

INAUGURAL LECTURE

Global strategies for reducing the burden from asthma

A report of a lecture given at The University of Edinburgh, Edinburgh, UK, October 1st 2012

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Abstract

Asthma is one of the most important chronic diseases in childhood. For several decades, a steady increase in prevalence has been observed worldwide. In the structural collaboration between the Centre for Population Health Services in Edinburgh and the Research Institute CAPHRI of Maastricht we investigated the possibilities for primary prevention of asthma in childhood. We found that a multifaceted approach might be effective in delaying or preventing asthma, whereas a mono-intervention does not seem to have such a protective effect. The most likely explanation is that the development of a multifactorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor.

Underdiagnosis of asthma is still a big problem in primary care. Most patients do not present bronchial symptoms to the general practitioner, even though they have decreased lung function, so they remain unknown and undiagnosed. However, patients who do present with respiratory problems and who have reduced lung function are not always recognised as such. We found that the perception of dyspnoea seems to determine, at least in part, the presentation to the general practitioner with symptoms.

These observations show that both the prevention of the development of asthma in early childhood, as well as case finding of asthma in adulthood, do not seem to be very effective in primary care. More research is needed to clarify what steps can be taken to reduce the global burden from asthma.

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Onno van Schayck is an Assistant Editor of the *PCRJ*. Following his Inaugural Lecture to the Centre for Population Health Sciences in October 2012, the Editors-in-Chief commissioned this article to celebrate the occasion and to give readers the opportunity to read about Professor van Schayck's contribution to primary care respiratory research over the last 25 years. We will publish summaries of other Inaugural lectures given by key figures in primary care respiratory medicine from time-to-time in future issues.

Introduction

In 1998 I was appointed as Professor of Medicine at the Departments of General Practice of both Maastricht University and Nijmegen University. Since 2008 the Research Institute CAPHRI of Maastricht University and the Centre for Population Health Services

of the University of Edinburgh have had a structural cooperation, especially in the area of childhood asthma. In 2010, I was invited to become Honorary Professor here at the Centre for Population Health Services in Edinburgh, and on October 1st, 2012 I had the honour to give my inaugural lecture at the University of Edinburgh.

My lecture focused on strategies for reducing the burden from asthma, covering the work of the research groups in Maastricht and Edinburgh, and especially the collaboration between these groups.

The burden of asthma

Asthma is one of the most important chronic diseases in childhood.¹ The prevalence of childhood asthma is high.² For several decades, a steady increase in prevalence has been observed worldwide.^{3,4} However, in some parts of the world, the first signs of stabilisation⁵ or even a decrease in prevalence² have been reported. Asthma poses a great burden on patients, their family members, health care

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services, and society. Asthma is the main cause of school absence.⁶ The number of asthma-related contacts and hospitalisations is high, which results in substantial costs of treating asthma (for instance 20.4% of the total health care costs in infants under the age of 1 year, and 24.1% in infants and children aged 1-14 years in the Netherlands).⁷

Research interests

a) The deleterious effects of continuous bronchodilatation

My research started in the late 1980s/early 1990s with the discovery that continuous use of bronchodilators in asthma resulted in deleterious effects, especially when no anti-inflammatory medication is used.⁸⁻¹¹ This finding was especially important for primary care as bronchodilators were until then often used as the sole medication for asthma in general practice. It stimulated efforts to ensure the early introduction of inhaled steroids in asthma as well as the use of combination drugs (inhaled long-acting bronchodilators together with corticosteroids in one device), which are nowadays the mainstay of asthma treatment both in primary and secondary care. But it also stimulated efforts to obtain an early diagnosis of asthma in order to avoid untreated progression. Moreover, it stimulated in our research groups the investigation of non-pharmacological preventive measures such as inhalant and food allergen avoidance in order to prevent asthma in genetically predisposed infants.

b) Risk factors for asthma

The risk of developing asthma is determined by genetic, as well as environmental, factors. Because specific genes for asthma have not been fully identified, the focus has been on a family history of

asthma. This approach is especially useful in primary care, with family doctors having access to all information of all family members. With regard to environmental factors, passive smoking and house dust mite, cat, and dog allergens are thought to be associated with sensitisation and allergic disease, whereas breast-feeding is thought to have a protective effect.¹²⁻¹⁶

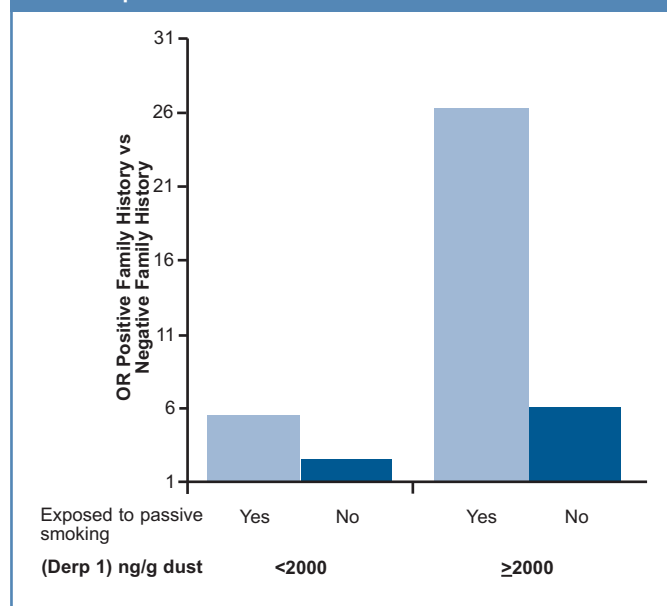
In the late 1990s, we began in the Netherlands a prospective birth cohort with almost 800 children recruited prenatally in primary care. Family history of asthma as determined in primary care was a significant risk factor for the occurrence of respiratory tract and asthma-related morbidity during the first 2 years of life. A particularly intriguing finding was that the relationship between a positive family history and respiratory morbidity was modified by postnatal exposure to parental smoking, house dust mite and breast-feeding.¹⁷ Parental smoking and house dust mite exposure increased the effect of a positive family history on wheezing. Moreover, when these infants were exposed to both parental passive smoking and house dust mite, this increase was even more pronounced (see Figure 1).

c) The interaction between genotype and environment – childhood asthma

On the basis that the interaction between genotype and environment plays a crucial role, it is reasonable to assume that reducing exposure to potentially relevant allergens should lead to a reduction in the risk of asthma. This concept is, however, mainly based on observations made in the early 1980s, which found that dramatic reduction of house dust mite (*Derp 1*) exposure, by moving children with asthma into a hospital or to a mountain sanatorium, could considerably reduce symptoms of asthma.^{18,19} But translating these secondary prevention findings into feasible-to-deliver primary prevention strategies had proved extremely difficult, as demonstrated by the disappointing results of large, carefully designed, randomised clinical trials of house dust mite avoidance strategies in birth cohorts.^{20,21} However, this is also true in relation to the more direct comparison of secondary prevention strategies.²² The reasons behind their lack of effectiveness remain unclear, however.

Since people with asthma are usually sensitised to more than one allergen, the successful elimination of one allergen is only likely to have limited clinical benefit. It is therefore logical, although experimentally somewhat complex, to test the efficacy and effectiveness of multifaceted approaches to allergen avoidance. The main potential disadvantage of a multifaceted approach is that it is difficult to disentangle the effects of one intervention from those of another. A number of randomised clinical trials have been conducted in new-born children to investigate whether the development of asthma can be prevented or delayed by reducing exposure to inhalant allergens, feeding allergens, or both. Although the majority of these studies investigated only one measure, others have used a multifaceted approach. Because there was no published systematic review on possible differences between these two approaches, researchers from Maastricht and Edinburgh together performed a search of the Cochrane Central Register of Controlled trials. In total, 10 high-quality studies (enrolling 3473 patients) were included, of

Figure 1. Interactive effect on wheezing of exposure to passive smoking and to house dust mite. Used with permission from the editor of *J Allergy Clin Immunol*. From Kuiper *et al. JACI* 2007;120:388-95¹⁷



which 1124 had a multifaceted intervention design²³⁻²⁵ and 2349 had a mono-intervention design.^{21,26-31} Several studies had repeated measurements on different ages of the children. The results suggested that a multifaceted approach might be effective in delaying or preventing asthma, whereas a mono-intervention does not seem to have such a protective effect. The most likely explanation is that the development of a multifactorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor.^{32,33}

d) Detecting and diagnosing adult asthma

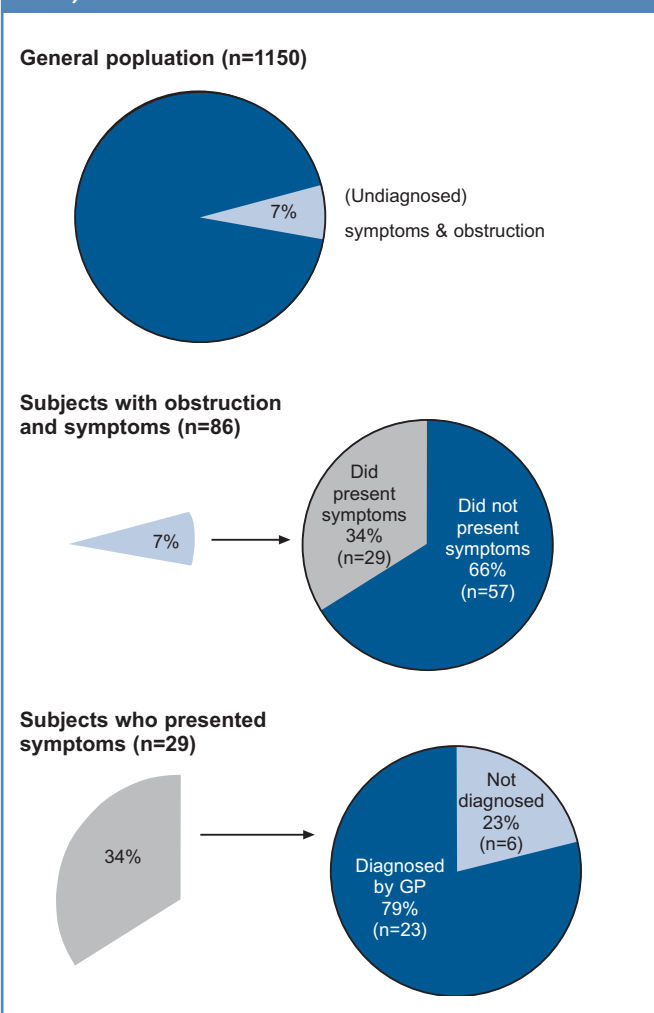
Asthma is not only a problem in childhood, but also in adulthood. In childhood the major challenge is to prevent the development of asthma. In adulthood the major challenge is to detect and diagnose asthma as early as possible. There is still an increase in the morbidity and mortality of adult asthma,^{34,35} which seems to apply to patients diagnosed as having asthma as well as to those in whom a diagnosis of asthma has not yet been made.³⁶ Under-diagnosis and consequent undertreatment might be important in the increased morbidity and mortality of asthma.^{37,38} Early detection and treatment of asthma might improve the long-term prognosis of these patients¹⁰ and this secondary prevention may also prevent irreversible loss of function.³⁹ It is not clear whether the physician or the patient is to blame: is under-diagnosis of asthma caused by the physician who does not adequately interpret the symptoms presented to him (or her)? Or is it caused by the patient who does not present his or her symptoms to the physician?⁴⁰ In the latter case, it is not clear why a patient does not present his or her symptoms to the general practitioner. Is this caused by poor perception of the symptom of dyspnoea in particular?⁴¹⁻⁴³

Our research group from the Department of General Practice in Nijmegen investigated several questions:

- 1. Is underdiagnosis of asthma caused by the physician or is it caused by the patient?
- 2. If it is caused by the patient why do patients not present their symptoms to their physicians?

We recruited a random sample of 1155 subjects aged 25-70 selected from 10 urban and rural general practices in the eastern part of the Netherlands.⁴⁴ In the Netherlands, all subjects in the general population are registered with a general practitioner. These 1155 subjects went through an extensive screening programme which included several measurements of forced expiratory volume in one second (FEV₁) and a questionnaire which included a question on whether they had ever presented with respiratory problems such as wheezing, coughing, or dyspnoea to the general practitioner.³⁶ Special attention was paid to the number of subjects with objective airway obstruction and symptoms suggestive of asthma (wheezing, recurrent coughing, or dyspnoea) to investigate further under-presentation and under-diagnosis in this group of higher risk subjects. FEV₁ was measured twice in a four-month period under standard conditions. The medical files at the surgeries of the general practitioner were analysed for asthma-related consultations. All files were checked if either asthma-related complaints and symptoms, or prescribed asthma drugs, or both, were present. All asthma-related

Figure 2. Underdiagnosed asthma in primary care (based on data from van Schayck CP, *et al. Thorax* 2000;55: 562-5)⁴⁴



consultations were scored.

Of the random sample of 1155 subjects, 86 (7%) had objective airflow obstruction as well as symptoms suggestive of asthma (see Figure 2).⁴⁴ The question of the extent to which the presentation of symptoms by the patient to the general practitioner is picked up and translated into a diagnosis is preceded by another question – namely, whether or not the patient presents the symptoms to the general practitioner. From the results of this study it appears that most patients (66%) do not present bronchial symptoms to their general practitioner, even though they have decreased lung function, so they remain unknown and undiagnosed. However, patients who do present with respiratory problems and who have reduced lung function are not always recognised as such. In this group, the interpretation of the complaint at presentation has probably been a wrong one. In looking for possible causes of under-diagnosis of asthma, this study indicated that the problem is mainly due to the patient and only partly to the general practitioner.

For the second question, a random sample of subjects with objective lung function was selected. Of the 86 subjects with

reduced lung function, 47 were further investigated to determine their ability to perceive dyspnoea by assessing the change in Borg score during a histamine provocation test carried out using the method described by Brand *et al.*⁴¹ After the measurements the subjects were classified into two groups: "good perceivers", in whom a decrease in FEV₁ was accompanied by an increase in the Borg score; and "poor perceivers", in whom there was a 20% decrease in FEV₁ or an observed decrease in FEV₁ after the last doubling dose of 32 mg/ml histamine which was not accompanied by any increase in the Borg score.⁴¹ It was then determined whether or not patients in the two groups with reduced lung function had consulted their general practitioner with asthma-related symptoms.

We investigated whether the ability to perceive airway obstruction determines whether or not a patient visits his or her general practitioner with concomitant airway symptoms (dyspnoea). This study showed that the perception of dyspnoea seems to determine, at least in part, the presentation to the general practitioner with symptoms. Of the subjects with bronchial obstruction who did visit the general practitioner with airways symptoms, 6% had poor perception of dyspnoea; however, of the subjects who did not visit the general practitioner in spite of bronchial obstruction, the percentage with a poor perception of dyspnoea was more than four times higher at 26%.⁴⁴

Future research

These observations show that both prevention of the development of asthma in early childhood, as well as case finding of asthma in adulthood, do not seem to be very effective in primary care. More research has to be done to clarify what steps can be taken to reduce the global burden from asthma.

There are at least three topics that require more attention in the coming years:

- Early detection of (high-risk) asthma in infancy by means of non-invasive measurements in exhaled breath (e.g. Exhaled Breath Condensate [EBC] and Volatile Organic Compounds [VOCs]).
- Studying gene-environment interaction in large cohorts with well-defined phenotypes of asthma.
- Studying the effects of (exposure to) smoking during pregnancy, infancy and adults, by using large cohorts of general practice registries.

All three of these topics are being studied as part of the structural cooperation between the Research Institute of Maastricht University and the Centre for Population Health Services of the University of Edinburgh.

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