health insurance systems and other health-care financing models invest on research and education for primary and secondary prevention and curative treatments.

G) A multidisciplinary scientific approach is essential. A group of 40 scientists and clinicians from all around the world and all fields of allergy, asthma and related disciplines gathered under the sponsorship of the Christine-Kühne Center of Allergy Research and Education (CK-CARE) in Davos, Switzerland from 17 to 20 July 2011 for the first 'Global Allergy Forum' under the topic "Barriers to Cure" and developed The Davos Declaration (Table 4).

In a parallel action that brings together political bodies and scientists, representatives of the European Academy of Allergy and Clinical Immunology, the European Respiratory Society, the International Primary Care Respiratory Group, the Polish Allergy Society, the WHO Global Alliance against Chronic Respiratory Diseases, and the European Federation of Allergy and Airway Diseases Patients' Associations were invited by the

TABLE 5

Council of the European Union Conclusions on prevention, early diagnosis and treatment of chronic respiratory diseases in children

- Tackle the problems that constitute the biggest risk factors that could trigger a chronic respiratory disease: tobacco smoke, poor indoor air quality, and outdoor air pollution. Prevention should begin before child birth, and stop-smoking programmes for pregnant women should be intensified. Additionally, future mothers and children should be protected against exposure to tobacco smoke, in particular at home and in closed spaces.
- Strengthen efforts to reduce the disability and premature death related to asthma by fostering best practices at an international level
- Strengthen knowledge and public awareness in the prevention and treatment of these diseases. Health education of children, parents, and teachers is recognised as important in this regard, as well as training of health professionals
- Foster cooperation and exchange of best practices and support member states in implementing their policies and improving networking, particularly international research networks, to find cost-effective procedures to improve the standards of health-care systems for chronic respiratory diseases
- Develop research for a better understanding of the reasons for the increase in prevalence of chronic respiratory diseases in children and the disparities between regions and throughout Europe

Polish Minister of Health to convene and discuss how to prevent and control chronic respiratory diseases in children on Sept 20–21, 2011 (Chapter D17). These conclusions were adopted during an Interministerial Conference of the 27 EU Member States, on Dec 2, 2011, and are outlined in Table 5.

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The European Academy of Allergy and Clinical Immunology (EAACI) is a non-profit organization active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. Its scope covers both basic science and clinical medicine.

Since its establishment in 1956, EAACI has grown to become the largest medical association in Europe in the field of allergy and clinical immunology. Its membership currently includes more than 8000 members from 121 countries, representing academicians, clinicians, and allied health professionals. In addition, EAACI includes 42 National Allergy Societies as members.

EAACI's mission is to provide the most efficient platform for scientific communication and education in the field of allergy and immunology, ultimately striving to ease the lives of patients suffering from these diseases. EAACI is regarded as the **primary source of expertise** in Europe for all aspects of allergy.

EAACI's activities

- Fostering science through dedicated platforms Annual Congress, Focused Meetings, Guidelines and Position Papers
- Educating professionals (Allergy Schools; CME system; knowledge examination in allergy and clinical Immunology; Research and Clinical Fellowships)
- Disseminating knowledge through EAACI Journals (Allergy, Pediatric Allergy Immunology, Clinical and Translational Allergy, EAACI Newletter) and online communication platforms
- Advocating change and raising awareness among the European Union's decision makers about the importance of allergy and clinical immunology and the opportunities to prevent and treat allergies through *Public Campaigns* and *Public Declarations*

EAACI's governance and structure is derived from its Constitution and By-Laws. The governing body of EAACI is its *General Assembly* representing all EAACI members. The *Executive Committee* acts as the main administrative body. Important structural units that facilitate various Academy functions and activities are the *Committees*, *Sections*, *Interest Groups*, the *Junior Members Assembly* and the *Task Forces*.

The Global Atlas of Asthma reviews and updates the existing data on asthma incidence and prevalence, risk and protective factors, pathogenic mechanisms and treatment options, focusing on prevention and control of asthma. The paramount role of allergy in the pathophysiology of asthma is strongly emphasized in order to highlight the importance of our core specialty and as a step forward for bringing the rest of the world closer to the understanding of allergy as a major public health/international problem.

The document is written by an international group of 80 World leaders in asthma research and is aimed to be a concise reference for all the stakeholders and a platform for a strategic planning for any aspect of the disease in a multifaceted way integrating research, education and global policies.

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