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The state of play in European asthma research in 2015

Introduction

The aim of this document is to provide an overview of the areas identified and previously published by experts in the field as key in asthma research to achieve the outcome of better asthma prevention, diagnosis, treatment and management and potentially a cure.

This document summarises existing pan-European and international overview documents that either directly look at or explicitly mention gaps in asthma research. It has been reviewed by experts in biological and clinical practice and health systems management to ensure a comprehensive review of the current state of play in European asthma research in 2015, and that no significant gaps have been missed or met since the publication of the overview documents. This document has also been reviewed by people with asthma to ensure its readability and relevance from their perspective.

This document is an outcome of the European Asthma Research and Innovation Partnership (EARIP; www.EARIP.eu), supported by the European Commission through the Seventh framework partnership (FP7). Therefore, the research gaps identified have been mapped against the Horizon 2020 research areas and European Innovation Partnership (EIP) criteria.

Methods

The overview documents have been produced by leading international and European medical societies, patient organisations and policy makers in the field of asthma, and identified research needs and gaps.

A literature review and reference searches identified the overview documents, along with recommendations from EARIP partners. Only documents within the date range 2010-2014 were used, as key gaps identified in earlier documents have now been addressed and advances, such as in phenotyping, have impacted the scope of asthma research.

The gaps identified have been presented under the following headings and cover asthma mechanisms and clinical practice as well as health systems management:

- Understanding asthma
- Asthma services and care
- Diagnosis and monitoring
- Treatment and management options
- Preventing and curing asthma
- Government policy
Please note that some topics will be presented under one heading but will also have significance for other areas. For example, research into phenotyping has implications for diagnosis, monitoring, treatment, management, prevention and cure. The topic will be presented under the first heading to which it relates, and may only receive a short reference under other headings to which it also relates.

**Background**

It is estimated that 30 million people in Europe under the age of 45 are currently living with asthma [1], with life-threatening symptoms leading to 500,000 hospitalisations a year [2], and an economic cost of €13.6 billion per year in lost productivity [3]. Asthma is the most common chronic respiratory condition in children and affects people across their lifetime, with the economic and medical burden further increased by people living longer with chronic conditions and comorbidities [1-2].

Poor asthma control is associated with increased risk of exacerbations, impaired quality of life, increased burden on healthcare services and resources, and reduced productivity [4-7]. Over 35% of children with asthma miss between 8 and 40 days of school a year due to their asthma symptoms [8] and the number of absentee day’s increases if a child’s parent also has asthma. There has been little improvement in the levels of asthma control over the last decade [4-5, 7].

Fourteen EU countries feature in the top 20 worst countries globally for asthma prevalence in adults [1]. There are also great differences in delivery and quality between countries across Europe, and the world, in the asthma services, diagnostic equipment and treatments available.

The information in this document will be used to guide the prioritisation of specific areas of research that the European Commission should fund, based on which areas are most likely to provide answers to the challenges of preventing, treating and living with asthma.

**Understanding asthma**

To be able to improve diagnosis, treatment and care, and to explore prevention and cure, asthma must first be understood better as a disease. It is important to extend current basic research into the causes and development of aspects of asthma and acute exacerbations; allergy, airway inflammation and bronchial hyperresponsiveness [1, 9]. Tools and analysis techniques to support this research must also be developed, such as sensitive and reliable multi-scale computational models and statistical modelling to accelerate the testing of new treatments [9, 14].

**Research gaps**

1. Genetics and biomarkers:
• Identify, understand and better classify the different forms of asthma by discovering specific genetic, epigenetic and inflammatory biomarkers for different phenotypes/endotypes, and how they are interlinked [1, 10-11].
• Identify biomarkers for asthma exacerbations, especially for acute exacerbations and severe asthma, and explore interactions between biomarkers, risk and comorbidities [10, 12-14].
• Better understand origins and progression of asthma subtypes across the lifetime, including genetic and epigenetic factors in asthma, airway inflammation and the immune system [1, 11, 13].
• Understand the role of each person’s genetics and gene expression in asthma susceptibility, airway structure, disease progression and severity [1, 10-11, 13].

2. Mechanisms:
• Longitudinal studies to understand the natural history and pathobiological mechanisms of different asthma endotypes including allergic and non-allergic asthma development and progression across the lifetime, including asthma in later life [3, 11, 13].
• Understand the biological mechanisms that cause acute worsening of and underlying chronic asthma or its spontaneous recovery (an improvement in symptoms without a change in treatment) [11, 13].

3. Comorbidities:
• Identify and understand the links between asthma and comorbid conditions, in particular between asthma and chronic obstructive pulmonary disease (COPD) (asthma COPD overlap syndrome (ACOS)), asthma and other allergic disorders (e.g. eczema, food allergy, rhinitis, anaphylaxis) and asthma and obesity [2, 14].

4. Immune tolerance:
• Understand the role of respiratory virus infections and microorganisms in the lung and gut in the manner in which asthma develops and how they respond to asthma treatments [9].
• Understand how the immune system responds in severe asthma, and identify and develop any new agents acting on specific pathways in pathogenesis [10, 13].
• Understand how immune tolerance to allergens can be developed using different types of immunotherapy (oral versus injected treatments), the mechanisms by which this takes place and why this does not occur in all people with asthma, hyperresponsiveness and allergies [9].

5. Environmental and lifestyle factors:
• Utilise already established longitudinal cohorts and establish new, longitudinal and population studies to investigate environment and lifestyle factors influencing asthma: exposures to air quality (indoor and outdoor air), allergens and microbes, urbanisation, occupation, climate, UV radiation, diet and nutrition, and direct skin contact [1-2, 11, 13].
• Explore active and passive tobacco smoke exposure as factors in developing and managing asthma [1-2, 14].
• The impact of environment and lifestyle factors on asthma exacerbations, especially for acute exacerbations and severe asthma [12-13].

6. Tools and models:
• Develop tools for complex data analyses: non-invasive imaging, cell culture, big data sharing platforms, European asthma registries and biobanks [10, 13-15].
• Design and validate models that mimic characteristics of asthma such as inflammation and exacerbations in humans, including better preclinical models for...
translational research in phenotyping, animal models and multi-scale airway modelling [1, 3, 10-11, 13].

Asthma services and care
The outcomes of research that develop the understanding of asthma needs to be communicated and used to inform the development of optimum asthma services, care pathways and professional-patient collaboration. Research in this area needs to assess current services and evaluate new services so that the best possible services with the best possible outcomes for the patient can be provided and be relevant for the context of the community and healthcare system [1].

Research gaps
1. Services and care programmes
   - Comparisons of asthma diagnosis, care pathways, asthma clinics (in countries that have them) and quality of care and quality of life between countries and settings, such as hospital, local doctor’s practices and community services, with international and longitudinal studies[1].
   - Assess the implementation and value of pulmonary rehabilitation programmes and best practice psychological support for asthma management [13, 15].
   - Implementation studies to learn the most efficient ways to adapt and transfer best practice care programmes: providing guidance on the establishment of integrated care pathways, developing local asthma physician, nurse and pharmacist networks, use of simple national guidelines, collaboration between primary care and specialists, providing patient-centred asthma education [15-16].
   - How to manage acute severe asthma in settings where emergency services and hospital are not accessible and in low-income countries [15-16].
   - The impact of European, national or regional programmes adapted for use in local or national contexts on healthcare spending and meeting locally identified gaps in asthma care [1].

3. Patient–professional partnership
   - Assess patient–professional communication in primary care practice, particularly in guided self-management, and developing patient–professional partnerships [11, 13-14].
   - Understand the challenges that professionals face when implementing asthma self-management, and how these knowledge, attitudinal and organisational barriers may be overcome [11, 15].
   - Understand and evaluate strategies for implementing supported self-management, with a focus on the educational needs of patients and skills training for professionals for ensuring that self-management is an integral, valued and monitored aspect of the long-term care of people with asthma [11, 15].

4. Patient involvement
   - Develop and assess systems for incorporating patient involvement in different roles and at all stages of asthma research, and measure the effectiveness and impact of these systems, different roles and involvement at different stages [13].

Diagnosis and monitoring
Accurate diagnosis and asthma monitoring ensures the appropriate care pathway, treatment and management of each person’s asthma [3, 11, 13]. Failure to diagnose or inaccurate diagnosis, due to the current lack of appropriate and precise diagnostic tests, and inadequate monitoring can have a huge impact on an individual’s quality of life [3, 11, 13-14]. Research is needed to ensure universal access and better approaches in diagnosis, with efficient ongoing monitoring of changes in the disease to prevent absenteeism, hospitalisation and asthma deaths [1, 11, 15].

Research gaps

1. Diagnostic tools
   - Low-cost, simple, and accurate diagnostic tools for use in primary care settings that can be distributed easily, and used repeatedly and regularly, especially in low-income countries [12-13, 17].
   - Tools that can identify differences between types of asthma and an update of the ICD-10 classification to ensure that professionals worldwide are using the same diagnostic criteria and treatments [14, 18].
   - Quick and accurate diagnosis of asthma within primary care settings across a person’s lifetime: practical algorithms that distinguish between recurrent wheeze and asthma in young children, and symptom-based tools for diagnosis in primary care [3, 12].

2. Improving diagnosis
   - Identify biomarkers that can be used to identify different asthma phenotypes/endotypes at the point of diagnosis [2].
   - Improvement of early diagnosis pathways and pathways for asthma diagnosis in patients presenting with other diseases, such as rhinitis and eczema; for example the impact of rapid referral for specialist consultation and definitive diagnosis [16].
   - Assessing strategies for improving earlier diagnosis in primary care [12].

3. Monitoring
   - The role of lung function testing and new ways of measuring airway inflammation non-invasively using breath analysis in the regular monitoring of asthma patients in primary care and in the assessment of severity and asthma control, including the routine incorporation of inflammatory diagnostics, such as exhaled feNO, eosinophilia in blood and sputum for diagnosis and monitoring [12-13].
   - Develop and assess mobile and telemonitoring technologies, such as mHealth and eHealth applications, to enable patients and physicians to monitor the individual’s asthma in daily life effectively, to inform when rescue medication is needed and to better understand the role of environmental exposure on asthma control [1, 13].
   - The role of other tools, as symptom-based questionnaires, in the regular monitoring of asthma patients in primary care and in assessment of severity and asthma control [12].

4. Quality of life
   - Standardise quality of life tools to monitor the real world impact of asthma on the individual, with evidence of the validity and usefulness of quality of life questionnaires when used for individual patients in routine primary care practice [12].
Treatment and management options

Selection of the best treatment for each person’s asthma will ensure good management and minimal impact of their asthma and their medication on their quality of life. Research is needed in a number of specific areas to advance personalised medicine and address exacerbation, infection reduction, self-management and adherence [1-3, 12, 14]. There is also a universal need for asthma drugs and inhalation devices that are available and affordable to all, including in low-income countries [15, 17].

Research gaps

1. New treatments
   - Drug development for: treatment-resistant asthma, to reverse corticosteroid resistance; to target small airways in severe asthma; using antibodies and antagonists that block or modify disease mechanisms, oncogenes and metabolic pathways [1, 3, 13, 15].
   - Drug treatments to prevent and treat acute exacerbations and treatment options for mild-to-moderate exacerbations in primary care settings [12-13].
   - Safe and effective biomarker-driven approaches to the therapy of severe asthma, through the identification of inflammatory and molecular phenotypes/endotypes, with novel specific therapies to benefit the individual patient (P4 (predictive, preventative, personalised and participatory) medicine) [1, 10, 13-15].
   - Investigate the properties of stem cells and their potential as a treatment approach [13].
   - Better target treatments and arrest the increasing prevalence of certain types of asthma, such as allergic and hyperresponsive (“brittle”) asthma, and with fewer side-effects than conventional drug treatments [3, 13-14].

2. Existing treatments
   - Assess existing drugs to identify the most effective add-on therapy option to inhaled corticosteroids in different sub-types of asthma, and how and when regular medication should be stepped down or stopped [12].
   - Assess the efficacy of existing and new drugs on different asthma phenotypes [2, 14].
   - Explore the influence of infections in early childhood and the long-term effects of anti-inflammatory treatment, and use of anti-viral drugs and vaccines [1, 13, 15].
   - Assess the impact of anti-microbial drugs to prevent and treat acute exacerbations [12-13].
   - Introduce and assess the impact of first line treatment with anti-inflammatory medication at the point of diagnosis [16].
   - Assess existing drugs to identify the most effective therapy options in low-income countries for both acute and maintenance treatment [12].

3. Drug delivery
   - Novel drug application methods, such as the inhalation of nanoparticle-based drugs and bioactive agents [13].
   - Appropriate inhalation devices to deliver exacerbation treatment [12-13].

4. Management tools
   - Simple tools and approaches to assess asthma control in primary care settings, including the identification of good and poor inhaler technique and strategies to ensure good technique [12-13].
Exhaled breath analysis for volatiles and temperature as a tool for measuring airway inflammation non-invasively to help improve management and monitoring of responses to existing and new therapies [3, 13].

5. Adherence
- Understand factors in adherence to treatment as a determinant of successful asthma management, and the impact of poor adherence to drug treatments. Key areas include adherence in adolescents with asthma; patients’ comprehension of asthma; different treatment strategies; treatment cost; patients’ concern about side effects in inhaled corticosteroids and other prescription treatments [2, 12, 14].

Preventing and curing asthma
Alongside diagnosis and treatment, efforts should be made to advance secondary prevention strategies and cure asthma that could benefit people both now and in the future. One aspect of this is to identify the barriers to prevention and cure, and to advance secondary prevention strategies to prevent asthma symptoms and exacerbations [6].

Research gaps
1. Prevention
- Intervention studies to evaluate primary and secondary preventive measures as an opportunity to prevent/reduce respiratory epithelial barrier damage [4].
- Understand the increase in prevalence of childhood asthma, and sub-types, such as allergic and hyperresponsive asthma, and develop efficient strategies for primary and secondary allergy and asthma prevention [4, 6, 8, 10-11].

2. Exacerbations
- Reduce the risk of severe asthma exacerbations by exploring the relationship between asthma, social, psychological and socio-economic factors and co-morbidity, especially psychological conditions, asthma COPD overlap syndrome (ACOS) and obesity [6, 12, 14].
- Understand the origins and triggers of asthma and exacerbations, specifically common cold viruses and environmental allergens [4-5, 11-12, 14].

3. Environment
- Distinguish between allergic, hyperresponsive and non-allergic asthma phenotypes when investigating environmental risk factors for asthma [1, 4, 11-12, 14].
- Understand the specific impact of smoking, indoor and outdoor air quality/pollution on asthma [8-9, 14].
- Develop and assess preventative work environments, including tools for full environmental control, in response to research on biological mechanisms experienced in high-risk professions, e.g. bakers, carpenters, painting, building, agriculture and hairdressing [4-5].

Government policy
Policy is underpinned by research, with studies informing the introduction or update and evaluation of local, regional and European government policy. Chronic conditions, such as asthma, have a societal and economic burden that can be limited, or potentially eradicated, through policies relating to asthma and asthma risk factors, such as indoor and outdoor air quality, including smoking and working environments [3]. However, asthma-
related policies will only be developed if the need and benefit of policy intervention is clearly evidenced by research.

Research gaps

1. Data collection and sharing
   - Epidemiological studies, accurate data collection and Europe-wide sharing on prevalence and incidence, and the reasons for disparities in different regions, countries and across Europe, with ongoing monitoring and comparison of prevalence, morbidity, hospitalisation and absenteeism, supported by European asthma registries [1-3, 13, 19-20].
   - Accurate data on the results and effects of recently implemented national asthma programmes in Europe [16].
   - Comparative studies between countries to assess national, regional and personal asthma programmes/plans [13, 15-16].
   - Comparative studies between countries evaluating the implementation and impact of national and EU policy focused on prevention, early diagnosis and treatment [1, 3].

2. Public health
   - Research on the effectiveness of public health interventions to tackle the greatest risk factors for chronic conditions, including lack of physical activity, tobacco smoke, diet and obesity [1-3, 13].
   - The impact of exposure to substances known to trigger asthma, such as in working environments (including schools), and the impact of strategies to regulate and control exposure [1-2, 13].

3. Health economics
   - Comparative health economics between countries and settings, such as hospital, local doctor’s practices and community services, with international and longitudinal studies, to identify impact and cost effectiveness [1-2].

It is important to note that whilst research is needed to inform government policy, policy is also needed to support research to ensure real-world changes for people with asthma. Governments need to support cross-boundary and interdisciplinary research and implementation with policy and funding [3, 13]. Research and policy can work together to close the gaps outlined in this document.

Conclusion

This document identifies the gaps in our understanding of asthma that need addressing to provide answers to the challenges of preventing, curing, treating and living with asthma. The information in this document, and the findings of all other EARIP work packages, will be used to develop an online survey that will enable key stakeholders in asthma research (researchers, clinicians, patients, patient organisations, industry and policymakers) to prioritise the most important research gaps that will deliver the biggest impact for people with asthma. The results of this survey, combined with a consensus workshop taking place at the European Respiratory Society’s International Congress 2015, will be used to produce an asthma roadmap with key priority areas for asthma research in Europe, to set the asthma research agenda, and make a compelling case for increased investment in asthma research in Europe.
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