Epidemiology of Asthma in the Netherlands with special reference to Childhood

J. Hess

ISBN: 90-9016524-X

Printed by Pasmans Offsetdrukkerij bv, Den Haag

EPIDEMIOLOGY OF ASTHMA IN THE NETHERLANDS WITH SPECIAL REFERENCE TO CHILDHOOD

Epidemiologie van astma in Nederland
in het bijzonder met betrekking tot kinderen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 19 februari 2003 om 13:45 uur

door
Johanna Hess
geboren te 's-Gravenhage

Promotiecommissie

Promotoren:

Prof.dr. J.C. de Jongste

Prof.dr. E.J. Duiverman

Overige leden:

Prof.dr. H.A. Büller

Prof.dr. A. Hofman

Prof.dr. H.C. Hoogsteden

Aan Rombout, Merel en Nander

Ter nagedachtenis aan mijn ouders

CONTENTS

CHAPTER 1
GENERAL INTRODUCTION

Asthma, treatment associated with excess mortality

Asthma is a disease characterised by airway narrowing. Consequently the primary aim of treatment has been for long to achieve bronchodilatation and treatment relied heavily on short acting bronchodilators. In the early to mid 1960s a temporary increase in mortality from asthma was noted in England and Wales, Australia, and New Zealand, especially in the age range 5-34 years [1-3]. This might have been the result of the introduction of pressurised aerosols containing the non-selective β-adrenergic receptor agonists isoprenaline and orciprenaline [1-4]. β-receptor systems are present in various organs, most importantly in heart and lung tissues. These drugs gave quick bronchodilatation, but could also lead to adverse cardiovascular effects, such as increased cardiac output, tachycardia, and hypoxemia. At the time it was shown that administration of non-selective β-agonists was followed by a decrease in arterial oxygen tension in chronic asthmatic patients [4], and it was thought that high doses in conjunction with frequently repeated inhalations might have caused a lethal outcome [3,4]. After warnings were given of the possible hazards of these pressurised aerosols, excessive mortality fell.

In the mid-seventies again an increase in mortality from asthma occurred, first observed in New Zealand in age group 5-34 years [5], then in other countries and also in other age groups [6-10] (figure 1.1). In New Zealand the total death rate doubled to 8 per 100,000 population in 1980, whereas the increases in Australia, England & Wales, Canada, and the United States were smaller and from a lower level. Total death rates in 1980 ranged from 1.5 (United States) to 3.7 (Australia) [6]. The introduction of the ninth revision of the International Classification of Diseases in 1979 may have affected the death rates to some extent. Unlike the eighth revision, death certificates that gave

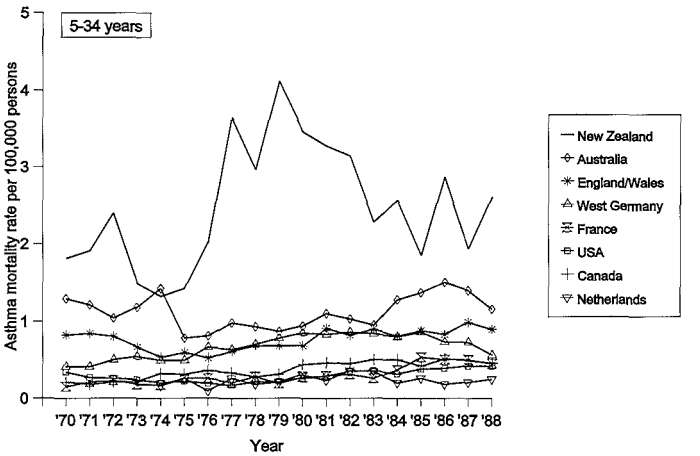

Figure 1.1 Mortality from asthma per 100,000 persons in age group 5-34 years in various countries, period from 1970 to 1988.

Source: Sears [10]; data from the Netherlands (1974-1988), Hess.

'bronchitis' or 'emphysema' as underlying cause were classified as 'asthma', when also mention was made of 'asthma' [6,7]. Sweden and Denmark [6,9] did not implement the ninth revision but showed nevertheless increased asthma death rates. Hence an increase in prevalence, severity or case fatality were suggested as explanatory factors [5-7]. This was a worrying development in view of the increased therapeutic possibilities with the introduction of prophylactic drugs such as sodium cromoglycate and inhaled corticosteroids, as well as new bronchodilator drugs such as selective β_2-agonists and sustained-release theophyllines. After the initially proposed subclassification of β-receptors in β-1-receptors, present in heart and adipose tissue, and β-2-receptors, present in airways, blood vessels, and uterus [11], it was demonstrated that in the smooth muscle of the human lung the β-receptors were entirely of the β_2-subtype [12,13]. The selective β_2-agonists effectively relax smooth muscle in the airways, inducing rapid bronchodilatation. They became first choice bronchodilators in asthma.

'The asthma paradox'

The coincidence of improving treatment with increasing mortality was referred to as the asthma paradox [7]. Asthma had been classified as a condition amenable to treatment, and it was to be expected that mortality should have been declining in view of the rising sales of all forms of anti-asthma treatment. It was hypothesised that treatment produced benefits but also risks, both indirectly by relying too much on bronchodilator drugs and hence delaying appropriate treatment, and directly [5,7,14]. Factors related to direct risks could have been tolerance to the bronchodilating action of the β-agonists, β-agonists-induced arrhythmias, or an additive toxic effect with oral theophyllines inducing cardiac arrest. However, studies did not provide support for a causal relationship of treatment with the increasing mortality and morbidity from asthma. Further, the possibility of drug-induced increase in bronchial hyperresponsiveness and consequently worsening of asthma was suggested [14]. Nevertheless, the increase in mortality in New Zealand was linked to the β_2-agonist fenoterol. It was not clear whether adverse effects could be ascribed to the class of drugs. Fenoterol appeared to have a similar effect on lung function and airway reactivity as the β_2-agonists salbutamol and terbutaline, but the adverse effects of cardiovascular changes, hypokalaemia, and tremor were substantially greater, suggesting a relatively greater potency [15]. Cardiovascular changes induced by fenoterol may be enhanced by hypoxemia, which is a complicating factor in a severe asthma attack [16].

Increase in asthma morbidity and β-agonists

Data on trends in morbidity from asthma became available. Increasing hospital admission rates in various countries were reported, especially in children [17-22] (figure 1.2). Since the mid-sixties, the hospital admission rate in age group 0-14 years showed a 10-fold increase in New Zealand, a 6.6-fold increase in England & Wales, a 4-fold increase in Canada, and a 3-fold increase in the United States over a fifteen-year period [19]. Also, indications for an increasing prevalence of asthma were reported [23-28]. As with asthma mortality and hospital admission rates, prevalence figures varied throughout the world, e.g. in the early eighties between 1.8% and 13.5% [10,29] (figure

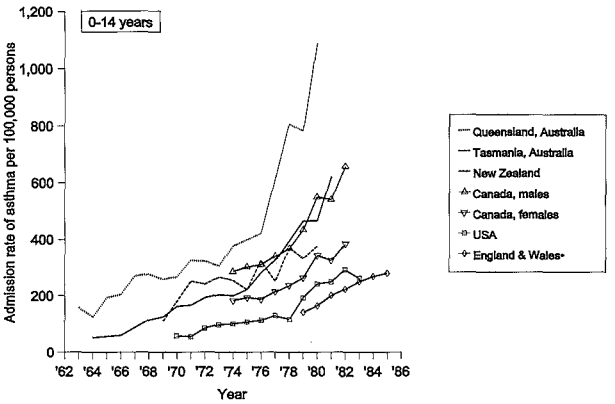

Figure 1.2 Hospital admissions for asthma per 100,000 persons in age group 0-14 years in various countries, period from 1963 to 1985. Source: Australia and New Zealand, Mitchell [19]; Canada, Bates [20]; USA, Evans [21]; England & Wales (*age group 5-14 years), Mitchell [22].

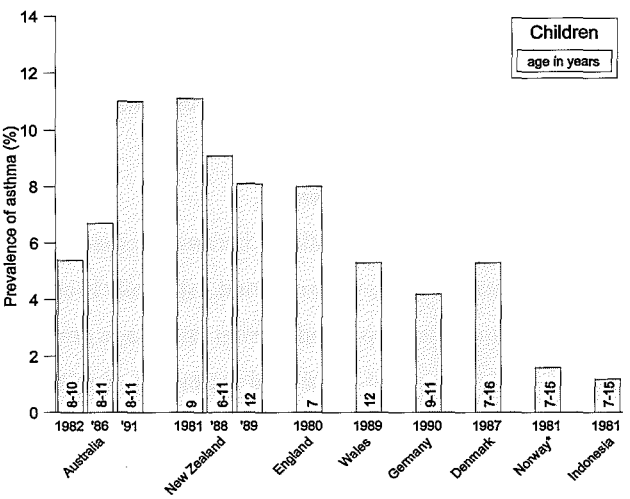

Figure 1.3 Prevalence of current asthma (%) in populations of children in various countries, period from 1980 to 1991.
Source: Woolcock [29]; *, Sears [10].

1.3), partly because of different methods used and different populations studied. However, worldwide substantial increases in the prevalence of asthma in schoolchildren and adolescents were reported, for example in the United States [23], England [24,25], New Zealand [26], Finland [27], and Australia [28]. This could not be explained by a change in diagnostic fashion and appeared for most part to be real. Moreover, in view of the increased hospital admissions and the increased sales and use of anti-asthma drugs [30,31], it was suggested that the prevalence of severe asthma had increased, possibly due to chronic use of high-dose inhaled bronchodilator β-agonist [10]. That an increasing use of β-adrenergic receptor agonists was contributing to the worldwide increase in asthma morbidity [10,32] was, however, questioned [33]. The quantitative use of β-agonists may have reflected severity of asthma, fenoterol used in particular by patients with more severe asthma and at higher risk of dying. Adverse effects of β_2-agonists have again been under debate, focusing on the β_2-agonist fenoterol as a main cause of the excess asthma deaths in New Zealand in the period 1976-91 [34-36]. The availability of the potent bronchodilator fenoterol may have contributed to delays in seeking appropriate care, but various factors associated with health care are likely to have contributed to the epidemic of asthma deaths in New Zealand [37]. Increased use of inhaled corticosteroids probably contributed to its termination [35,37].

Asthma, from a 'spastic' disease to an 'inflammatory' disease

The concept of the pathogenesis of asthma has changed [38]. Rather than a disease of abnormal airway smooth muscle contractility, asthma is now regarded as an inflammatory disorder of the airways, where complex interaction of numerous resident and infiltrating cells in the airway walls are responsible for airway inflammation and airway narrowing [38-40]. Even in a clinically early stage of disease infiltration of inflammatory cells in the airway wall was observed [41]. The individual inflammatory cells and mediators have different pathophysiological effects. Mast cells are in particular involved in the acute inflammatory response to triggers, and eosinophils, lymphocytes, and macrophages play an important part in the chronic inflammatory response. A central role is attributed to the T-lymphocytes and their cytokine mediators

[40]. The inflammatory processes give rise to bronchoconstriction, airway mucosal oedema, and mucus hypersecretion leading to bronchial hyperresponsiveness, asthma symptoms and variable airway obstruction. The airway inflammation may result in chronic structural changes in the airways and irreversible airway obstruction. A clear definition of asthma has been lacking, but the recognition of inflammation as the characteristic feature in asthma is now universally agreed and has been included in various definitions of asthma [29].

Management guidelines

The rising mortality and morbidity from asthma in the seventies and eighties prompted to develop guidelines which consolidated in international consensus statements on diagnosis and management of asthma [42,43], and led to the Global Initiative for Asthma (GINA) by collaboration between the National Heart, Lung, and Blood Institute and the World Health Organization. GINA published the global strategy for asthma management and prevention report in 1995 and produced regular updates [44].

The definition of asthma given by GINA was as follows: "Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli."

GINA emphasised the importance of preventive treatment directed to the inflammatory processes in the airways. Treatment primarily involved anti-inflammatory drugs, especially corticosteroids, with bronchodilators as relief medication. Instituting treatment with inhaled steroids in newly diagnosed asthmatic patients proved to have better clinical results compared to treatment with bronchodilators only [45,46]. Also,

steroids proved to have better clinical results in asthmatic patients already on maintenance treatment with β_2-agonists when compared to placebo or inhaled anticholinergics [47-49]. Early intervention with inhaled steroids showed beneficial effects in terms of lung function [50,51], and is considered especially important as it may protect against persistent symptoms and consequent decline in lung function. Delayed introduction showed poorer responses to treatment [51-53]. The recommendations of early intervention with inhaled steroids with respect to both severity and onset of asthma have, however, raised concerns about the possible adverse effects. These may include accelerated bone loss in adults and growth retardation in children [54,55], especially when inhaled steroids are used in high doses or for prolonged periods. This pointed to the need of monitoring the patient for such potential side effects. It has become clear that the inflammatory process in asthma leads to permanent changes in lung function by an altered structure of the bronchial wall known as airway remodelling [56], which is already present in an early stage of the disease. The inflammatory process can be directly assessed by analysing bronchial biopsies. Biopsy studies in adults reported that treatment with inhaled steroids reduced the numbers of inflammatory cells, and that bronchial epithelial damage may be restored [57]. The efficacy of inhaled corticosteroids in preventing or controlling the various other aspects of airway remodelling is not yet clear.

Impact of treatment on asthma mortality and morbidity

It was suggested that inhaled corticosteroids could reduce the risk of fatal and near-fatal asthma [58,59]. Likewise, regular treatment with inhaled corticosteroids reduced the risk of hospitalisation for asthma [60]. From large population studies a reduction in mortality and hospital admission rates in the nineties have been reported from New Zealand and the United States [37,61]. Swedish studies showed the same for childhood admissions [62,63], which findings were ascribed to the increased use of inhaled steroids.

Classification problems

The observed trends in mortality and morbidity from asthma in different parts of the world were reason to analyse mortality data and hospital admission data in the Netherlands. However, when focusing on asthma only, there are a few problems like diagnostic accuracy, nosology, and shifts in diagnostic labelling. Asthma may present with symptoms of cough, wheeze, shortness of breath and chest tightness, and with airflow limitation. These variables are not specific. Studies on death certificates indicated the highest accuracy of asthma diagnosis under the age of 44 years, accuracy declining with increasing age [64,65]. Especially in the elderly, accuracy of asthma death certification appeared to be low, other respiratory disorders and medical problems complicating the accurate identification of the cause of death [66]. Also in the very young it is difficult to distinguish between asthma and other obstructive respiratory diseases with asthma-like symptoms [67,68]. Prospective studies were set up with the aim to clarify the natural history of asthma in childhood [69-71]. In the Netherlands, asthma was for long not viewed as a separate disease, but was viewed along with chronic bronchitis and emphysema as part of a disease-entity named 'chronic non-specific lung disease' (CNSLD), in Dutch "chronische aspecifieke respiratoire aandoeningen" ("CARA"). Chronic bronchitis and emphysema together are usually referred to as chronic obstructive pulmonary disease (COPD). In contrast to other countries, the umbrella-term "CARA" was often used in the Netherlands as a diagnostic term, rather than making a distinction between asthma and COPD [72,73]. Recently, it was shown that an increased longitudinal decline in lung function, thought to be characteristic for COPD, can occur in asthma as well, thus making asthma a risk factor for COPD [74].

Asthma in early life

In infancy, respiratory symptoms often appear to be transient [69-71]. Lower levels of lung function prior to the illness may contribute as a mechanical factor [70]. In young children the symptom of wheeze is the classic expression of variable airflow obstruction in asthma. It is now thought that there are several distinct wheezing phenotypes in

childhood at different ages with different clinical expressions [70,75,76]. Viral infections may cause transient wheeze in infants, nevertheless most childhood asthma begins in infancy, but when should wheezing be labelled 'asthma'? [77]. Also, in school age children distinction between 'wheezy bronchitis' and asthma is difficult. Concern about underdiagnosis and undertreatment of asthma and overtreatment with antibiotics in childhood [68,78], could have favoured diagnostic labelling of asthma. An increased use of asthma as a diagnostic label in schoolchildren in the late eighties has been reported in the UK [79].

Analysis of Dutch data

In view of the problems of a clear-cut asthma label, we thought it essential to extend the analysis of the Dutch data on asthma to other obstructive airway disorders. We obtained mortality and morbidity data on asthma and COPD in the total population, according to the International Classification of Diseases (ICD) codes. COPD comprises the codes for bronchitis not specified as acute or chronic, chronic bronchitis, emphysema, and chronic obstructive airway disease not classified elsewhere. Furthermore, data on acute bronchi(oli)tis and on pneumonia and influenza in children were analysed as well. There might be a relationship between respiratory syncytial virus bronchiolitis and asthma [80-83], and between pneumonia and asthma [84], but the nature is not clear. It is questioned whether asthma predisposes for these infections or occurs as a result. By including these diseases, we estimated the true respiratory morbidity in childhood.

'COPD' in children

Classical COPD in adults refers to chronic bronchitis and emphysema, but COPD usually includes the codes for 'bronchitis' and 'chronic obstructive airway disease', covered by the Dutch diagnostic "CARA" term, as well. In this sense, we use the term 'COPD' in children. We note that it is not equivalent to the term 'paediatric COPD' which has been proposed by Avital c.s. and refers to the chronic obstructive lung diseases cystic fibrosis, bronchiolitis obliterans, primary ciliary dyskinesia and bronchiectasis [85].

Scope of this thesis

The aim of this thesis is to examine trends in mortality and morbidity attributed to asthma in the Netherlands in the light of the changing concepts of asthma and the improved pharmacotherapy, against the background of other airway disorders. We analysed national statistics on asthma and COPD from 1980 to 1999, which data are presented in the first part of the thesis. Chapter 2 presents the data on mortality in different age groups. Chapter 3 presents the data on hospital admissions in different age groups. Complementary, chapter 4 presents trends in consultations and prescriptions of anti-asthma drugs in patients having ambulatory care for asthma and COPD over the period 1981 to 1993, reflecting prevalence and (changes in) disease management in the Netherlands. Chapter 5 describes the pharmacotherapy for asthma in the Netherlands from 1999 through 2001.

The second part of this thesis deals with clinical registration on asthma in children aged 0-4 years, carried out at the Juliana Children's Hospital in The Hague. In this age group, the rising morbidity from asthma is of great concern. Studies pointed to increasing hospital admissions for asthma especially in children aged 0-4 years [86-88], which age group appeared to be at highest risk for hospital readmissions as well [88-90]. Early recognition of risk of (severe) asthma in clinical practice and improvement of asthma management could help to reduce morbidity in children. The aim of the registration study was to examine prognostic characteristics of asthma diagnosis, to identify predisposing risk factors related to exacerbations and hospital admissions, and to assess whether threshold of admission and severity of episode differed in first admissions and readmissions.

References

1. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. Br Med J 1968; i: 335-339.
2. Inman WHW, Adelstein AM. Rise and fall of asthma mortality in England and Wales in relation to use of pressurised aerosols. Lancet 1969; ii: 279-285.
3. Stolley PD, Schinnar R. Association between asthma mortality and isoproterenol aerosols: a review. Prev Medicine 1978; 7: 519-538.
4. Tai E, Read J. Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. Thorax 1967; 22: 543-549.
5. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: a new epidemic in New Zealand. Br Med J 1982; 285: 771-774.
6. Sly RM. Increases in deaths from asthma. Ann Allergy 1984; 53: 20-25.
7. Burney PGJ. Asthma mortality in England and Wales: evidence for a further increase, 1974-84. Lancet 1986; ii: 323-326.
8. Bousquet J, Hatton F, Godard P, Michel FB. Asthma mortality in France. J Allergy Clin Immunol 1987; 80(\$uppl): 389-394.
9. Juel K, Pedersen PA. Increasing asthma mortality in Denmark 1969-88 not a result of a changed coding practice. Ann Allergy 1992; 68: 180-182.
10. Sears MR. Epidemiology. In: PJ Barnes, IW Rodger, NC Thomson, eds. Asthma: Basic Mechanisms and Clinical Management, second edition. London: Academic Press Limited, 1992, pp. 1-19.
11. Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG. Differentiation of receptor systems activated by sympathomimetic amines. Nature 1967; 214: 597-598.
12. Zaagsma J, van der Heijden PJCM, van der Schaar MWG, Bank CMC. Comparison of functional β-adrenoceptor heterogeneity in central and peripheral airway smooth muscle of guinea pig and man. J Receptor Research 1983; 3: 89-106.
13. Carstairs JR, Nimmo AJ, Barnes PJ. Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. Am Rev Respir Dis 1985; 132: 541-547.
14. Mitchell EA. Is current treatment increasing asthma mortality and morbidity [editorial]? Thorax 1989; 44: 81-84.
15. Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. Lancet 1990; 336: 1396-1399.
16. Bremner P, Burgess CD, Crane J, McHaffie D, Galletly D, Pearce N, Woodman K, Beasley R. Cardiovascular effects of fenoterol under conditions of hypoxaemia. Thorax 1992; 47: 814-817.

17. Anderson HR. Increase in hospitalisation for childhood asthma. Arch Dis Child 1978; 53: 295-300.

18. Jackson RT, Mitchell EA. Trends in hospital admission rates and drug treatment of asthma in New Zealand. NZ Med J 1983; 96: 728-730.

19. Mitchell EA. International trends in hospital admission rates for asthma. Arch Dis Child 1985; 60: 376-378.

20. Bates DV, Baker-Anderson M. Asthma mortality and morbidity in Canada. J Allergy Clin Immunol 1987; 80(suppl): 395-397.

21. Evans R III, Mullally DI, Wilson RW, Gergen PJ, Rosenberg HM, Grauman JS, Chevarley FM, Feinleib M. National trends in the morbidity and mortality of asthma in the US. Prevalence, hospitalization and death from asthma over two decades: 1965-1984. Chest 1987; 91(suppl): 65S-74S.

22. Mitchell EA, Anderson HR, Freeling P, White PT. Why are hospital admission and mortality rates for childhood asthma higher in New Zealand than in the United Kingdom? Thorax 1990; 45: 176-182.

23. Gergen PJ, Mullally DI, Evans R III. National survey of prevalence of asthma among children in the United States, 1976 to 1980. Pediatrics 1988; 81: 1-7.

24. Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child 1989; 64: 1452-1456.

25. Burney PGJ, Chinn S, Rona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973-86. Br Med J 1990; 300: 1306-1310.

26. Shaw RA, Crane J, O'Donnell TV, Porteous LE, Coleman ED. Increasing asthma prevalence in a rural New Zealand adolescent population: 1975-89. Arch Dis Child 1990; 65: 1319-1323.

27. Haahtela T, Lindholm H, Björkstén F, Koskenvuo K, Laitinen LA. Prevalence of asthma in Finnish young men. Br Med J 1990; 301: 266-268.

28. Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. Br Med J 1991; 302: 1116-1118.

29. Woolcock AJ, Peat JK. Definition, classification, epidemiology and risk factors for asthma. In: O'Byrne P, Thomson NC, eds. Manual of asthma management. London: WB Saunders Company Ltd, 1995:3-27.

30. Keating G, Mitchell EA, Jackson R, Beaglehole R, Rea H. Trends in sales of drugs for asthma in New Zealand, Australia, and the United Kingdom, 1975-81. Br Med J 1984; 289: 348-351.

31. Bosco LA, Knapp DE, Gerstman B, Graham CF. Asthma drug therapy trends in the United States, 1972 to 1985. J Allergy Clin Immunol 1987; 80(suppl): 398-402.

32. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, Yates DM, Lucas MK, Herbison GP. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990; 336: 1391-1396.

33. Wever AMJ, Wever-Hess J. β-adrenerge agonisten en sterfte en morbiditeit wegens astma. Ned Tijdschr Geneeskd 1992; 136: 460-465.

34. Lanes SF, Birmann B, Raiford D, Walker AM. International trends in sales of inhaled fenoterol, all inhaled β-agonists, and asthma mortality, 1970-1992. J Clin Epidemiol 1997; 50: 321-328.

35. Suissa S, Ernst P. Optical illusions from visual data analysis: example of the New Zealand asthma mortality epidemic. J Clin Epidemiol 1997; 50: 1079-1088.

36. Time trends in fenoterol and asthma deaths: optical illusion or reality check? Letter to the Editors. J Clin Epidemiol 1998; 51: 633-635.

37. Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand: what lessons have been learned? Thorax 1995; 50: 303-311.

38. Kay AB. Asthma and inflammation. J Allergy Clin Immunol 1991; 87: 893-910.

39. Lee TH, Lane SJ. The role of macrophages in the mechanisms of airway inflammation in asthma. Am Rev Respir Dis 1992; 145: S27-S30.

40. Stirling RG, Chung KF. New immunological approaches and cytokine targets in asthma and allergy. Eur Respir J 2000; 16: 1158-1174.

41. Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. Am Rev Respir Dis 1993; 147: 697-704.

42. Warner JO, Götz M, Landau LI, Levison H, Milner AD, Pedersen S, Silverman M. Management of asthma: a consensus statement. Arch Dis Child 1989; 64: 1065-1079.

43. International consensus report on the diagnosis and management of asthma. Clin Exp Allergy 1992; 22(Suppl 1): 1-72.

44. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention NHLBI/WHO workshop report. National Institutes of Health, National Heart, Lung, and Blood Institute. Bethesda, Maryland, USA. 1995; Publication No. 95-3659.

45. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Reinikainen K, Selroos O, Sovijärvi A, Stenius-Aarniala B, Svahn T, Tammivaara R, Laitinen LA. Comparison of a β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991; 325: 388-392.

46. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β_2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. J Allergy Clin Immunol 1992; 90: 32-42.

47. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990; 142: 832-836.

48. Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF, and the Dutch Chronic Non-Specific Lung Disease Study Group. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992; 146: 547-554.

49. Kerstjens HAM, Brand PLP, Hughes MD, Robinson NJ, Postma DS, Sluiter HJ, Bleecker ER, Dekhuijzen PNR, de Jong PM, Mengelers HJJ, Overbeek SE, Schoonbrood DFME, and the Dutch Chronic Non-Specific Lung Disease Study Group. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. N Engl J Med 1992; 327: 1413-1419.

50. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Selroos O, Sovijärvi A, Stenius-Aarniala B, Svahn T, Tammivaara R, Laitinen LA. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994; 331: 700-705.

51. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994; 88: 373-381.

52. Selroos O, Pietinalho A, Löfroos A-B, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest 1995; 108: 1228-1234.

53. Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder PGH, Postma DS, and the Dutch CNSLD study group. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? Chest 1996; 110: 35-41.

54. Drazen JM, Israel E. Treating mild asthma - when are inhaled steroids indicated [editorial]? N Engl J Med 1994; 331: 737-739.

55. Foucard T. Aggressive treatment of childhood asthma with local steroids. Good or bad? Allergy 1996; 51: 367-371.

56. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000; 161: 1720-1745.

57. Barnes NC, Burke CM, Poulter LW, Schleimer RP. The anti-inflammatory profile of inhaled corticosteroids: biopsy studies in asthmatic patients. Respir Med 2000; 94(suppl F): S16-S21.

58. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, Boivin J-F, McNutt M, Buist AS. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. JAMA 1992; 268: 3462-3464.

59. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000; 343: 332-336.

60. Blais L, Suissa S, Boivin J-F, Ernst P. First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma. Thorax 1998; 53: 1025-1029.

61. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997; 277: 887-891.

62. Wennergren G, Kristjánsson S, Strannegård I-L. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in the prevalence of asthma. J Allergy Clin Immunol 1996; 97: 742-748.

63. Strömberg L. Decreasing admissions for childhood asthma to a Swedish county hospital. Acta Paediatr 1996; 85: 173-176.

64. A subcommittee of the BTA Research Committee. Accuracy of death certificates in bronchial asthma. Thorax 1984; 39: 505-509.

65. Sears MR, Rea HH, de Boer G, Beaglehole R, Gillies AJD, Holst PE, O'Donnell TV, Rothwell RPG. Accuracy of certification of deaths due to asthma. A national study. Am J Epidemiol 1986; 124: 1004-1011.

66. Waters Barger L, Vollmer WM, Felt RW, Buist AS. Further investigation into the recent increase in asthma death rates: a review of 41 asthma deaths in Oregon in 1982. Ann Allergy 1988; 60: 31-39.

67. McConnochie KM. Bronchiolitis. What's in the name? Am J Dis Child 1983; 137: 11-13.

68. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-1199.

69. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood – a birth cohort study. Arch Dis Child 1991; 66: 1050-1053.

70. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, and the Group Health Medical Associates. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332: 133-138.

71. Dodge R, Martinez FD, Cline MG, Lebowitz MD, Burrows B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. J Allergy Clin Immunol 1996; 98: 48-54.

72. Sluiter HJ, Koëter GH, de Monchy JGR, Postma DS, de Vries K, Orie NGM. The Dutch Hypothesis (chronic non-specific lung disease) revisited. Eur Respir J 1991; 4: 479-489.

73. Vermeire PA, Pride NB. A "splitting" look at chronic nonspecific lung disease (CNSLD): common features but diverse pathogenesis. Eur Respir J 1991; 4: 490-496.

74. Vestbo J, Prescott E. Update on the "Dutch hypothesis" for chronic respiratory disease. Thorax 1998; 53(suppl 2): S15-S19.

75. Silverman M, Wilson N. Wheezing phenotypes in childhood [editorial]. Thorax 1997; 52: 936-937.

76. Wright AL, Taussig LM. Lessons from long-term cohort studies. Eur Respir J 1998; 12(suppl 27): 17S-22S.

77. Silverman M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. Thorax 1993; 48: 1200-1204.

78. Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. Br Med J 1983; 286: 1253-1256.

79. Hill R, Williams J, Tattersfield A, Britton J. Change in use of asthma as a diagnostic label for wheezing illness in schoolchildren. Br Med J 1989; 299: 898.

80. Godfrey S. Bronchiolitis and asthma in infancy and early childhood. Thorax 1996; 51 (suppl 2): S60-S64.

81. Everard ML. What link between early respiratory viral infections and atopic asthma [commentary]? Lancet 1999; 354: 527-528.

82. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999; 354: 541-545.

83. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000; 161: 1501-1507.

84. Clark CE, Coote JM, Silver DAT, Halpin DMG. Asthma after childhood pneumonia: six year follow up study. Br Med J 2000; 320: 1514-1516.

85. Avital A, Springer C, Bar-Yishay E, Godfrey S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. Thorax 1995; 50: 511-516.

86. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.

87. Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA 1990; 264: 1688-1692.

88. To T, Dick P, Feldman W, Hernandez R. A cohort study on childhood asthma admissions and readmissions. Pediatrics 1996; 98: 191-195.

89. Mitchell EA, Bland JM, Thompson JMD. Risk factors for readmission to hospital for asthma in childhood. Thorax 1994; 49: 33-36.

90. Farber HJ. Risk of readmission to hospital for pediatric asthma. J Asthma 1998; 35: 95-99.

CHAPTER 2
DUTCH NATIONAL ASTHMA MORTALITY DATA, 1980-1999

Abstract

Asthma mortality increased in various countries in the eighties. Consensus guidelines on diagnosis and management of asthma were published from 1989. The possible impact of these guidelines on asthma mortality in the Netherlands is unknown. In this perspective we evaluated national mortality data from the Netherlands over the period 1980-1999 on asthma as well as on chronic obstructive pulmonary disease (COPD) according to the codes of the International Classification of Diseases (ICD): revision-9 (1980-1995), asthma 493, COPD 490-492, 496; revision-10 (1996-1999), asthma J45-46, COPD J40-44. Mortality rates per million persons per year were calculated for age groups 0-4, 5-34, 35-64, and ≥65 years by gender. We performed time trend analyses by linear least squares regression over the period 1980-1999, and the subperiods 1980-1989 and 1990-1999. In childhood, mortality rates were also calculated for age group 5-14 years, and extended to acute bronchi(oli)tis, ICD-9 466, ICD-10 J20-22, and pneumonia/influenza, ICD-9 480-487, ICD-10 J10-18. Asthma mortality showed a large decline in males and females in age group ≥65 years in the early nineties, and a gradual, significant decrease in age group 35-64 years in subperiod 1990-1999. COPD mortality in age group ≥65 years increased significantly in females throughout, but in males the increase in the 1980s levelled off in the 1990s. COPD mortality in age group 35-64 years showed a significant increase in females in the subperiod 1980-1989, and a significant decrease in males in the subperiod 1990-1999. In age groups 0-4 years and 5-34 years, mortality from asthma and COPD concerned small numbers. The only trend found was a decrease in asthma mortality in males aged 5-34 years, predominantly in the 1980s. In age group 0-4 years mortality from acute bronchi(oli)tis and pneumonia/influenza decreased significantly.

In conclusion, mortality from asthma showed a favourable development in the Netherlands over the period 1980-1999. Mortality from other respiratory diseases showed stable or decreasing trends, except for the significant increase in mortality from COPD in older females.

2.1 Introduction

In the sixties a strong transient increase in asthma mortality was reported from New Zealand, Australia, and England and Wales, particularly in younger age groups [1,2]. It was assumed that the introduction of non-specific β-adrenergic receptor agonists per inhalation, particularly of the stronger dose preparations, could be held responsible for the increase because of cardiotoxic side effects [3,4]. The availability of the more selective β_2-agonists per inhalation in the 1970s was a step forward in the treatment of asthma. In the mid to late seventies and in the eighties, however, the asthma mortality increased again. This was first observed in New Zealand [5], later also in other countries [6-8]. In possible explanations, the main concern was the adequacy of treatment of the asthmatic patient, especially with respect to adverse effects and reduction in effectiveness (decreased protection) due to treatment with β-agonists [9,10]. Underassessment of the severity by the patients and the doctors, delays in seeking or providing help, and a rapid progression of fatal attacks were identified as important factors contributing to death from asthma [11].

Consensus guidelines on diagnosis and management of asthma have been developed and updated nationally and internationally since 1989 [12-17]. In 1995 the Global Initiative for Asthma (GINA) was published by a joint effort of the National Heart, Lung, and Blood Institute and the World Health Organization, presenting a global strategy for asthma management and prevention [18]. It is to be expected that these efforts will eventually reduce asthma mortality.

Earlier reports showed no trends in asthma mortality in childhood between 1980 and 1994 in the Netherlands [19,20]. In adults, asthma mortality decreased in both sexes from age 35, and decreased substantially from age 65 in the early nineties [20]. However, a definite distinction between asthma and chronic obstructive pulmonary disease (COPD) is difficult, particularly in the elderly [21,22]. In young children asthma is also not a clear-cut diagnosis [23,24]. In age group 5-34 years, asthma mortality rates are probably most reliable, but a labelling shift from acute bronchitis to asthma was thought to have contributed to mortality trends in the United Kingdom [25]. Moreover, asthma, (chronic) bronchitis and emphysema were regarded as part of the disease-entity chronic non-specific lung disease (CNSLD) in the Netherlands [26], and the Dutch equivalent umbrella term "CARA" (chronische aspecifieke respiratoire aandoeningen) was used as diagnostic label. Therefore, the analysis of the Dutch data extended to other respiratory diseases.

The aim of the present study was to examine trends in mortality from asthma in the Netherlands in different age groups in the period 1980-1999 against the background of other (obstructive) respiratory diseases, and to evaluate whether trends in the 1990s differed from those in the 1980s.

2.2 Material and methods

Mortality data

Annual crude mortality data were obtained from the Central Bureau of Statistics (CBS) by gender, age in 5-year groups, and primary cause of death according to the International Classification of Diseases (ICD) over the period 1980-1999 [27]. The ninth revision of the ICD was used from 1980-1995, in which asthma was coded as 493. The ICD-codes on the following lung diseases were also analysed: bronchitis not specified as acute or chronic, ICD 490; chronic bronchitis, ICD 491; emphysema, ICD 492; chronic obstructive airway disease not classified elsewhere, ICD 496. The ICD

codes 490, 491, 492, and 496 were combined, and will be referred to as chronic obstructive pulmonary disease (COPD) in all age groups. From 1996 the tenth revision of the ICD was in operation at the CBS, in which subgroups of diseases are described in more detail for coding purposes. The coding is not fully comparable with the ICD-9. In ICD-10 asthma is coded as J45 (asthma) and J46 (acute asthma), and COPD comprises the codes J40, J41, J42, J43, and J44. The main difference between ICD-9 and ICD-10 is that ICD-9 code 490 in children under 14 years of age has been transferred to acute bronchitis, being code J20 in ICD-10.

For the purpose of international comparisons and identifying age-specific trends, the analysis was carried out for four major age groups: 0-4 years, 5-34 years, 35-64 years, and ≥65 years. Annual mean population age structures [28] were used to calculate mortality rates for asthma and COPD per million persons in each calender year for the total population, and for males and females separately in each age group. The size of the population in the four age groups for the years from 1980 to 1999 is listed in appendix A.

In childhood, the analysis was extended to the respiratory diseases acute bronchi(oli)tis, ICD-9: 466; ICD-10: J20-J22, including ICD-9: 490 at ages 0-14 years, and influenza and pneumonia, ICD-9: 480-487; ICD-10: J10-J18. Three age groups were considered: 0-4 years, 5-9 years, and 10-14 years. Under the age of 15 years, however, the mortality concerned small numbers of deaths, and rates were calculated in age groups 0-4 years and 5-14 years for males and females combined.

Statistical analysis

The statistical package SPSS for Windows was used for time trend analyses which were performed by linear least squares regression. In a few situations, linear regression was clearly inappropriate and results will not be presented. The coefficient of the slope presents the annual change in the respective rate. The slope and its standard error (SE) offer the possibility to test the annual change to be significantly positive or negative

over the study period. A p-value <0.05 was considered significant to give a slope different from zero. In order to compare the trends in the two decades of the period 1980-1999 the linear regressions were also performed for the periods 1980-1989 and 1990-1999 separately. The slopes of these two periods, b_1 and b_2, were compared by the formula: $q=(b_1 - b_2)/SE(b_1 - b_2)$. Considering this quotient as a standard normal variate we tested whether the two slopes differed.

2.3 Results

2.3.1 Asthma in the total population

The actual number of deaths and the rates per million persons are presented in Appendix B, tables I-III. Text tables 2.1a (1980-1999) and 2.1b (1980-1989 and 1990-1999) list the results of the linear regression analyses. In age group 0-4 years, mortality from asthma concerned very small numbers, the rates fluctuated and no trends were found. Results in this age group are described in more detail in section 2.3.3. In age group 5-34 years, mortality rates were also very low; in males a slight but significant decrease was found, to which the first rather than the second decade contributed. In age group 35-64 years, asthma mortality decreased significantly in males and females, mainly because of the decrease in the second decade of the study period. The slopes in females differed significantly between the two subperiods (table 2.1b). Asthma mortality in age group ≥65 years showed no significant trend in the period 1980-1989, but in the 1990s a steep decline occurred from a level of about 100 per million persons, rates increasing again from the very low level of 3 per million persons in 1995 to about 30 per million persons in 1999. Figures 2.1 to 2.4 show the asthma mortality rates for males and females in the respective age groups.

Table 2.1a Results of the linear regression y=a+b*(year-1980), y: mortality from asthma respectively chronic obstructive pulmonary disease (COPD), 1980-1999

	intercept (SE)	slope (SE) p-value
ASTHMA		
0-4 years		
Males	3.58 (1.06)	-0.128 (0.095) 0.20
Females	1.96 (0.84)	-0.080 (0.076) 0.31
5-34 years		
Males	3.64 (0.33)	-0.156 (0.030) <0.001
Females	2.18 (0.32)	-0.054 (0.029) 0.08
35-64 years		
Males	15.8 (1.08)	-0.721 (0.097) <0.001
Females	14.9 (1.19)	-0.581 (0.107) <0.001
≥65 years[1]		
Males		
Females		
COPD		
0-4 years		
Males	3.10 (1.04)	-0.101 (0.094) 0.30
Females	1.75 (0.59)	-0.044 (0.053) 0.42
5-34 years		
Males	1.48 (0.29)	-0.032 (0.026) 0.24
Females	0.95 (0.17)	-0.010 (0.015) 0.52
35-64 years		
Males	144 (3.66)	-3.45 (0.330) <0.001
Females	39.2 (1.88)	+1.47 (0.169) <0.001
≥65 years		
Males	3897 (161)	+56.5 (14.5) 0.001
Females	620 (30.6)	+61.3 (2.75) <0.001

a, intercept; b, slope; SE, standard error.
[1)] Linear regression not carried out.
Asthma, ICD-9 code 493, 1980-1995; ICD-10 codes J45-J46, 1996-1999; COPD, ICD-9 codes 490-492, 496, 1980-1995; ICD-10 codes J40-J44, 1996-1999.

Table 2.1b Results of the linear regression y=a+b*(year-1980) by subperiod, y: mortality from asthma respectively COPD

Period	1980-1989 intercept (SE)	slope (SE) p-value	1990-1999 intercept (SE)	slope (SE) p-value	slope difference[1] p-value
ASTHMA					
0-4 years					
Males	1.52 (1.36)	+0.445 (0.255) 0.12	2.25 (3.31)	-0.073 (0.224) 0.75	>0.10
Females	2.97 (1.17)	-0.404 (0.218) 0.10	5.69 (2.61)	-0.305 (0.176) 0.12	>0.20
5-34 years					
Males	4.04 (0.60)	-0.242 (0.112) 0.06	2.28 (0.57)	-0.062 (0.039) 0.15	>0.10
Females	2.41 (0.52)	-0.106 (0.097) 0.31	1.56 (1.08)	-0.010 (0.073) 0.89	>0.20
35-64 years					
Males	14.6 (1.81)	-0.438 (0.339) 0.23	18.9 (2.99)	-0.939 (0.202) <0.01	>0.20
Females	11.6 (1.44)	+0.296 (0.270) 0.30	14.7 (2.36)	-0.614 (0.159) <0.01	<0.01
≥65 years[2]					
Males	113 (8.02)	+1.99 (1.50) 0.22			
Females	67.9 (4.43)	+1.72 (0.831) 0.07			
COPD					
0-4 years					
Males	1.26 (1.46)	+0.357 (0.273) 0.23	5.51 (3.39)	-0.283 (0.229) 0.25	>0.05
Females	0.94 (0.94)	+0.150 (0.175) 0.42	3.45 (1.70)	-0.165 (0.115) 0.19	>0.10
5-34 years					
Males	1.50 (0.44)	-0.043 (0.083) 0.62	1.87 (1.09)	-0.056 (0.073) 0.47	>0.20
Females	0.82 (0.27)	+0.024 (0.050) 0.65	1.04 (0.56)	-0.018 (0.038) 0.65	>0.20
35-64 years					
Males	136 (3.28)	-1.04 (0.615) 0.13	130 (11.2)	-2.65 (0.757) 0.01	=0.10
Females	38.9 (2.71)	+1.41 (0.507) 0.02	49.0 (6.60)	+0.835 (0.447) 0.10	>0.20
≥65 years					
Males	3384 (85.5)	+177 (16.0) <0.001	5114 (415)	-29.4 (28.0) 0.32	<0.001
Females	583 (33.7)	+69.8 (6.32) <0.001	710 (135)	+54.9 (9.11) <0.001	>0.10

a, intercept; b, slope; SE, standard error.

[1)] slope 1980-1989 versus slope 1990-1999. [2)] Linear regression not carried out for the period 1990-1999.

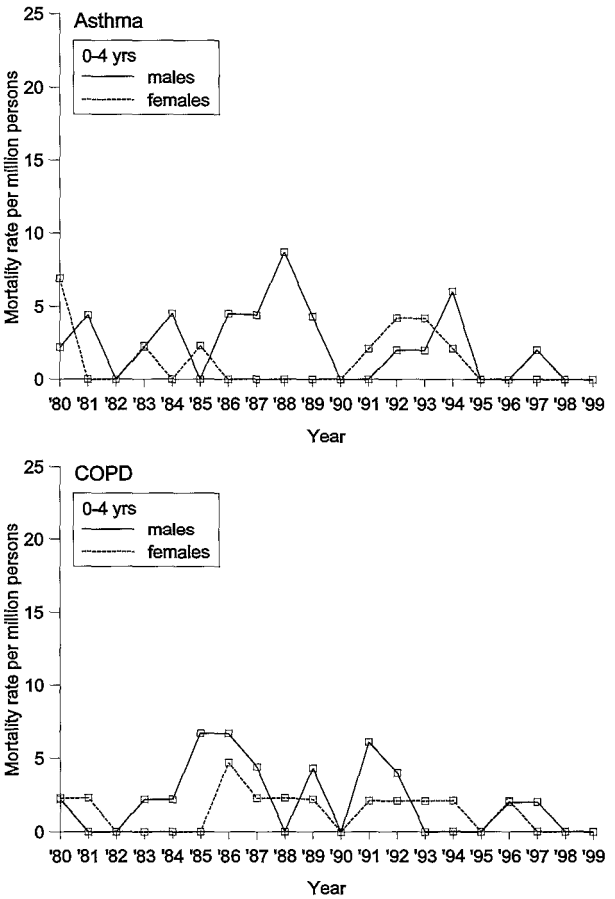

Figure 2.1 Mortality from asthma (ICD-9 code 493, 1980-1995; ICD-10 codes J45-J46, 1996-1999) (upper panel) and 'chronic obstructive pulmonary disease' (COPD) (ICD-9 codes 490-492, 496, 1980-1995; ICD-10 codes J40-J44, 1996-1999) (lower panel) in age group 0-4 years by gender in the period 1980-1999.

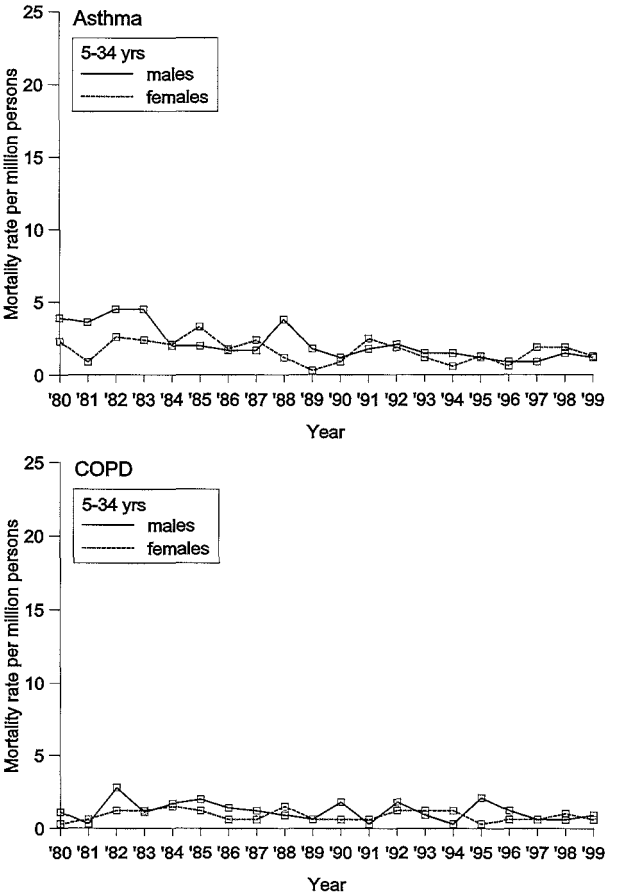

Figure 2.2 Mortality from asthma (ICD-9 code 493, 1980-1995; ICD-10 codes J45-J46, 1996-1999) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496, 1980-1995; ICD-10 codes J40-J44, 1996-1999) (lower panel) in age group 5-34 years by gender in the period 1980-1999.

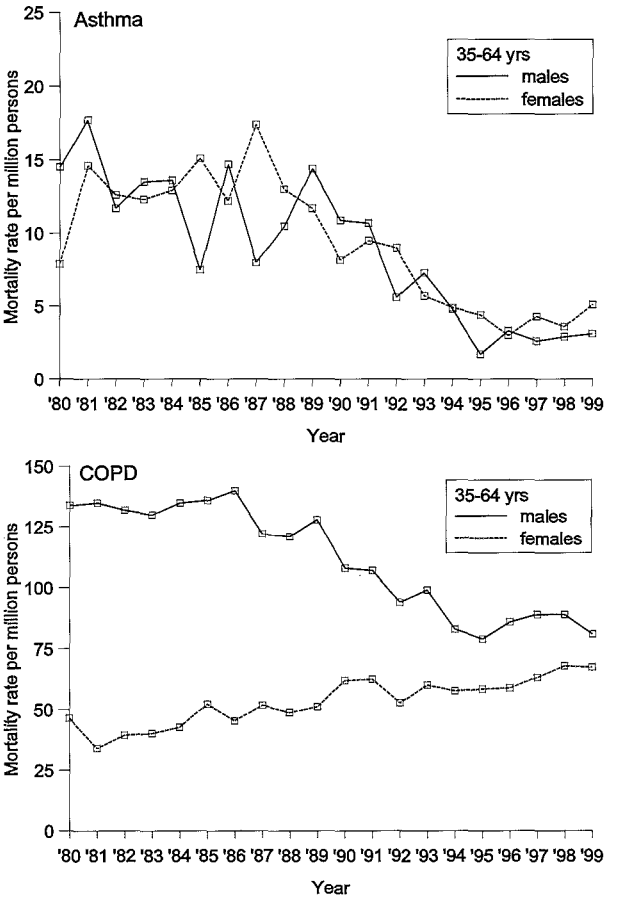

Figure 2.3 Mortality from asthma (ICD-9 code 493, 1980-1995; ICD-10 codes J45-J46, 1996-1999) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496, 1980-1995; ICD-10 codes J40-J44, 1996-1999) (lower panel) in age group 35-64 years by gender in the period 1980-1999.

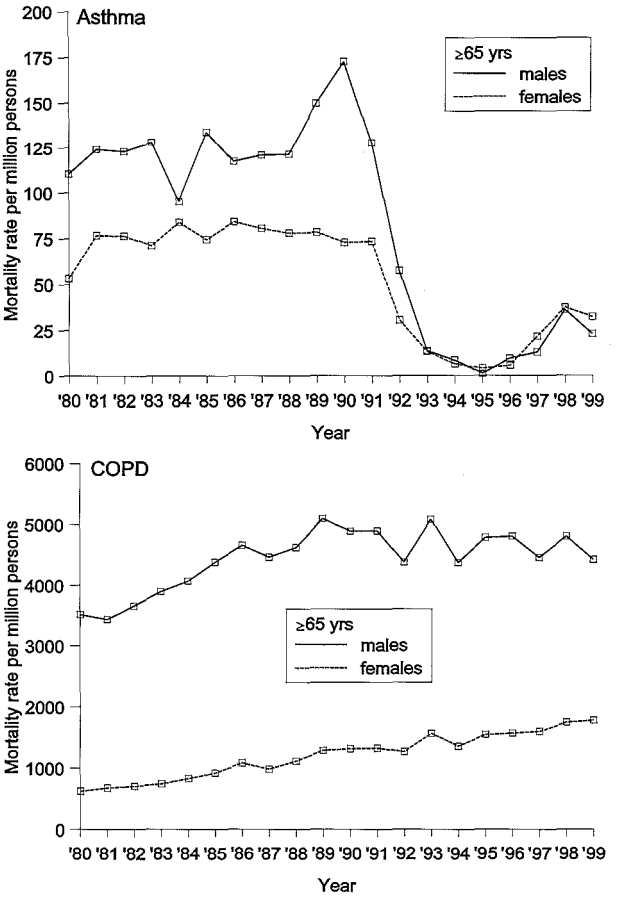

Figure 2.4 Mortality from asthma (ICD-9 code 493, 1980-1995; ICD-10 codes J45-J46, 1996-1999) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496, 1980-1995; ICD-10 codes J40-J44, 1996-1999) (lower panel) in age group ≥65 years by gender in the period 1980-1999.

A plausible explanation for the large fall in asthma mortality in the early 1990s is a labelling shift from asthma to COPD.

2.3.2 Chronic obstructive pulmonary disease (COPD) in the total population

The actual number of deaths and the rates per million persons are presented in Appendix B, tables IV-VI. Results from the linear regression analyses are added in the text tables 2.1a and 2.1b. Mortality from COPD in age groups 0-4 years and 5-34 years was very low and no trends were observed. In age groups 35-64 years and ≥65 years, mortality from COPD in females increased significantly in the first decade, and in females ≥65 years in the second decade as well. In males, mortality from COPD showed discrepant trends in these two age groups. In age group 35-64 years, mortality decreased significantly, to which the subperiod 1990-1999 contributed most. In males aged ≥65 years, an overall significant increase was found, but the trends in the two subperiods differed significantly and mortality tended to decrease in the 1990s (table 2.1b). Mortality from COPD is predominant in males, but the ratio of males to females in age group 35-64 years decreased from approximately 3 in 1980 to 1.5. in 1999, and in age group ≥65 years from approximately 5 in 1980 to 3 in 1999. The age-specific trends in COPD mortality are also shown in the figures 2.1 to 2.4. The scales of the y-axis differ depending on the levels of the rate.

2.3.3 Obstructive airways disease in childhood

The actual numbers of deaths and the age-specific mortality rates per million persons per year in children for asthma, acute bronchi(oli)tis, pneumonia and influenza, and COPD in age groups 0-4 years and 5-14 years are presented in Appendix B, tables VII-VIII. In age group 0-4 years very small numbers of deaths from asthma occurred, a total of 33 actual deaths over the 20-year study period, which was similar to the number of deaths registered under COPD. The rates for acute bronchi(oli)tis and for pneumonia and influenza fluctuated, but were lower in the nineties. Linear regression analysis showed a significant decrease for both acute bronchi(oli)tis (slope=-0.616, SE=0.107, $p<0.001$) and pneumonia and influenza (slope=-1.33, SE=0.316, $p<0.001$). In age group 5-14 years an average of 1 death from asthma per year was observed, the mortality from

the other respiratory diseases was also very low with no trends.

2.4 Discussion

We observed a decrease in mortality from asthma in the Netherlands over the period 1980-1999. From age 5, asthma mortality showed a lower level in the 1990s than in the 1980s. Most striking is the large reduction in mortality that occurred in age group ≥65 years in the early 1990s. This was followed by a slight increase after 1995. Under the age of 65 mortality declined more gradually, and from a much lower level. The trends in males and females were similar. Possible explanations for this decline can be better management, beneficial effects of prescribing anti-inflammatory drugs more frequently and as maintenance treatment, or a labelling shift with a preference for COPD diagnosis. From middle age, there is an increasing influence of e.g. smoking, occupation and pollution on the respiratory system, leading to a more difficult distinction between asthma and COPD. Inaccuracies of asthma death certification have been observed [21,29-39], accuracy declining with increasing age [21,29,30,32,36,39]. In the elderly, numerous other medical problems may exist to complicate correct diagnostic coding [21,34,35,37,38]. Misclassification of asthma as COPD [34,35] and vice versa [21,39] was found. Nevertheless, most deaths from asthma occur at higher ages.

On average two-thirds of all asthma deaths occurred in the age group ≥65 years, but death from COPD is much more frequent and a labelling shift from asthma to COPD will therefore not be apparent. However, the abruptness of the fall in asthma mortality rate in the age group ≥65 years at the time of the appearances of guidelines on asthma diagnosis and management might rather point to a reluctance to label deaths as asthma than to a sudden effect of better treatment. A labelling shift from asthma to COPD is also plausible in view of the publication in 1987 of the American Thoracic Society (ATS) standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. These stated that a typical abnormality in

asthma includes an increase of 15% or greater in the forced expiratory volume in one second (FEV_1) in response to a bronchodilator [40]. However, in older, more severe asthmatics, airways obstruction becomes gradually more irreversible, possibly because of the remodelling process in the airways [41].

Under the age of 65, a labelling shift from asthma to COPD is less plausible to explain the observed trends in asthma mortality in view of the magnitude of the slopes and the time periods in which they occurred: in age group 35-64 years asthma mortality decreased both in males and females in the 1990s, but reciprocal trends in mortality from COPD were seen only in females and the increase was strongest between 1980 and 1989. Favouring COPD diagnosis in females is not in line with the finding that, regardless respiratory symptoms and smoking, older females rather than males were labelled with a diagnosis of asthma [42]. Moreover, the observed trends in COPD mortality in the Netherlands were similar to trends in COPD mortality in several other countries, and follow the patterns of cigarette smoking [43-46]. In the United States, rates of deaths with any mention of obstructive lung disease (COPD and asthma) increased much more compared to underlying cause of death, suggesting an underestimation of its role in mortality [47]. The trends were the same, stabilising among males (<85 years) and increasing among females from 1979 through 1993 [47].

COPD presents a growing cause for concern, as highlighted by the consensus statement of the European Respiratory Society [48] and the statement of the American Thoracic Society [49] in 1995. Smoking accounts for an estimated 80 to 90% of the risk of developing COPD [49]. In the Netherlands, female mortality rates for COPD in age group 35-64 years are now approaching the rates in males, notwithstanding a lower percentage of female smokers [50], but women may be even more susceptible to the deleterious effects of smoking on lung function and consequently on admissions and mortality [51]. Poor lung function is a risk factor for death from COPD, even in patients considered to have had asthma [52,53]. It can be questioned whether elderly patients ever suffer from uncomplicated asthma, and it seems most important to direct treatment

to preserving lung function independent of the diagnostic label asthma or COPD.

The highest accuracy of asthma diagnosis in death certification was found under the age of 45 years [29,30]. Hence trend analyses on asthma mortality have often been focused on the age group 5-34 years, which showed increased death rates in various countries from mid 1970s to the early 1980s [5,7,8,10,54]. The increase continued in the United States [54], but mortality showed downward trends in the United Kingdom in the late 1980s and early 1990s [55]. In the Netherlands, mortality from asthma decreased in the age group 5-34 years from 1980 through 1999, but especially in the eighties and in males. No trend was found in the mortality from COPD, neither in the mortality from acute bronchitis [20], making a change in coding practices or labelling unlikely. However, mortality in this age group concerned small numbers, and the level for asthma in the 1990s was similar to the level in 1974-76 [56].

Mortality from asthma and from COPD in childhood (0-14 years) is extremely low in the Netherlands, and no trends were found. In the age group 0-4 years, hospital admissions for asthma increased [19,20], which may reflect increased prevalence of more severe disease. It is unlikely that an increase in asthma mortality has been masked in view of the observed decreased mortality from acute bronchi(oli)tis and from pneumonia and influenza in this age group.

Several studies have indicated that recent hospital admissions for asthma are a risk factor for death from asthma [57,58]. In the Netherlands, hospital admissions for asthma decreased in all age groups, except for the 0-4 year-olds [20]. The decrease in mortality from asthma may thus be real, and is in accordance with findings from other countries. Since the late eighties, increasing rates stabilised in the United States [54], and decreased in Britain [55] and New Zealand [59] for most ages, possibly due to improvement of asthma care, while better management of acute asthma has been reported [59,60].

Mortality from asthma in the Netherlands over the study period was low compared to other countries [7,8,54,55,59]. It may have been underestimated in view of the diagnostic labelling of "CARA" that will have been coded under COPD. However, internationally the level of mortality from COPD in the Netherlands was moderate [61]. On the other hand, overestimation of asthma mortality was suggested from Denmark [39] and the United Kingdom [36]. International comparisons require caution as differences in diagnostic labelling of chronic airflow obstruction [62] and death certification practices [63-65] have been found. Besides, populations differ and social factors rather than medical ones may contribute to ethnic variations in asthma mortality [54,66-68].

From 1996, ICD-9 code 490 (bronchitis not specified as acute or chronic) changed to ICD-10 code J20 (acute bronchitis) for ages 0-14 years. From 1980-1995 a total of 10 deaths from 'bronchitis not specified as acute or chronic' occurred and in age group 0-4 years only. Under ICD-10, the conclusions on mortality from acute bronchi(oli)tis (a significant decrease) and COPD (no significant trend) would have been the same.

In summary, mortality from asthma declined in the Netherlands over the period 1980-1999. Trends in males and females were similar. Changes in coding practices or diagnostic labelling under the age of 65 years are unlikely to have been responsible, there might be a real decrease. In subjects over 65 years diagnostic transfer from asthma to COPD is a plausible explanation for the fall in asthma mortality in the early 1990s. The guidelines on diagnosis and management of asthma may have contributed by more diagnostic awareness and improvement of asthma management. Mortality from COPD increased in females ≥35 years and initially in males ≥65 years. In age group 0-4 years asthma mortality concerned very small numbers and showed no trend, while mortality from acute bronchi(oli)tis and from pneumonia and influenza decreased.

References

1. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. Br Med J 1968; i: 335-339.
2. Inman WHW, Adelstein AM. Rise and fall of asthma mortality in England and Wales in relation to use of pressurised aerosols. Lancet 1969; ii: 279-285.
3. Tai E, Read J. Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. Thorax 1967; 22: 543-549.
4. Stolley PD, Schinnar R. Association between asthma mortality and isoproterenol aerosols: a review. Prev Med 1978; 7: 319-338.
5. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: a new epidemic in New Zealand. Br Med J 1982; 285: 771-774.
6. Sly RM. Increases in deaths from asthma. Ann Allergy 1984; 53: 20-25.
7. Burney PGJ. Asthma mortality in England and Wales: evidence for a further increase, 1974-84. Lancet 1986; ii: 323-326.
8. Bousquet J, Hatton F, Godard P, Michel FB. Asthma mortality in France. J Allergy Clin Immunol 1987; 80(suppl): 389-394.
9. Mitchell EA. Is current treatment increasing asthma mortality and morbidity [editorial]? Thorax 1989; 44: 81-84.
10. Sears MR. Epidemiology. In: PJ Barnes, IW Rodger, NC Thomson, eds. Asthma: Basic Mechanisms and Clinical Management, second edition. London: Academic Press Limited, 1992, pp. 1-19.
11. Johnson AJ, Nunn AJ, Somner AR, Stableforth DE, Stewart CJ. Circumstances of death from asthma. Br Med J 1984; 288: 1870-1872.
12. Warner JO, Götz M, Landau LI, Levison H, Milner AD, Pedersen S, Silverman M. Management of asthma: a consensus statement. Arch Dis Child 1989; 64: 1065-1079.
13. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: I - chronic persistent asthma. Br Med J 1990; 301: 651-653.
14. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: II - acute severe asthma. Br Med J 1990; 301: 797-800.
15. International consensus report on the diagnosis and management of asthma. Clin Exp Allergy 1992; 22 (Suppl. 1): 1-72.
16. Warner JO, et al. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992; 67: 240-248.

17. British Thoracic Society, British Paediatric Association, Royal College of Physicians, King's Fund Centre, National Asthma Campaign, Royal College of General Practitioners, General Practitioners in Asthma Group, British Association of Accident and Emergency Medicine, British Paediatric Respiratory Group. Guidelines on the management of asthma. Thorax 1993; 48(suppl. 2): S1-S24.

18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention NHLBI/WHO workshop report. National Institutes of Health, National Heart, Lung, and Blood Institute. Bethesda, Maryland, USA. 1995; Publication No. 95-3659.

19. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.

20. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.

21. Waters Barger L, Vollmer WM, Felt RW, Buist AS. Further investigation into the recent increase in asthma death rates: a review of 41 asthma deaths in Oregon in 1982. Ann Allergy 1988; 60: 31-39.

22. Vestbo J, Prescott E. Update on the "Dutch hypothesis" for chronic respiratory disease. Thorax 1998; 53(suppl 2): S15-S19.

23. McConnochie KM. Bronchiolitis. What's in the name? Am J Dis Child 1983; 137: 11-13.

24. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-1199.

25. Whallett EJ, Ayres JG. Labelling shift from acute bronchitis may be contributing to the recent rise in asthma mortality in the 5-34 age group. Respir Med 1993; 87: 183-186.

26. Sluiter HJ, Koëter GH, de Monchy JGR, Postma DS, de Vries K, Orie NGM. The Dutch Hypothesis (chronic non-specific lung disease) revisited. Eur Respir J 1991; 4: 479-489.

27. Centraal Bureau voor de Statistiek. Overledenen naar doodsoorzaak, leeftijd en geslacht. Jaargangen 1980-1999. Voorburg: Centraal Bureau voor de Statistiek.

28. Centraal Bureau voor de Statistiek. Leeftijdsopbouw naar burgelijke staat en geslacht, gemiddeld 1980-1999. Voorburg: Centraal Bureau voor de Statistiek.

29. A subcommittee of the BTA Research Committee. Accuracy of death certificates in bronchial asthma. Thorax 1984; 39: 505-509.

30. Sears MR, Rea HH, de Boer G, Beaglehole R, Gillies AJD, Holst PE, O'Donnell TV, Rothwell RPG. Accuracy of certification of deaths due to asthma. A national study. Am J Epidemiol 1986; 124: 1004-1011.

31. Hunt LW, Silverstein MD, Reed CE, O'Connell EJ, O'Fallon WM, Yunginger JW. Accuracy of the death certificate in a population-based study of asthmatic patients. JAMA 1993; 269: 1947-1952.

32. Wright SC, Evans AE, Sinnamon DG, MacMahon J. Asthma mortality and death certification in Northern Ireland. Thorax 1994; 49: 141-143.

33. Model D. Preventable factors and death certification in death due to asthma. Respir Med 1995; 89: 21-25.

34. Smyth ET, Wright SC, Evans AE, Sinnamon DG, MacMahon J. Death from airways obstruction: accuracy of certification in Northern Ireland. Thorax 1996; 51: 293-297.

35. Guite HF, Burney PGJ. Accuracy of recording of deaths from asthma in the UK: the false negative rate. Thorax 1996; 51: 924-928.

36. Reid DWEC, Hendrick VJ, Aitken TC, Berrill WT, Stenton SC, Hendrick DJ. Age-dependent inaccuracy of asthma death certification in Northern England, 1991-1992. Eur Respir J 1998; 12: 1079-1083.

37. Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, Arthurs R, Hodges IGC. A confidential inquiry into asthma deaths in Wales. Thorax 1999; 54: 985-989.

38. Jones K, Berrill WT, Bromly CL, Hendrick DJ. A confidential enquiry into certified asthma deaths in the North of England, 1994-96: influence of co-morbidity and diagnostic inaccuracy. Respir Med 1999; 93: 923-927.

39. Sidenius KE, Munch EP, Madsen F, Lange P, Viskum K, Søes-Petersen U. Accuracy of recorded asthma deaths in Denmark in a 12-months period in 1994/95. Respir Med 2000; 94: 373-377.

40. American Thoracic Society. Medical section of the American Lung Association. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136: 225-244.

41. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000; 161: 1720-1745.

42. Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. Am Rev Respir Dis 1986; 133: 981-986.

43. Feinleib M, Rosenberg HM, Collins JG, Delozier JE, Pokras R, Chevarley FM. Trends in COPD morbidity and mortality in the United States. Am Rev Respir Dis 1989; 140: S9-S18.

44. Speizer FE. The rise in chronic obstructive pulmonary disease mortality. Overview and summary. Am Rev Respir Dis 1989; 140: S106-S107.

45. Backhouse A, Holland WW. Trends in mortality from chronic obstructive airways disease in the United Kingdom. Thorax 1989; 44: 529-532.

46. Lacasse Y, Brooks D, Goldstein RS. Trends in the epidemiology of COPD in Canada, 1980 to 1995. Chest 1999; 116: 306-313.

47. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993: an analysis using multiple-cause mortality data. Am J Respir Crit Care Med 1997; 156: 814-818.

48. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J, on behalf of the Task Force. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995; 8: 1398-1420.

49. Statement of the American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152(suppl): S77-S120.

50. Stichting Volksgezondheid en Roken (Stivoro). Jaarverslag 1999. Den Haag: Stichting Volksgezondheid en Roken; 2000.

51. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. Eur Respir J 1997; 10: 822-827.

52. Lange P, Ulrik CS, Vestbo J. Mortality in adults with self-reported asthma. Lancet 1996; 347: 1285-1289.

53. Connolly CK, Mamun M, Alcock SM, Prescott RJ. The Darlington and Northallerton prospective asthma study: best function predicts mortality during the first 10 years. Respir Med 1998; 92: 1274-1280.

54. Sly RM, O'Donnell R. Stabilization of asthma mortality. Ann Allergy Asthma Immunol 1997; 78: 347-354.

55. Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983-95: results of an observational study. Br Med J 1997; 314: 1439-1441.

56. Wever AMJ, Wever-Hess J. β-adrenerge agonisten en sterfte en morbiditeit wegens astma. Ned Tijdschr Geneeskd 1992; 136: 460-465.

57. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. Thorax 1986; 41: 833-839.

58. Crane J, Pearce N, Burgess C, Woodman K, Robson B, Beasley R. Markers of risk of asthma death or readmission in the 12 months following a hospital admission for asthma. Int J Epidemiol 1992; 21: 737-744.

59. Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand: what lessons have been learned? Thorax 1995; 50: 303-311.

60. Bucknall CE, Slack R, Godley CC, Mackay TW, Wright SC, on behalf of SCIAD collaborators. Scottish confidential inquiry into asthma deaths (SCIAD), 1994-6. Thorax 1999; 54: 978-984.

61. Hurd S. The impact of COPD on lung health worldwide. Epidemiology and incidence. Chest 2000; 117(suppl): 1S-4S.

62. Pride NB, Vermeire P, Allegra L. Diagnostic labels applied to model case histories of chronic airflow obstruction. Responses to a questionnaire in 11 North American and Western European Countries. Eur Respir J 1989; 2: 702-709.

63. Kelson MC, Heller RF. The effect of death certification and coding practices on observed differences in respiratory disease mortality in 8 E.E.C. countries. Rev Epidem Santé Publ 1983; 31: 423-432.

64. Mackenbach JP, Van Duyne WMJ, Kelson MC. Certification and coding of two underlying causes of death in the Netherlands and other countries of the European Community. J Epidemiol Comm Health 1987; 41: 156-160.

65. Burney PGJ. The effect of death certification practice on recorded national asthma mortality rates. Rev Epidem Santé Publ 1989; 37: 385-389.

66. Sears MR, Rea HH, Beaglehole R, Gillies AJ, Holst PE, O'Donnell TV, Rothwell RP, Sutherland DC. Asthma mortality in New Zealand: a two year national study. NZ Med J 1985; 98: 271-275.

67. Ng TP, Tan WC. Temporal trends and ethnic variations in asthma mortality in Singapore, 1976-1995. Thorax 1999; 54: 990-994.

68. Kaliner MA. Asthma deaths. A social or medical problem [editorial]? JAMA 1993; 269: 1994-1995.

CHAPTER 3
DUTCH NATIONAL DATA ON HOSPITAL ADMISSIONS FOR ASTHMA, 1980-1999

Abstract

The rising morbidity associated with asthma in various countries in the 1980s resulted in changes in treatment strategies, reflected in guidelines on diagnosis and management of asthma. To assess trends in hospital admissions in the Netherlands, we evaluated national data on asthma as well as on chronic obstructive pulmonary disease (COPD) over the period 1980-1999, according to the codes of the ninth revision of the International Classification of Diseases (ICD): asthma, 493; COPD, 490-492 and 496. Admission rates per million persons per year are presented for age groups 0-4, 5-34, 35-64, and ≥65 years by gender. Time trend analyses were performed by linear least squares regression over the period 1980-1999, and the subperiods 1980-1989 and 1990-1999. For children, the analysis included data on acute bronchi(oli)tis (ICD 466) and pneumonia/influenza (ICD 480-487). A Dutch consensus meeting on asthma in children was held in 1992, so we analysed the subperiods 1980-1992 and 1993-1999. Admission rates are presented for age groups 0-4, 5-9, and 10-14 years by gender. Between 1980 and 1999, hospital admissions for asthma increased significantly in age group 0-4 years and decreased in the other age groups. Between 1990 and 1999, these trends levelled off, except for a continuing decrease in males ≥65 years. In the age groups between 5 and 34 years, admissions for asthma tended to increase in the 1990s. In this decade, admissions for COPD showed a concurrent significant decrease in childhood and young adulthood, suggestive of a shift in diagnostic labelling. COPD admissions in age group 35-64 years increased continuously in females, but decreased in males in the 1990s. In age group ≥65 years, COPD admissions increased again continuously in females, and levelled off in males. Furthermore, admissions for acute bronchi(oli)tis showed a

significant increase in age group 0-4 years.

In conclusion, our results indicate an overall favourable development in hospital admissions for asthma in the Netherlands over the period 1980-1999. However, hospital admission rates increased for acute bronchi(oli)tis in age group 0-4 years, as did the rates for COPD in females ≥35 years.

3.1 Introduction

From the mid-sixties well into the 1980s hospitalisation rates for asthma increased in various countries, especially for children [1-4]. Increasing hospitalisation rates might have been due to an increase in the prevalence of asthma over time, which has now been observed worldwide [5], and/or an increase in severity of asthma [6,7]. Also changes in medical care, such as the introduction of in-hospital treatment with nebuliser therapy in the 1970s [8], and the increasing provision and utilisation of health services [9,10] may have contributed. Hospital admissions may reflect asthma management practices and asthma severity rather than prevalence, but indicators for severity threshold for admission have not yet been defined [6,11].

In the 1980s a continuing increase in hospital admissions in young children was reported [6,12-15], whereas in older children and adults indications for declining admission rates were found [13,15]. The more recent reductions in hospitalisation for asthma have been linked with increases in prophylactic treatment [16-19]. Guidelines on diagnosis and management of asthma have been developed and updated nationally and internationally since 1989 [20-25], and a report on 'Global Strategy for Asthma Management and Prevention' was published in 1995 [26]. These emphasise the importance of early recognition and preventive treatment directed to diminish the inflammatory processes in the airways, with the aim to reduce asthma morbidity.

In the Netherlands, hospital admission rates decreased significantly over the period 1980-1994, except for a significant increase in age group 0-4 years [27]. The increase in males aged 5-9 years observed in the eighties [28] did not continue. In the present study the data on hospital admissions are extended to cover the period 1980 to 1999.

The lack of a clear definition of asthma may have hampered correct diagnostic labelling. In admitted patients and in school children with a history of wheeze, underdiagnosis and undertreatment of asthma was observed [29-31]. Concern about overtreating 'bronchitic' patients with antibiotics [31,32] could consequently have favoured asthma labelling [33], to achieve better management of the disease. A changing content of the asthma diagnosis may have provided bias in the reported increasing asthma prevalences [34], and affects the accuracy of time trend analyses. Especially in the (very) young [32,35] and in the elderly [36], diagnostic coding for asthma is less secure. Therefore, (chronic) bronchitis and emphysema, incorporated in chronic obstructive pulmonary disease (COPD), as well as other reactive airway disorders in childhood were included in the analysis. Moreover, in the Netherlands asthma and COPD have traditionally been combined and referred to as "CARA" [37]. In 1992 a consensus meeting of a Central Advisory Committee discouraged the use of the diagnostic term "CARA" in children, after which it became obsolete [38].

The aim of the present study was to examine trends in hospital admissions for asthma in the Netherlands in different age groups in the period 1980-1999 against the background of other airway disorders, and to evaluate whether trends in the 1990s differed from those in the 1980s.

3.2 Material and methods

Hospital admission data

Annual crude hospital morbidity data were obtained from the Dutch Centre for Health

Care Information[1] by gender, age in 5-year groups, and diagnosis of discharge according to the ninth revision of the International Classification of Diseases (ICD-9, Clinical Modification) over the period 1980-1999. The Dutch Centre for Health Care Information covered on average 98.3% (range 94-99.7%) over the years 1980-1994 and 99.9% over the years 1995-1999 of all hospital admissions in the Netherlands, and the data were adjusted to a 100% level [39].

The ICD-codes on the following lung diseases were analysed: asthma, ICD 493; bronchitis not specified as acute or chronic, ICD 490; chronic bronchitis, ICD 491; emphysema, ICD 492; chronic obstructive airway disease not classified elsewhere, ICD 496. The codes ICD 490, 491, 492, and 496 were combined and will be referred to as chronic obstructive pulmonary disease (COPD) in all age groups. Thus, 'COPD' in childhood in this chapter refers to these same ICD codes.

Annual mean population age structures [40] were used to calculate admission rates for asthma and COPD per million persons in each calender year for the total population, and for males and females separately in the age groups 0-4 years, 5-34 years, 35-64 years, and ≥65 years. The size of the population in the four age groups for the years from 1980 to 1999 is listed in appendix A.

In childhood, the analysis was extended to the respiratory diseases acute bronchi(oli)tis, ICD 466, and influenza and pneumonia, ICD 480-487. Gender-specific rates were calculated for the age groups 0-4 years, 5-9 years, and 10-14 years per million persons [40].

Statistical analysis

The statistical package SPSS for Windows was used for time trend analyses which were

[1] From 1 January 2000 the Dutch Centre for Health Care Information is part of "Prismant", Utrecht.

performed by linear least squares regression. The coefficient of the slope presents the annual change in the respective rate. The slope and its standard error (SE) offer the possibility to test the annual change to be significantly positive or negative over the study period. A p-value <0.05 was considered significant to give a slope different from zero. In order to compare the trends in the two decades of the period 1980-1999 the linear regressions were also performed for the periods 1980-1989 and 1990-1999 separately for the four main age groups. The slopes of these two periods, b_1 and b_2, were compared by the formula: $q=(b_1 - b_2)/SE(b_1 - b_2)$. Considering this quotient as a standard normal variate we tested whether the two slopes differed. To assess the possible impact of the national consensus meeting on asthma in children in 1992 [38], we compared the subperiods 1980-1992 and 1993-1999 for the age groups 0-4 years, 5-9 years, and 10-14 years.

3.3 Results

3.3.1 Asthma in the total population

The actual number of hospital admissions and rates per million persons by age group in the Netherlands from 1980 to 1999 are presented in Appendix C, tables I-III. Admission rates for asthma were highest in age group 0-4 years, the rates in males nearly twice the rates in females. In age groups 5-34 years and 35-64 years rates were higher in females than in males. Hospital admission rates decreased significantly in all age groups, except for a significant increase in age group 0-4 years (table 3.1a). Results for this age group are further described in section 3.3.3. Most slopes differed significantly between the subperiods 1980-1989 and 1990-1999 (table 3.1b). Under the age of 65 years the observed decreases occurred primarily in the 1980s. The trends levelled off in the 1990s, but the decrease in males aged ≥65 years was larger than in the 1980s. In age group 5-34 years, the slight increase in admission rates was significant in males (table 3.1b). Figures 3.1 to 3.4 illustrate the admission rates for males and

Table 3.1a Results of the linear regression y=a+b*(year-1980), y: hospital admissions for asthma respectively chronic obstructive pulmonary disease (COPD), 1980-1999

	intercept (SE)	slope (SE) p-value
ASTHMA		
0-4 years		
Males	1385 (94.5)	+86.5 (8.50) <0.001
Females	893 (60.0)	+34.9 (5.40) <0.001
5-34 years		
Males	337 (14.8)	-8.01 (1.33) <0.001
Females	370 (9.46)	-4.25 (0.851) <0.001
35-64 years		
Males	520 (19.4)	-22.2 (1.75) <0.001
Females	630 (23.3)	-20.2 (2.10) <0.001
≥65 years		
Males	1116 (29.8)	-49.8 (2.68) <0.001
Females	752 (21.6)	-26.8 (1.94) <0.001
COPD		
0-4 years[1]		
Males		
Females		
5-34 years		
Males	147 (8.90)	-3.37 (0.800) <0.001
Females	155 (9.62)	-2.39 (0.866) 0.01
35-64 years		
Males	1287 (28.3)	-19.9 (2.54) <0.001
Females	673 (23.6)	+19.3 (2.12) <0.001
≥65 years		
Males	7990 (315)	+207 (28.4) <0.001
Females	1819 (55.7)	+152 (5.01) <0.001

a, intercept; b, slope; SE, standard error.
[1)] Linear regression not carried out.
Asthma, ICD-9 code 493; COPD, ICD-9 codes 490-492, 496.

Table 3.1b Results of the linear regression y=a+b*(year-1980), y: hospital admissions for asthma respectively COPD

Period	1980-1989 intercept (SE)	slope (SE) p-value	1990-1999 intercept (SE)	slope (SE) p-value	slope difference[1] p-value
ASTHMA					
0-4 years					
Males	1383 (84.3)	+78.4 (15.8) 0.001	1976 (425)	+48.4 (28.8) 0.13	>0.20
Females	762 (58.4)	+69.0 (10.9) <0.001	970 (230)	+28.1 (15.6) 0.11	<0.05
5-34 years					
Males	357 (12.3)	-10.4 (2.30) <0.01	142 (25.9)	+4.89 (1.75) 0.02	<0.001
Females	373 (10.7)	-3.56 (2.00) 0.11	272 (25.6)	+2.10 (1.73) 0.26	<0.05
35-64 years					
Males	570 (14.7)	-32.4 (2.76) <0.001	292 (31.6)	-6.79 (2.14) 0.01	<0.001
Females	679 (18.1)	-29.1 (3.39) <0.001	332 (37.5)	-0.285 (2.54) 0.91	<0.001
≥65 years					
Males	1036 (25.7)	-27.6 (4.81) <0.001	1060 (83.8)	-47.3 (5.67) <0.001	<0.01
Females	740 (16.8)	-20.1 (3.15) <0.001	517 (57.2)	-11.8 (3.87) 0.02	>0.05
COPD					
0-4 years[2]					
Males	1464 (80.4)	+30.0 (15.1) 0.08			
Females	886 (51.9)	+7.18 (9.73) 0.48			
5-34 years					
Males	133 (8.34)	-0.818 (1.56) 0.61	232 (30.3)	-9.01 (2.05) <0.01	<0.01
Females	135 (6.53)	+1.52 (1.22) 0.25	263 (27.1)	-9.65 (1.83) <0.001	<0.001
35-64 years					
Males	1217 (42.6)	-2.06 (7.98) 0.80	1346 (40.7)	-24.8 (2.75) <0.001	<0.01
Females	606 (21.3)	+35.7 (4.00) <0.001	793 (68.8)	+10.6 (4.65) 0.053	<0.001
≥65 years					
Males	7127 (337)	+408 (63.2) <0.001	10173 (752)	+54.1 (50.9) 0.32	<0.001
Females	1743 (74.4)	+173 (13.9) <0.001	1797 (208)	+152 (14.1) <0.001	>0.20

a, intercept; b, slope; SE, standard error;
[1)] slope 1980-1989 versus slope 1990-1999. [2)] Linear regression not carried out for the period 1990-1999.

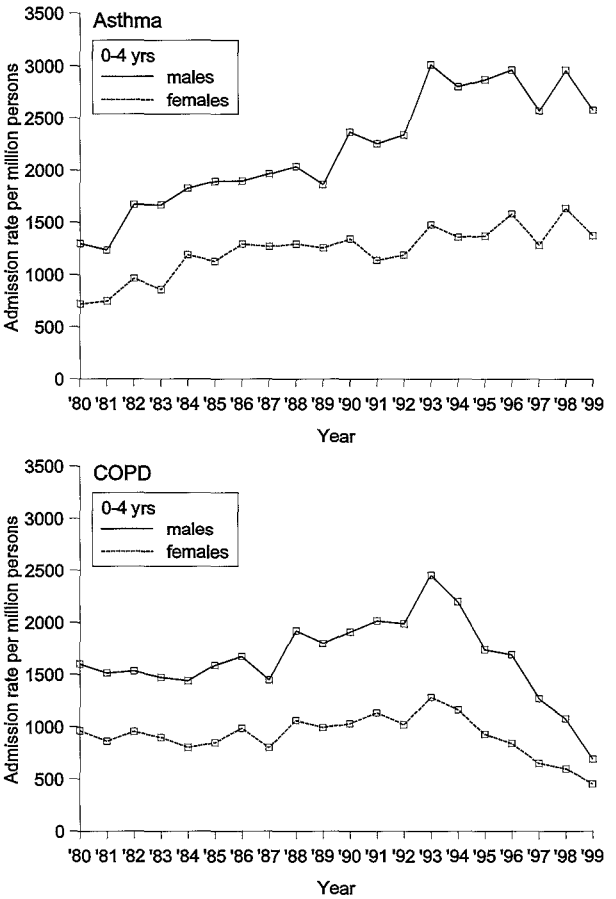

Figure 3.1 Hospital admissions for asthma (ICD-9 code 493) (upper panel) and 'chronic obstructive pulmonary disease' (COPD) (ICD-9 codes 490-492, 496) (lower panel) in age group 0-4 years by gender in the period 1980-1999.

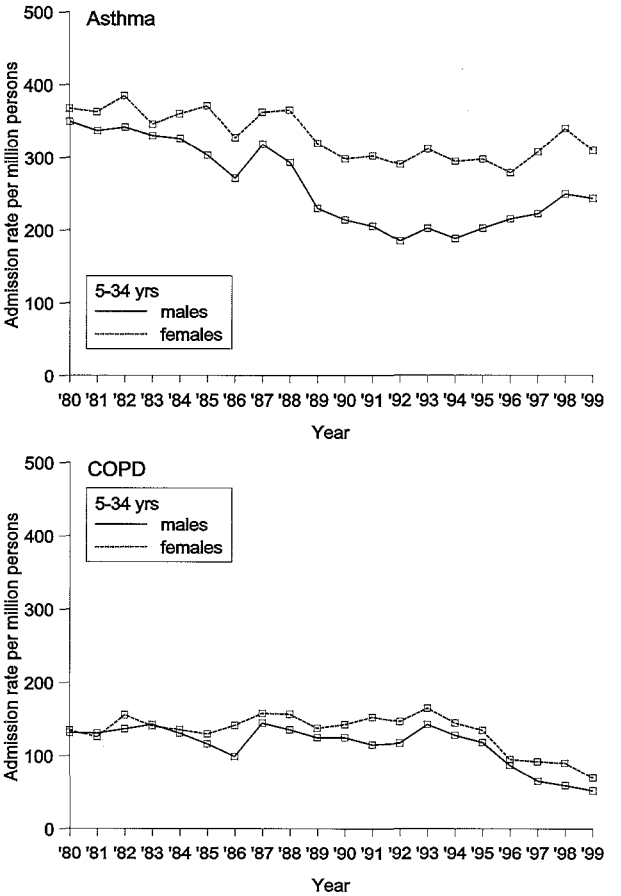

Figure 3.2 Hospital admissions for asthma (ICD-9 code 493) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496) (lower panel) in age group 5-34 years by gender in the period 1980-1999.

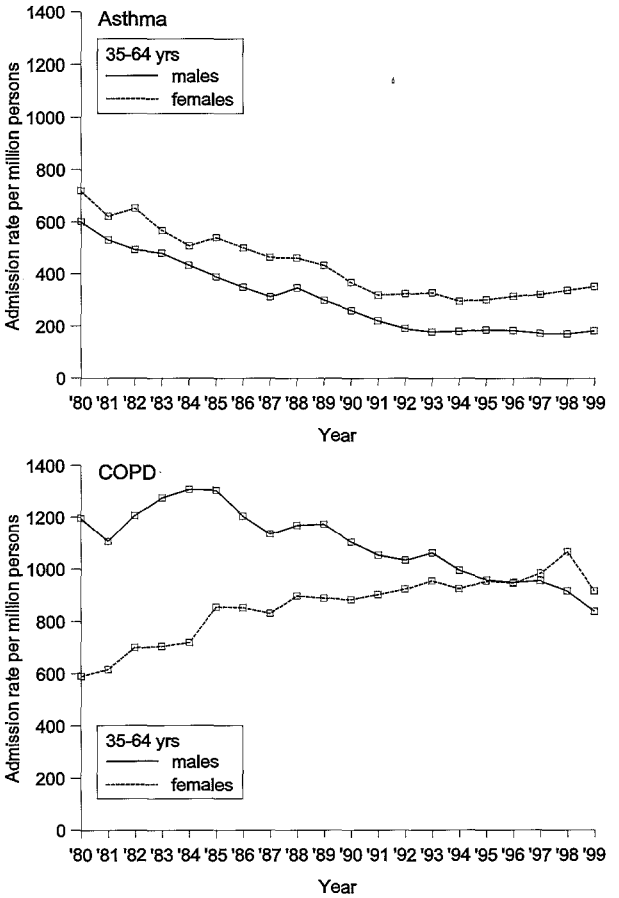

Figure 3.3 Hospital admissions for asthma (ICD-9 code 493) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496) (lower panel) in age group 35-64 years by gender in the period 1980-1999.

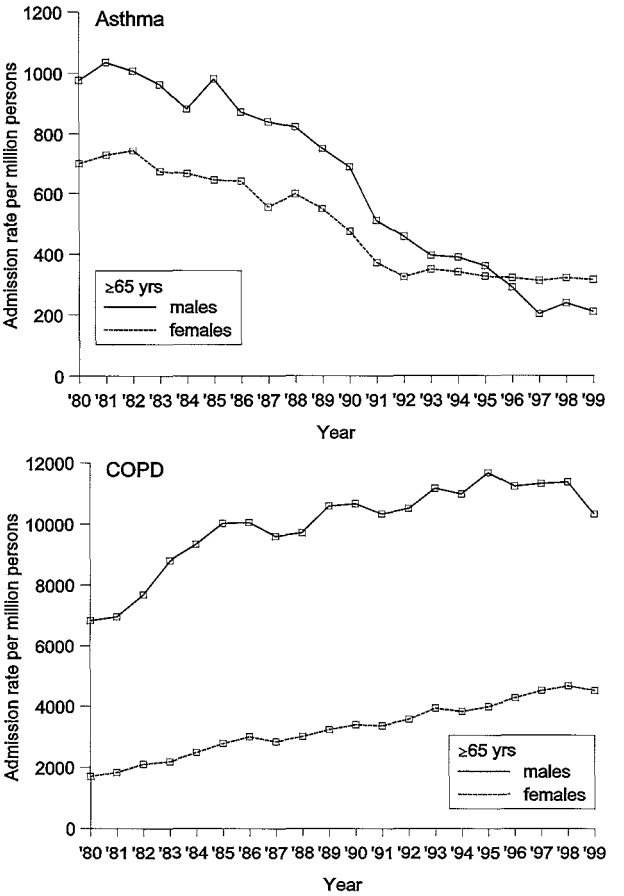

Figure 3.4 Hospital admissions for asthma (ICD-9 code 493) (upper panel) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490-492, 496) (lower panel) in age group ≥65 years by gender in the period 1980-1999.

females in the respective age groups. Note that the scales of the y-axis differ, depending on the levels of the rate.

3.3.2 Chronic obstructive pulmonary disease (COPD) in the total population

The actual number of hospital admissions and rates per million persons by age group in the Netherlands from 1980 to 1999 are presented in Appendix C, tables IV-VI. Rates show a U-shaped age-dependency with highest rates in age group ≥65 years. Significant trends (table 3.1a) and differences in slopes between the two subperiods (table 3.1b) were found.

Notable are the decreasing trends in admissions for COPD in males and females under the age of 35 years in the 1990s (figures 3.1 and 3.2). In age group 35-64 years, the admission rate in females increased and outnumbered the decreasing rate in males in the late nineties (figure 3.3). The admission rates of COPD in age group ≥65 years levelled off in males in the 1990s, but continued to increase in females (figure 3.4), and male/female ratio decreased from approximately 4 in the early 1980s to 2.5 at the end of study period.

3.3.3 Obstructive airways disease in childhood

The actual numbers and rates per million persons of the hospital admissions for asthma, COPD, acute bronchi(oli)tis, and pneumonia and influenza in the age groups 0-4 years, 5-9 years, and 10-14 years are presented in Appendix C, tables VII-XII. Admission rates were inversely related with age and highest in males, especially in age group 0-4 years. In tables 3.2a (1980-1999) and 3.2b (1980-1992 and 1993-1999) the results of the linear regression analyses are listed. For COPD, the assumption of linear regression was not valid for the total period. With respect to pneumonia and influenza in childhood, comparison of the two subperiods was not done because of the considerable fluctuations in admissions over the total period 1980-1999.

Table 3.2a Results of the linear regression y=a+b*(year-1980), y: hospital admission for the respective respiratory diseases[1] in childhood, 1980-1999

	intercept (SE)	slope (SE) p-value
ASTHMA		
0-4 years		
Males	1385 (94.5)	+86.5 (8.50) <0.001
Females	893 (60.0)	+34.9 (5.40) <0.001
5-9 years		
Males	778 (43.0)	-12.6 (3.87) <0.01
Females	435 (21.9)	-5.84 (1.97) <0.01
10-14 years		
Males	429 (24.0)	-11.2 (2.16) <0.001
Females	276 (14.0)	-3.65 (1.26) <0.01
ACUTE BRONCHI(OLI)TIS		
0-4 years		
Males	151 (321)	+180 (28.9) <0.001
Females	65.9 (241)	+128 (21.7) <0.001
5-9 years		
Males	76.6 (11.7)	-0.706 (1.05) 0.51
Females	54.3 (6.66)	-0.474 (0.599) 0.44
10-14 years		
Males	24.2 (5.26)	-0.008 (0.473) 0.99
Females	15.4 (2.65)	-0.144 (0.238) 0.55
PNEUMONIA/INFLUENZA		
0-4 years		
Males	3666 (181)	+13.3 (16.3) 0.42
Females	2713 (155)	+13.7 (14.0) 0.34
5-9 years		
Males	809 (65.7)	-2.24 (5.91) 0.71
Females	633 (47.5)	-2.34 (4.28) 0.59
10-14 years		
Males	212 (20.9)	+1.47 (1.88) 0.44
Females	163 (14.7)	+2.41 (1.32) 0.08

a, intercept; b, slope; SE, standard error.

[1)] Linear regression not carried out for COPD (ICD-9 codes 490-492, 496) for the period 1980-1999. Asthma, ICD-9 code 493; Acute bronchi(oli)tis, ICD-9 code 466; Pneumonia/influenza, ICD-9 codes 480-487.

Table 3.2b Results of the linear regression y=a+b*(year-1980), y: hospital admissions for the respective respiratory diseases[1] in childhood

Period	1980-1992 intercept (SE)	slope (SE) p-value	1993-1999 intercept (SE)	slope (SE) p-value	slope difference[2] p-value
ASTHMA					
0-4 years					
Males	1369 (70.2)	+83.9 (9.92) <0.001	3559 (509)	-45.6 (31.6) 0.21	<0.001
Females	851 (73.1)	+42.8 (10.3) <0.01	1350 (429)	+5.86 (26.6) 0.83	>0.10
5-9 years					
Males	802 (58.6)	-16.4 (8.29) 0.07	290 (156)	+17.8 (9.68) 0.13	<0.01
Females	442 (28.9)	-7.07 (4.08) 0.11	336 (147)	+0.429 (9.11) 0.96	>0.20
10-14 years					
Males	472 (26.1)	-19.9 (3.69) <0.001	168 (83.2)	+6.04 (5.16) 0.29	<0.001
Females	296 (16.4)	-7.50 (2.32) <0.01	103 (54.0)	+7.50 (3.35) 0.08	<0.001
COPD					
0-4 years					
Males	1416 (68.1)	+44.7 (9.64) <0.001	6162 (258)	-286 (16.0) <0.001	<0.001
Females	862 (44.9)	+15.0 (6.35) 0.04	3066 (129)	-139 (8.01) <0.001	<0.001
5-9 years					
Males	300 (22.0)	+5.55 (3.12) 0.10	1153 (100)	-56.3 (6.22) <0.001	<0.001
Females	190 (10.6)	+4.23 (1.50) 0.02	668 (89.2)	-31.3 (5.53) <0.01	<0.001
10-14 years					
Males	136 (9.46)	+0.242 (1.34) 0.86	459 (47.3)	-22.8 (2.93) <0.001	<0.001
Females	96.7 (10.5)	-0.071 (1.49) 0.96	271 (19.3)	-12.2 (1.20) <0.001	<0.001
ACUTE BRONCHI(OLI)TIS					
0-4 years					
Males	496 (131)	+108 (18.5) <0.001	-831 (3843)	+251 (238) 0.34	>0.20
Females	321 (101)	+75.1 (14.3) <0.001	-665 (2889)	+181 (179) 0.36	>0.20
5-9 years					
Males	55.8 (14.2)	+3.62 (2.01) 0.10	129 (25.6)	-4.57 (1.59) 0.03	<0.01
Females	45.2 (7.60)	+1.39 (1.07) 0.22	86.1 (44.0)	-2.71 (2.73) 0.37	>0.10
10-14 years					
Males	14.8 (5.70)	+2.07 (0.806) 0.03	3.43 (19.8)	+0.929 (1.23) 0.48	>0.20
Females	13.1 (3.00)	+0.335 (0.424) 0.45	25.3 (21.7)	-0.821 (1.35) 0.57	>0.20

a, intercept; b, slope; SE, standard error.
[1)] Linear regression was not carried out for pneumonia and influenza for the periods 1980-1992 and 1993-1999. [2)] slope 1980-1992 versus slope 1993-1999.

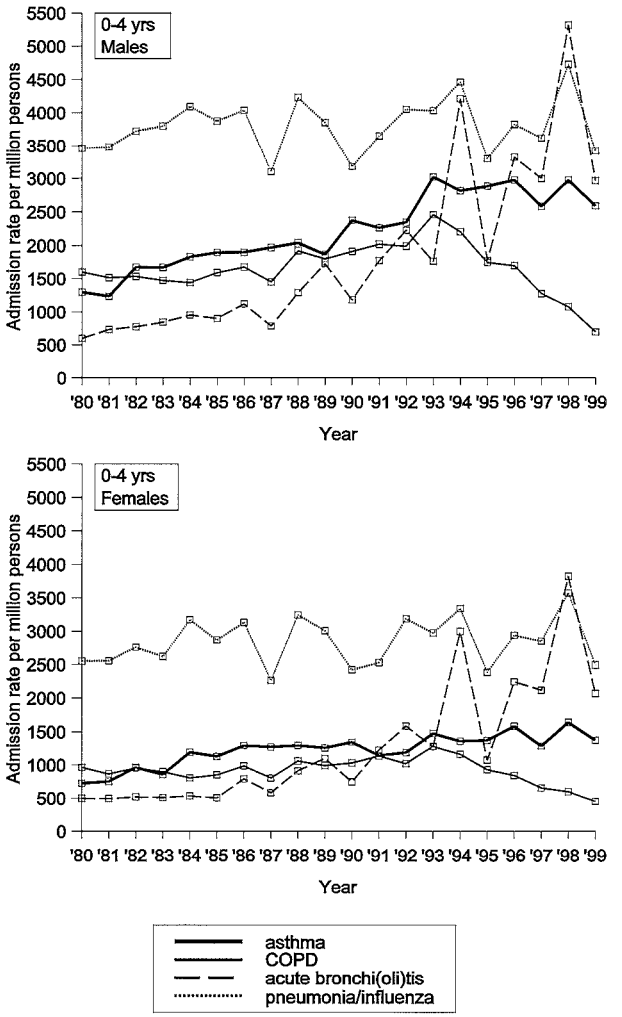

Figure 3.5 Hospital admissions for asthma (ICD-9 code 493), 'chronic obstructive pulmonary disease' (COPD) (ICD-9 codes 490-492, 496), acute bronchi(oli)tis (ICD-9 code 466), and pneumonia and influenza (ICD-9 codes 480-487) in males (upper panel) and females (lower panel) in age group 0-4 years in the period 1980-1999.

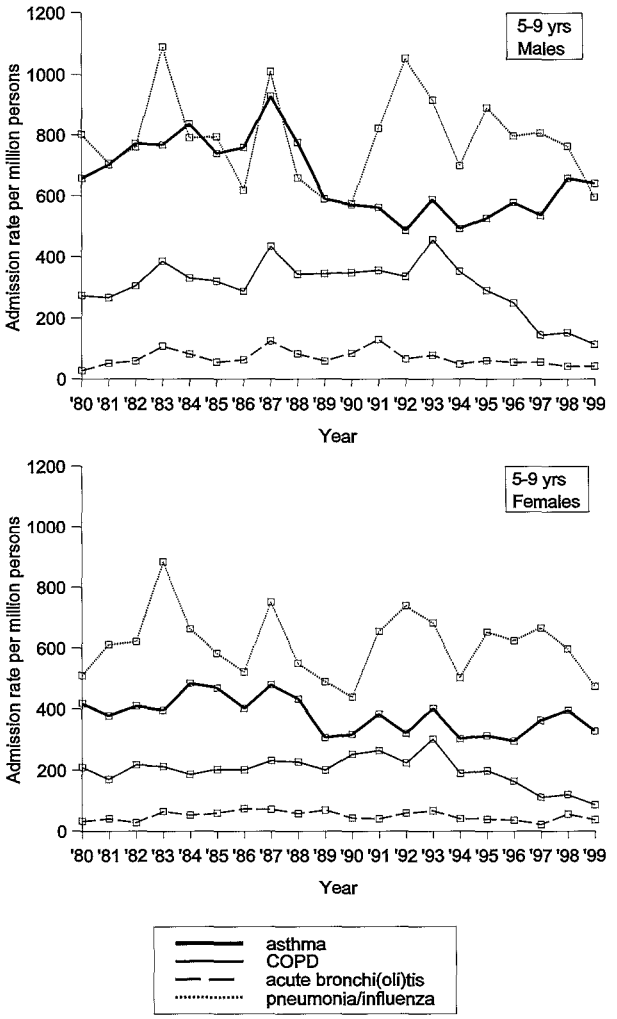

Figure 3.6 Hospital admissions for asthma (ICD-9 code 493), 'chronic obstructive pulmonary disease' (COPD) (ICD-9 codes 490-492, 496), acute bronchi(oli)tis (ICD-9 code 466), and pneumonia and influenza (ICD-9 codes 480-487) in males (upper panel) and females (lower panel) in age group 5-9 years in the period 1980-1999.

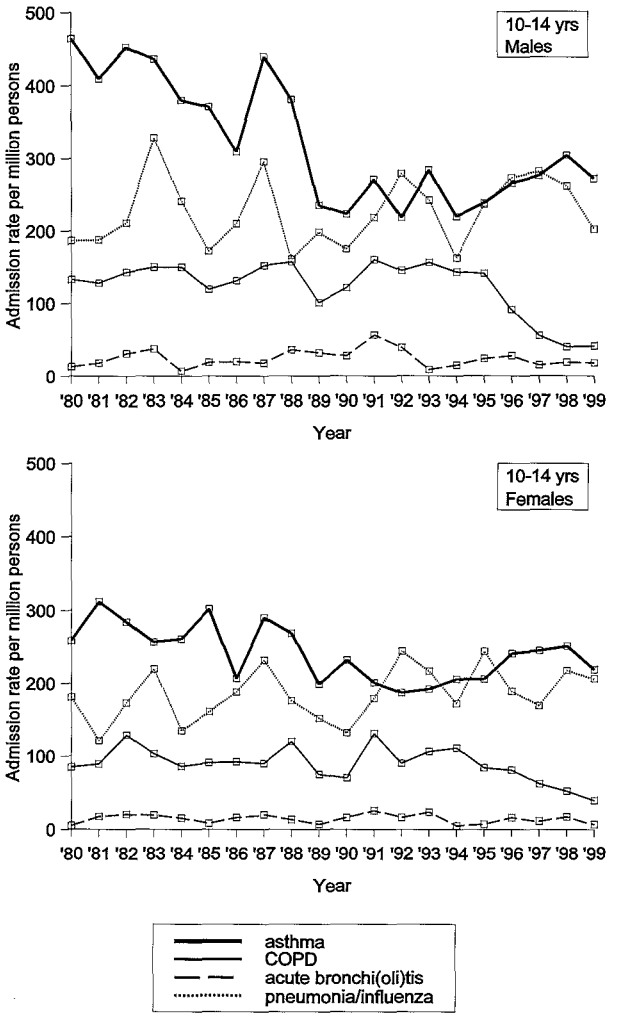

Figure 3.7 Hospital admissions for asthma (ICD-9 code 493), 'chronic obstructive pulmonary disease' (COPD) (ICD-9 codes 490-492, 496), acute bronchi(oli)tis (ICD-9 code 466), and pneumonia and influenza (ICD-9 codes 480-487) in males (upper panel) and females (lower panel) in age group 10-14 years in the period 1980-1999.

In age group 0-4 years (figure 3.5), hospital admissions for asthma increased, primarily in the subperiod 1980-1992. Notably, admissions for COPD and acute bronchi(oli)tis increased as well. After 1993 admissions for asthma levelled off and for COPD decreased strongly (table 3.2b). The hospital admissions for acute bronchi(oli)tis continued to increase, albeit not significantly, showing large fluctuations, but the slopes did not differ significantly between the two subperiods (table 3.2b).

In age groups 5-9 years (figure 3.6) and 10-14 years (figure 3.7), hospital admissions for asthma decreased significantly, in males more strongly than in females, due to the decreases in the subperiod 1980-1992. In the period 1993-1999, there was a trend towards increasing rates, the slopes differing between the two subperiods, except for females in age group 5-9 years (table 3.2b). Hospital admissions for COPD decreased significantly in both age groups after 1993. Additionally, admissions for acute bronchi(oli)tis showed a significant decrease in males in age group 5-9 years in the subperiod 1993-1999.

Hospital admissions for pneumonia and influenza fluctuated in all three age groups over the period 1980-1999, without significant trends (table 3.2a).

3.4 Discussion

We found an increase in hospital admissions for asthma in age group 0-4 years in contrast to an overall decreasing trend in the Netherlands. The trends levelled off in the 1990s, and in age group 5-34 years a slight increase occurred. Admissions for acute bronchi(oli)tis increased as well in age group 0-4 years. Hospital admissions for COPD increased continuously in females ≥35 years, which was different from trends in males. In children, we observed a marked decrease in admissions for COPD after 1993. Rates may be influenced by factors such as changes in coding practices, diagnostic labelling, prevalence and severity of asthma, health care policies, and asthma management.

Coding practices and diagnostic labelling. Changes in coding can be excluded, as for the full period under study the ninth revision of the ICD was in use by the Dutch Centre for Health Care Information, but changes in diagnostic labelling could have contributed to the observed trends. The view on the pathophysiology and subsequent treatment of asthma changed in the eighties, and guidelines for diagnosis and management of asthma were published. In the Netherlands, the umbrella-term "CARA" (equivalent to chronic non-specific lung disease (CNSLD)) was used as diagnostic label, rather than asthma or chronic bronchitis and emphysema (COPD) [37]. Moreover, a consensus meeting on asthma in children was held in 1992 [38], and "CARA" as diagnostic term became obsolete. "CARA" corresponds to ICD code 496, which is included in the codes for 'COPD'. Therefore, a change in diagnostic labelling from COPD to asthma is likely to have contributed to the trends for asthma and COPD in childhood and young adulthood in the last decade.

To what extent diagnostic transfer from "CARA" to asthma occurred in age groups 35-64 years and ≥65 years is unclear. The admission rates for COPD are high compared to those for asthma, especially at higher age. COPD is characterised by a slowly progressive and irreversible airflow limitation, caused mainly by smoking, and morbidity increases steeply with age [41]. Female gender may be an extra risk factor for hospitalisation for COPD [42]. In the Netherlands, the percentage male smokers (≥15 years) decreased from 90 in 1958 to 37 in 1999. The overall percentage female smokers was around 30, with a temporary 40% in the mid-sixties to the late-seventies, but in females between 20-49 years percentages were higher [43]. The admission rate for COPD showed in females a continuing increase, particularly in age group ≥65 years, whereas in males admissions decreased in age group 35-64 years and levelled off in age group ≥65 years in the 1990s. These trends correspond with observations in age-sex-specific prevalence of physician diagnosed COPD in the United Kingdom [44]. Notably, in age group 35-64 years the admission rate for COPD became in females even higher than in males. The trends in admissions and mortality are similar for COPD [Chapter 2]. We have argued that a labelling shift from asthma to COPD is plausible to

explain the fall in asthma mortality in age group ≥65 years in the early nineties. In the admission data, support for such a labelling shift is only found in males ≥65 years, in whom admissions for asthma decreased strongly in the 1990s.

In infancy, differentiation between acute bronchiolitis and asthma is very difficult [35]. Interestingly, in age group 0-4 years hospital admissions for acute bronchi(oli)tis showed a striking increase over the study period. From 1980 to 1987 acute bronchiolitis (ICD-9 code 466.1) contributed on average 40% and acute bronchitis (ICD code 466.0) on average 60% to the admission rate of ICD code 466 [28]. In the recent years 1997, 1998, and 1999 acute bronchiolitis made up 82%, 89%, and 84% respectively of the admission rate of ICD 466, and occurred mainly in children under the age of 1 year. In the United States, hospitalisation rates for bronchiolitis in infants increased substantially between 1980 and 1996 [45]. Attendance of day care centres is associated with respiratory infections [46], bronchial obstruction [47], and frequent wheezing [48] in early life, and increased use, especially for children <1 year, may lead to bronchiolitis at younger age when hospitalisation is more likely [45]. Respiratory syncytial virus (RSV) is the commonest cause of acute bronchiolitis. It is questioned whether RSV respiratory morbidity is a marker or a cause for the development of wheezing phenotypes including asthma [49-52]. Only a minority of the children with RSV infection need hospitalisation, and the observed increased rates are especially worrying if the hypothesis is true that RSV infection promotes the development of asthma and allergy in children [52]. The relationship between day care [46-48,53], siblings [46-48,53,54], (respiratory) infections [46,47,55], atopic sensitisation [53,54], and asthma in childhood [46-48,55] has still to be further clarified. Without regard to diagnostic difficulties, our findings that hospital admissions increased for asthma as well as for acute bronchi(oli)tis in age group 0-4 years, while admissions for pneumonia and influenza remained stable, indicate increased respiratory morbidity in young children.

Prevalence and severity of asthma. Hospital admission rates may be an indicator for the prevalence of severe asthma [56]. It has been postulated that increasing hospitalisation

of very young children may be an early reflection of the increased prevalence of asthma reported among school children [19]. Increases in the prevalence of asthma were observed in various countries [5], but also criticised [34]. In the Netherlands, an increase in percentage of primary schoolchildren with asthmatic symptoms and doctor-diagnosed asthma has been reported [57], but data on trends in severity are not available. Admission rates for asthma are low compared with data from other countries, but patterns in gender are similar [13,58,59]. The low rates may be explained by differences in diagnostic labelling, as "CARA" would have been coded as ICD 496 (COPD). However, in adults admission rates for COPD were also lower than reported from other countries [60,61]. When admissions for asthma and COPD in childhood were combined, rates were still lower than admission rates for asthma in childhood in other countries [12,19]. Substantial geographical differences in prevalence of asthma symptoms and diagnosed asthma exist in children [62] and adults [63]. High prevalences were reported from centres in the British Isles, New Zealand, Australia, and the United States in the early nineties [62,63]. The prevalence of diagnosed asthma in adults was lower in the Netherlands, but the prevalence of some symptoms ('wheeze with breathlessness' and 'cough at night') reached a similar level as in these centres [63].

Health care policies. Health service characteristics may affect admission rates for asthma [64]. It was also suggested that the observed rise in hospitalisation in childhood in the United Kingdom may reflect trends in provision and utilisation of health services rather than major changes in morbidity [10]. In the Netherlands, an actual reduction in the number of hospital beds was forced in the eighties, and a decrease in admissions for all causes and length of stay in hospital in childhood occurred [28]. Despite this development, admissions for asthma increased in young children. Length of stay for asthma might give an indication about severity threshold for hospital admissions within the management of childhood asthma [11]. Although decreasing, it was high compared with other countries in the 1980s [28]. Despite a further substantial 35-40% decrease from 1990 to 1999, the length of stay still remained higher than in other countries [17,58,65,66]. However, in one study more than 80% of the hospitalisations in children

aged 2-14 years was shorter than 24 hours [66], drawing attention to the possibility of differences in management of acute asthma in hospital, or differences in coding practices of the admission, i.e. between day care and ward admissions, hampering international comparisons. It is remarkable though, that in a Dutch study a readmission rate of 26% was found [67], similar to findings in the age group 0-4 years from other countries [14,15,68]. In that study, as in the present data, admissions were ward admissions with at least one overnight stay. In the Netherlands, day care admissions for asthma were negligible in the 1980s, but started to rise in the late 1990s. From 1993 more than 95% of the day care admissions are registered by the Dutch Centre for Health Care Information according to the ICD codes. In 1993 the admission ratio of ward to day care for asthma was about 60:1 in age group 0-4 years and 54:1 in the total population, and had decreased in 1999 to 18:1 and 8.6:1, respectively. Hence, it is not plausible that a shift to day care was a contributory factor for the observed trends in admissions for asthma in the study period, but it may be a factor to take into account in future analyses.

Readmissions may contribute to the increasing admission rates for asthma [1], but this was not found by others [14]. In a more recent study, first admissions for asthma increased, but readmissions decreased, particularly in 0-3 years olds, possibly due to increasing use of anti-inflammatory treatment which reduces severity of disease [19]. Apart from severity of asthma, social factors can play a role in hospitalisation. Ethnicity rather than deprivation seems to be a risk factor, which may be due to undertreatment with inhaled steroids rather than to a higher prevalence of asthma [69,70]. In the Netherlands, ethnicity was not coded at admission. Also, no national data are available on first admissions and repeat admissions. Hence, their contribution to the age-specific trends in hospitalisation cannot be estimated.

Asthma management. In children [71] and adults [72] admitted to hospital for asthma in the United States, management was found not to comply with the guidelines. In general, the goals for asthma control appeared not to be met [73]. However, reductions

in hospital admissions for asthma in various countries have been linked with increases in prophylactic treatment [16-19]. In the Netherlands, the trends might reflect better asthma management as well. Hospital admissions for asthma decreased from the age of 5 years and the recent increases at the ages between 5 and 34 years were smaller than the concurrent decreases in admissions for COPD. Prescriptions for anti-inflammatory agents increased from 1981 in all age groups [74,75]. A substantial increase was found in age group 0-4 years between 1990 and 1993 [Chapter 4]. Inhaler devices have been adapted for treatment of asthma in young children, but only recently attempts are made to enhance their therapeutic efficacy [76]. The levelling off of the increase in age group 0-4 years in the 1990s with a concurrent decrease in admissions for COPD suggests a true improvement in management.

Summary. In the Netherlands, hospital admission rates for asthma showed an overall decrease over the period 1980-1999, except for the increase in age group 0-4 years. The trends levelled off in the 1990s. The guidelines on diagnosis and management of asthma, and the Dutch consensus on asthma in children, may have contributed to the observed trends by their influence on diagnostic labelling and by stimulating prophylactic treatment for asthma. A diagnostic transfer from COPD to asthma is likely to have occurred in childhood and young adulthood after 1993. The increasing hospital admission rates for acute bronchi(oli)tis in age group 0-4 years, and the increasing hospital admission rates for COPD in females over 35 years are cause for concern.

References

1. Anderson HR. Increase in hospitalisation for childhood asthma. Arch Dis Child 1978; 53: 295-300.
2. Jackson RT, Mitchell EA. Trends in hospital admission rates and drug treatment of asthma in New Zealand. NZ Med J 1983; 96: 728-730.
3. Mitchell EA. International trends in hospital admission rates for asthma. Arch Dis Child 1985; 60: 376-378.
4. Evans R III, Mullally DI, Wilson RW, Gergen PJ, Rosenberg HM, Grauman JS, Chevarley FM, Feinleib M. National trends in the morbidity and mortality of asthma in the US. Prevalence, hospitalization and death from asthma over two decades: 1965-1984. Chest 1987; 91(suppl): 65S-74S.
5. Grant EN, Wagner R, Weiss KB. Observations on emerging patterns of asthma in our society. J Allergy Clin Immunol 1999; 104: S1-S9.
6. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.
7. Baldwin DR, Ormerod LP, Mackay AD, Stableforth DE. Changes in hospital management of acute severe asthma by thoracic and general physicians in Birmingham and Manchester during 1978 and 1985. Thorax 1990; 45: 130-134.
8. Storr J, Barrell E, Lenney W. Rising asthma admissions and self referral. Arch Dis Child 1988; 63: 774-779.
9. Anderson HR, Bailey P, West S. Trends in the hospital care of acute childhood asthma 1970-8: a regional study. Br Med J 1980; 281: 1191-1194.
10. Strachan DP, Anderson HR. Trends in hospital admission rates for asthma in children. Br Med J 1992; 304: 819-820.
11. Anderson HR. Is the prevalence of asthma changing? Arch Dis Child 1989; 64: 172-175.
12. Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA 1990; 264: 1688-1692.
13. Hyndman SJ, Williams DRR, Merrill SL, Lipscombe JM, Palmer CR. Rates of admission to hospital for asthma. Br Med J 1994; 308: 1596-1600.
14. Senthilselvan A. Effect of readmissions on increasing hospital admissions for asthma in children. Thorax 1995; 50: 934-936.
15. To T, Dick P, Feldman W, Hernandez R. A cohort study on childhood asthma admissions and readmissions. Pediatrics 1996; 98: 191-195.

16. Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand: what lessons have been learned? Thorax 1995; 50: 303-311.

17. Wennergren G, Kristjánsson S, Strannegård I-L. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in the prevalence of asthma. J Allergy Clin Immunol 1996; 97: 742-748.

18. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997; 277: 887-891.

19. Jónasson G, Carlsen K-H, Lødrup Carlsen KC, Mowinckel P, Leegaard J, Halvorsen KS. Trends in hospital admissions for childhood asthma in Oslo, Norway, 1980-95. Allergy 2000; 55: 232-239.

20. Warner JO, Götz M, Landau LI, Levison H, Milner AD, Pedersen S, Silverman M. Management of asthma: a consensus statement. Arch Dis Child 1989; 64: 1065-1079.

21. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: I - chronic persistent asthma. Br Med J 1990; 301: 651-653.

22. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: II - acute severe asthma. Br Med J 1990; 301: 797-800.

23. International consensus report on the diagnosis and management of asthma. Clin Exp Allergy 1992; 22(Suppl 1): 1-72.

24. Warner JO, et al. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992; 67: 240-248.

25. British Thoracic Society, British Paediatric Association, Royal College of Physicians, King's Fund Centre, National Asthma Campaign, Royal College of General Practitioners, General Practitioners in Asthma Group, British Association of Accident and Emergency Medicine, British Paediatric Respiratory Group. Guidelines on the management of asthma. Thorax 1993; 48(Suppl 2): S1-S24.

26. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention NHLBI/WHO workshop report. National Institutes of Health, National Heart, Lung, and Blood Institute. Bethesda, Maryland, USA. 1995; Publication No. 95-3659.

27. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.

28. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.

29. Conway SP, Littlewood JM. Admission to hospital with asthma. Arch Dis Child 1985; 60: 636-639.

30. Bucknall CE, Robertson C, Moran F, Stevenson RD. Management of asthma in hospital: a prospective audit. Br Med J 1988; 296: 1637-1639.

31. Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. Br Med J 1983; 286: 1253-1256.

32. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-1199.

33. Hill R, Williams J, Tattersfield A, Britton J. Change in use of asthma as a diagnostic label for wheezing illness in schoolchildren. Br Med J 1989; 299: 898.

34. Magnus P, Jaakkola JJK. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. Br Med J 1997; 314: 1795-1799.

35. McConnochie KM. Bronchiolitis. What's in the name? Am J Dis Child 1983; 137: 11-13.

36. Reed CE. The natural history of asthma in adults: the problem of irreversibility. J Allergy Clin Immunol 1999; 103: 539-547.

37. Sluiter HJ, Koëter GH, de Monchy JGR, Postma DS, de Vries K, Orie NGM. The Dutch Hypothesis (chronic non-specific lung disease) revisited. Eur Respir J 1991; 4: 479-489.

38. Kerrebijn KF. Consensus on asthma in children (English summary). Ned Tijdschr Geneeskd 1993; 137: 1239-1246.

39. Stichting Informatiecentrum voor de Gezondheidszorg. Ontslagen patienten naar geslacht, hoofddiagnose en leeftijd. Diagnose Ziekenhuizen Jaarwerk Tabellen 1980-1999. Utrecht: Stichting Informatiecentrum voor de Gezondheidszorg.

40. Centraal Bureau voor de Statistiek. Leeftijdsopbouw naar burgelijke staat en geslacht, gemiddeld 1980-1999. Voorburg: Centraal Bureau voor de Statistiek.

41. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J, on behalf of the Task Force. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995; 8: 1398-1420.

42. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. Eur Respir J 1997; 10: 822-827.

43. Stichting Volksgezondheid en Roken (Stivoro). Jaarverslag 1999. Den Haag: Stichting Volksgezondheid en Roken; 2000.

44. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, Pride NB. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000; 55: 789-794.

45. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999; 282: 1440-1446.

46. Nystad W, Skrondal A, Magnus P. Day care attendance, recurrent respiratory tract infections and asthma. Int J Epidemiol 1999; 28: 882-887.

47. Nafstad P, Magnus P, Jaakkola JJK. Early respiratory infections and childhood asthma. Pediatrics 2000; 106: (3) e38.

48. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000; 343: 538-543.

49. Godfrey S. Bronchiolitis and asthma in infancy and early childhood. Thorax 1996; 51 (suppl 2): S60-S64.

50. Everard ML. What link between early respiratory viral infections and atopic asthma [commentary]? Lancet 1999; 354: 527-528.

51. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999; 354: 541-545.

52. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000; 161: 1501-1507.

53. Krämer U, Heinrich J, Wjst M, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. Lancet 1999; 353: 450-454.

54. Von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann H-H. Skin test reactivity and number of siblings. Br Med J 1994; 308: 692-695.

55. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, Wahn U, MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. Br Med J 2001; 322: 390-395.

56. Jalaludin B, Chey T, Holmwood M, Chipps J, Hanson R, Corbett S, Leeder S. Admission rates as an indicator of the prevalence of severe asthma in the community. Aust N Z J Public Health 1998; 22: 214-219.

57. Van der Wal MF, Uitenbroek DG, Verhoeff AP. Increased proportion of elementary school pupils with asthmatic symptoms in the Netherlands, 1984/'85-1994/'95; a study of the literature (English summary). Ned Tijdschr Geneeskd 2000; 144: 1780-1784.

58. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. JAMA 1992; 268: 3437-3440.

59. Harju T, Keistinen T, Tuuponen T, Kivelä S-L. Hospital admissions of asthmatics by age and sex. Allergy 1996; 51: 693-696.

60. Lacasse Y, Brooks D, Goldstein RS. Trends in the epidemiology of COPD in Canada, 1980 to 1995. Chest 1999; 116: 306-313.

61. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest 2000; 117(suppl): 5S-9S.

62. The international study of asthma and allergies in childhood (ISAAC) steering committee. Worldwide variations in the prevalence of asthma symptoms: the international study of asthma and allergies in childhood (ISAAC). Eur Respir J 1998; 12: 315-335.

63. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1996; 9: 687-695.

64. Burney PGJ, Papacosta AO, Withey CH, Colley JRT, Holland WW. Hospital admission rates and the prevalence of asthma symptoms in 20 local authority districts. Thorax 1991; 46: 574-579.

65. Strömberg L. Decreasing admissions for childhood asthma to a Swedish county hospital. Acta Paediatr 1996; 85: 173-176.

66. Benito J, Lopez Bayon J, Montiano J, Sanchez J, Mintegui S, Vazquez C. Time trends in acute childhood asthma in Basque Country, Spain. Pediatr Pulmonol 1995; 20: 184-188.

67. Wever-Hess J, Hermans J, Kouwenberg JM, Duiverman EJ, Wever AMJ. Hospital admissions and readmissions for asthma in the age group 0-4 years. Pediatr Pulmonol 2001: 31: 30-36.

68. Farber HJ. Risk of readmission to hospital for pediatric asthma. J Asthma 1998; 35: 95-99.

69. Gilthorpe MS, Lay-Yee R, Wilson RC, Walters S, Griffiths RK, Bedi R. Variations in hospitalization rates for asthma among Black and minority ethnic communities. Respir Med 1998; 92: 642-648.

70. Gottlieb DJ, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates. A small area analysis in Boston. Chest 1995; 108: 28-35.

71. Dakin CJ, Wales S, Field P, Henry RL, Morton J. A quality assurance review of outpatient care of children with life-threatening asthma exacerbations. J Paediatr Child Health 2000; 36: 23-26.

72. Hartert TV, Windom HH, Peebles RS, Freidhoff LR, Togias A. Inadequate outpatient medical therapy for patients with asthma admitted to two urban hospitals. Am J Medicine 1996; 100: 386-394.

73. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the asthma insights and reality in Europe (AIRE) study. Eur Respir J 2000; 16: 802-807.

74. Wever-Hess J, Kouwenberg JM, Wever AMJ. Trends in consultations and prescriptions for obstructive airways disease in children (English summary). Ned Tijdschr Geneeskd 1993; 137: 1246-1251.

75. Wever AMJ, Wever-Hess J. Trends in consultations and prescriptions for obstructive airways disease in the Netherlands. Proceedings of the British Thoracic Society. Thorax 1993; 48: 444-445.

76. Janssens HM, Heijnen EMEW, de Jong VM, Hop WCJ, Holland WPJ, de Jongste JC, Tiddens HAWM. Aerosol delivery from spacers in wheezy infants: a daily life study. Eur Respir J 2000; 16: 850-856.

CHAPTER 4
CONSULTATIONS AND PRESCRIPTIONS FOR ASTHMA AND COPD IN THE NETHERLANDS, 1981-1993

Abstract

The rising mortality and morbidity associated with asthma in the eighties prompted to develop guidelines on diagnosis, treatment and management of asthma. To evaluate their impact in the Netherlands, we analysed national data on consultations (first and repeat) and prescriptions in those having ambulatory care for asthma and chronic obstructive pulmonary disease (COPD) by age group (0-4 years, 5-11 years, 12-19 years, 5-39 years, 40-64 years, and ≥65 years) and doctor's category (general practitioners (GPs) and specialists) over the period 1981-1993. Prescriptions were subdivided into (1) pulmonary medication: β_2-agonists, anticholinergics, ketotifen, methylxanthines, sodium cromoglycate, inhaled steroids, oral steroids, (2) antibiotics, (3) other drugs. We calculated age-specific rates per 1000 persons per year and analysed time trends by least squares regression. Rates of first consultations remained steady, except for the increase in age group 0-4 years in specialists. Rates of repeat consultations increased in age groups 0-4 years and 5-11 years for both GPs and specialists, as well as in age groups 12-19 years and 5-39 years for specialists. Specialist consultations decreased in age group 40-64 years. Prescription rates of pulmonary medication increased in all age groups, except for 40-64 years, both by GPs and specialists. In age groups 0-4 years and 40-64 years, a decrease in GP prescriptions for the 'other drugs' occurred. Trends in prescriptions for the various classes of drugs within the pulmonary medication group were in line with the guidelines. Prescriptions for antibiotics showed no trends. The ratios of prescription rate to consultation rate for the anti-inflammatory drugs increased significantly in all age groups. In conclusion, the findings suggest a stable incidence of asthma and COPD in the Netherlands,

improvement in care, and an increase in prevalence and (or) severity of obstructive airways disease in children over the period 1981-1993.

4.1 Introduction

The rising mortality and morbidity associated with asthma in the eighties was not expected. The therapeutic possibilities had greatly improved by the introduction of cromones and inhaled corticosteroids as anti-inflammatory agents together with selective β_2-agonists and methylxanthines as bronchodilators. Sales and prescriptions of anti-asthma drugs had increased [1-3], but the use of β_2-agonists was associated with negative effects [4,5]. Guidelines on diagnosis, treatment and management of asthma have been developed and updated nationally and internationally since 1989 [6-12], resulting in a Global Initiative for Asthma by the National Heart, Lung, and Blood Institute and the World Health Organization in 1995 [13]. Dutch guidelines were issued in 1991 for specialists [14,15] and in 1992 for general practitioners [16-18]. The establishment of asthma as an inflammatory disorder implied anti-inflammatory drugs as mainstay treatment and bronchodilators as relief medication.

The Institute of Medical Statistics (IMS) in the Netherlands can provide national data on consultations and prescriptions in patients receiving ambulatory care. Previous reports indicated an increase in prescriptions for anti-asthma medication over the period 1981-1990 [19,20]. This chapter presents the data on consultations and prescriptions from 1981 up to 1993. The aim was to evaluate parameters of asthma management in ambulatory care, and to determine whether changes were in line with the published guidelines.

4.2 Material and methods

IMS data

In the Netherlands, the IMS obtains information on consultations and prescriptions in ambulatory care by quarterly samples of 325 general practitioners (GPs) and specialists. The physicians are asked to record all doctor-patient contacts on special forms during 1 week. This results in information from circa 1300 physicians per year, 660 GPs and 640 specialists. The information is processed anonymously and is used to calculate national consultation and prescription data. The doctor's diagnosis is recorded according to the International Classification of Diseases (ICD) codes. For the purpose of this study we obtained the national data from the Diagnosis Index of the IMS on asthma (ICD code 493) and chronic obstructive pulmonary disease (COPD) (comprising ICD codes 490, 491, 492, and 496) for the following age groups: 0-4 years, 5-11 years, 12-19 years, 5-39 years, 40-64 years, and ≥65 years, and the following years: 1981, 1983, 1986, 1988 (consultations only), 1990, and 1993. Emphysema (ICD code 492) was evaluated from age 40. Code 496 (chronic obstructive airway disease not classified elsewhere) turned out to be hardly used and was thus excluded from the analysis. From 1981-1987 ICD revision 8 was in operation, and from 1988-1993 ICD revision 9. The major difference is that under ICD-8 the diagnostic label "CARA" was coded as asthma, code 493, and under ICD-9 "CARA" was coded separately from asthma as 493.93. "CARA" stands for Chronische Aspecifieke Respiratoire Aandoeningen, which is equivalent to the English term chronic nonspecific lung disease (CNSLD). In the Netherlands, contrary to other countries, the term "CARA" has been widely used [21,22]. Therefore, data on asthma and COPD were combined in the trend analysis.

Consultations were divided into first and repeat consultations. The prescriptions were divided into 3 main categories:

- pulmonary medication, comprising β_2-agonists, anticholinergics (including deptropine in childhood), ketotifen, methylxanthines, sodium cromoglycate, inhaled steroids, and oral steroids,

- antibiotics, and
- other drugs (such as antitussives, expectorants, mucolytics).

The data from GPs and specialists were analysed separately.

Data analysis

We used annual mean population age structures [23] to calculate rates per 1000 persons for the number of consultations and the number of prescriptions in the respective calender years in the respective age groups. We performed time trend analyses over the period 1981-1993 on the age specific rates for consultations and for prescriptions for the 3 main categories by means of least squares linear regression, using the statistical package SPSS. The coefficient of the slope reflected the annual change in the respective rate, and we tested whether the change was significantly positive or negative over the study period. A p-value <0.05 was considered significant to give a slope different from zero. Additionally, the trends in prescriptions of the drugs in the pulmonary medication category were examined within the different classes. These data are descriptively presented.

We calculated ratios of prescription rate to consultation rate for GP and specialist by age group, as proxy for drug treatment intensity. This was done for all drugs combined, for anti-inflammatory drugs (sodium cromoglycate, inhaled steroids, and oral steroids), and for bronchodilators (β_2-agonists, anticholinergics, and methylxanthines). Time trend analyses were performed on these ratios.

1993

The change by IMS from ICD-8 to ICD-9 for coding since 1988 allowed to analyse the data on asthma separate from "CARA". The 1993 data were evaluated by the diagnostic labels asthma (ICD 493), "CARA" (ICD 493.93), chronic bronchitis (ICD 491), bronchitis not specified as acute or chronic (ICD 490), and emphysema (ICD 492), with the aim to address the issue whether diagnostic label carried relevance to treatment pattern.

4.3 Results

4.3.1 Trends in consultations and prescriptions in the total population

The number of first consultations in GPs showed no significant trends, but in specialists a significant increase in age group 0-4 years ($p=0.02$) was found and a significant, small decrease in age group 40-64 years ($p=0.04$). Repeat consultations increased significantly in age group 0-4 years in both GPs ($p<0.01$) and specialists ($p<0.001$), and in age group 5-39 years in specialists ($p=0.02$), whereas repeat consultations decreased in age group 40-64 years in specialists ($p<0.01$). Figure 4.1 illustrates the trends in the consultation rates.

Prescriptions by GPs for pulmonary medication increased significantly in the age groups 0-4 years ($p<0.001$), 5-39 years ($p=0.02$), and ≥65 years ($p=0.02$), as did the prescriptions by specialists in these age groups ($p<0.001$, $p=0.04$, and $p=0.02$ respectively) (figure 4.2). No trends were seen regarding antibiotics. The prescription rates of the 'other drugs' showed a significant decrease in age groups 0-4 years ($p<0.01$) and 40-64 years ($p=0.03$) for GP prescriptions (figure 4.2).

The trends in prescription rates of the different classes of drugs within the pulmonary medication category are shown in figure 4.3 (GP) and figure 4.4 (specialist). Most marked is the increase in prescriptions for inhaled steroids in all age groups and for anticholinergics in age groups 0-4 years and ≥65 years, and the decrease in prescriptions for xanthines in all age groups.

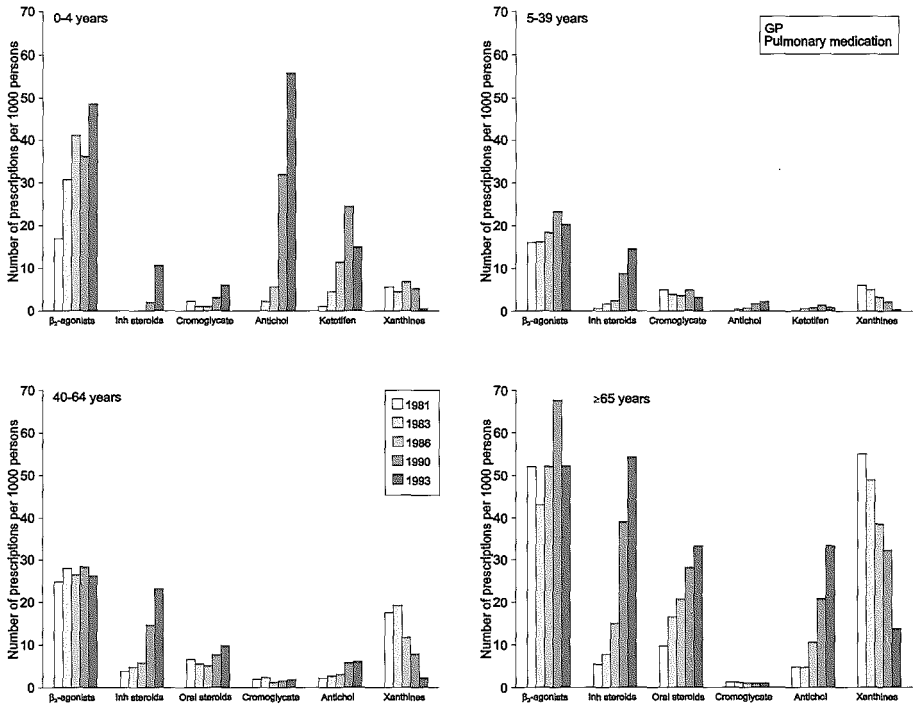

Figure 4.3 Number of prescriptions for pulmonary medication for asthma and COPD per 1000 persons by GP in the four age groups in the total population, in column presented for the years 1981, 1983, 1986, 1990, and 1993 successively, broken down into pharmacological groups of drugs.
Age groups 0-4 years and 5-39 years: β_2-agonists, inhaled steroids, sodium cromoglycate, anticholinergics, ketotifen, and methylxanthines; age groups 40-64 years and ≥65 years: β_2-agonists, inhaled steroids, oral steroids, sodium cromoglycate, anticholinergics, and methylxanthines.

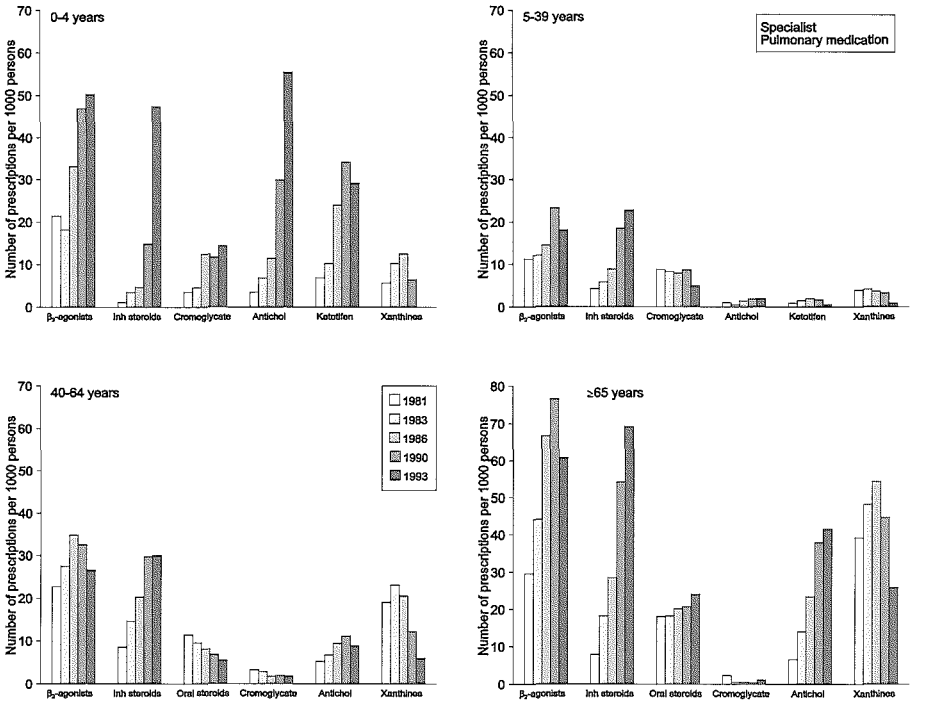

Figure 4.4 Number of prescriptions for pulmonary medication for asthma and COPD per 1000 persons by specialist in the four age groups in the total population, in column presented for the years 1981, 1983, 1986, 1990, and 1993 successively, broken down into pharmacological groups of drugs.

Age groups 0-4 years and 5-39 years: β_2-agonists, inhaled steroids, sodium cromoglycate, anticholinergics, ketotifen, and methylxanthines; age groups 40-64 years and ≥65 years: β_2-agonists, inhaled steroids, oral steroids, sodium cromoglycate, anticholinergics, and methylxanthines.

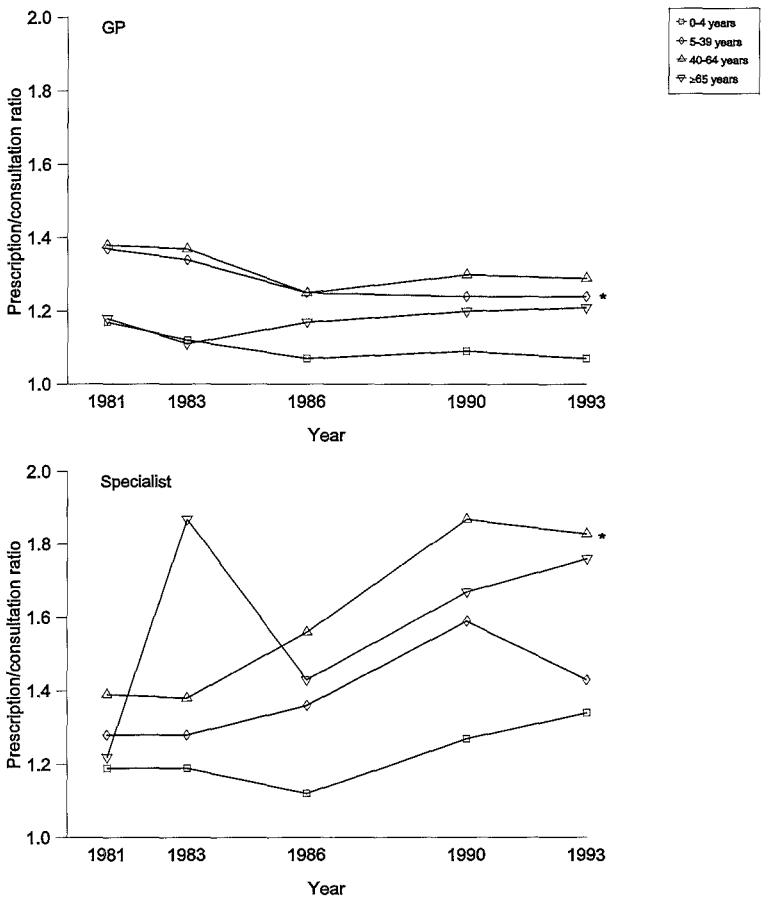

Figure 4.5 Number of prescriptions per consultation for asthma and COPD by GP (upper panel) and specialist (lower panel) by age group in the total population, 1981-1993. *, Trend statistically significant ($p<0.05$).

The rates of consultations and prescriptions per 1000 persons were higher in the youngest and the oldest age group compared to the middle age groups. However, taking into account the ratios of prescription rate to consultation rate, treatment intensity was overall similar (figure 4.5). The GP's ratio in age group 5-39 years decreased ($p=0.04$) and the specialist's ratio in age group 40-64 years increased ($p=0.01$).

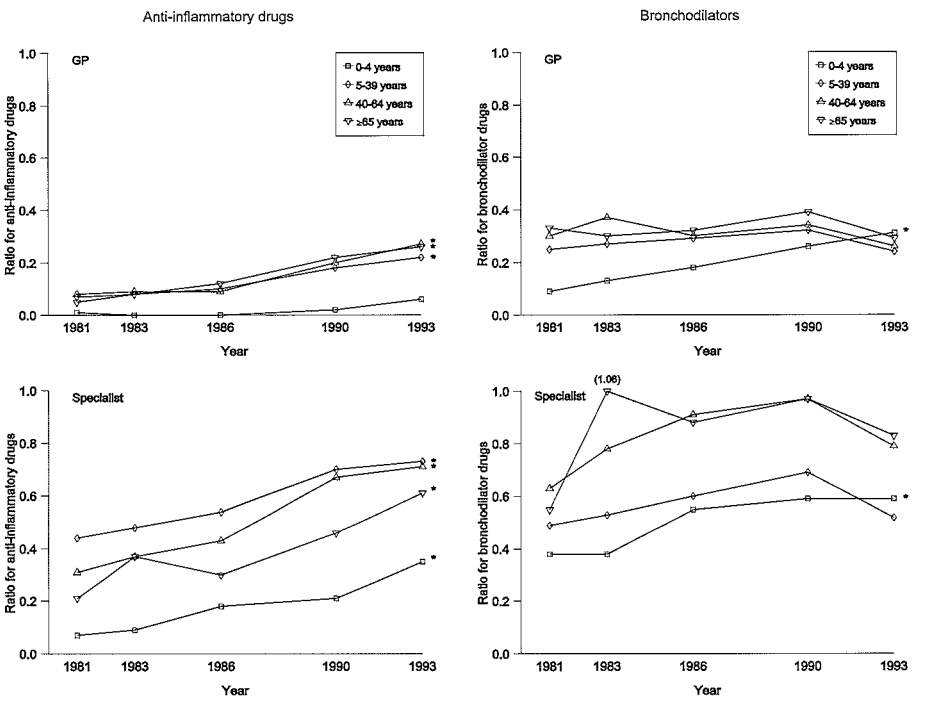

Figure 4.6 Number of prescriptions per consultation for asthma and COPD for anti-inflammatory drugs (on the left) and bronchodilators (on the right) by GP (upper panels) and specialist (lower panels) by age group in the total population, 1981-1993. Anti-inflammatory drugs: inhaled steroids, sodium cromoglycate, and oral steroids; bronchodilators: β_2-agonists, anticholinergics, and methylxanthines.

*, Trend statistically significant ($p<0.05$).

For the anti-inflammatory drugs (inhaled steroids, sodium cromoglycate, oral steroids), the number of prescriptions per consultation (ratio) increased significantly in the 4 age groups between 1981 and 1993 except for the GP's ratio in age group 0-4 years (p-values in the respective age groups for GP: 0.09, <0.01, 0.02, and <0.001; for specialist: 0.01, <0.01, 0.01, and 0.03) (figure 4.6). The prescription/consultation ratios for bronchodilators (β_2-agonists, anticholinergics, methylxanthines) increased in the 1980s, but bronchodilators were consistently less frequently prescribed per consultation in

1993 than in 1990, except for the increase in the ratio in age group 0-4 years (GP: $p<0.001$, specialist: $p=0.01$) (figure 4.6).

4.3.2 Trends in consultations and prescriptions in childhood

This section concerns the age groups 0-4 years, 5-11 years, and 12-19 years. The age group 0-4 years was also represented in section 4.3.1 as part of the total population.

No significant trends were found in first consultations, with the exception of an increase for age group 0-4 years in specialists ($p=0.02$). Repeat consultations increased significantly in all age groups, except for GPs in age group 12-19 years (0-4 years: GP, $p<0.01$; specialist, $p<0.001$; 5-11 years: GP, $p=0.02$; specialist, $p<0.01$; and 12-19 years: GP, $p=0.07$; specialist, $p<0.05$). Figure 4.7 illustrates the trends in consultation rates between 1981 and 1993.

Prescriptions by GPs for pulmonary medication increased significantly in all three age groups (0-4 years: $p<0.001$; 5-11 years: $p<0.01$; 12-19 years: $p=0.04$). Prescriptions by specialists increased significantly in the age groups 0-4 years ($p<0.001$) and 5-11 years ($p<0.01$), while the trend in age group 12-19 years nearly reached statistical significance ($p=0.054$). Prescriptions for antibiotics showed no significant trends. Prescriptions by GPs for the 'other drugs' decreased significantly in age group 0-4 years ($p<0.01$). Figure 4.8 shows the rates of prescriptions for these 3 main categories of drugs.

The trends in prescription rates of the different classes of drugs within the pulmonary medication category are shown in figure 4.9 (GP) and figure 4.10 (specialist). In all 3 age groups prescription rates of inhaled steroids increased markedly, as did prescription rates of β_2-agonists and anticholinergics in age group 0-4 years. In age groups 5-11 years and 12-19 years, prescriptions for β_2-agonists increased as well until 1990.

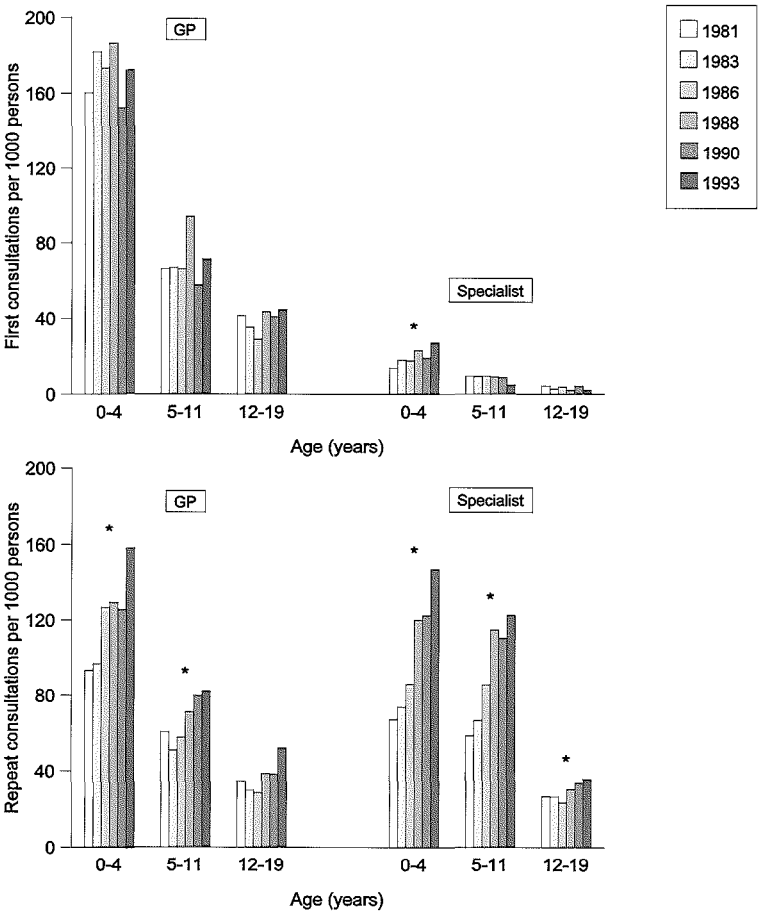

Figure 4.7 Number of first consultations (upper panel) and repeat consultations (lower panel) for asthma and COPD per 1000 persons by doctor's category and age group in childhood, in column presented for the years 1981, 1983, 1986, 1988, 1990, and 1993 successively.
*, Trend statistically significant ($p<0.05$).

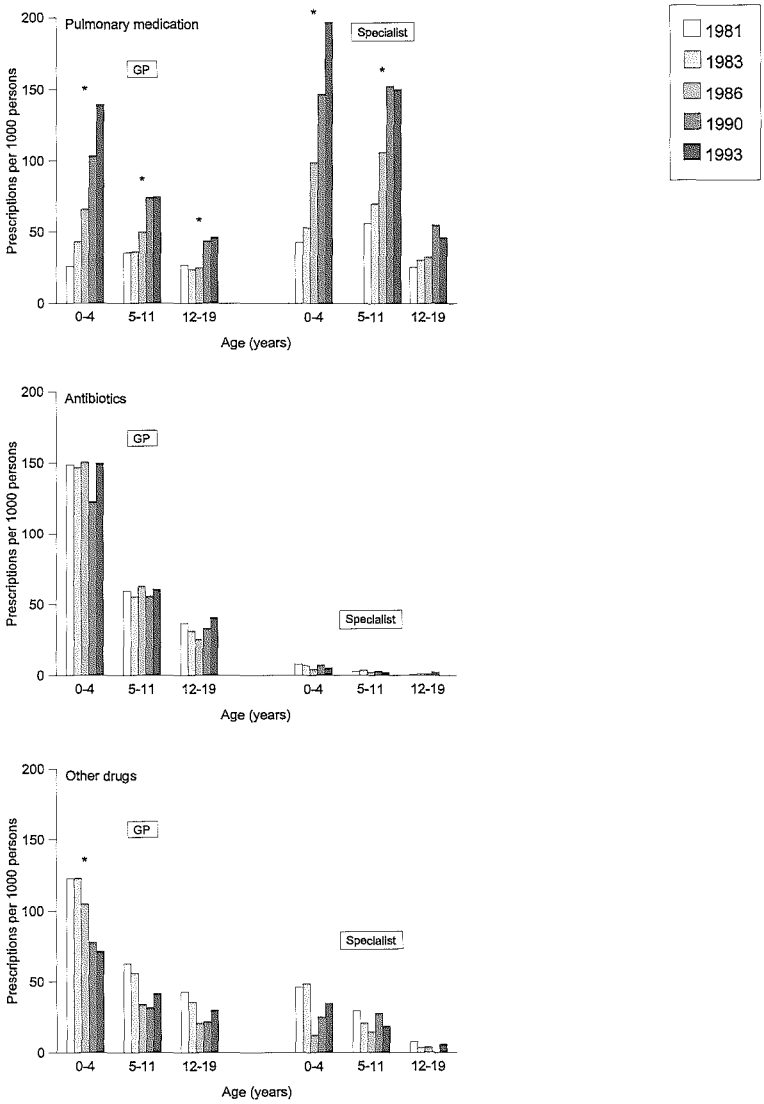

Figure 4.8 Number of prescriptions for asthma and COPD per 1000 persons for pulmonary medication (upper panel), antibiotics (middle panel), and the 'other drugs' (lower panel), by doctor's category and age group in childhood, in column presented for the years 1981, 1983, 1986, 1990, and 1993 successively. *, Trend statistically significant ($p<0.05$).

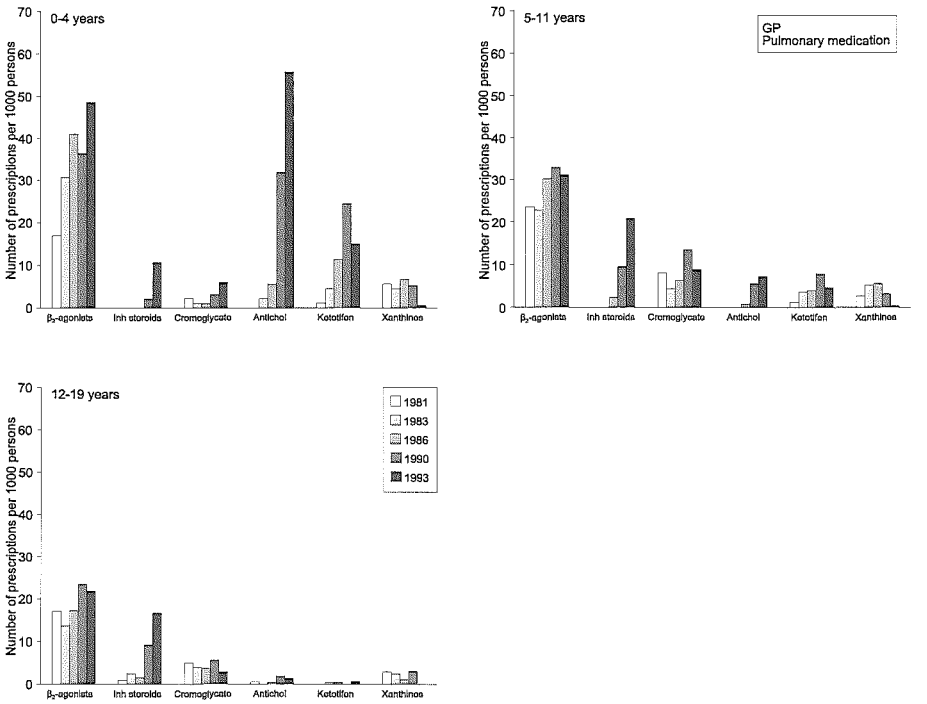

Figure 4.9 Number of prescriptions for pulmonary medication for asthma and COPD per 1000 persons by GP in the three age groups in childhood, in column presented for the years 1981, 1983, 1986, 1990, and 1993 successively, broken down into pharmacological groups of drugs: β_2-agonists, inhaled steroids, sodium cromoglycate, anticholinergics, ketotifen, and methylxanthines.

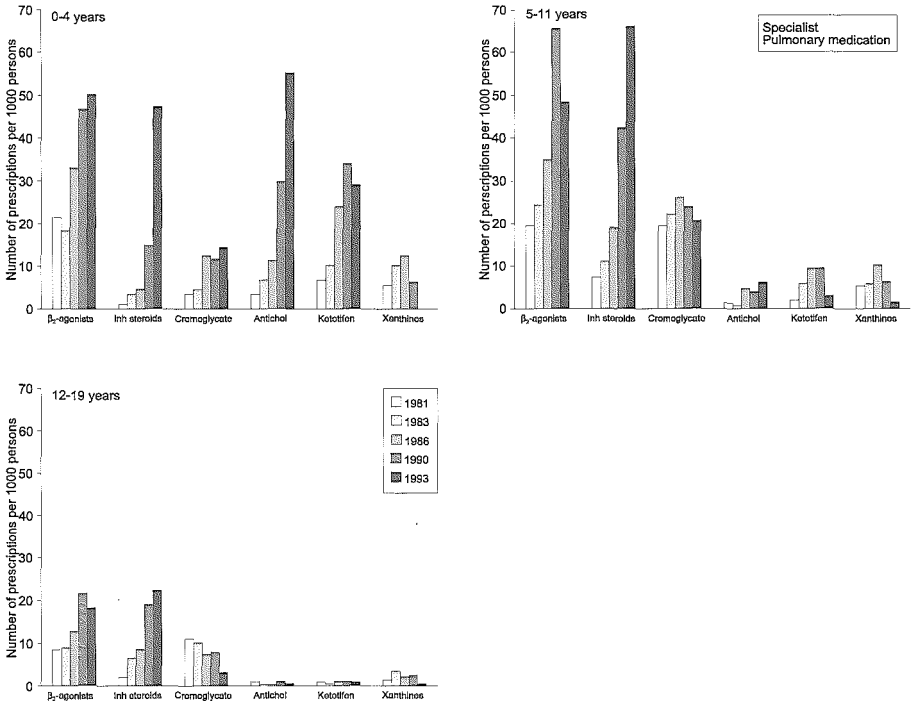

Figure 4.10 Number of prescriptions for pulmonary medication for asthma and COPD per 1000 persons by specialist in the three age groups in childhood, in column presented for the years 1981, 1983, 1986, 1990, and 1993 successively, broken down into pharmacological groups of drugs: β_2-agonists, inhaled steroids, sodium cromoglycate, anticholinergics, ketotifen, and methylxanthines.

Prescription rates in age group 12-19 years were lower than in the younger age groups, however in relation to the consultation rate (ratio) treatment intensity was not (figure 4.11). The ratios for the anti-inflammatory drugs (inhaled steroids, sodium cromoglycate, oral steroids) increased significantly for GP in age groups 5-11 years ($p=0.02$) and 12-19 years ($p=0.01$), and for specialists in age groups 0-4 years ($p<0.01$) and 5-11 years ($p<0.01$). The ratios for bronchodilators (β_2-agonists, anticholinergics, methylxanthines) increased throughout in age group 0-4 years (GP: $p<0.001$; specialist: $p=0.03$), but in the other two age groups the increasing trend in the eighties was followed by a decline in 1993 (figure 4.11).

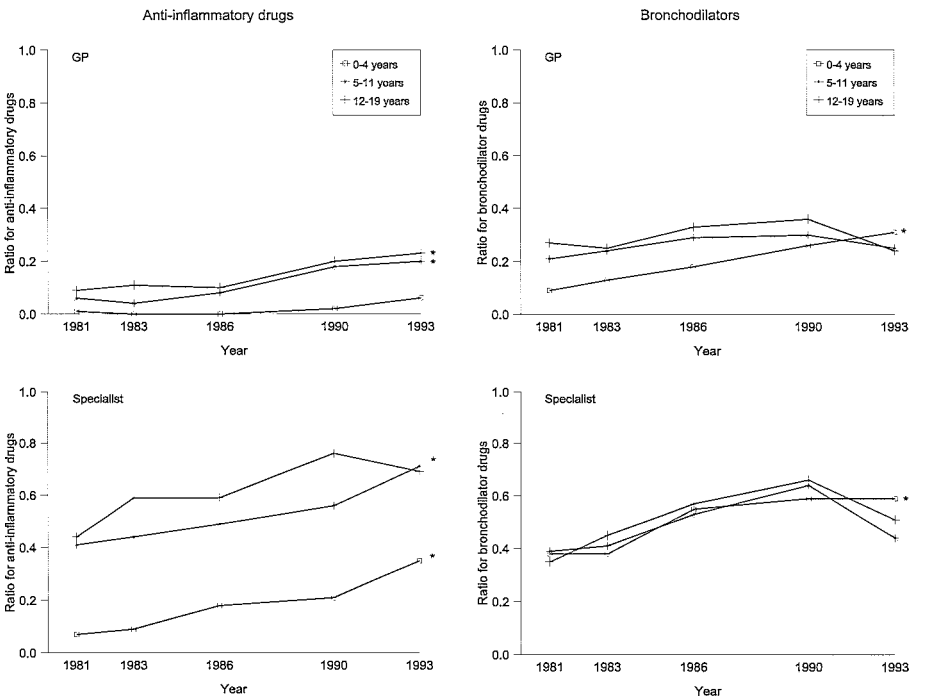

Figure 4.11 Number of prescriptions per consultation for asthma and COPD for anti-inflammatory drugs (on the left) and bronchodilators (on the right) by GP (upper panels) and specialist (lower panels) by age group in childhood, 1981-1993. Anti-inflammatory drugs: inhaled steroids, sodium cromoglycate, and oral steroids; bronchodilators: β_2-agonists, anticholinergics, and methylxanthines.

*, Trend statistically significant ($p<0.05$).

4.3.3 Consultations and prescriptions for asthma and the other obstructive pulmonary diseases as separate diagnostic entities in 1993

The total number of consultations by age group and doctor's category are listed in table 4.1, according to diagnostic label. At GP consultations the "CARA" label was more prevalent than the asthma label, especially at ages under 5 years and over 40 years, except in age group 12-19 years. However, the majority of GP consultations were labelled bronchitis, not specified as acute or chronic. The majority of specialist consultations were labelled asthma or "CARA", with asthma labelling predominant between the ages 5 and 64 years, particularly in young adults. Consultations for bronchitis played a minor role.

Drug prescriptions were related to diagnostic label in the total population (figure 4.12) and in childhood (figure 4.13). We evaluated 3 main disease categories: asthma, "CARA", and the other labels combined in a 'bronchitis'-group (chronic bronchitis, bronchitis not specified as acute or chronic, and emphysema (from age 40)). For the purpose of this section, drugs were grouped as bronchodilators: β_2-agonists and anticholinergics; anti-inflammatory drugs: inhaled steroids, sodium cromoglycate, and oral steroids; antibiotics; and remainder: ketotifen, methylxanthines, and the 'other drugs'. The pattern of treatment by GP in asthma and in "CARA" was remarkably similar in all age groups, mainly bronchodilators and anti-inflammatory treatment, whereas in the 'bronchitis'-group prescriptions for antibiotics were most prevalent. In specialists prescriptions for bronchodilators and anti-inflammatory drugs were predominant, except for 'bronchitis' in age group 0-4 years, for which prescriptions for the remainder group were more prevalent.

Table 4.1 Number of consultations for the obstructive pulmonary diseases by diagnostic labelling in general practitioners and specialists by age group in 1993

	Age group in years					
	0-4	5-11	12-19	5-39	40-64	≥ 65
General practitioner						
Asthma	49113	39352	40378	158479	84247	72801
"CARA"	73784	57196	33811	200599	192750	288775
Chronic bronchitis	3290	3811	2748	16945	36506	40402
Bronchitis, not specified	204290	99566	67651	362201	270693	222921
Emphysema					10911	61751
Specialist						
Asthma	81919	99809	39686	216074	142236	98389
"CARA"	76291	55931	16193	83325	53726	110898
Chronic bronchitis	2004	501	320	4556	13911	31998
Bronchitis, not specified	13527	9018	1258	12365	8837	7197
Emphysema					19636	59173

Asthma: international classification of diseases (ICD)-9 code 493
"CARA": ICD-9 code 493.93
Chronic bronchitis: ICD-9 code 491
Bronchitis not specified as acute or chronic: ICD-9 code 490
Emphysema: ICD-9 code 492 (from age 40 years).

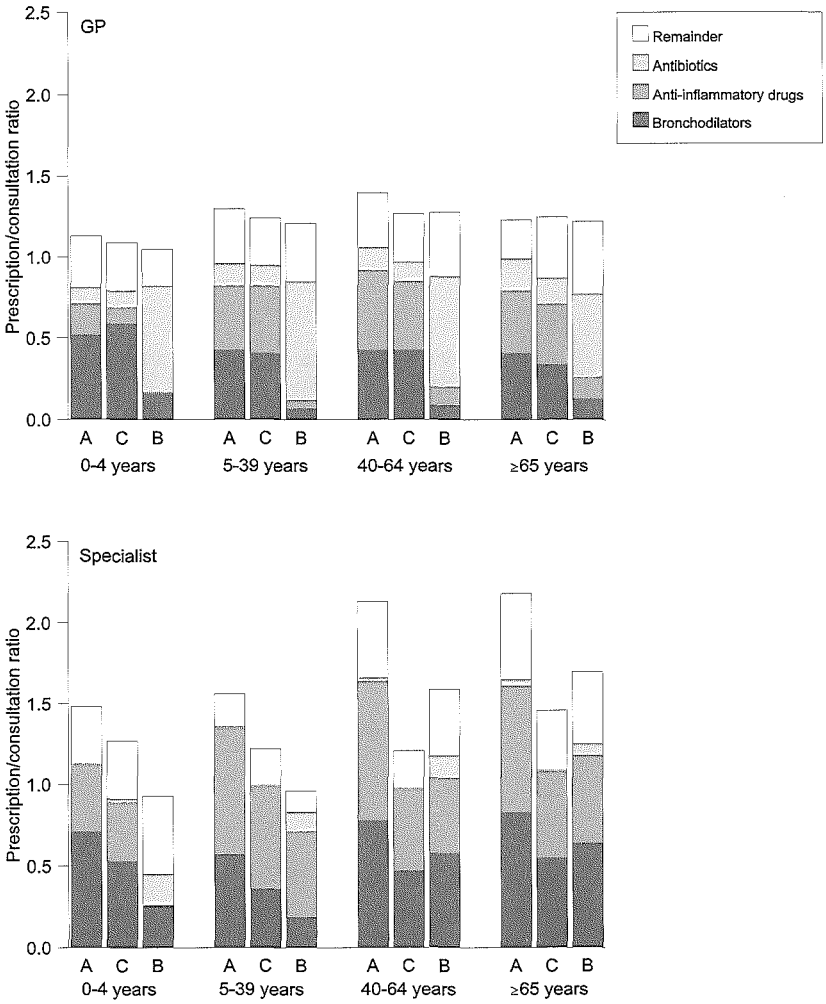

Figure 4.12 Number of prescriptions by class of drugs per consultation for GP (upper panel) and specialist (lower panel) by diagnostic label, asthma (A), "CARA" (C), and chronic bronchitis, bronchitis not specified as acute or chronic, and emphysema (B), by age group in the total population in 1993. A: ICD-9 493; C: ICD-9 493.93; B: ICD-9 490-492. Class of drugs: bronchodilators (β_2-agonists and anticholinergics); anti-inflammatory drugs (inhaled steroids, sodium cromoglycate, and oral steroids); antibiotics; remainder (ketotifen, methylxanthines, and 'other drugs').

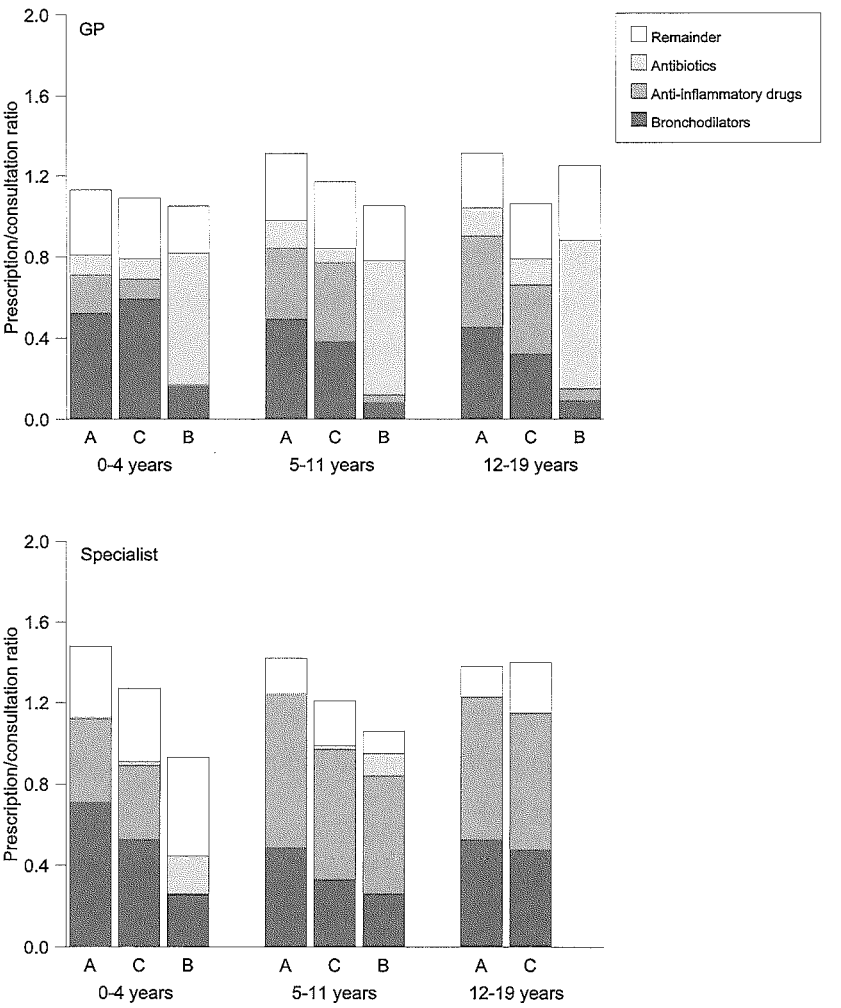

Figure 4.13 Number of prescriptions by class of drugs per consultation for GP (upper panel) and specialist (lower panel) by diagnostic label, asthma (A), "CARA" (C), and chronic bronchitis and bronchitis not specified as acute or chronic (B), by age group in childhood in 1993. A: ICD-9 493; C: ICD-9 493.93; B: ICD-9 490-491. Class of drugs: bronchodilators (β_2-agonists and anticholinergics); anti-inflammatory drugs (inhaled steroids, sodium cromoglycate, and oral steroids); antibiotics; remainder (ketotifen, methylxanthines, and 'other drugs').

4.4 Discussion

We observed a change in prescriptions of drugs for asthma and COPD in the Netherlands from 1981 to 1993, in accordance with the guidelines. Importantly, an increase in the number of prescriptions for anti-inflammatory drugs was observed in relation to the number of consultations. Other findings were an overall stable rate of first consultations, and an increase in the rate of repeat consultations in the age groups between 0 and 40 years. Consultation rates may reflect need for care, but also the outcome of care.

The absence of trends in first consultations for asthma and COPD in GPs and specialists suggests a stable incidence in the Netherlands over the period 1981-1993. An exception was the increase in first consultations in age group 0-4 years in specialists. In the Netherlands, it is common practice that patients are being referred to the specialist by GP, so this finding indicates either an increase in severity of disease or (and) a shift in medical care. The latter is not in line with the Dutch guidelines for asthma in children [16], whereas an increase in severity is in line with the reported increase in hospital admissions in this age group [24].

The significant increases found in repeat consultations in patients under 40 years may point to a better management, i.e. more frequent follow-up visits for a review of treatment, which is in accordance with the guidelines, particularly with respect to inhaled steroids in children. Alternatively, benefit from increased prescribing of anti-asthma drugs may result in a decrease in consultations, which occurred in the age group 40-64 years for specialists. Other factors in the increase in repeat consultations may be more severe disease or increased prevalence of the disease at younger ages. The increase in age group 5-39 years appeared to be mainly due to the increasing rates in age group 5-11 years. It has been argued that a cohort effect in asthma prevalence could have occurred [25]. Worldwide increases in prevalence of asthma have been observed, especially at younger ages [26]. In the Netherlands, prevalence of asthma in

schoolchildren might have increased [27]. An increase in prevalence of very mild-to-moderate asthma/COPD in subjects aged 25-70 years was found [28], but stratification by age was not done.

Over the period 1981-1993 inhaled steroids were more frequently prescribed in all age groups by GPs and specialists, prescriptions for β_2-agonists showing only a moderate increase. In the age groups 0-4 years and ≥65 years prescriptions for anticholinergics increased considerably. A Dutch study in patients with asthma and chronic bronchitis indicated that older patients (>60 years) benefited more from inhaling anticholinergics (ipratropium bromide) than β_2-agonists [29]. So in the Dutch GP guidelines on CNSLD in adults, treatment with anticholinergics is recommended in patients >60 years [18]. It should be mentioned that anticholinergics included deptropine. Deptropine was frequently used for childhood respiratory diseases in the Netherlands and was included in the Dutch national guidelines for asthma in children <4 years [15,16]. However, because of adverse events deptropine was removed from the Dutch guidelines in the late nineties, and a strong decrease in prescriptions for deptropine followed the negative reporting [30]. Prescriptions by GP for pulmonary medication in the age group 0-4 years increased whereas prescriptions for the 'other drugs' decreased. Along with the decrease in prescriptions for methylxanthines, the prescription patterns observed were in accordance with the asthma guidelines. No information was provided on dosages of drugs or on multiple prescriptions for the same patient, so no additional trends in prescribing patterns could be assessed in the drug therapy of patients with asthma and COPD.

The prevalence of consultations and prescriptions was higher at younger and older ages than at middle ages. However, the ratios of prescription rate to consultation rate in the age groups point to similar drug treatment intensities. Importantly, in all age groups the ratio for anti-inflammatory drugs increased. This increase was mainly due to prescriptions for inhaled steroids. The prescription rate of the nonsteroid drug sodium cromoglycate increased in age group 0-4 years, but showed a tendency to decrease in

the age groups 5-11 years and 12-19 years. This follows the guidelines, where sodium cromoglycate has a place in the course of mild asthma, whereas inhaled steroids are first choice for long-term suppression of the inflammatory process in the airways.

Studies in the eighties pointed to the importance of the diagnostic label for the treatment of chronic respiratory symptoms [31,32]. Especially in older patients [33], but also in younger ones [34], it is often difficult to make a proper diagnosis. In a Dutch study on respiratory diseases based on data from general practices, it was found that many mutations in diagnostic labelling occurred, shifting between the "CARA" categories as well as from respiratory diseases classified as infections to especially the "CARA" categories asthma and chronic bronchitis [35]. Drug prescription patterns for patients labelled asthma and "CARA" were similar in 1993, primarily bronchodilators and inhaled steroids were prescribed. A different pattern was found in the 'bronchitis'-group, that is chronic bronchitis, bronchitis not specified as acute or chronic, and emphysema combined. Treatment of 'bronchitis' occurred primarily by GP and antibiotics were predominantly prescribed, as well as when bronchitis was labelled as chronic. The practice of prescribing antibiotics for symptoms associated with bacterial infections in CNSLD patients has been questioned [36]. Also in childhood, when the most frequent triggers for acute episodes of asthma and bronchitis are viral infections [37-39], routine treatment with antibiotics is not beneficial [40]. Symptoms of chronic and recurrent cough in young children may be an expression of asthmatic disease for which anti-asthma drugs are indicated [41], while episodes labelled as acute bronchitis in adults may be exacerbations of CNSLD [35]. It has recently been suggested that antibiotics in early childhood may even contribute to development of atopy through effects on the gastrointestinal flora, by affecting the balance of T-helper lymphocyte types 1 and 2 [42]. The risk of development of asthma and allergic diseases was highest in children with a predisposition to atopic immune responses [43]. In our study, stable prescription rates of antibiotics were observed in all age groups up to 1993.

Enhanced diagnostic awareness could have occurred in the last decades and a shift in

labelling may have contributed to an increased prevalence of asthma [44]. An 'asthma' label in favour of a 'bronchitis' label may reduce the antibiotic treatment of wheezy children [31,39]. The increased prescription rate of anti-inflammatory drugs in childhood accompanied by a stable prescription rate of antibiotics suggest an increase in prevalence and (or) severity of asthma rather than a shift in labelling in the Netherlands. In 1993, the prescriptions of drugs for 'asthma' and "CARA" appeared to be similar and this might point to asthma treatment in the Netherlands reaching a broad spectrum of asthmatic children [45].

In general practice, the ratio of corticosteroid to bronchodilator prescriptions for asthma appeared to be an important factor in the outcome of asthma care and may be a measure of quality of prescribing, with a higher ratio leading to less severe symptoms [46]. In 1993, inhaled steroids were as often prescribed as bronchodilators. An increased co-use of inhaled steroids and brochodilators was found in Dutch asthma patients, aged 5-50 years, over the period 1986-1991 [47]. Compared to other countries in Europe, the Netherlands scored high in knowledge of and attitude to asthma according to the guidelines [48]. Although data suggest good asthma drug management in the Netherlands, in individual patients goals may not be met [49]. There may be a need for education and increased use of inhaled steroids [49,50], nevertheless continuing morbidity may exist in patients on (high doses of) inhaled steroids [50,51] and high levels of GP attendances [51].

The present data on consultations and prescriptions concerned patients in ambulatory care, and were based on diagnostic codes. We emphasise that the data were part of the overall information about doctor-patient contacts obtained by IMS, therefore bias because of special interest in asthma and COPD on the part of the participating doctor is unlikely to have occurred.

In conclusion, health care utilisation for asthma and COPD increased in the Netherlands over the period 1981-1993. Steady first consultation rates suggested a stable incidence.

Repeat consultation rates increased in the age groups under 40 years, whereas a decrease in age group 40-64 years was found. Trends in prescription rates were in line with the guidelines, in particular inhaled steroids were more frequently prescribed. The results may indicate better management of asthma and COPD, but also increase in prevalence an (or) severity of obstructive airways disease at younger ages.

References

1. Jackson RT, Mitchell EA. Trends in hospital admission rates and drug treatment of asthma in New Zealand. NZ Med J 1983; 96: 728-730.
2. Keating G, Mitchell EA, Jackson R, Beaglehole R, Rea H. Trends in sales of drugs for asthma in New Zealand, Australia, and the United Kingdom, 1975-81. Br Med J 1984; 289: 348-351.
3. Bosco LA, Knapp DE, Gerstman B, Graham CF. Asthma drug therapy trends in the United States, 1972 to 1985. J Allergy Clin Immunol 1987: 80(suppl): 398-402.
4. Editorial. β2 agonists in asthma: relief, prevention, morbidity. Lancet 1990; 336: 1411-1412.
5. Wever AMJ, Wever-Hess J. β-adrenerge agonisten en sterfte en morbiditeit wegens astma. Ned Tijdschr Geneeskd 1992; 136: 460-465.
6. Warner JO, Götz M, Landau LI, Levison H, Milner AD, Pedersen S, Silverman M. Management of asthma: a consensus statement. Arch Dis Child 1989; 64: 1065-1079.
7. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. J Allergy Clin Immunol 1990; 85: 1098-1111.
8. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: I - chronic persistent asthma. Br Med J 1990; 301: 651-653.
9. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: II - acute severe asthma. Br Med J 1990; 301: 797-800.
10. International consensus report on the diagnosis and management of asthma. Clin Exp Allergy 1992; 22 (Suppl 1): 1-72.
11. Warner JO, et al. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992; 67: 240-248.
12. British Thoracic Society, British Paediatric Association, Royal College of Physicians, King's Fund Centre, National Asthma Campaign, Royal College of General Practitioners, General Practitioners in Asthma Group, British Association of Accident and Emergency Medicine, British Paediatric Respiratory Group. Guidelines on the management of asthma. Thorax 1993; 48(Suppl 2): S1-S24.
13. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention NHLBI/WHO workshop report. National Institutes of Health, National Heart, Lung, and Blood Institute. Bethesda, Maryland, USA. 1995; Publication No. 95-3659.
14. Van der Laag J, van Aalderen WMC, Duiverman EJ, van Essen-Zandvliet EEM, Nagelkerke AF, van Nierop JC. Astma bij kinderen; consensus van kinderlongartsen over lange-termijnbehandeling. I. Diagnostiek. Ned Tijdschr Geneeskd 1991; 135: 2316-2319.

15. Van der Laag J, van Aalderen WMC, Duiverman EJ, van Essen-Zandvliet EEM, Nagelkerke AF, van Nierop JC. Astma bij kinderen; consensus van kinderlongartsen over langetermijnbehandeling. II. Behandeling. Ned Tijdschr Geneeskd 1991; 135: 2319-2323.

16. Dirksen WJ, Geyer RMM, De Haan M, Kolnaar BGM, Merkx JAM, Romeijnders ACM, Dijkstra RH, Van der Laan JR. NHG-standaard astma bij kinderen. Huisarts Wet 1992; 35: 355-362.

17. Bottema BJAM, Fabels EJ, Van Grunsven PM, Van Hensbergen W, Muris JWM, Van Schayck CP, Schreuder F, Starmans R, Rosmalen CFH. NHG-standaard Cara bij volwassenen: diagnostiek. Huisarts Wet 1992; 35: 430-436.

18. Van der Waart MAC, Dekker FW, Nijhoff S, Thiadens HA, Van Weel C, Helder M, Starmans R, Rosmalen CFH. NHG-standaard Cara bij volwassenen: behandeling. Huisarts Wet 1992; 35: 437-443.

19. Wever-Hess J, Kouwenberg JM, Wever AMJ. Trends in consultations and prescriptions for obstructive airways disease in children (English summary). Ned Tijdschr Geneeskd 1993; 137: 1246-1251.

20. Wever AMJ, Wever-Hess J. Trends in consultations and prescriptions for obstructive airways disease in the Netherlands. Proceedings of the British Thoracic Society. Thorax 1993; 48: 444-445.

21. Sluiter HJ, Koëter GH, de Monchy JGR, Postma DS, de Vries K, Orie NGM. The Dutch Hypothesis (chronic non-specific lung disease) revisited. Eur Respir J 1991; 4: 479-489.

22. Vermeire PA, Pride NB. A "splitting" look at chronic nonspecific lung disease (CNSLD): common features but diverse pathogenesis. Eur Respir J 1991; 4: 490-496.

23. Centraal Bureau voor de Statistiek. Leeftijdsopbouw naar burgelijke staat en geslacht, gemiddeld 1981-1993. Voorburg: Centraal Bureau voor de Statistiek.

24. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.

25. Pearce N, Sunyer J, Cheng S, Chinn S, Björkstén B, Burr M, Keil U, Anderson HR, Burney P, on behalf of the ISAAC Steering Committee and the European Community Respiratory Health Survey. Comparison of asthma prevalence in the ISAAC and the ECRHS. Eur Respir J 2000; 16: 420-426.

26. Grant EN, Wagner R, Weiss KB. Observations on emerging patterns of asthma in our society. J Allergy Clin Immunol 1999; 104: S1-9.

27. Van der Wal MF, Uitenbroek DG, Verhoeff AP. Increased proportion of elementary school pupils with asthmatic symptoms in the Netherlands, 1984/'85-1994/'95; a study of the literature (English summary). Ned Tijdschr Geneeskd 2000; 144: 1780-1784 .

28. Tirimanna PRS, van Schayck CP, den Otter JJ, van Weel C, van Herwaarden CLA, van den Boom G, van Grunsven PM, van den Bosch WJHM. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract 1996; 46: 277-281.

29. Van Schayck CP, Folgering H, Harbers H, Maas KL, van Weel C. Effects of allergy and age on responses to salbutamol and ipratropium bromide in moderate asthma and chronic bronchitis. Thorax 1991; 46: 355-359.

30. Schirm E, Gebben HJ, Tobi H, de Jong-van den Berg LTW. Deptropine still prescribed for the 1-4-year-old (English summary). Ned Tijdschr Geneeskd 2000; 144: 2409-2411.

31. Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. Br Med J 1983; 286: 1253-1256.

32. Littlejohns P, Ebrahim S, Anderson R. Treatment of adult asthma: is the diagnosis relevant? Thorax 1989; 44: 797-802.

33. Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. Am Rev Respir Dis 1986; 133: 981-986.

34. Manfreda J, Becker AB, Wang P-Z, Roos LL, Anthonisen NR. Trends in physician-diagnosed asthma prevalence in Manitoba between 1980 and 1990. Chest 1993; 103: 151-157.

35. Bottema BJAM. Diagnostiek van CARA in de huisartspraktijk. Thesis, Amsterdam 1993. ISBN 90-9006655-1.

36. Sachs APE, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995; 50: 758-763.

37. Carlsen KH, Ørstavik I, Leegaard J, Høeg H. Respiratory virus infections and aeroallergens in acute bronchial asthma. Arch Dis Child 1984; 59: 310-315.

38. Conway SP, Littlewood JM. Admission to hospital with asthma. Arch Dis Child 1985; 60: 636-639.

39. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-1199.

40. Taylor B, Abbott GD, Kerr MMcK, Fergusson DM. Amoxycillin and co-trimoxazole in presumed viral respiratory infections of childhood: placebo-controlled trial. Br Med J 1977; 2 : 552-554.

41. Spelman R. Two-year follow up of the management of chronic or recurrent cough in children according to an asthma protocol. Br J Gen Practice 1991: 41: 406-409.

42. Holt PG, Sly PD, Björkstén B. Atopic versus infectious diseases in childhood: a question of balance? Pediatr Allergy Immunol 1997; 8: 53-58.

43. Droste JHJ, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, van Bever HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? Clin Exp Allergy 2000; 30: 1547-1553.

44. Magnus P, Jaakkola JJK. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. Br Med J 1997; 314: 1795-1799.

45. Silverman M, Wilson N. Wheezing phenotypes in childhood [editorial]. Thorax 1997; 52: 936-937.

46. Shelley M, Croft P, Chapman S, Pantin C. Is the quality of asthma prescribing, as measured by the general practice ratio of corticosteroid to bronchodilator, associated with asthma morbidity? J Clin Epidemiol 2000; 53: 1217-1221.

47. Van Ganse E, van der Linden PD, Leufkens HGM, Herings RMC, Vincken W, Ernst P. Asthma medications and disease exacerbations: an epidemiological study as a method for asthma surveillance. Eur Respir J 1995; 8 : 1856-1860.

48. Lagerløv P, Veninga CCM, Muskova M, Hummers-Pradier E, Stålsby Lundborg C, Andrew M, Haaijer-Ruskamp FM, on behalf of the Drug Education Project (DEP) group. Asthma management in five European countries: doctors' knowledge, attitudes and prescribing behaviour. Eur Respir J 2000; 15: 25-29.

49. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the asthma insights and reality in Europe (AIRE) study. Eur Respir J 2000; 16: 802-807.

50. Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. Thorax 1999; 54: 296-300.

51. Nolan D, White P. Symptomatic asthma: attendance and prescribing in general practice. Respir Med 2002; 96: 102-109.

CHAPTER 5
PHARMACOTHERAPY FOR ASTHMA IN THE NETHERLANDS, 1999-2001

Abstract

To review current asthma therapy, we analysed data on consultations and prescriptions by general practitioners (GPs) and specialists for asthma in the age groups 0-4 years, 5-11 years, 12-19 years, 20-39 years, 40-64 years, and ≥65 years in the Netherlands for the years 1999, 2000, and 2001. Drugs were grouped as bronchodilators: β_2-agonists and anticholinergics; anti-inflammatory drugs: inhaled corticosteroids, mast cell stabilisers, and oral and parenteral corticosteroids; combined inhaled β_2-agonists and corticosteroids; antileukotrienes; and other drugs. We calculated ratios of number of prescriptions to number of consultations for the pulmonary drugs. Overall, prescriptions for pulmonary medication accounted for 90% of all prescriptions for asthma, and were primarily for β_2-agonists and inhaled corticosteroids. The GPs' prescription/consultation ratios for bronchodilators ranged from 0.5 in children to 0.7 in adults and for anti-inflammatory drugs from 0.4 to 0.6. Bronchodilators and anti-inflammatory drugs were prescribed by specialists in similar frequencies, and the prescription/consultation ratios ranged from 0.7 in age group 0-4 years to over 0.9 in age group ≥65 years. The increased ratios observed for inhaled combined β_2-agonists and corticosteroids indicate the greater use of long acting β_2-agonists in asthma management.

5.1 Introduction

In chapter 4, parameters of asthma management in ambulatory care were evaluated over the period 1981-1993, when the first international consensus guidelines on asthma

diagnosis and management were published. Guidelines for asthma have recently been updated for children [1,2] and adults [3]. The updated guidelines recommend asthma treatment primarily by inhaled short acting β_2-agonists and inhaled steroids, and include an increasing role for long acting β_2-agonists, along with educational processes, such as patient information, self-management plans, and educational programs for caregivers. Early intervention with a higher dose of steroids is advised to achieve rapid control of symptoms, and then stepping down the treatment. Cromones (sodium cromoglycate and nedocromil) and xanthines have a limited place in asthma therapy, while deptropine and ketotifen have become obsolete. New agents were introduced to play a role in asthma management, such as leukotriene antagonists. For the purpose of this thesis, the Institute of Medical Statistics (IMS) provided data on consultations and prescriptions for asthma in the Netherlands for the years 1999, 2000, and 2001. We aimed to review the current treatment pattern for asthma in the Netherlands.

5.2 Material and methods

For detailed information about IMS data, we refer to chapter 4, section 2. For the present chapter, we analysed data for asthma according to the International Classification of Diseases (ICD), tenth revision, code J45. ICD-10 code J46 covers 'status asthmaticus'. Consultations for asthma coded under J46 were less than 0.1% and were excluded from the analysis.

We divided age into the age groups: 0-4 years, 5-11 years, 12-19 years, 20-39 years, 40-64 years, and ≥65 years. Consultations were divided into first and repeat consultations. IMS grouped the drugs for asthma as follows: bronchodilators: β_2-agonists and anticholinergics (including deptropine); anti-inflammatory drugs: inhaled corticosteroids, mast cell stabilisers (cromones and ketotifen), and oral and parenteral corticosteroids; combined inhaled β_2-agonists and corticosteroids; antileukotrienes; and other drugs: antibiotics, expectorants, and other pharmacotherapy. We analysed the data

for general practitioners (GPs) and specialists separately.

To present the prevalence of consultations with physicians in 1999, we calculated age-specific rates per 1000 persons, based on the mean Dutch population age structure [4]. To assess asthma treatment, we related the number of prescriptions to the number of consultations and calculated ratios for bronchodilators, anti-inflammatory drugs, combined inhaled β_2-agonists and corticosteroids, and leukotriene antagonists by age group and doctor's category for the years 1999, 2000, and 2001. The results are descriptively presented.

5.3 Results

Consultations

Prevalence of first consultations was highest in age group 0-4 years and decreased with age. Repeat consultations occurred most frequently in age groups 0-4 years and 5-11

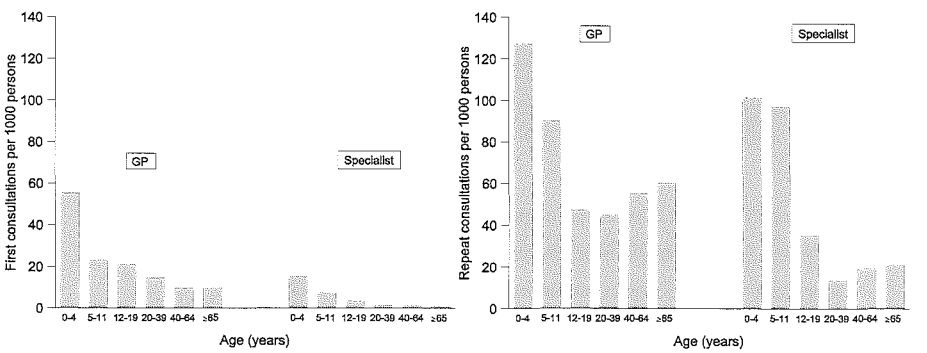

Figure 5.1 Number of first consultations (left panel) and repeat consultations (right panel) for asthma per 1000 persons by doctor's category and age group in 1999. Asthma: international classification of diseases (ICD)-10 code J45.

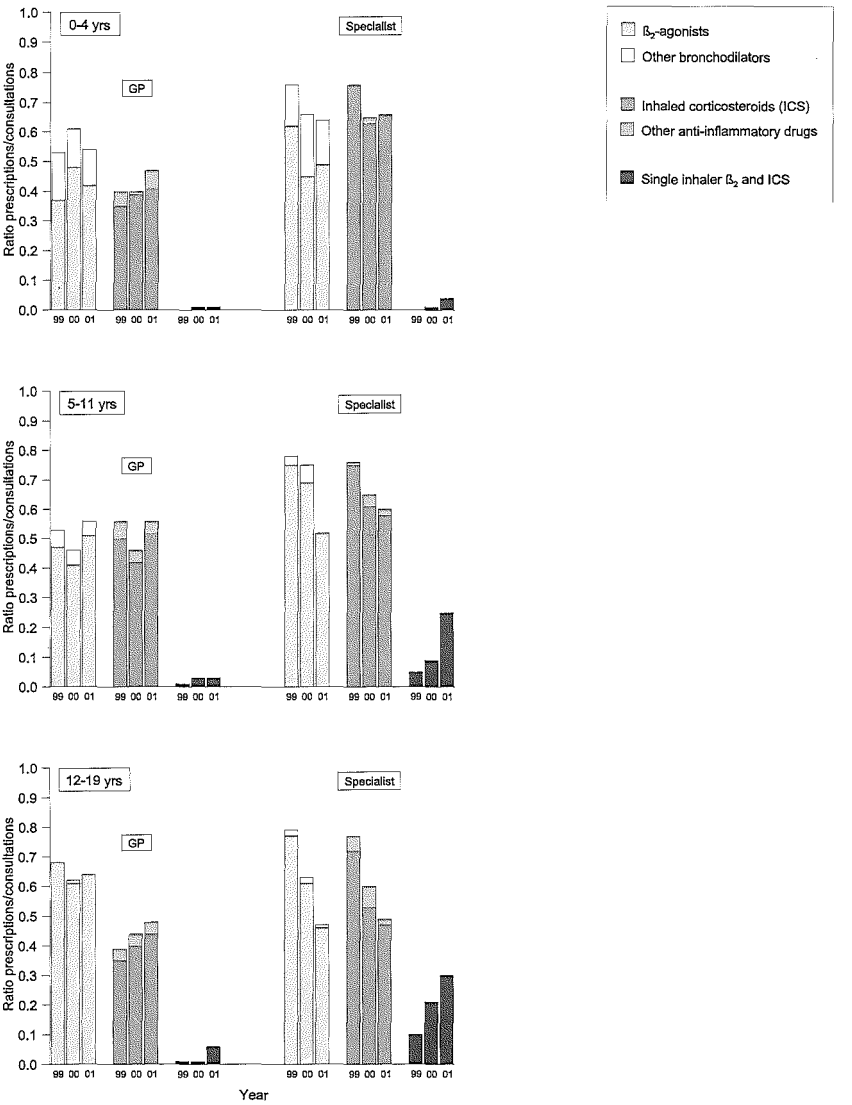

Figure 5.2 Number of prescriptions per consultation for asthma by doctor's category for β_2-agonists, other bronchodilators (anticholinergics), inhaled corticosteroids (ICS), other anti-inflammatory drugs (cromones, ketotifen, noninhaled corticosteroids), and β_2-agonists + ICS by single inhaler in age groups 0-4 years (upper panel), 5-11 years (middle panel), and 12-19 years (lower panel), 1999-2001.

Asthma: international classification of diseases (ICD)-10 code J45.

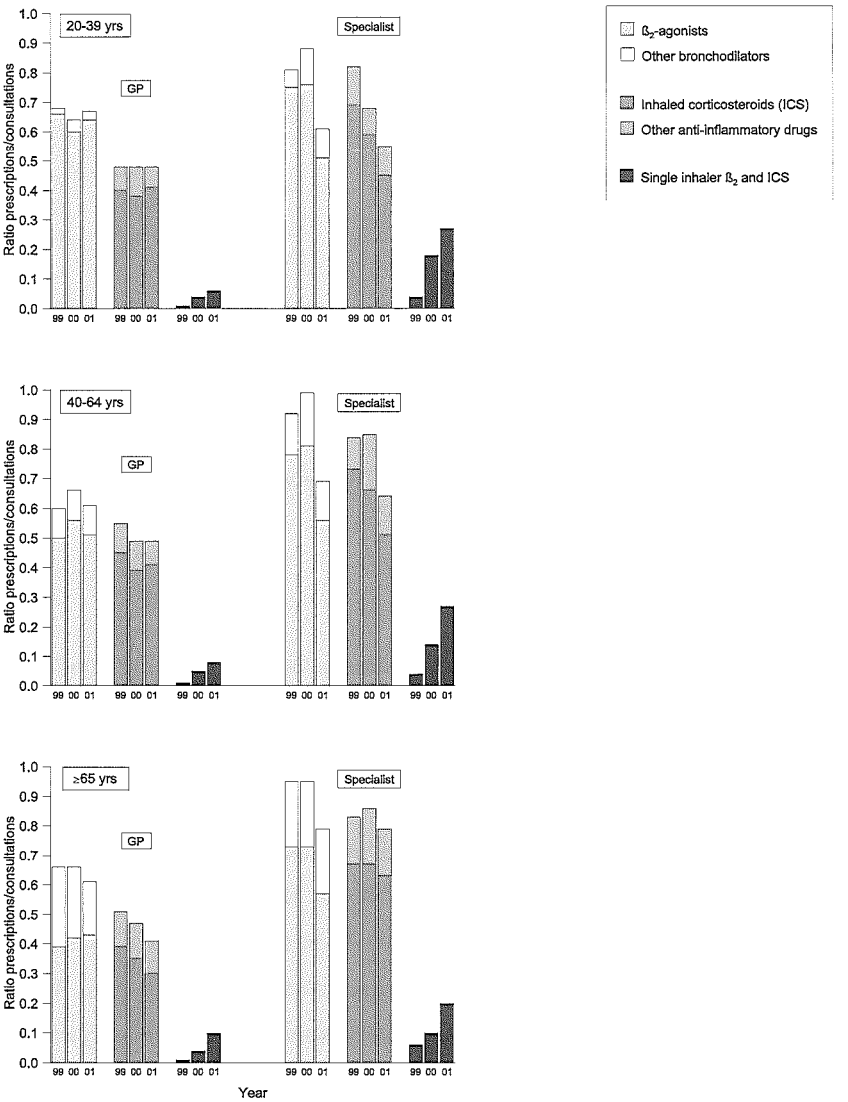

Figure 5.3 Number of prescriptions per consultation for asthma by doctor's category for β_2-agonists, other bronchodilators (anticholinergics), inhaled corticosteroids (ICS), other anti-inflammatory drugs (cromones, ketotifen, noninhaled corticosteroids), and β_2-agonists + ICS by single inhaler in age groups 20-39 years (upper panel), 40-64 years (middle panel), and ≥65 years (lower panel), 1999-2001.

Asthma: international classification of diseases (ICD)-10 code J45.

Table 5.1 Ratio of number of prescriptions to number of consultations for combined β_2-agonists and corticosteroids by single inhaler for asthma, by age and doctor's category, 1999-2001

	Age (years)					
	0-4	5-11	12-19	20-39	40-64	≥65
General practitioner						
1999	0	0.01	0.01	0.01	0.01	0.01
2000	0.01	0.03	0.01	0.04	0.05	0.04
2001	0.01	0.03	0.06	0.06	0.08	0.10
Specialist						
1999	0	0.05	0.10	0.04	0.04	0.06
2000	0.01	0.09	0.21	0.18	0.14	0.10
2001	0.04	0.25	0.30	0.27	0.27	0.20

Asthma: international classification of diseases (ICD)-10 code J45.

years, especially for specialists, and showed the lowest rates in age group 20-39 years (figure 5.1).

Prescriptions

Prescriptions for the pulmonary medication accounted for 90% (GPs) or more (specialists) of all prescriptions for asthma.

Prescriptions for bronchodilators and anti-inflammatory drugs concerned primarily β_2-agonists and inhaled corticosteroids, in children (figure 5.2) as well as in adults (figure 5.3). Anticholinergics were mainly prescribed in the age groups 0-4 years and ≥65 years. Bronchodilators were prescribed by GPs at over half of the consultations and anti-inflammatory drugs to nearly the same extent. For specialists, the ratios of prescriptions to consultations for bronchodilators and anti-inflammatory drugs showed similar frequencies and decreased from age 5 over the period 1999-2001. However, the ratios for combined inhaled β_2-agonists and corticosteroids increased over time (table 5.1). Prescriptions for cromones and ketotifen were minor, as well as for xanthines which were included in the 'other drugs' by IMS.

Leukotriene antagonists, a new class of drugs, were prescribed very rarely. Prescriptions by GPs started in 2001 from age 5, and the ratios ranged from 0.01 in age group 5-11

years to 0.02 in age group 20-39 years. Prescriptions by specialists increased from 1999 to ratios which ranged from 0.01 in age group 0-4 years to 0.10 in age group 12-19 years in 2001.

5.4 Discussion

The rate of first consultations with GPs might be proxy for the incidence of asthma. From the United States, incidence rates from 1964-1983 were reported to be highest in infants <1 year of age and to fall progressively through childhood to be lowest in adults [5]. Dividing age group 0-4 years in under 1-year-olds and 1-4-year-olds, rates were 66.2 and 52.7 respectively. The distribution in our results was less skewed than in those data, where <1-year-olds had a nearly 3 times higher incidence than 1-4-year-olds, but levels were higher [5]. It is estimated that 75% of childhood asthma is infrequent episodic, 20% frequent episodic, and 5% persistent [2]. Infrequent episodic asthma can be managed by β-agonists alone. For frequent episodic and persistent asthma prophylactic treatment is considered necessary. The relatively high prescription ratio for inhaled steroids by GPs in age group 0-4 years may point to diagnostic labelling of asthma by GP in children with more frequent or recurrent symptoms. Whether the right patients are being diagnosed and treated may be an issue especially in childhood [6]. Prevalence data are often based on questionnaires. The present data concerned patients seeking medical help. Also in the other age groups patients with more troublesome and severe symptoms might have been labelled with the diagnosis 'asthma', in view of the relatively high frequency of anti-inflammatory therapy.

Anticholinergics were prescribed mainly in age group 0-4 years and ≥65 years, but played a small part. In children, this accords with the Dutch asthma guidelines, which stated that there was no indication for deptropine any more [1]. In line with the guidelines, asthma management was mostly by β_2-agonists and inhaled steroids [1-3].

References

1. Hoekstra MO. Treatment of asthma in children; revised guidelines from paediatric pneumonologists (English summary). Ned Tijdschr Geneeskd 1997; 141: 2223-2229.
2. Warner JO, Naspitz CK, Cropp GJA. Third international pediatric consensus statement on the management of childhood asthma. Pediatr Pulmonol 1998; 25: 1-17.
3. British asthma guidelines coordinating committee. The British guidelines on asthma management: 1995 review and position statement. Thorax 1997; 52(Suppl 1): S1-24.
4. Centraal Bureau voor de Statistiek. Leeftijdsopbouw naar burgelijke staat en geslacht, gemiddeld 1999. Voorburg: Centraal Bureau voor de Statistiek.
5. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. Am Rev Respir Dis 1992; 146: 888-894.
6. Keeley DJ, Silverman M. Are we too ready to diagnose asthma in children? Thorax 1999; 54: 625-628.
7. Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. Eur Respir J 1992; 5: 1062-1067.
8. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344: 219-224.
9. Woolcock A, Lundbeck B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996; 153: 1481-1488.
10. Pauwels RA, Löfdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997; 337: 1405-1411.
11. Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 μg) in combination in a Diskus™ inhaler (Seretide™) is effective and safe in children with asthma. Pediatr Pulmonol 2000; 30: 97-105.
12. Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S, Ekström T. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. Eur Respir J 2001; 18: 262-268.
13. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting β_2-agonists and corticosteroids. Eur Respir J 2002; 19: 182-191.
14. Lipworth BJ. Leukotriene-receptor antagonists. Lancet 1999; 353: 57-62.

CHAPTER 6
ASTHMA IN AGE GROUP 0-4 YEARS. A REGISTRATION STUDY FROM THE JULIANA CHILDREN'S HOSPITAL, THE HAGUE

6.1 Introduction to the study

Since the mid-sixties an increase in hospital admissions for asthma in children in several countries was observed [1]. Factors that could have played a role were an increase in prevalence and (or) severity of asthma, an increase in the number of admissions per patient, a change in hospital admission criteria, and a change in medical management. Several studies from the United Kingdom were aimed at assessing these explanatory aspects. A study in children aged 5-14 years pointed to an increased readmission rate, whereas self referrals had increased as well, possibly due to a tendency of hospitals to partake in primary care functions [2]. A later study, however, showed a relative fall in readmissions in 5-14-year-olds, but together with data from children aged 0-4 years, the findings indicated an increase in number of asthmatic children experiencing severe attacks [3]. Another study pointed to an increase in the number of admitted children as cause for the rising admissions, both in children aged 0-4 years and 5-14 years [4]. In this latter study 72% of the admissions were due to self referrals, to which parental preference for nebuliser treatment in hospital played a part. It has been questioned whether the increase in admissions was associated with a reduction in threshold of severity on admission. From routine case notes the severity assessed by pulse rate and respiration rate on admission and by duration of the episode before admission, provided however no evidence for a threshold reduction [2,3].

In the eighties a striking increase in hospital admissions was also found in the Netherlands in age group 0-4 years [5]. Extrapolation of the British results to the Dutch

situation needs to be viewed with caution, in particular as admission rate in the Netherlands is much lower and stay in hospital much longer than in other countries. Therefore, a registration study was set up in children aged 0-4 years who were newly referred to the outpatient department of the Juliana Children's Hospital in the Hague with symptoms suggestive of asthma. The aim was to examine prognostic characteristics of asthma diagnosis and to identify predisposing risk factors related to exacerbations and hospital admissions. Furthermore, hospital admission data were evaluated, to asses whether threshold of admission and severity of episode differed in first admissions and readmissions. This study resulted in three publications which are presented in the next three sections.

References

1. Mitchell EA. International trends in hospital admission rates for asthma. Arch Dis Child 1985; 60: 376-378.
2. Anderson HR, Bailey P, West S. Trends in the hospital care of acute childhood asthma 1970-8: a regional study. Br Med J 1980; 281: 1191-1194.
3. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.
4. Storr J, Barrell E, Lenney W. Rising asthma admissions and self referral. Arch Dis Child 1988; 63: 774-779.
5. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.

Reprinted from: Acta Paediatr 1999; 88: 827-834.

6.2 PROGNOSTIC CHARACTERISTICS OF ASTHMA DIAGNOSIS IN EARLY CHILDHOOD IN CLINICAL PRACTICE

J Wever-Hess[1], JM Kouwenberg[1], EJ Duiverman[1], J Hermans[2] and AMJ Wever[3]

[1]Department of Paediatric Respiratory Medicine, Juliana Children's Hospital, The Hague, [2]Department of Medical Statistics, University of Leiden, [3]Department of Respiratory Medicine, Red Cross Hospital, The Hague, The Netherlands.

Abstract

A registration study from clinical practice was set up to assess the prognostic value of symptoms and laboratory data at first visit for doctor-diagnosed 'asthma' in early childhood. A total of 419 children aged 0-4 years, who were newly referred to the outpatient department of the Juliana Children's Hospital with possible asthma were enrolled over a 2-year period. Data from history taking, physical examination, laboratory tests for atopic status at first visit and data from follow-up visits were recorded. Two years after the first visit all medical records were reviewed for diagnostic label. The age groups 0-1 year and 2-4 years were analysed separately, because respiratory symptoms are often transient and sensitization to inhalant allergens is uncommon before the age of 2 years. The clinical diagnosis 'asthma' was made in 113 of 231 (49%) children aged 0-1 year and in 144 of 188 (77%) children aged 2-4 years. Characteristics from history taking indicated shortness of breath was the most prognostic symptom in both age groups. Eczema, wheeze and non- allergic provoking factors (weather conditions) were further predisposing factors in the 0-1-year group, as were allergic provoking factors (inhalant allergens) and absence of ear-nose-throat-history in the 2-4-year group. Adding laboratory data to history total serum IgE had prognostic value, but specific serum IgE against inhalant allergens (Phadiatop®) was a strong predisposing factor, especially in the 2-4-year group. These prognostic characteristics may enhance early recognition of asthma in infants and

improve asthma care in clinical practice.

Introduction

Increasing hospital admissions for asthma in childhood in many countries in the last two decades [1], particularly in the age group 0-4 years [2,3] raises questions about asthma management in young children. The initial concern about underdiagnosis and undertreatment of asthma in childhood and overtreating patients with antibiotics [4,5] has changed to efforts to identify children at risk of developing asthma, as respiratory symptoms in infancy often appear to be transient [6-8].

Diagnosing asthma in very young children is still a rather arbitrary process. At this age no real diagnostic tests are available and objective physiological measurements cannot be used routinely. Different criteria, such as three or more wheezy episodes, or presence of atopy [9] have been used, and recently it has been under debate whether the term 'asthma' in childhood should be used [10]. Studies tend to focus on the symptom wheeze, as asthma is an obstructive disorder. Wheezy subjects have been characterized in population based studies [7,11] and in hospital in-patients [12,13] for obtaining predictive variables. Although wheeze may be the classic expression of variable airway obstruction in asthma in young children, asthma may present with symptoms other than wheeze [8,14].

Whatever the problems in diagnosing asthma in very young children may be, in day-to-day clinical practice general practitioners and paediatricians have to deal with young patients presenting with various symptoms suggestive of asthma. To study this difficult and ill-defined area in more detail a registration study from clinical practice was set up in the Juliana Children's Hospital in The Hague, The Netherlands. New referrals under the age of 5 years presenting with asthmatic symptoms were enrolled and followed-up. The paediatrician finally recorded for each child whether he or she considered the clinical diagnosis 'asthma' to be present or not.

The aim of this paper is to assess the prognostic value of symptoms and laboratory data

at first visit for the children who were eventually diagnosed as having 'asthma' by the doctor. The study population was analysed for age groups 0-1 and 2-4 years separately because it has been reported that respiratory symptoms before the age of 2 years are often transient [6-8] and that persistence of wheeze is associated with atopy [6,7] and atopy in itself is associated with age [6].

Patients and methods

Patients

The Juliana Children's Hospital in The Hague has a regional role, covering a population of 325 000. From 1 January 1991 to 1 January 1993 all children, aged 0-4 years, newly referred to the outpatient department with symptoms that were suggestive of asthma were enrolled in the study. Patients with asthma-like symptoms that could be explained by other respiratory disorders, such as respiratory syncytial virus (RSV) bronchiolitis, cystic fibrosis and gastro-oesophageal reflux, were excluded [15]. Patients with RSV bronchiolitis were subsequently entered into the study if after 6 weeks of the initial episode respiratory symptoms persisted or reoccurred.

Clinical history and physical examination

At the initial visit a history was taken and a physical examination carried out according to a standard questionnaire in use in the paediatric respiratory medicine department. Data on asthmatic symptoms, age when symptoms started, allergic provoking factors (food, animals, pollen, house dust), non-allergic provoking factors (infections, exercise/activity, weather conditions, changes in temperature, air pollution, tobacco smoke, emotions), past history including ear, nose and throat (ENT) history and family history were collected. Environmental factors, such as pets in the home, and exposure to tobacco smoke, were documented, as well as data on medication, including the precise drug and method of administration.

Follow-up and diagnosis

Patients were followed-up by their paediatrician. Frequency of follow-up visits was according to medical need, but parents were also advised to contact the paediatrician by telephone when troubled. Two years after the first visit the patient's medical records were reviewed for a doctor's diagnosis of 'asthma' or 'non-asthma', and if in doubt parents were contacted by telephone for additional information. The patients were diagnosed by the paediatrician as 'asthma' or 'non-asthma' on clinical grounds, based on recurrence of symptoms and need for and response to therapy, according to the guidelines for diagnosis of asthma in young children [15].

Laboratory tests

At the initial visit blood was drawn for eosinophil count and total and specific immunoglobulin E (IgE). Number of eosinophils was considered elevated when $\geq 0.400 \times 10^9$ cells/l. Total IgE was considered elevated according to age in years (y) as follows: 0 y: ≥10.1, 1 y: ≥13.1, 2 y: ≥23.1, 3 y: ≥32.1, and 4 y: ≥40.1 kU/l, according to the manufacturer's specifications (Pharmacia & Upjohn AB). Screening for inhalant allergy was done by Phadiatop® and for food allergy by RAST testing with food mix (fx5) from Pharmacia Diagnostics & Upjohn AB. Phadiatop contains a balanced mixture of common inhalant allergens. Fx5 contains the allergens egg white, milk, fish/cod, wheat, peanut and soy bean. Both tests yield a positive/negative answer.

Data analysis

The statistical package SPSS/PC+ was used for analysis of the data. The characteristics of the patients with the clinical diagnosis 'asthma' were compared with those of the 'non-asthma' patients for both age subgroups. χ^2 test on contingency tables, Student's t-test on means, and in cases when Levene's test for equality of variances resulted in a p-value <0.05 the non-parametric Mann-Whitney U test were used in univariate analyses.

Characteristics from history taking on symptoms, provoking factors, social factors and laboratory variables that differed significantly in prevalence between the two diagnostic

groups, were entered in a stepwise logistic regression analysis as possible prognostic variables. The diagnosis 'asthma or 'non-asthma' was the dependent variable. All variables were dichotomized for this analysis, data from history taking being present or absent. Wheeze at auscultation came out as a strong prognostic variable in both age subgroups, and because of the temporal nature of this sign it was not included in the final analyses. The first logistic regression analysis was restricted to investigating the predisposing value of history taking for asthma diagnosis. In the second analysis the prognostic value of laboratory tests additional to history taking was examined.
In an attempt to simplify the results from the logistic regression analyses indices were compiled based on selected significant variables from history taking and laboratory tests. For each individual patient an index value was computed, representing the number of prevalent/positive predisposing factors; this value was then related to the clinical diagnosis of 'asthma' or 'non-asthma'.

Ethics

The study was approved by the Medical Ethics committee of the Juliana Children's Hospital.

Results

Over a 2-year period a total of 419 children entered the study with symptoms of possible asthma, the numbers being at age 0 y: 128, 1 y: 103, 2 y: 89, 3 y: 75, and 4 y: 24. The clinical diagnosis of 'asthma' was made in 113 of the 231 children aged 0-1 year (49%); in the children aged 2-4 years this proportion was substantially higher: 144 out of 188 (77%).

Characteristics in the 0-1-year-olds

History. Data from the history taking and physical examination at initial presentation

Table 6.2.1 Prevalence data from history taking and physical examination at presentation, patients aged 0-1 year

	All (n=231) n (%)	Asthma (n = 113) n (%)	Non-asthma (n=118) n (%)	p-value
Gender, males	147 (64)	82 (73)	65 (55)	0.006
Mean age (mo) (SD)				
at registration	11 (5.4)	11 (5.7)	11 (5.2)	ns
at first symptoms	5.5 (4.6)	5.8 (5.0)	5.2 (4.3)	ns
Symptoms				
cough	195 (84)	91 (81)	104 (88)	ns
wheeze	155 (67)	87 (77)	68 (58)	0.002
cough and wheeze	130 (56)	69 (61)	61 (52)	ns
shortness of breath	121 (52)	78 (69)	43 (36)	<0.001
phlegm	74 (32)	33 (29)	41 (35)	ns
colds	89 (39)	37 (33)	52 (44)	ns
past or present				
rhinitis/otitis	132 (57)	67 (59)	65 (55)	ns
eczema	83 (36)	51 (45)	32 (27)	0.004
Provoking factors				
allergic factors	34 (15)	22 (19)	12 (10)	0.046
food allergens	23 (10)	16 (14)	7 (6)	0.037
inhalant allergens	17 (7)	12 (11)	5 (4)	ns
non-allergic factors	164 (71)	88 (78)	76 (64)	0.024
infections	118 (51)	68 (60)	50 (42)	0.007
exercise	73 (32)	42 (37)	31 (26)	ns
weather conditions	68 (29)	42 (37)	26 (22)	0.012
Social factors*				
family history P/M +	109 (48)	60 (54)	49 (43)	ns
maternal smoking	89 (39)	48 (43)	41 (35)	ns
smoking in household	129 (57)	67 (60)	62 (53)	ns
pets present	88 (38)	46 (41)	42 (36)	ns
Medication				
β_2-agonists	41 (18)	30 (27)	11 (9)	<0.001
deptropine	69 (30)	32 (28)	37 (31)	ns
anticholinergics	7 (3)	5 (4)	2 (2)	ns
antihistamines	27 (12)	17 (15)	10 (8)	ns
anti-inflammatory	7 (3)	5 (4)	2 (2)	ns
antibiotics (or past)	130 (56)	54 (48)	76 (64)	0.011
Physical examination				
wheeze at auscultation	95 (41)	68 (60)	27 (23)	<0.001

* Missing observations on family history (n = 6), smoking (n = 3), and pets (n = 2).

are shown in table 6.2.1 with test results from the univariate analysis. The variables that were found to be significantly different between the asthma and non-asthma patients were gender, wheeze, shortness of breath, eczema, allergic provoking factors and non-allergic provoking factors. Only the three most prevalent non-allergic provoking factors are shown.

Data on drug therapy at presentation showed a relatively high percentage of prescriptions for antibiotics, a low percentage for β_2-agonists and few prescriptions for anti-inflammatory drugs (table 6.2.1). During the study anti-inflammatory therapy was prescribed in 50% of the asthmatics and in none of the non-asthmatics. In the asthmatics with a positive Phadiatop test result anti-inflammatory therapy was prescribed more frequently than in those with a negative test result (80% versus 47%, $p = 0.017$). β_2-agonists were significantly more prescribed in asthmatics than in non-asthmatics (78% versus 31%, $p < 0.001$), mainly on an as-needed basis.

Laboratory tests. Most variables had a low frequency of positivity. Laboratory tests on total IgE, Phadiatop and food mix were significantly different between the 'asthma' and 'non-asthma' patients (table 6.2.2), and the results were added in the stepwise logistic regression analysis. Eosinophil count proved not to be significant in the logistic regression analysis and was not included in the final analysis because of missing observations (9.5%).

Table 6.2.2 Results from laboratory tests at presentation, patients aged 0-1 year

	All (n = 231)* n (%)	Asthma (n = 113) n (%)	Non-asthma (n = 118) n (%)	p-value
Total serum IgE				
elevated	90 (42)	58 (55)	32 (30)	<0.001
geometric mean (kU/l)	11.1	18.1	6.78	<0.001
Eosinophils				
≥0.400 x 10^9/l	31 (15)	22 (21)	9 (8)	0.009
mean number	0.224	0.264	0.186	ns
Phadiatop positive	17 (8)	15 (14)	2 (2)	0.001
Food mix (fx5) positive	43 (20)	29 (28)	14 (13)	0.008
Phadiatop + fx5 positive	10 (5)	10 (10)	0 (0)	0.001

* Missing data on total serum IgE (n = 19), eosinophil count (n = 22), Phadiatop (n = 21), and RAST food mix (n = 21).

Stepwise logistic regression analysis. Running the analysis with the significant variables from history taking, the results showed shortness of breath, eczema, wheeze and weather conditions to be predictive for labelling 'asthma' (table 6.2.3). Gender, allergic provoking factors and non-allergic provoking factors were shown not to be predictive.

Table 6.2.3 Results of the stepwise logistic regression analyses in the patients aged 0-1 year using history (A) and history and laboratory tests combined (B) in discriminating between the clinical diagnostic groups 'asthma' and 'non-asthma'. Variables are placed in order of prognostic value.

Variable	n	Odds ratio	95% Confidence interval
History (n = 231)			
Shortness of breath			
absent	110	1.00	
present	121	4.23	2.36-7.60
Eczema			
absent	148	1.00	
present	83	2.32	1.27-4.26
Wheeze			
absent	76	1.00	
present	155	2.43	1.31-4.52
Weather conditions as provoking factor			
absent	163	1.00	
present	68	2.30	1.21-4.38
History and laboratory tests (n = 209)			
Shortness of breath			
absent	96	1.00	
present	113	4.71	2.44-9.08
Total serum IgE			
normal	121	1.00	
elevated	88	2.64	1.37-5.09
Phadiatop			
negative	193	1.00	
positive	16	7.59	1.42-40.6
Gender			
female	77	1.00	
male	132	1.94	1.001-3.75
Weather conditions as provoking factor			
absent	145	1.00	
present	64	2.13	1.06-4.27
Wheeze			
absent	66	1.00	
present	143	2.07	1.05-4.07

Combining the significant variables from both history and laboratory tests resulted in shortness of breath, total IgE, Phadiatop, gender, weather conditions and wheeze being prognostic for 'asthma' (table 6.2.3). Eczema, allergic and non-allergic provoking factors and food mix were the variables that were not predictive. Figure 6.2.1 shows the percentage and number of patients at each index value (i.e. the number of prevalent predisposing factors) divided by diagnostic group for both analyses, history alone (A) and history and laboratory tests combined (B). The results confirm the higher the index

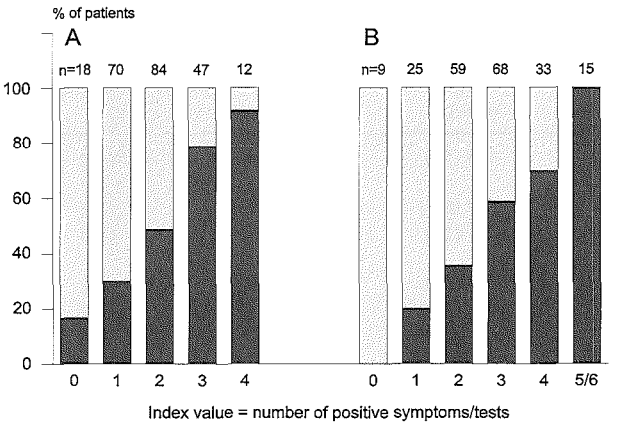

Figure 6.2.1 Number and percentage of patients, aged 0-1 year, divided according to diagnosis by index value based on the number of significant variables indicated from (A) history taking alone: namely shortness of breath, eczema, wheeze and weather conditions as provoking factor; and (B) from both history taking and laboratory tests: namely shortness of breath, total serum IgE, Phadiatop, gender, weather conditions as provoking factor and wheeze.
Asthmatics, non-asthmatics.

value the higher the chance of having asthma diagnosed.

Characteristics in the 2-4-year-olds

History. Data from the history taking and physical examination at initial presentation are shown in table 6.2.4, with test results from the univariate analysis. The variables shortness of breath and eczema (more prevalent in the asthmatics), and ear-nose-throat symptoms (more prevalent in the non-asthmatics) were found to be significant and were entered in the stepwise logistic regression analysis, as well as inhalant allergens as provoking factor.

Data on drug therapy at presentation showed that β_2-agonists and antibiotics were prescribed more frequently, anti-inflammatory drugs were hardly used (table 6.2.4). During the study anti-inflammatory therapy was prescribed in 53% of the asthmatics

Table 6.2.4 Prevalence data from history taking and physical examination at presentation, patients aged 2-4 years

	All (n = 188) n (%)	Asthma (n = 144) n (%)	Non-asthma (n = 44) n (%)	p-value
Gender, males	108 (57)	86 (60)	22 (50)	ns
Mean age (mo) (SD)				
at registration	37 (8.4)	38 (8.2)	36 (8.9)	ns
at first symptoms	17 (14)	18 (13)	17 (15)	ns
Symptoms				
cough	168 (89)	127 (88)	41 (93)	ns
wheeze	97 (52)	78 (54)	19 (43)	ns
cough and wheeze	88 (47)	70 (49)	18 (41)	ns
shortness of breath	130 (69)	109 (76)	21 (48)	<0.001
phlegm	44 (23)	32 (22)	12 (27)	ns
colds	68 (36)	56 (39)	12 (27)	ns
past or present				
rhinitis/otitis	124 (66)	89 (62)	35 (80)	0.030
eczema	78 (41)	67 (47)	11 (25)	0.011
Provoking factors				
allergic factors	64 (34)	56 (39)	8 (18)	0.011
food allergens	26 (14)	22 (15)	4 (9)	ns
inhalant allergens	54 (29)	50 (35)	4 (9)	0.001
non-allergic factors	155 (82)	117 (81)	38 (86)	ns
infections	108 (57)	86 (60)	22 (50)	ns
exercise	90 (48)	70 (49)	20 (45)	ns
weather conditions	93 (49)	71 (49)	22 (50)	ns
Social factors*				
family history P/M +	82 (44)	63 (44)	19 (43)	ns
maternal smoking	66 (35)	47 (33)	19 (43)	ns
smoking in household	96 (52)	70 (49)	26 (59)	ns
pets present	76 (40)	58 (40)	18 (41)	ns
Medication				
β_2-agonists	79 (42)	69 (48)	10 (23)	0.003
deptropine	18 (10)	11 (8)	7 (16)	ns
anticholinergics	6 (3)	5 (3)	1 (2)	ns
antihistamines	38 (20)	27 (19)	11 (25)	ns
anti-inflammatory	10 (5)	10 (7)	0 (0)	ns
antibiotics (or past)	92 (49)	67 (47)	25 (57)	ns
Physical examination				
wheeze at auscultation	67 (36)	65 (45)	2 (5)	<0.001

* Missing observations on family history (n = 2) and smoking (n = 2).

and in two (5%) non-asthmatics. In asthmatics with a positive Phadiatop test result anti-inflammatory therapy was prescribed more frequently than in those with a negative test result (60% versus 42%, $p = 0.031$). β_2-agonists were prescribed significantly more in asthmatics than in non-asthmatics (82% versus 41%, $p < 0.001$), mainly on an as-needed basis.

Table 6.2.5 Results from laboratory tests at presentation, patients aged 2-4 years

	All (n = 188)* n (%)	Asthma (n = 144) n (%)	Non-asthma (n = 44) n (%)	p-value
Total serum IgE				
elevated	119 (65)	107 (75)	12 (29)	<0.001
geometric mean (kU/l)	66.8	105	14.7	<0.001
Eosinophils				
≥0.400 x 10^9/l	56 (33)	49 (38)	7 (18)	0.018
mean number	0.343	0.375	0.237	0.030
Phadiatop positive	88 (47)	86 (60)	2 (5)	<0.001
Food mix (fx5) positive	70 (38)	64 (46)	6 (14)	<0.001
Phadiatop + fx5 positive	53 (29)	51 (36)	2 (5)	<0.001

* Missing data on total serum IgE (n = 4), eosinophil count (n = 18), Phadiatop (n = 2), and RAST food mix (n = 5).

Table 6.2.6 Results of the stepwise logistic regression analyses in the patients aged 2-4 years using history (A) and history and laboratory tests combined (B) in discriminating between the clinical diagnostic groups 'asthma' and 'non-asthma'. Variables are placed in order of prognostic value

Variable	n	Odds ratio	95% Confidence interval
History (n = 188)			
Shortness of breath			
absent	58	1.00	
present	130	3.10	1.49-6.47
Inhalant allergens as provoking factor			
absent	134	1.00	
present	54	4.71	1.56-14.3
ENT history			
present	124	1.00	
absent	64	2.39	1.02-5.59
History and laboratory tests (n = 182)			
Phadiatop			
negative	96	1.00	
positive	86	17.4	3.78-80.2
Total serum IgE			
normal	65	1.00	
elevated	117	2.65	1.11-6.34
Shortness of breath			
absent	55	1.00	
present	127	2.47	1.07-5.68

Laboratory tests. The laboratory tests showed significantly higher values and percentages of positive test results in asthmatics than in non-asthmatics (table 6.2.5). Specific IgE against inhalant allergens (Phadiatop) was present in 60% of the asthmatics. Total IgE, Phadiatop and food mix results were added in the stepwise

logistic regression analysis. Eosinophil count proved not to be significant in the logistic regression analysis and was not included in the final analysis because of missing observations (9.6%).

Stepwise logistic regression analysis. Results from the stepwise regression analyses are presented in table 6.2.6, the data from history resulted in shortness of breath, inhalant allergens as provoking factor and absence of ENT-history being prognostic for 'asthma'. Wheeze and eczema were the variables shown not to be prognostic. Data from both history and laboratory tests indicated Phadiatop being a very strong predisposing variable to which total IgE and shortness of breath were added in the selection process (table 6.2.6). Wheeze, eczema, allergic and non-allergic provoking factors, ENT-history, and food mix results were shown not to contribute any more. Figure 6.2.2 shows the breakdown of the patients according to their diagnosis of asthma or non-asthma at each index value for both analyses, (A) history alone and (B) history and laboratory tests combined.

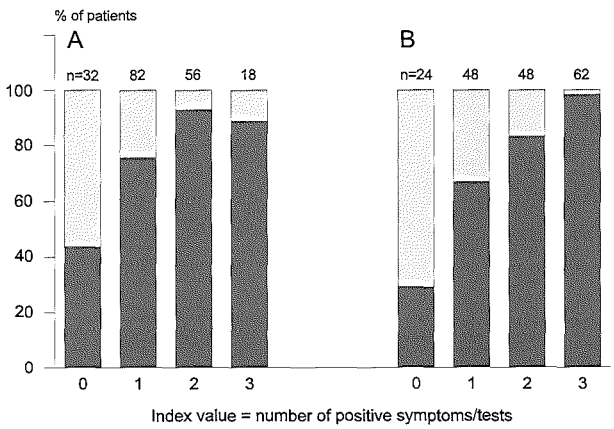

Figure 6.2.2 Number and percentage of patients, aged 2-4 years, divided according to diagnosis by index value based on the number of significant variables indicated from (A) history taking alone: namely shortness of breath, inhalant allergens as provoking factor and absence of ENT-history; and (B) from both history taking and laboratory tests: namely Phadiatop, total serum IgE and shortness of breath.
Asthmatics, non-asthmatics.

Discussion

The patients in this study came from daily clinical practice referred to the outpatient department of the Children's Hospital for help and advice. They presented with asthmatic symptoms, not only wheeze, but also cough and shortness of breath. The decreasing number of referrals to the outpatient department by increasing age seems to indicate that the biggest problem in diagnosing and managing asthmatic symptoms lies with the youngest ages. In the first 2 years of life viral infections and altered lung mechanics are influencing the expression of asthmatic symptoms, whereas later atopy and bronchial hyperresponsiveness in connection with atopy is increasingly important [16]. In the 2-4-year group 77% of the children had doctor diagnosed asthma versus 49% in the 0-1-year group, onset of symptoms being 18 versus 5.8 months. It supports the findings from other study populations that transient symptoms frequently occur before the age of 2 years [6-8,13]. Different variables proved to carry different prognostic value for clinical diagnosis of asthma between the two age groups (0-1 year and 2-4 years), using the same method of history taking and laboratory testing. Thus the subdivision of the age group 0-4 years seems justified.

From the history data the symptom of shortness of breath was the variable with the most prognostic value between asthma and non-asthma in both age groups. This is in accordance with findings from population based samples in children under 5-year-old in which shortness of breath with wheezing attacks was associated with doctor diagnosed asthma [8,11], possibly indicating more disease severity in children reporting shortness of breath as a symptom.

The importance of the symptom of wheeze may vary with age. Wheeze had a higher prevalence in the youngest age group, and in contrast to the older age group, proved to be a prognostic variable between asthma and non-asthma. The importance of viral infections/colds predisposing for wheeze and acute asthma attacks has already been indicated in population based [11] and hospital based samples [17], but in relation to asthma diagnosis they are not a contributing factor [11]. In the youngest age group infections as a provoking factor differed in prevalence between asthmatics and

non-asthmatics in the univariate analysis, but again had no prognostic value with regard to diagnosis. Non-allergic provoking factors were very prevalent in both diagnostic groups, pointing to the non-specificity of these factors in asthma. Only weather conditions appeared to be prognostic before the age of 2 years, agreeing with another Dutch study in the same age group in which this factor was related to persistence of asthmatic symptoms [18]. Inhalant allergens (animals, pollen, house dust) as a predictive factor was negligible in the 0-1-year group, but played a role in the 2-4-year group. This is in agreement with findings that the prevalence of inhalant precipitants increases with increasing age [11] and that inhalant allergen sensitization usually starts from about 2 years of age [17,19], being a risk factor for wheeze at hospitalization [17] and associated with recurrent wheezing under the age of 5 years [19].

Overall, the important role of atopic markers was observed in this study with eczema relevant in the youngest age group and Phadiatop and more modestly total IgE relevant in both age groups, being in agreement with other findings [7,12]. However, despite the relatively high odds ratio of Phadiatop in the youngest age group, one could argue that in the diagnostic procedure at this age adding this test is not that relevant because of the low prevalence of a positive test result. Phadiatop in the very young may be less sensitive than skin prick tests [12], but sensitization to inhalant allergens before the age of 2 years is uncommon [17,19]. Furthermore, eczema from history taking as predisposing factor appears to be overtaken by laboratory tests when they are added to the analysis. In the 2-4-year group a positive Phadiatop test result was much more prevalent (47%) and a strong predictive factor for an asthma diagnosis. Confirming sensitization to inhalant allergens is of value in the diagnostic procedure in this age group. It is noted that at the end of the study period more atopics, as defined by a positive Phadiatop test, were on maintenance anti-inflammatory therapy compared with the non-atopics, suggesting that the disease is more severe in the atopic children [20].

No association was found between asthma diagnosis and family history in this study population. This partly disagrees with findings in wheezy children in which maternal asthma was more prevalent in those with a diagnosis of asthma than in those without the diagnosis, but it was not a major factor in the logistic regression [11]. It is well

known that family history and smoking are risk factors for asthmatic symptoms in young children when compared with healthy controls, but within a group of children with asthmatic symptoms these factors seem not to be prognostic for asthma diagnosis. Exposure to tobacco smoke in wheezy infants might, however, be a risk factor for persistent asthma later in childhood [21].

The findings from the present study population presenting with various respiratory symptoms point, notably, to shortness of breath, eczema and sensitization to inhalant allergens being associated with asthma diagnosis, similar to findings from population based and hospital in-patients based wheezy children. When restricting studies to only wheezers one should be aware that a number of potential asthmatics might be overlooked, especially in older infants. Although asthma may be seen as a syndrome and in future patients may be divided into several phenotypes and with specific pharmacotherapeutic interventions, diagnosing asthma in clinical practice remains essential to ensure correct treatment [10]. Early recognition of asthma may contribute to improved care and consequently to reduced morbidity [22]. Diagnosis may be facilitated by considering predictive variables from history taking, particularly in patients under the age of 2 years, and by adding tests for sensitization to inhalant allergens, particularly in older infants, aged 2-4 years.

Acknowledgement.—This study was supported financially by the 'Stichting Astmabestrijding', Amsterdam, The Netherlands.

References

1. Mitchell EA. International trends in hospital admission rates for asthma. Arch Dis Child 1985; 60: 376-378.
2. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.
3. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.
4. Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. Br Med J 1983; 286: 1253-1256.
5. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-1199.
6. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood—a birth cohort study. Arch Dis Child 1991; 66: 1050-1053.
7. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, Group Health Medical Associates. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332: 133-138.
8. Dodge R, Martinez FD, Cline MG, Lebowitz MD, Burrows B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. J Allergy Clin Immunol 1996; 98: 48-54.
9. Carlsen KH. What distinguishes the asthmatic amongst the infant wheezers? Pediatr Allergy Immunol 1997; 8(Suppl 10): 40-45.
10. Silverman M, Wilson N. Asthma—time for a change of name? Arch Dis Child 1997; 77: 62-65.
11. Luyt DK, Burton P, Brooke AM, Simpson H. Wheeze in preschool children and its relation with doctor diagnosed asthma. Arch Dis Child 1994; 71: 24-30.
12. Delacourt C, Labbé D, Vassault A, Brunet-Langot D, de Blic J, Scheinmann P. Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma. Allergy 1994; 49: 843-847.
13. Wennergren G, Hansson S, Engström I, Jodal U, Åmark M, Brolin I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. Acta Paediatr 1992; 81: 40-45.
14. Green R, Luyt D. Clinical characteristics of childhood asthmatics in Johannesburg. S Afr Med J 1997; 87: 878-882.
15. Warner JO. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992; 67: 240-248.
16. Wennergren G, Wilson N. Short- and long-term efficacy. Eur Respir J 1998; 12(Suppl 27): 52s-58s.

17. Duff AL, Pomeranz ES, Gelber LE, Price GW, Farris H, Hayden FG, et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatrics 1993; 92: 535-540.

18. Brand PLP, Van Aalderen WMC. Asthma in young children: differences in treatment between GP's and paediatricians, and evolution of symptoms over 1-2.5 years (English summary). Ned Tijdschr Geneeskd 1998; 142: 1501-1504.

19. Van Asperen PP, Kemp AS. The natural history of IgE sensitisation and atopic disease in early childhood. Acta Paediatr Scand 1989; 78: 239-245.

20. Zimmerman B, Chambers C, Forsyth S. Allergy in asthma. II. The highly atopic infant and chronic asthma. J Allergy Clin Immunol 1988; 81: 71-77.

21. Wennergren G, Åmark M, Åmark K, Oskarsdóttir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. Acta Paediatr 1997; 86: 351-355.

22. Charlton I, Jones K, Bain J. Delay in diagnosis of childhood asthma and its influence on respiratory consultation rates. Arch Dis Child 1991; 66: 633-635.

Reprinted from: Pediatr Pulmonol 2000; 29: 250-256.

6.3 RISK FACTORS FOR EXACERBATIONS AND HOSPITAL ADMISSIONS IN ASTHMA OF EARLY CHILDHOOD

J. Wever-Hess, MD,[1] J.M. Kouwenberg, MD,[1] E.J. Duiverman, MD, PhD,[2] J. Hermans, PhD,[3] and A.M.J. Wever, MD, PhD[4]

[1]Department of Pediatric Respiratory Medicine, Juliana Children's Hospital, The Hague, The Netherlands. [2]Academic Hospital Groningen/Beatrix Children's Hospital, The Netherlands. [3]Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands. [4]Department of Respiratory Medicine, Red Cross Hospital, The Hague, The Netherlands.

Grant sponsor: Stichting Astmabestrijding, Amsterdam.

Abstract

Hospital admissions and readmissions for asthma in early childhood remain causes for concern. The purpose of this study was to identify predisposing risk factors related to asthma exacerbations as precursors of hospital admissions in young children. Subjects were patients with doctor-diagnosed asthma from a clinical registration study, aged 0-4 years, and followed up for 2 years. Data from histories and laboratory tests for atopic status at initial presentation, and the patient's condition at visits over the 2-year follow-up period were evaluated. Exacerbation was defined as increases in cough and/or wheeze and/or breathlessness, increase in β_2-agonist use, and a clinical need for a short course of oral corticosteroids. Age groups 0-1 year and 2-4 years, based on age at initial presentation, were analyzed separately.

In the age group 0-1 year, 71/113 (63%) patients had at least one exacerbation, and 20 experienced recurrent exacerbations (≥3). Predisposing risk factors for exacerbation were damp housing (odds ratio (OR) 7.6 (2.0-28.6)) and colds (OR 3.6 (1.4-9.6)), and for recurrent exacerbations sensitization to inhalant allergens (Phadiatop®) (OR 8.1 (1.6-40.5)) and damp housing (OR 3.8 (1.1-12.8)). Hospital admissions were significantly associated with number of exacerbations. In the age group 2-4 years,

58/144 (40%) patients had at least one exacerbation, and 21 experienced recurrent exacerbations (≥2). Predisposing risk factors for exacerbation were mean age at initial presentation (OR 0.92 (0.88-0.97)) and level of total IgE (OR 2.3 (1.4-3.9)), whereas for recurrent exacerbations no predictor variables were found. Hospital admissions were significantly associated with damp housing.

Results from this study may facilitate recognition of young asthmatic patients at risk of (recurrent) exacerbations, and help to identify those in whom early intervention with anti-inflammatory therapy may be necessary. We also emphasize the importance of preventive measures in decreasing damp housing.

Introduction

Hospital admission rates for asthma in childhood are high and have increased in the last two decades in several parts of the world, especially in children aged 0-4 years [1-3]. Other studies have indicated that readmissions for asthma in childhood occur mainly under the age of 5 [3-5]. In the Netherlands, rates of hospital admissions for asthma are relatively low [6], but are highest and still on the increase in the age group 0-4 years [7]. A number of event-orientated studies have identified clinical evaluation of the attack to be predictive for hospital admission for asthma [8,9], with pulse oximetry being particularly helpful [8-10]. Besides asthma severity, health services and hospital strategies may play a part in hospitalizing asthmatic patients [11,12]. There are indications that inadequate therapy and suboptimal treatment of the asthmatic child by caregivers and caretakers may contribute to acute asthma manifestations leading to hospital admission [12,13]. However, from studies on readmissions, the number of previous admissions and age were the main risk factors for admission, irrespective of factors related to asthma management [4,5].

The present study aimed to identify predisposing risk factors related to asthma exacerbations being precursors of hospital admissions in children with asthma aged 0-4 years. This information may serve to optimize asthma management in these children.

The age group 0-4 years was subdivided into a 0-1 year and a 2-4 year age group, as different factors may play a role in the disease at different ages [14].

Materials and methods

Patients

Between January 1, 1991 and January 1, 1993 all children aged 0-4 years, who were newly referred to the outpatient department of the Juliana Children's Hospital in The Hague with a suspected diagnosis of asthma, were enrolled in a registration study and followed for 2 years [15]. Out of a total of 419 children, 257 had doctor-diagnosed asthma: 113 patients were 0 up to 2 years old at initial presentation (age group 0-1 year), and 144 patients were 2-4 years old (age group 2-4 years). These 257 patients are the subjects of the present paper.

Clinical History and Physical Examination

At the initial visit a history was taken, using a standard questionnaire of the department of pediatric respiratory medicine. Data on asthmatic symptoms, age when symptoms started, provoking factors, eczema, ear-nose-and-throat signs and symptoms, and family history were collected. Environmental factors, such as pets in the home, exposure to tobacco smoke, housing conditions, and medications prescribed and method of administration were listed.

Frequency of follow-up visits was at the discretion of the physician or according to medical need. At each visit the patient's condition was evaluated by an interim history and physical examination, and exacerbation status was assessed (yes/no). Exacerbation was defined as any increase in cough, wheeze, or breathlessness, an increase in β_2-agonist use (more than 3 oral doses a day, or more than 6 inhalations a day), and a need for a short course of oral corticosteroids. Prescriptions for anti-asthma drugs were documented, considering sodium cromoglycate and inhaled corticosteroids as preventive anti-inflammatory therapy.

Laboratory Tests

At the initial visit blood was drawn for total and specific immunoglobulin E (IgE). Total IgE was considered elevated according to age in years and specifications of the manufacturer (Pharmacia & Upjohn AB, Uppsala, Sweden): 0 years (y): ≥10.1, 1 y: ≥13.1, 2 y: ≥23.1, 3 y: ≥32.1, and 4 y: ≥40.1 kU/L. Screening for inhalant allergy was done by Phadiatop® testing and for food allergy by RAST testing with food mix (fx5) (Pharmacia Diagnostics & Upjohn AB). Phadiatop® contains a balanced mixture of common inhalant allergens, and fx5 contains the allergens egg white, milk, fish/cod, wheat, peanut, and soy bean. Both tests yield a positive/negative answer. A positive Phadiatop® test result was followed up by RAST tests for specific IgE antibodies against house dust mite, cat dander, and dog dander. Results were classified semiquantitatively in RAST classes 0-4; class ≥1 was considered positive.

Data Evaluation and Statistical Analysis

The patients with at least one exacerbation over the 2-year follow-up period made up the *exacerbation group*, and patients without exacerbations the *nonexacerbation group*. Recurrent exacerbations were defined as 3 or more in age group 0-1 year, and 2 or more in age group 2-4 years. Patients in the *exacerbation group* with at least one hospital admission for asthma over the 2-year follow-up period were considered the *admission group*, and those without hospital admissions for asthma the *nonadmission group*.

The statistical package SPSS/PC+ 5.0 was used for the analysis of the data. Pearson Chi-square test, Fisher's exact test, and the Mantel-Haenszel linear association Chi-square were used to compare different groups in crosstables. Student's two-sample t-test on means, and in cases when Levene's test for equality of variances resulted in a P-value < 0.05, the nonparametric Mann-Whitney U test were used in univariate analyses to compare groups on quantitative variables.

The variables that differed significantly between the *exacerbation* and *nonexacerbation groups* were entered in a stepwise logistic regression analysis, with *exacerbation group* (yes/no) as the dependent variable. Within the *exacerbation group* a stepwise logistic regression analysis was carried out with recurrent exacerbations (yes/no) as dependent

variable, and the variables that differed significantly by number of exacerbations as independent variables. Variables were dichotomized for these analyses except for level of total IgE, which was logtransformed, and age. Predictor variables are presented with odds ratios (OR) and 95% confidence intervals (CI). Stepwise logistic regression analysis on *admission group* (yes/no) was not done in view of the absence of sufficient significant differences.

Ethics

The study was approved by the Medical Ethical Committee of the Juliana Children's Hospital.

Results

Of the 113 asthmatic children in the age group 0-1 year, 71 (63%) experienced a total of 143 exacerbations (Ex) over the 2-year study period: n = 34 (1 Ex), n = 17 (2 Ex), n = 13 (3 Ex), n = 4 (4 Ex), n = 1 (5 Ex), n = 1 (6 Ex), and n = 1 (9 Ex). Of the 144 asthmatic children in the age group 2-4 years, 58 (40%) experienced a total of 96 exacerbations: n = 37 (1 Ex), n = 8 (2 Ex), n = 10 (3 Ex), n = 2 (4 Ex), and n = 1 (5 Ex). The respective admission groups consisted of 49 children having a total of 77 subsequent hospital admissions, and 47 children experienced a total of 58 subsequent hospital admissions. In the age group 0-1 year, 5/113 (4%) children, and in the age group 2-4 years, 2/144 (1%) children were hospitalized without exacerbation according to the criteria set in this study.

Exacerbations

Data from the histories and laboratory tests at initial presentation in the age group 0-1 year are shown in Table 6.3.1. In the *exacerbation group*, prevalences of reported colds, living in damp houses, and geometric mean total IgE proved to be significantly higher than in the *nonexacerbation group*. Entering these three variables in a stepwise logistic

Table 6.3.1 Prevalence data from histories and laboratory tests at presentation in asthmatic patients aged 0-1 year[1]

	All (N = 113)[2] n (%)[2]	Exacerbation (n = 71) n (%)	Nonexacerbation (n = 42) n (%)	P-value
History				
Gender, males	82 (73)	52 (73)	30 (71)	0..835
Mean age in months ± SD				
At registration	11 ± 5.7	12 ± 5.7	11 ± 5.6	0.506
At first symptoms	5.8 ± 5.0	6.5 ± 5.7	4.5 ± 3.2	0.118
Past or present history				
Colds	37 (33)	29 (41)	8 (19)	0.017
Rhinitis/otitis	67 (59)	42 (59)	25 (60)	0.969
Eczema	51 (45)	31 (44)	20 (48)	0.683
Social factors				
Family history P/M+	60 (54)	40 (56)	20 (49)	0.440
Maternal smoking	48 (43)	29 (41)	19 (45)	0.693
Smoking in household	67 (60)	44 (63)	23 (55)	0.398
Pets present	46 (41)	28 (39)	18 (43)	0.721
Damp housing	28 (26)	23 (34)	5 (13)	0.017
Siblings	72 (65)	44 (64)	28 (67)	0.756
First child	42 (38)	26 (38)	16 (38)	0.965
Laboratory tests				
Total serum IgE				
Elevated	58 (55)	41 (59)	17 (47)	0.266
Geometric mean (kU/L)	18.1	23.6	10.8	0.031
Phadiatop® test positive	15 (14)	11 (16)	4 (11)	0.502
Food mix (fx5) RAST positive	29 (28)	20 (29)	9 (25)	0.633

[1]P, father; M, mother; RAST, radioallergosorbent test.
[2]Missing observations on family history (n = 1), smoking (n = 1), damp housing (n = 6), siblings (n = 2), IgE (n = 7), Phadiatop® test (n = 8), food mix (n = 9).

regression analysis resulted in damp housing (OR 7.6 (2.0-28.6)) and colds (OR 3.6 (1.4- 9.6)) as predictor variables for the *exacerbation group*. Table 6.3.2 shows the data for the age group 2-4 years. Mean age at registration differed significantly between the *exacerbation* and *nonexacerbation groups*. Laboratory results showed significantly higher prevalences of elevated total IgE and positive Phadiatop® results, and a significantly higher geometric mean total IgE in the *exacerbation group* compared to the *nonexacerbation group*. A stepwise logistic regression analysis with these four variables showed age at registration (OR 0.92 (0.88-0.97)) and level of total IgE (OR 2.3 (1.4-3.9)) to be significant predictor variables.

Table 6.3.2 Prevalence data from histories and laboratory tests at presentation in asthmatic patients aged 2-4 years[1]

	All (N = 144)[2] n (%)[2]	Exacerbation (n = 58) n (%)	Nonexacerbation (n = 86) n (%)	P-value
History				
Gender, males	86 (60)	38 (66)	48 (56)	0.244
Mean age in months ± SD				
At registration	38 ± 8.2	35 ± 8.0	39 ± 7.9	0.001
At first symptoms	18 ± 13	19 ± 13	17 ± 14	0.403
Past or present history				
Colds	56 (39)	24 (41)	32 (37)	0.615
Rhinitis/otitis	89 (62)	33 (57)	56 (65)	0.319
Eczema	67 (47)	25 (43)	42 (49)	0.499
Social factors				
Family history P/M+	63 (44)	29 (50)	34 (40)	0.262
Maternal smoking	47 (33)	20 (35)	27 (32)	0.680
Smoking in household	70 (49)	28 (49)	42 (49)	0.973
Pets present	58 (40)	23 (40)	35 (41)	0.900
Damp housing	41 (30)	20 (37)	21 (25)	0.143
Siblings	110 (78)	48 (84)	62 (74)	0.143
First child	64 (46)	27 (48)	37 (44)	0.628
Laboratory tests				
Total serum IgE				
Elevated	107 (75)	51 (88)	56 (67)	0.004
Geometric mean (kU/L)	105	173 74		0.003
Phadiatop® test positive	86 (60)	41 (71)	45 (53)	0.033
Food mix (fx5) RAST positive	64 (46)	29 (52)	35 (42)	0.239

[1]P, father; M, mother; RAST, radioallergosorbent test.
[2]Missing observations on family history (n = 2), smoking (n = 2), damp housing (n = 7), siblings (n = 3), IgE (n = 2), Phadiatop® test (n = 1), food mix (n = 4).

Table 6.3.3 Prevalence of variables, showing a significantly linear association with number of exacerbations in the patients aged 0-1 year

	Variable				
Number of exacerbations	Colds n/N (%)	Damp house n/N (%)	IgE ≥90 kU/L n/N (%)	Phadiatop® test n/N (%)	Food mix (RAST) n/N (%)
0	8/42 (19)	5/39 (13)	3/36 (8)	4/36 (11)	9/36 (25)
1	11/34 (32)	7/32 (22)	4/33 (12)	3/33 (9)	5/33 (15)
2	10/17 (59)	6/16 (38)	6/17 (35)	1/16 (6)	6/16 (38)
≥3	8/20 (40)	10/20 (50)	9/20 (45)	7/20 (35)	9/19 (47)
P-value	0.018	0.001	<0.001	0.041	0.047

ratio in the patients aged 2-4 years who experienced only one exacerbation.

In patients with a positive Phadiatop® result, specific IgE antibodies were detected against house dust mite, cat dander, and dog dander in 6, 8, and 9 patients aged 0-1 year, respectively, and in 65, 56, and 42 patients aged 2-4 years, respectively. In this study, no associations were found between prevalence of these specific IgEs and asthma exacerbations, hospital admissions, or damp housing (data not presented).

Preventive Treatment

At initial presentation, only 5 (4%) patients aged 0-1 year and 10 (7%) patients aged 2-4 years were on maintenance anti-inflammatory treatment, all using inhaled steroids. Exacerbations occurred mainly in the first year of observation, with over 50% in the first 3 months. Prescriptions for preventive therapy over the study period by number of exacerbations is shown in Table 6.3.6. These results indicate a linear association between prescription of preventive therapy and number of exacerbations in age group 0-1 year, reaching 90% for patients with 3 or more exacerbations. In the age group 2-4 years, the linear association was weak, but preventive medication was prescribed significantly more often in the patients with two or more exacerbations (95%).

Table 6.3.6 Prescriptions for anti-inflammatory therapy over the study period by number of exacerbations, for age groups 0-1 year and 2-4 years

		Preventive therapy			
No. of exacerbations	N	1-3 months n (%)	4-12 months n (%)	13-24 months n (%)	Total n (%)
Age group 0-1 year					
0	42	11 (26)	9 (21)	4 (10)	24 (57)
1	34	11 (32)	9 (26)	3 (9)	23 (68)
2	17	10 (59)	4 (24)	0 (0)	14 (82)
≥3	20	6 (30)	6 (30)	6 (30)	18 (90)
P-values					0.038[1]
					0.004[2]
Age group 2-4 years					
0	86	35 (41)	17 (20)	6 (7)	58 (67)
1	37	16 (43)	7 (19)	1 (3)	24 (65)
≥2	21	12 (57)	7 (33)	1 (5)	20 (95)
P-values					0.028[1]
					0.045[2]

[1]Pearson Chi-square.
[2]Linear-by-linear association.

Discussion

This study concerned children aged 0-4 years who were newly referred to the outpatient department of the Juliana Children's Hospital in The Hague, diagnosed as having asthma, and followed up for 2 years under specialist's care. The aim of the study was to investigate whether predisposing factors for asthma exacerbations and subsequent hospital admissions could be identified in young asthmatic children. Consequently, the patient group under study was by nature a selected group. Management of the asthmatic patient is aimed at preventing exacerbations which may lead to emergency visits and hospital admissions. Asthma exacerbation implies temporal worsening of the disease, but criteria to define exacerbations are arbitrary. In this study the criteria included a need for a short course of oral corticosteroids. It is noted that oral corticosteroids had been prescribed for asthma exacerbations prior to referral in only a few patients. About half of the exacerbations resulted in hospital admission; thus, patients with recurrent exacerbations are at highest risk for hospital admission and readmission.

Exacerbations are often triggered by viral infections [16]; sensitization to inhalant allergens such as house dust mite and cat dander has been associated with acute hospital visits in older children [17,18]. In this study, reported cold and sensitization to inhalant allergens were also significantly associated with exacerbations. However, reported colds had only prognostic value in the age group 0-1 year for the *exacerbation group*, second to damp housing. More importantly, sensitization to inhalant allergens (positive Phadiatop® test), although overall low in prevalence in age group 0-1 year, proved to be of predictive value for recurrent exacerbations. In the age group 2-4 years, prevalence of sensitization to inhalant allergens was substantially higher, but Phadiatop® test results did not come out as a predictor variable, possibly because more than half of the patients in the *nonexacerbation group* also had a positive test result. In this group, the level of total IgE had predictive value for exacerbations. It has already been reported that elevated levels of total IgE are a risk factor for persistence of wheeze in infancy [19], but whether total IgE is a predisposing factor in itself or an indicator for other risk factor(s), such as airway hyperresponsiveness [20], remains to be clarified.

Damp housing was an important predictor variable in both age groups. Data on damp housing were self-reported at initial presentation. Results from case-control studies have suggested no overreporting of dampness in the home in asthmatics [21,22], but rather the reverse [22]. Several studies have indicated damp housing to be associated with house dust mite and mould sensitization and development of asthma [23]. In young asthmatic children an association between damp housing and asthma was found, particularly in those sensitized to pets [21]. Results from this study suggest that damp housing may be a variable that contributes independently of sensitization to aggravating symptoms in young asthmatics. Damp housing was the prognostic variable for recurrent exacerbations in the age group 0-1 year second to Phadiatop® test results, and was associated with hospital admission within the *exacerbation group* in the age group 2-4 years, possibly pointing to more severe asthma in those children living in damp houses [22] not explained by atopic status.

Inadequate therapy may be a contributing factor to hospital admissions [12,13]. Early intervention with anti-inflammatory drugs in childhood asthma contributes to lower morbidity [24], but varying results have been reported in preschool children perhaps because of dose and method of administration [25]. Recent studies in preschool children showed that treatment with inhaled corticosteroids had no effect in children with predominantly episodic viral wheeze [26]. However, in infants with moderate to severe asthma, a beneficial effect of inhaled steroids was observed [27,28], pointing to the chronic nature of asthmatic symptoms as a factor that may influence treatment effect. In this study the proportion of patients in whom preventive therapy was initiated in the first 3 months was similar in the different exacerbation groups; patients with recurrent exacerbations had significantly more frequently preventive therapy prescribed over the study period than those with 0 or 1 exacerbations, indicating that exacerbations may still occur despite preventive therapy. This is in accordance with findings from a study in which medical treatment did not affect the chance of readmissions [4], and another one in which bronchoalveolar lavage findings in children suggested that ongoing airways inflammation was present despite anti-inflammatory treatment [29]. However, factors such as dose of anti-inflammatory drugs, duration of therapy, and compliance may have

played a role in the efficacy of treatment.

There is great concern about application and long-term safety of inhaled steroids in young children [24,25]. Therefore, recognition of asthmatic children at risk for recurrent exacerbations and hospital admissions is an important issue. These children might benefit from early intervention with inhaled corticosteroids to prevent future severe episodes needing short courses of oral corticosteroids and hospital admissions. Children with asthma under the age of 5 have the highest risk of admission and readmission [1-6]. The results from this study indicate that total IgE production and sensitization to inhalant allergens predispose to exacerbations of asthma in this age group. Damp housing emerged as an independent risk factor for recurrent exacerbations in patients aged 0-1 year and for hospital admission in patients aged 2-4 years. Preventive measures in damp housing such as increasing ventilation and the use of dryers in homes may benefit the asthmatic child.

References

1. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.
2. Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA 1990; 264: 1688-1692.
3. To T, Dick P, Feldman W, Hernandez R. A cohort study on childhood asthma admissions and readmissions. Pediatrics 1996; 98: 191-195.
4. Mitchell EA, Bland JM, Thompson JMD. Risk factors for readmission to hospital for asthma in childhood. Thorax 1994; 49: 33-36.
5. Farber HJ. Risk of readmission to hospital for pediatric asthma. J Asthma 1998; 35: 95-99.
6. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.
7. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.
8. Kerem E, Tibshirani R, Canny G, Bentur L, Reisman J, Schuh S, Stein R, Levison H. Predicting the need for hospitalization in children with acute asthma. Chest 1990; 98: 1355-1361.
9. Jalaludin B, Chey T, Holmwood M, Chipps J, Hanson R, Corbett S, Leeder S. Admission rates as an indicator of the prevalence of severe asthma in the community. Aust N Z J Public Health 1998; 22: 214-219.
10. Geelhoed GC, Landau LI, Le Souëf PN. Evaluation of SaO_2 as a predictor of outcome in 280 children presenting with acute asthma. Ann Emerg Med 1994; 23: 1236-1241.
11. Strachan DP, Anderson HR. Trends in hospital admission rates for asthma in children. Br Med J [Clin Res] 1992; 304: 819-820.
12. Homer CJ, Szilagyi P, Rodewald L, Bloom SR, Greenspan P, Yazdgerdi S, Leventhal JM, Finkelstein D, Perrin JM. Does quality of care affect rates of hospitalization for childhood asthma? Pediatrics 1996; 98: 18-23.
13. Ordoñez GA, Phelan PD, Olinsky A, Robertson CF. Preventable factors in hospital admissions for asthma. Arch Dis Child 1998; 78: 143-147.
14. Silverman M, Wilson N. Wheezing phenotypes in childhood. Thorax 1997; 52: 936-937.
15. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatr 1999; 88: 827-834.
16. Carlsen KH, Ørstavik I, Leegaard J, Høeg H. Respiratory virus infections and aeroallergens in acute bronchial asthma. Arch Dis Child 1984; 59: 310-315.

17. Nelson RP, DiNicolo R, Fernandez-Caldas E, Seleznick MJ, Lockey RF, Good RA. Allergen-specific IgE levels and mite allergen exposure in children with acute asthma first seen in an emergency department and in nonasthmatic control subjects. J Allergy Clin Immunol 1996; 98: 258-263.

18. Sarpong SB, Karrison T. Sensitization to indoor allergens and the risk for asthma hospitalization in children. Ann Allergy Asthma Immunol 1997; 79: 455-459.

19. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, Group Health Medical Associates. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332: 133-138.

20. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991; 325: 1067-1071.

21. Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL. Indoor environmental risk factors in young asthmatics: a case-control study. Arch Dis Child 1995; 73: 408-412.

22. Williamson IJ, Martin CJ, McGill G, Monie RDH, Fennerty AG. Damp housing and asthma: a case-control study. Thorax 1997;.52: 229-234.

23. Billings CG, Howard P. Damp housing and asthma. Monaldi Arch Chest Dis 1998; 53: 43-49.

24. Bisgaard H. Use of inhaled corticosteroids in pediatric asthma. Pediatr Pulmonol [Suppl] 1997; 15: 27-33.

25. Price JF. Corticosteroids and other anti-inflammatory agents in the treatment of children. Eur Respir Rev 1994; 4: 27-32.

26. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. Arch Dis Child 1995; 72: 317-320.

27. de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, Scheinmann P. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol 1996; 98: 14-20.

28. Wennergren G, Nordvall SL, Hedlin G, Möller C, Wille S, Åsbrink Nilsson E. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. Acta Paediatr 1996; 85: 183-189.

29. Stevenson EC, Turner G, Heaney LG, Schock BC, Taylor R, Gallagher T, Ennis M, Shields MD. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. Clin Exp Allergy 1997; 27: 1027-1035.

Reprinted from: Pediatr Pulmonol 2001; 31: 30-36.

6.4 HOSPITAL ADMISSIONS AND READMISSIONS FOR ASTHMA IN THE AGE GROUP 0-4 YEARS

J. Wever-Hess, MD,[1] J. Hermans, PhD,[2] J.M. Kouwenberg, MD,[1] E.J. Duiverman, MD, PhD,[3] and A.M.J. Wever, MD, PhD[4]

[1]Department of Pediatric Respiratory Medicine, Juliana Children's Hospital, The Hague, The Netherlands. [2]Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands. [3]Academic Hospital Groningen/Beatrix Children's Hospital, The Netherlands. [4]Department of Respiratory Medicine, Red Cross Hospital, The Hague, The Netherlands.

Grant sponsor: Stichting Astmabestrijding, Amsterdam, The Netherlands.

Abstract

Childhood rates for admission and readmission for asthma are highest under the age of 5 years. From a registration study in 0-4-year-olds, 100 patients (68 male) were admitted to hospital for asthma and followed for 1 year, yielding a total of 136 admissions. To examine factors that may play a role in admissions and readmissions, histories and laboratory tests for atopic status at initial presentation, and clinical data on admission were evaluated. Age groups 0-1 year (n=54) and 2-4 years (n=46) were analyzed separately, of whom 20 (37%) and 9 (20%) patients, respectively, had at least one readmission.

In the age group 2-4 years, patients with antibodies against inhalant allergens, determined by radioallergosorbent test (RAST), had a significantly higher risk of readmission (RR=1.54; 95% CI, 1.22-1.95). In the age group 0-1 year, prevalence of sensitization to inhalant allergens was low (20% vs. 72% in age group 2-4 years) and constituted only a slight risk (P=0.097) for readmission. A history of eczema showed a negative association in the age group 0-1 year. Treatment of the first admission did not differ between children only admitted once and those requiring readmission. In both age groups, clinical features at admission did not differ significantly between first and

subsequent admissions, and neither did length of stay. Number of readmissions were higher in the age group 0-1 year than in the age group 2-4 years (27/81 (33%) vs. 9/55 (16%), P=0.028), with no indication of a lower threshold for admission. In the age group 0-1 year, 60% of the readmissions occurred within 2 months of first hospitalization. Moreover, in the age group 0-1 year a trend was observed that inhaled steroids were prescribed less frequently on discharge following first admission in those children who were readmitted than in the children who had a first admission only (4/20 (20%) vs. 15/34 (44%), P=0.073).

More "aggressive" therapy with anti-inflammatory drugs and close medical follow-up after discharge seem to be indicated.

Introduction

Anti-inflammatory treatment has become the mainstay in the pharmacologic management of asthma. Epidemiological studies have indicated beneficial effects of inhaled steroids on hospital admission rates for asthma in New Zealand and the USA [1,2]. A decrease in hospitalization for asthma in children in the early 1990s was reported from Sweden [3,4], but in children under the age of 5 years changes were not significant or clear-cut [3]. A favourable development in asthma statistics was also observed in the Netherlands, but in the age group 0-4 years the hospital admission rate for asthma was still on the increase in the 1990s [5]. This occurred despite an increase in prescriptions for anti-inflammatory drugs in this age group, the national data being obtained from the Institute of Medical Statistics in The Hague [6]. Another factor in childhood asthma is the risk for readmissions being higher in children under the age of 5 years [7-9], with an increasing probability of readmission with increasing number of previous admissions [10].

In a previous paper from a clinical registration study in patients aged 0-4 years risk factors for exacerbations and hospital admissions have been indicated [11]. This study describes the children who were admitted to hospital for asthma, with a follow-up of 1

year. The goal was to examine factors that may play a role in readmission, as the majority of readmissions appeared to take place in the 12 months following the original admission [7,10]. Furthermore, admission data were evaluated to assess whether the threshold leading to an admission and the severity of episode differed between first admission and readmission. Age groups 0-1 year and 2-4 years at initial presentation, were analyzed separately.

Materials and methods

Patients

Subjects came from a registration study of patients aged 0-4 years who were newly referred to the outpatient department of the Juliana Children's Hospital in The Hague with a suspected diagnosis of asthma. Patients with asthma-like symptoms that were suggestive of respiratory syncytial virus bronchiolitis were excluded, but were subsequently enrolled if after 6 weeks of the initial episode, respiratory symptoms persisted or recurred. This cohort was followed for 2 years, in which period 257 children were diagnosed with asthma on clinical grounds, based on recurrence of symptoms and need for and response to therapy according to the guidelines for diagnosis of asthma in young children [12]. One hundred and three children had one or more hospital admissions for asthma. Those children with an admission within the first year after initial presentation were followed-up for 1 year, yielding the present study population of 100 patients.

Clinical History, Physical Examination, and Laboratory Tests

At the initial visit a history was taken, using the standard questionnaire of the Department of Pediatric Respiratory Medicine. Physical examination was carried out and blood drawn for total and specific immunoglobulin E (IgE). Total IgE was considered elevated according to the specifications of the manufacturer (Pharmacia & Upjohn AB, Uppsala, Sweden): 0 years (y), ≥10.1; 1 y, ≥13.1; 2 y, ≥23.1; 3 y, ≥32.1;

and 4 y, ≥40.1 kU/L. Screening for sensitivity to inhalant allergens was done by radioallergosorbent (Phadiatop®) test and for food allergy by RAST testing with food mix (fx5) (Pharmacia Diagnostics & Upjohn AB). Phadiatop® contains a balanced mixture of common inhalant allergens, and fx5 contains the allergens egg white, milk, fish/cod, wheat, peanut, and soy bean. Both tests yield a positive/negative answer. Follow-up visits were at the discretion of the physician or according to medical need, and the patient's condition was evaluated by an interim history and physical examination. Further details are described elsewhere [11,12].

Admission Data

Outpatient treatment of asthma exacerbation consisted of salbutamol and ipratropium bromide aerosol administered by jet nebulizer. If no sufficient improvement occurred within 2-3 h, the child was admitted to hospital. This was judged on clinical grounds, taking into account respiratory effort and auscultation. When admitted, data were collected on duration of symptoms before admission (0-12 h, 13-24 h, >24 h), date and time of admission, date of discharge, clinical assessment, and capillary carbon dioxide tension (PCO_2 mmHg). Severity of the attack was assessed based on a scoring system based on degree of wheeze at auscultation (range 0 (none)-3 (heard without stethoscope)), use of accessory muscles (range 0 (none)-3 (severe)), and pulse rate per minute (range 0 (≤80)-3 (>140)); total scores ranged from 0-9 [13]. Inpatient asthma treatment was documented.

Data Analysis

The statistical package SPSS/PC+8.0 was used for the analysis of data. Pearson's Chi-square test and Fisher's exact test were used to compare groups in crosstables. We used Student's two-sample t-test on means, and in cases when Levene's test for equality of variances resulted in a P-value < 0.05, the nonparametric Mann-Whitney U test was used to compare groups on quantitative variables. Time to first readmission was presented graphically by Kaplan Meier survival curves and compared by logrank test.

Ethics

The study was approved by the Medical Ethics Committee of the hospital.

Results

The study population consisted of 100 patients (68 male) experiencing 136 hospital admissions (93 male). Table 6.4.1 shows the number of patients by number of hospital admissions. The difference in number of children requiring readmission between the age groups 0-1 year and 2-4 years was 20/54 (37%) vs. 9/46 (20%) and failed to reach statistical significance (P=0.055). The difference in number of readmissions for the two respective age groups, 27/81 (33%) vs. 9/55 (16%), proved to be significant (P=0.028); the overall readmission rate in age group 0-4 years was 26% (36/136).

Table 6.4.1 Hospital admissions for asthma

Age group	Total number of children admitted	Number of children with admissions				Total number of admissions	Number of readmissions, n (%)
		1	2	3	4		
0-1 year	54	34	14	5	1	81	27 (33)
2-4 years	46	37	9	0	0	55	9 (16)
All	100	71	23	5	1	136	36 (26)

Patients

The time interval between the initial admission and the first readmission over the 1-year follow-up period is shown in figure 6.4.1. The risk of readmission was significantly greater in the age group 0-1 year compared to 2-4 years (P=0.044). In the age group 0-1 year, 60% of the readmissions occurred within 2 months of initial admission, whereas in the age group 2-4 years readmissions occurred more gradually. In the age group 0-1 year, second readmissions occurred six times; 5 readmissions took place within 2 months after the first readmission.

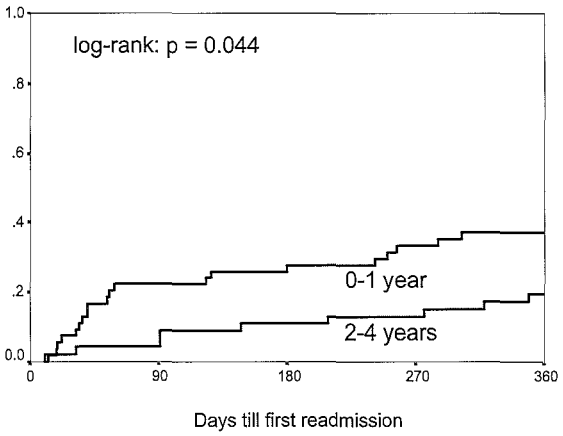

Figure 6.4.1 Risk for readmission by age group in the year following first admission.

Data from histories and laboratory tests at time of referral are shown in table 6.4.2 for the patients aged 0-1 year, with a breakdown by number of admissions (one vs. two or more). Table 6.4.3 shows the same data for the age group 2-4 years. Significant differences between patients with one admission and with more admissions were found in the age group 0-1 year in regard to prevalence of history of eczema (lower in the

Table 6.4.2 Results derived from history and laboratory tests at time of referral (patients aged 0-1 year)[1]

	All (n=54), n (%)	One admission (n=34), n (%)	≥2 admissions (n=20), n (%)	P-value
History				
Male gender	37 (69)	23 (68)	14 (70)	0.857
Family history P/M+	27 (50)	18 (53)	9 (45)	0.573
Maternal smoking	22 (42)	14 (42)	8 (40)	0.862
Smoking in household	34 (64)	21 (64)	13 (65)	0.920
Pets present	22 (41)	13 (38)	9 (45)	0.625
Damp housing	16 (32)	11 (34)	5 (28)	0.631
History of eczema	24 (44)	20 (59)	4 (20)	0.006
Laboratory tests				
Total IgE elevated	30 (58)	21 (64)	9 (47)	0.253
Geometric mean IgE (kU/L)	22.0	26.4	16.1	0.366
Inhalant allergen test positive	10 (20)	4 (12.5)	6 (32)	0.097
Food mix (fx5) positive	15 (30)	12 (37.5)	3 (17)	0.123

[1]Data missing on smoking (n=1), damp housing (n=4), IgE (n=2), inhalant allergen test by Phadiatop® (n=3), and food mix (n=4).

Table 6.4.3 Results derived from history and laboratory tests at time of referral (patients aged 2-4 years)[1]

	All (n=46), n (%)	One admission (n=37), n (%)	Two admissions (n=9), n (%)	P-value
History				
Male gender	31 (67)	26 (70)	5 (56)	0.445
Family history P/M+	22 (48)	17 (46)	5 (56)	0.718
Maternal smoking	17 (38)	12 (33)	5 (56)	0.265
Smoking in household	24 (53)	18 (50)	6 (67)	0.469
Pets present	20 (43)	17 (46)	3 (33)	0.711
Damp housing	18 (43)	14 (41)	4 (50)	0.706
History of eczema	20 (43)	17 (46)	3 (33)	0.711
Laboratory tests				
Total IgE elevated	41 (89)	32 (86)	9 (100)	0.566
Geometric mean IgE (kU/L)	185	171	252	0.526
Inhalant allergen test positive	33 (72)	24 (65)	9 (100)	0.044
Food mix (fx5) positive	23 (52)	18 (49)	5 (71)	0.416

[1]Data missing on smoking (n=1), damp housing (n=4), food mix (n=2); inhalant allergen test by Phadiatop®.

readmission group), and in the age group 2-4 years in the prevalence of positive Phadiatop® result, presenting a relative risk of 1.54 for readmission (95% CI, 1.22-1.95). Age at first admission did not differ between patients with one admission and those with readmissions: mean age (SD) at time of first admission was in the age group 0-1 year 358 days (151) vs. 400 days (185), (P=0.374), and in the age group 2-4 years, 1,052 (228) vs. 1,199 (272), (P=0.102).

Table 6.4.4 Treatment during first admission in children with one admission and in those with readmission(s)

	0-1 year		2-4 years	
	One admission (n=34), n (%)	≥2 admissions (n=20), n (%)	One admission (n=37), n (%)	Two admissions (n=9), n (%)
Corticosteroids[1]				
Oral (± nebulized)	28 (82)	15 (75)	35 (95)	7 (78)
Nebulized	3 (9)	1 (5)	0 (0)	2 (22)
Salbutamol				
Nebulized (± oral)	33 (97)	18 (90)	37 (100)	9 (100)
Oral	1 (3)	1 (5)	0 (0)	0 (0)
Ipratropium bromide (nebulized)	33 (97)	19 (95)	33 (89)	9 (100)
Xanthines (intravenous)	3 (9)	1 (5)	4 (11)	1 (11)
Antibiotics	8 (24)	3 (15)	7 (19)	0 (0)
Steroid maintenance therapy following discharge first admission	15 (44)	4 (20)	14 (38)	5 (56)

[1]Combination with intravenous corticosteroids in both age groups in 3 patients.

Table 6.4.5 Clinical characteristics on first admission and readmission(s)

	Age group 0-1 year[1]		Age group 2-4 years[2]	
	First admission (n=54), n (%)	Readmissions (n=27), n (%)	First admission (n=46), n (%)	Readmissions (n=9), n (%)
Duration of symptoms before admission				
0-12 h	18 (33)	5 (19)	19 (42)	7 (78)
13-24 h	8 (15)	8 (30)	15 (33)	0 (0)
>24 h	28 (52)	14 (52)	11 (24)	2 (22)
Physical examination				
Auscultatory wheeze	52 (96)	27 (100)	44 (96)	9 (100)
Wheeze without stethoscope	17 (31)	7 (26)	5 (11)	2 (22)
Accessory muscle use	48 (89)	23 (92)	39 (93)	9 (100)
Temperature				
≥39.0°C	8 (16)	3 (12.5)	6 (13)	0 (0)
≥38.5°C	17 (33)	6 (25)	9 (20)	0 (0)
Mean ± SD	38.0 ± 0.8	38.0 ± 0.9	37.8 ± 0.9	37.2 ± 0.8
Pulse rate/min > 140	20 (53)	6 (40)	9 (26)	1 (20)
Mean ± SD	145 ± 26	140 ± 26	132 ± 22	127 ± 28
Respiratory rate/min				
Mean ± SD	54 ± 11	55 ± 18	45 ± 14	43 ± 4
PCO_2 mmHg				
Mean ± SD	37.4 ± 5.1	37.4 ± 8.0	35.6 ± 4.7	36.6 ± 1.7
Clinical score[3]				
Mean ± SD	6.0 ± 1.4	5.4 ± 1.7	5.4 ± 1.6	4.8 ± 2.2
Severe (≥7)	16 (42)	5 (36)	4 (12)	1 (20)
Time of admission				
Daytime (8 h AM-8 h PM)	33 (62)	15 (56)	26 (57)	5 (56)
Nighttime	20 (38)	12 (44)	20 (43)	4 (44)
Length of stay (days)				
Mean ± SD	8.4 ± 3.0	8.6 ± 5.2	7.2 ± 2.9	7.0 ± 1.9
Median	8.0	9.0	7.0	7.0

[1]Missing data on accessory muscle use (n=2), temperature (n=6), pulse rate (n=28), respiratory rate (n=18), PCO_2 (n=35), time of admission (n=1), and clinical score (n=29).
[2]Missing data on duration of symptoms (n=1), accessory muscle use (n=4), temperature (n=2), pulse rate (n=15), respiratory rate (n=16), PCO_2 (n=25), and clinical score (n=17).
[3]Based on Conway and Littlewood [13].

Treatment during first admission is shown in table 6.4.4. No significant differences between the patients with one admission and those with two or more admissions were observed. In the age group 0-1 year, a trend was noted, showing that inhaled steroids were prescribed less frequently at discharge in the children with readmissions than in those with only one admission (P=0.073), but this was not the case in the age group 2-4 years (P=0.456).

Admissions

In both age groups no significant differences were found in admission data between first admission and readmissions (table 6.4.5). Number of missing data at first admission and at readmission differed significantly only for the measure of capillary PCO_2 in the age group 0-1 year; 19/54 children (35%) had this value not measured at the time of first admission, while 16/27 (59%) had this value not assessed on readmission (P=0.039). Comparison of the overall admission data between the two age groups showed significant differences in duration of symptoms, length of stay in hospital, and vital signs, as listed in table 6.4.6. Number of missing data did not differ significantly between the two age groups. Season of admission has been added in table 6.4.6; the difference between the age groups failed to reach statistical significance (P=0.051).

Table 6.4.6 Characteristics on admission that differed in age groups 0-1 and 2-4 years[1]

	0-1 year (n=81), n (%)	2-4 years (n=55), n (%)	P-value
Duration of symptoms before admission			
0-12 h	23 (28)	26 (48)	
13-24 h	16 (20)	15 (28)	
>24 h	42 (52)	13 (24)	0.005
Physical examination			
Wheeze without stethoscope	24 (30)	7 (13)	0.021
Temperature, mean ± SD	38.0 ± 0.8	37.7 ± 0.9	0.043
Pulse rate/min >140	26 (49)	10 (25)	0.018
Mean ± SD	144 ± 26	131 ± 22	0.014
Respiratory rate/min, mean ± SD	55 ± 14	45 ± 13	0.001
Clinical score			
Mild/moderate (0-6)	31 (60)	33 (87)	
Severe (≥7)	21 (40)	5 (13)	0.005
Length of stay (days)			
Mean ± SD	8.5 ± 3.9	7.2 ± 2.7	0.028
Median	8.0	7.0	0.007
Season of admission			
Spring (March-May)	22 (27)	8 (15)	
Summer (June-August)	10 (12)	11 (20)	
Autumn (September-November)	22 (27)	24 (44)	
Winter (December-February)	27 (33)	12 (22)	0.051

[1]For missing data and clinical score, see footnotes in Table 6.4.5.

Discussion

Studies on asthma admissions in childhood commonly cover a wide age span [3,4,7-9], in which age <5 years has been identified as a risk factor for readmission [7-9]. The present study examined the age group 0-4 years. The ratio of males to females for hospital admissions in this study (2.2:1) was similar to the national figure of 2.1:1 in the Netherlands in this period, obtained from the Dutch Centre for Health Care Information [14]. The same is true for mean length of stay in our 0–4 year age group, i.e., 8 days in our study, which compares to the Dutch national figure for length of stay declining from 13.8 days in 1980 [15] to 7.2 days in 1991-1992 [14]. This indicates that the population in this study was representative for the Netherlands. The age group 0-1 year consisted of 54 children with a total of 27 readmissions. The age group 2-4 years consisted of 46 children with a total of only 9 readmissions.

In both age groups, no significant differences were found in the clinical data between first admission and readmission, indicating a similar hospital practice regarding hospitalization and readmission for these young asthmatic patients. The overall readmission rate within 1 year was 26%, similar to findings in the age group 0-4 years from other studies [8,9,16]. The observed gender ratio of 2:1 was also similar [8,10,16-18]. Female gender has been reported to be a risk factor for readmission in childhood asthma [7,16], but in the latter study this was not observed in age group 0-4 years [16]. In the present study, gender was again not a risk factor for readmission, being 27% in males and 26% in females.

A significantly higher readmission rate was found in the age group 0-1 year (33%) than in the age group 2-4 years (16%). Results from physical examinations suggest more rather than less severe acute asthma in the youngest age group. However, it should be noted that at a younger age, pulse and respiratory rates are normally higher. The clinical score used to assess severity of the asthma attack was based on auscultatory wheeze, accessory muscle use, and pulse rate [13], and has been found to be useful for discriminative purposes [19]. A drawback was the number of missing data on pulse rates and respiratory rates, varying from 22-35%; however, no significant differences

in number of missing data between the age groups were noted. Overall, 71% of acute asthma proved to be mild/moderate, in accordance with 70% in the study by Conway and Littlewood [13]. Although mean score did not differ between age groups, a significant difference was observed regarding grade of severity, with 40% of acute asthma being severe in the age group 0-1 year vs. 13% in the age group 2-4 years. In the age group 0-1 year, duration of symptoms before admission and mean length of stay in hospital were significantly longer than in the age group 2-4 years. Therefore, the results do not indicate a lower threshold for admission, but rather a true higher readmission rate in the age group 0-1 year. Mean length of stay was much longer than reported from other countries, where it varied from 2.5-3.6 days [3,4,13,20,21]. However, in this study hospitalizations were real ward admissions with overnight stay. The seasonally occurring peaks in admissions favour viral infections as the most likely responsible trigger for asthma exacerbations [22]. It is noticeable, however, that all readmitted children in the age group 2-4 years had antibodies against inhalant allergens; Phadiatop® test positivity showed a relative risk of 1.54. In the age group 0-1 year, the prevalence of positive Phadiatop® test results was low, and only a trend could be observed, but a previous paper reported positive Phadiatop® results to be a risk factor for recurrent exacerbations [11]. Thus atopic children may be especially vulnerable to viral infections. However, the pathophysiological mechanisms responsible are not yet clear [23]. The negative association of history of eczema with hospital readmissions in this age group remains to be explained. Previous results from this registration study showed eczema to be one of the predisposing factors associated with asthma diagnosis [12], but in asthma exacerbations it played no role [11], and no indication was found for an association between eczema and treatment with anti-inflammatory therapy.

Readmissions in the age group 0-1 year occurred primarily within 2 months after initial admission. Readmissions in the age group 2-4 years occurred throughout the subsequent year, but were low in number. Other studies have pointed to a high risk of readmissions in age group 0-4 years within 3 months after the previous admission [7,8,10], the interval being significantly shorter than in children aged 5-17 years [8].

Educational programs targeted at children hospitalized for asthma have shown

promising results in reducing readmissions [24,25], but were carried out in children 2 years and over. It also seems worthwhile to target children under the age of 2 years for educational programs. Asthma management in preschool children is difficult, and treatment with inhaled corticosteroids raises concern. Children aged 0-1 year having been hospitalized for asthma should be closely followed because of the high risk of readmission in the first months following the admission. Besides, more "aggressive" therapy seems indicated, because a trend towards less frequent prescription for inhaled steroids at discharge from the first admission was found in those children who were readmitted. This is supported by a recent study in which a beneficial effect of inhaled steroids was found on asthma exacerbations in 1-3-year-olds with moderate asthma [26]. Thus, inhaled steroids may be efficacious in preventing initial hospitalizations and readmissions for asthma in very young children, but further research is needed to support this recommendation.

References

1. Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand: what lessons have been learned? Thorax 1995; 50: 303-311.
2. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997; 277: 887-891.
3. Wennergren G, Kristjánsson S, Strannegård I-L. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in the prevalence of asthma. J Allergy Clin Immunol 1996; 97: 742-748.
4. Strömberg L. Decreasing admissions for childhood asthma to a Swedish county hospital. Acta Paediatr 1996; 85: 173-176.
5. Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.
6. Wever-Hess J, Kouwenberg JM, Wever AMJ. Trends in consultations and prescriptions for obstructive airways disease in children. Ned Tijdschr Geneeskd 1993; 137: 1246-1251 [English-language summary].
7. Mitchell EA, Bland JM, Thompson JMD. Risk factors for readmission to hospital for asthma in childhood. Thorax 1994; 49: 33-36.
8. To T, Dick P, Feldman W, Hernandez R. A cohort study on childhood asthma admissions and readmissions. Pediatrics 1996; 98: 191-195.
9. Farber HJ. Risk of readmission to hospital for pediatric asthma. J Asthma 1998; 35: 95-99.
10. Schaubel D, Johansen H, Mao Y, Dutta M, Manfreda J. Risk of preschool asthma: incidence, hospitalization, recurrence, and readmission probability. J Asthma 1996; 33: 97-103.
11. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Risk factors for exacerbations and hospital admissions in asthma of early childhood. Pediatr Pulmonol 2000; 29: 250-256.
12. Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatr 1999; 88: 827-834.
13. Conway SP, Littlewood JM. Admission to hospital with asthma. Arch Dis Child 1985; 60: 636-639.
14. SIG Zorginformatie Utrecht. Landelijke medische registratie (LMR), 1991-1992. Utrecht: SIG Zorginformatie.
15. Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.

16. Senthilselvan A. Effect of readmissions on increasing hospital admissions for asthma in children. Thorax 1995; 50: 934-936.

17. Hyndman SJ, Williams DRR, Merrill SL, Lipscombe JM, Palmer CR. Rates of admission to hospital for asthma. Br Med J [Clin Res] 1994; 308: 1596-1600.

18. Harju T, Keistinen T, Tuuponen T, Kivelä S-L. Hospital admissions of asthmatics by age and sex. Allergy 1996; 51: 693-696.

19. van der Windt DAWM, Nagelkerke AF, Bouter LM, Dankert- Roelse JE, Veerman AJP. Clinical scores for acute asthma in preschool children. A review of the literature. J Clin Epidemiol 1994; 47: 635-646.

20. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. JAMA 1992; 268: 3437-3440.

21. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989; 44: 614-619.

22. Dales RE, Schweitzer I, Toogood JH, Drouin M, Yang W, Dolovich J, Boulet J. Respiratory infections and the autumn increase in asthma morbidity. Eur Respir J 1996; 9: 72-77.

23. Openshaw PJM, Walzl G. Infections prevent the development of asthma—true, false or both [editorial]? J R Soc Med 1999; 92: 495-499.

24. Madge P, McColl J, Paton J. Impact of a nurse-led home management training programme in children admitted to hospital with acute asthma: a randomised controlled study. Thorax 1997; 52: 223-228.

25. Wesseldine LJ, McCarthy P, Silverman M. Structured discharge procedure for children admitted to hospital with acute asthma: a randomised controlled trial of nursing practice. Arch Dis Child 1999; 80: 110-114.

26. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children. A dose comparison study. Am J Respir Crit Care Med 1999; 160: 126-131.

CHAPTER 7
SUMMARY, GENERAL DISCUSSION, AND FUTURE RESEARCH

7.1 Summary

The aim of this thesis was to examine trends in mortality and morbidity attributed to asthma in the Netherlands, in the light of the changing concepts of asthma and the improved pharmacotherapy, against the background of other airway disorders. Furthermore, prognostic characteristics of asthma diagnosis and predisposing risk factors related to asthma exacerbations and hospital (re)admissions were examined in children aged 0-4 years.

Chapter 1 contains the general introduction. This introduction describes trends in mortality and hospital admissions associated with asthma in various parts of the world in the last 30-40 years, with special reference to drug management of asthma. The concept of asthma has changed from a 'spastic' disease to an 'inflammatory' disease. Guidelines have been developed nationally and internationally, which emphasised the importance of preventive treatment directed to the inflammatory processes in the airways, and recommended bronchodilators as relief medication. Most childhood asthma begins in infancy. In the very young, as in the elderly, it is often difficult to differentiate between asthma and other pulmonary diseases, especially chronic obstructive pulmonary disease (COPD). In the Netherlands, asthma and COPD have been combined and termed "chronische aspecifieke respiratoire aandoeningen" ("CARA"). The term "CARA" was often used as diagnostic label. Therefore, we evaluated asthma as well as other obstructive respiratory diseases with asthma-like symptoms, according to the codes of the International Classification of Diseases.

Chapter 2 presents the national data on mortality from asthma and COPD in the Netherlands over the period 1980-1999. For the age groups 0-4 years, 5-34 years, 35-64 years, and ≥65 years gender-specific mortality rates per million persons were calculated. In childhood, mortality rates were also evaluated for acute bronchi(oli)tis, and pneumonia-influenza for age groups 0-4 years and 5-14 years. Mortality from asthma was inversely related with age, most deaths occurring in age group ≥65 years. In this age group, asthma mortality declined strongly in the 1990s. No trend was found in age group 0-4 years and a gradual, modest decrease was observed in age groups 5-34 years and 35-64 years over the study period. In age group 0-4 years, mortality from acute bronchi(oli)tis, and pneumonia-influenza decreased. COPD mortality increased in age groups 35-64 years and ≥65 years in females throughout the study period, while rates in males respectively levelled off and decreased in the 1990s. We concluded that mortality from asthma showed a favourable development, and that the mortality rates of the other respiratory diseases showed stable or decreasing trends, except for the increase in mortality from COPD in older females, over the period 1980-1999.

Chapter 3 presents the national data on hospital admissions for asthma and COPD in the Netherlands over the period 1980-1999. For the age groups 0-4 years, 5-34 years, 35-64 years, and ≥65 years gender-specific hospital admission rates per million persons were calculated, as well as gender-specific rates for age groups 5-9 years and 10-14 years in childhood. Furthermore, admission rates for acute bronchi(oli)tis and pneumonia-influenza in childhood were evaluated. Admission rates for asthma increased in age group 0-4 years, whereas rates decreased in the other age groups. These trends levelled off in the 1990s. In childhood and young adulthood, the trends in admissions for asthma and COPD suggested a shift in diagnostic labelling from COPD to asthma after 1993. In age groups 35-64 years and ≥65 years, rates of admissions for COPD increased continuously in females, while rates in males respectively decreased and levelled off in the 1990s. In age group 0-4 years, admissions for acute bronchi(oli)tis increased substantially. In conclusion, the rates of hospital admission for asthma showed an overall favourable development in the Netherlands over the period 1980-1999, but the

admission rates for respiratory diseases in the very young and the increasing hospital admission rates for COPD in older females are causes for concern.

Chapter 4 presents data on consultations and prescriptions in patients having ambulatory care for asthma and chronic obstructive pulmonary disease (COPD) by age group (0-4 years, 5-11 years, 12-19 years, 5-39 years, 40-64 years, and ≥65 years) and doctor's category (general practitioner (GP), specialist) in the Netherlands over the period 1981-1993. We divided consultations into first and repeat consultations, and the prescriptions into (1) pulmonary medication: β_2-agonists, anticholinergics, ketotifen, methylxanthines, sodium cromoglycate, inhaled steroids, oral steroids, (2) antibiotics, and (3) other drugs. We calculated age-specific consultation and prescription rates per 1000 persons. Overall, rates of first consultations were stable, and rates of repeat consultations increased in the age groups under 40 years. For specialists, however, first consultations increased in age group 0-4 years, and all consultations decreased in age group 40-64 years. Rates of prescriptions for pulmonary medication increased, except in age group 40-64 years. Rates for antibiotics were stable. Rates of prescriptions by GP for 'other drugs' decreased in age groups 0-4 years and 40-64 years. The ratio of prescription rate to consultation rate for the anti-inflammatory drugs increased significantly at all ages. In conclusion, the results suggest improved care for asthma and COPD in the Netherlands according to published guidelines, and increased prevalence and (or) severity of obstructive airways disease in children, over the period 1981-1993.

Chapter 5 reviews prescriptions by GPs and specialists for asthma in the Netherlands in the years 1999, 2000, and 2001. We calculated ratios for the number of prescriptions to the number of consultations in the age groups 0-4 years, 5-11 years, 12-19 years, 20-39 years, 40-64 years, and ≥65 years. Drugs were grouped as follows:

- bronchodilators: β_2-agonists, anticholinergics;
- anti-inflammatory drugs: inhaled corticosteroids, mast cell stabilisers, oral and parenteral corticosteroids;
- combined inhaled β_2-agonists and corticosteroids;

- antileukotrienes;
- other drugs.

Overall, 90% of the prescriptions for asthma concerned pulmonary medication, particularly β_2-agonists and inhaled corticosteroids in rather similar frequencies. Anticholinergics were mainly prescribed in the age groups 0-4 years and ≥65 years. Prescriptions for combined inhaled β_2-agonists and corticosteroids increased in the age groups ≥5 years from 1999 to 2001. For specialists, the increase roughly mirrored a decrease in prescriptions for inhaled corticosteroids and for β_2-agonists.

Chapter 6 describes the results from a registration study, set up in children aged 0-4 years who were newly referred to the outpatient department at the Juliana Children's Hospital, the Hague, with symptoms suggestive of asthma. Age groups 0-1 year and 2-4 years, based on age at initial presentation, were analysed separately. A history was taken, using a standard questionnaire of the department of paediatric respiratory medicine, and blood was drawn for total and specific immunoglobulin E (IgE).

Firstly, we analysed prognostic characteristics of asthma diagnosis in early childhood in clinical practice. In total, 419 children were enrolled over a 2-year period and followed for 2 years. Age group 0-1 year comprised 231 patients, of whom 113 (49%) were diagnosed as having asthma. Prognostic variables from history taking were shortness of breath, eczema, wheeze and non-allergic provoking factors. Age group 2-4 years comprised 188 patients, of whom 144 (77%) were diagnosed as having asthma. Prognostic variables were shortness of breath, allergic provoking factors, and absence of ear-nose-throat history. Adding laboratory data, sensitisation to inhalant allergens (presence of specific IgE) was a strong predisposing factor.

Secondly, we analysed risk factors for exacerbations and hospital admissions in asthma of early childhood. In age group 0-1 year, 71 patients (63%) had exacerbations, associated with damp housing, colds, and sensitisation to inhalant allergen (presence of specific IgE), while hospital admissions were associated with the number of

exacerbations. In age group 2-4 years, 58 patients (40%) had exacerbations, for which age at presentation and level of total IgE were predisposing risk factors, while hospital admissions were associated with damp housing.

Thirdly, we analysed factors associated with readmissions for asthma in the children who were admitted to hospital within the first year after initial presentation (54 patients aged 0-1 year and 46 patients aged 2-4 years), yielding a follow-up of 1 year. In age group 0-1 year, the number of readmissions was higher than in age group 2-4 years (33% versus 16%, p-value 0.028), with no indication for lower threshold of admission. Clinical features at admission did not differ between first admission and subsequent admission in both age groups. In age group 0-1 year, a history of eczema showed a negative association with readmission. Sensitisation to inhalant allergens (presence of specific IgE) was positively associated, but its prevalence was low and significance was not reached. In age group 2-4 years, patients sensitised to inhalant allergens had a higher risk of readmission (relative risk 1.54, confidence interval 1.22-1.95). In age group 0-1 year, 60% of the readmissions occurred within two months of initial admission, and prescriptions for inhaled steroids at discharge might be indicated in preventing readmission.

7.2 General Discussion

Trends

Overall, a decrease was observed in mortality and hospital admissions associated with asthma in the Netherlands over the period 1980-1999, but different trends occurred in the 1980s and the 1990s. Between ages 5-64 years, mortality and hospital admissions decreased stronger in the 1980s. In age group ≥65 years, the decreasing trends were more strongly in the 1990s, especially in males. Hospital admissions for asthma showed an increase over the study period in age group 0-4 years only. In infancy, it is difficult to distinguish between asthma and acute bronchiolitis. Whatever label, both diseases

showed increasing hospital admission rates. This had no impact on asthma mortality, while mortality from acute bronchi(oli)tis decreased.

Trends in the 1980s may reflect the improved possibilities for treatment of different age groups with various anti-asthma drugs and inhaler devices. The changing concept of asthma from a 'spastic' disease to an 'inflammatory' disease may have promoted the use of anti-inflammatory drugs, besides the use of bronchodilators. The trends in the 1990s may additionally reflect the impact of consensus guidelines on diagnosis and management of asthma. These guidelines emphasised the importance of early recognition and treatment of asthma and the use of inhaled corticosteroids as maintenance therapy in chronic asthma. Therefore, shifts in diagnostic labelling and changes in asthma management may have contributed to the observed trends.

Diagnostic labelling

Asthma has escaped an exact definition so far. The description of a 'chronic inflammatory disorder of the airways' has been agreed upon, but the variability of the disease between and within individuals may provide variation in diagnostic labelling. The American Thoracic Society published standards for the diagnosis of patients with chronic obstructive pulmonary disease (COPD) and asthma in 1987 [1]. At older ages, however, COPD with features of asthma and vice versa exist, and in young children several wheezing phenotypes including asthma exist. In the Netherlands, asthma was traditionally clustered with 'bronchitis' and 'emphysema' (COPD) and labelled as "chronische aspecifieke respiratoire aandoeningen" ("CARA"). The data on consultations in 1993 indicated that the prevalence of the diagnostic label "CARA" was higher in childhood and in the age group ≥65 years [chapter 4]. This likely reflects the more difficult distinction at younger ages and at older ages between asthma on the one hand and COPD / 'wheezy bronchitis' on the other. "CARA" will be covered by International Classification of Diseases (ICD)-9 code 496 and ICD-10 code J44 'chronic obstructive airway disease not classified elsewhere' and thus by 'COPD'. The term "CARA" as diagnostic label became obsolete in the Netherlands in the 1990s. In

children and young adults, hospital admissions for COPD decreased in the 1990s, whereas admissions for asthma tended to increase [chapter 3]. In age group ≥65 years, asthma mortality showed a fall in the early 1990s [chapter 2] and hospital admissions for asthma decreased, albeit more gradually, in males in the 1990s [chapter 3]. These trends could not affect those of COPD, because of the much higher frequency of COPD. A shift in diagnostic labelling in children from COPD to asthma and in the elderly, especially in males, from asthma to COPD is likely to have contributed to the observed trends.

Asthma management

Trends in prescription rates were in line with the asthma guidelines. A major finding was the increase in prescriptions for anti-inflammatory drugs between 1981 and 1993. The ratio of the number of prescriptions for anti-inflammatory drugs to the number of consultations increased in all age groups [chapter 4]. Improvement in management of childhood asthma may, however, mask an increase in prevalence, if any. Worldwide increases in prevalence of asthma have been reported, but data are lacking in the Netherlands. The increase in hospital admissions in age group 0-4 years may be an early reflection of increased prevalence of asthma in childhood. Initially, an increase in admissions for asthma was found in age group 5-9 years in the 1980s, but there were no further indications for a cohort effect in the admissions. Admissions for childhood asthma ("CARA") are now decreasing [chapter 3]. This might be the result of improvement in ambulatory care, reflected by increased consultations and prescriptions for pulmonary medication for asthma and COPD in childhood [chapter 4]. But also, the increase in consultations and prescriptions may point to an increased prevalence and (or) severity of childhood asthma. From the United Kingdom an increase in respiratory morbidity in preschool children was reported [2]. Prevalence data over time are needed in the Netherlands to clarify this issue, along with data on hospital admissions. However, there are indications from studies comparing data from Eastern and Western Europe and studies from Italy and the United States that the increase in prevalence of asthma may have come to an end [3-5].

Control of asthma appears to be best achieved at middle age (35-64 years), although the degree of pharmacotherapy was similar to that in the other age groups over 1981-1993. Mortality and hospital admissions for asthma decreased, as did specialist consultations for asthma and COPD. Consultations of GPs remained stable, accompanied by improvement in GP asthma management: prescriptions increased for inhaled steroids, and decreased for xanthines and non anti-asthma drugs. However, part of the ambulatory care will have been directed to COPD. At middle age, trends in mortality and hospital admissions for COPD differed between males and females. It is likely that the impact of smoking has been more important than pharmacotherapeutic management in the decreasing trend for males and increasing trend for females with COPD. In order to assess the role of ambulatory care, we need information about consultations and prescriptions by gender.

Recent changes in therapeutic asthma management

We evaluated changes in prescription patterns from 1981 through 1993 for asthma and COPD combined, as separation of the data for asthma could not been done. However, we found that the changes observed were in line with the guidelines for asthma at the time. Therefore, the data may serve as baseline for asthma treatment in the 1980s. The updated guidelines for asthma in the second part of the 1990s [6-8], recommended short acting β_2-agonists and inhaled steroids as first choice, and a lower threshold for long acting β_2-agonists. Recent data (1999-2001) for asthma in the Netherlands confirmed that most prescriptions were for β_2-agonists and inhaled steroids, with an increase in combination treatment with long acting β_2-agonists and corticosteroids by single inhaler [chapter 5]. Except for anticholinergics in young and elderly patients, prescriptions for other drugs played a minor role. Thus in patients labelled 'asthma', the prescription pattern was in accordance with the guidelines. However, this does not need to imply correct treatment in individual patients.

Vital statistics on asthma and COPD in the Netherlands

The prevalence data on asthma and COPD showed different pictures regarding mortality

and hospital admissions. Asthma mortality showed a positive and asthma morbidity a negative association with age, whereas COPD mortality and COPD morbidity were both positively associated with age. Asthma trends in males and females were similar, but COPD trends in males and females ≥35 years differed. Although most asthma deaths occurred in age group ≥65 years, numbers were low compared to the mortality from COPD. Hospital admission rates for asthma were highest in age group 0-4 years. Moreover, hospital admissions for acute bronchi(oli)tis increased in age group 0-4 years and reached a higher level than admissions for asthma in the late 1990s. Thus there is a high burden of respiratory diseases in young children, accompanied by low mortality, and a high burden in the elderly, accompanied by a high mortality. Trends in admissions for COPD were similar to trends in mortality from COPD. COPD is a progressive and disabling disease. Therefore, the increase in admissions for COPD in females predicts a further increase in mortality in females in the next decade(s).

Figure 7.1 shows the rates for mortality, hospital admissions, and consultations for asthma and COPD in 1993. The figure illustrates that the highest prevalences occur at ages when the diagnosis of asthma is most difficult. It is questioned whether

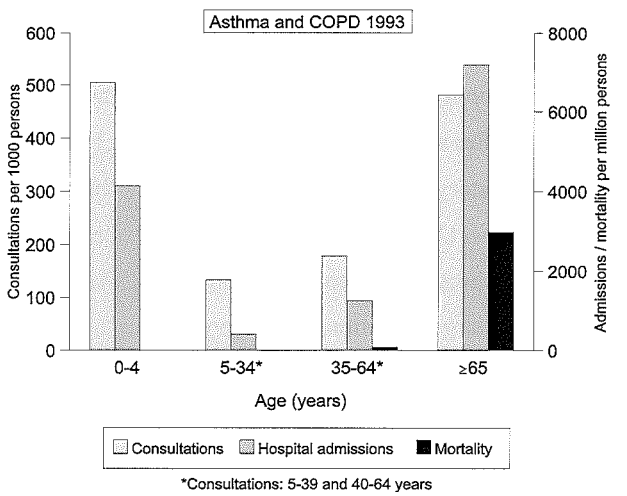

Figure 7.1 Consultations per 1000 persons, hospital admissions and mortality per million persons for asthma and chronic obstructive pulmonary disease (COPD) by age in the Netherlands, 1993.

measurements may contribute. At the other end of the age spectrum, young children are at risk for inadequate treatment [15], while the increase in asthma and asthma-like morbidity in age group 0-4 years in the past decades is cause for concern. Figure 7.2 shows asthma morbidity and mortality statistics in the Netherlands in 1999. Rates of consultations and hospital admissions were high in the age group 0-4 years. There are still no markers that can be used in routine clinical practice to recognise children at risk for asthma [7], and clinical history and evaluation are still the cornerstones for diagnosis. We therefore examined prognostic characteristics and predisposing risk factors related to asthma morbidity in the Netherlands in children aged 0-4 years at the Juliana's Children Hospital in the Hague [chapter 6].

Age group 0-4 years

We found an inverse association between number of referrals to the hospital's outpatient department and age. Also, younger age proved to be a risk factor for exacerbations of asthma and hospital readmissions for asthma. Diagnosing and managing asthmatic symptoms is obviously the biggest problem in the youngest patients. Early recognition may enhance early treatment to achieve disease control. Besides variables from history taking (trigger factors, damp housing), sensitisation to inhalant allergens proved to be a risk factor for exacerbations and hospital (re)admissions. In infants, however, positive allergy tests showed low prevalences. Once admitted to hospital, clinical evaluation after discharge is important in view of the high risk of readmission within the first months. In infants, inhaled steroids may then be recommended to prevent readmission. In older children, inhaled anti-inflammatory therapy showed a protective effect of risk for hospitalisation and emergency room visits [16]. Conventional dosages in preschool children seem to present no risk for systemic effects, but careful evaluation (monitoring growth) is advocated [17]. Furthermore, educational programmes were effective in older children and adults, and should be targeted at preschool children as well, although it might be more difficult to produce effects [18]. Asthma is a multifactorial disease with complex genetic and environmental components, possibly even starting before birth [19]. Further research may indicate if primary prevention is possible for asthma. The

effect of preventative measures on disease prevalence should be studied continuously.

7.3 Future research

We recommend the following directions for future research:

- Continuing epidemiological evaluation of asthma and asthma-like diseases statistics in the Netherlands.
- Good documentation of hospital ward admissions, hospital day care admissions, and hospital emergency visits, especially in young children, as measures for (trends in) the prevalence of severe asthma.
- Systemic recording of medical history taking in patients, especially the very young, in order to further improve the early recognition / identification of children at risk for asthma. Furthermore, data on ethnicity in children are needed to evaluate whether differences in asthma prevalence and severity exist between ethnic groups in the Netherlands, and consequently to explore and prevent risk factors in asthma.
- Gathering data on factors playing a role in the increasing number of hospital admissions for respiratory syncytial virus (RSV) bronchiolitis in young children and the relation between prevalence of RSV and childhood asthma in the Netherlands.
- Developing educational programmes on asthma management for preschool children and their parents and caregivers.
- Developing effective strategies to discourage smoking, especially in young females.
- Participating in international studies for generating hypotheses, for providing comparative prevalence data and assessing environmental risk factors in the Netherlands, in order to find explanations for geographical differences in disease prevalence and to develop interventions tailored to the Dutch situation.

References

1. American Thoracic Society. Medical section of the American Lung Association. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136: 225-244.
2. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet 2001; 357: 1821-1825.
3. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, Jarvis D, Kuenzli N, Leynaert B, Luczynska C, Neukirch F, Svanes C, Sunyer J, Wjst M, on behalf of the European Community Respiratory Health Survey II. The European Community Respiratory Health Survey: what are the main results so far? Eur Respir J 2001; 18: 598-611.
4. Ronchetti R, Villa MP, Barreto M, Rota R, Pagani J, Martella S, Falasca C, Paggi B, Guglielmi F, Ciofetta G. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. Eur Respir J 2001; 17: 881-886.
5. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002; 110: 315-322.
6. Hoekstra MO. Treatment of asthma in children; revised guidelines from paediatric pneumonologists (English summary). Ned Tijdschr Geneeskd 1997; 141: 2223-2229.
7. Warner JO, Naspitz CK, Cropp GJA. Third international pediatric consensus statement on the management of childhood asthma. Pediatr Pulmonol 1998; 25: 1-17.
8. British asthma guidelines coordinating committee. The British guidelines on asthma management: 1995 review and position statement. Thorax 1997; 52(Suppl 1): S1-24.
9. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, Strachan D, Weiland SK, Williams HC. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur Respir J 1995; 8: 483-491.
10. The international study of asthma and allergies in childhood (ISAAC) steering committee. Worldwide variations in the prevalence of asthma symptoms: the international study of asthma and allergies in childhood (ISAAC). Eur Respir J 1998; 12: 315-335.
11. Waters Barger L, Vollmer WM, Felt RW, Buist AS. Further investigation into the recent increase in asthma death rates: a review of 41 asthma deaths in Oregon in 1982. Ann Allergy 1988; 60: 31-39.
12. Parameswaran K, Hildreth AJ, Chadha D, Keaney NP, Taylor IK, Bansal SK. Asthma in the elderly: underperceived, underdiagnosed and undertreated; a community survey. Respir Med 1998; 92: 573-577.

13. Dow L, Fowler L, Phelps L, Waters K, Coggon D, Kinmonth AL, Holgate ST. Prevalence of untreated asthma in a population sample of 6000 older adults in Bristol, UK. Thorax 2001; 56: 472-476.

14. van Schayck CP, van der Heijden FMMA, van den Boom G, Tirimanna PRS, van Herwaarden CLA. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. Thorax 2000; 55: 562-565.

15. Keeley DJ, Silverman M. Are we too ready to diagnose asthma in children? Thorax 1999; 54: 625-628.

16. Adams RJ, Fuhlbrigge A, Finkelstein JA, Lozano P, Livingston JM, Weiss KB, Weiss ST. Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. Pediatrics 2001; 107: 706-711.

17. Allen DB. Inhaled corticosteroid therapy for asthma in preschool children: growth issues. Pediatrics 2002; 109: 373-380.

18. Stevens CA, Wesseldine LJ, Couriel JM, Dyer AJ, Osman LM, Silverman M. Parental education and guided self-management of asthma and wheezing in the pre-school child: a randomised controlled trial. Thorax 2002; 57: 39-44.

19. Becker AB. Is primary prevention of asthma possible? Pediatr Pulmonol 2000; 30: 63-72.

SAMENVATTING

Het doel van dit proefschrift was trends te onderzoeken in de sterfte en morbiditeit wegens astma in Nederland, in het licht van de veranderde inzichten betreffende astma en de verbeterde farmacotherapie, tegen de achtergrond van andere luchtwegaandoeningen. Verder werden voorspellende kenmerken voor de diagnosestelling van astma en ontvankelijk makende risicofactoren voor exacerbaties en ziekenhuis(her)opnamen wegens astma onderzocht bij kinderen in de leeftijd van 0-4 jaar.

Hoofdstuk 1 omvat de algemene inleiding. Deze inleiding beschrijft trends in sterfte en ziekenhuisopnamen wegens astma in verscheidene delen van de wereld in de afgelopen 30-40 jaar, vooral in verband met de medicamenteuze behandeling van astma. Het inzicht in astma veranderde. Astma wordt niet meer beschouwd als een "spastische" aandoening, maar als een "inflammatoire" aandoening. Richtlijnen werden nationaal en internationaal opgesteld, die het belang van preventieve behandeling van de ontstekingsprocessen in de luchtwegen benadrukten en luchtwegverwijders aanbevolen voor symptoombestrijding. Astma bij kinderen ontwikkelt zich meestal op zeer jonge leeftijd. Bij zeer jonge kinderen, als ook bij ouderen, is het vaak moeilijk onderscheid te maken tussen astma en andere longaandoeningen, vooral COPD ('chronic obstructive pulmonary disease'). In Nederland werden astma en COPD samengevat onder de term chronische aspecifieke respiratoire aandoeningen (CARA). De term CARA werd vaak als diagnostisch label gebruikt. Daarom evalueerden we zowel astma als andere obstructieve luchtwegaandoeningen die gepaard gaan met astmatische klachten, overeenkomstig de codes van de internationale classificatie van ziekten (ICD).

Hoofdstuk 2 presenteert de nationale gegevens betreffende de sterfte aan astma en COPD in Nederland over de periode 1980-1999. Sterftecijfers per geslacht per miljoen inwoners werden berekend voor de leeftijdsgroepen 0-4 jaar, 5-34 jaar, 35-64 jaar en

≥65 jaar. Bij kinderen werd de sterfte aan acute bronchi(oli)tis en pneumonie-influenza eveneens geëvalueerd voor de leeftijdsgroepen 0-4 jaar en 5-14 jaar. De sterfte aan astma verhield zich omgekeerd met leeftijd, de meeste sterfgevallen kwamen voor in de leeftijdsgroep ≥65 jaar. In deze leeftijdsgroep nam de sterfte sterk af in de negentiger jaren. Geen trend werd gevonden in de leeftijdsgroep 0-4 jaar en een geleidelijke, bescheiden afname werd waargenomen in de leeftijdsgroepen 5-34 jaar en 35-64 jaar. In de leeftijdsgroep 0-4 jaar nam de sterfte aan acute bronchi(oli)tis en pneumonie-influenza af. In de leeftijdsgroepen 35-64 jaar en ≥65 jaar steeg de sterfte aan COPD bij de vrouwen over de gehele onderzoeksperiode, terwijl de cijfers bij de mannen zich stabiliseerden respectievelijk daalden in de negentiger jaren. We concludeerden dat de sterfte aan astma een gunstige ontwikkeling toonde en dat de sterftecijfers van de andere respiratoire aandoeningen stabiele of dalende trends toonden, met uitzondering van de toename in de sterfte aan COPD bij oudere vrouwen, over de periode 1980-1999.

Hoofdstuk 3 presenteert de nationale gegevens betreffende de ziekenhuisopnamen wegens astma en COPD in Nederland over de periode 1980-1999. Ziekenhuisopnamecijfers per geslacht per miljoen inwoners werden berekend voor de leeftijdsgroepen 0-4 jaar, 5-34 jaar, 35-64 jaar en ≥65 jaar, evenals bij kinderen voor de leeftijdsgroepen 5-9 jaar en 10-14 jaar. Verder werden ziekenhuisopnamecijfers geëvalueerd voor acute bronchi(oli)tis en pneumonie-influenza voor de kinderleeftijdsgroepen. De opnamecijfers voor astma stegen in de leeftijdsgroep 0-4 jaar, terwijl de cijfers daalden in de andere leeftijdsgroepen. Deze trends stabiliseerden zich in de negentiger jaren. De trends in de ziekenhuisopnamen wegens astma en COPD bij kinderen en jong volwassenen suggereerden een verschuiving in diagnosestelling van COPD naar astma na 1993. In de leeftijdsgroepen 35-64 jaar en ≥65 jaar stegen de ziekenhuisopnamecijfers voor COPD bij de vrouwen continu, terwijl de opnamecijfers bij de mannen afnamen respectievelijk zich stabiliseerden in de negentiger jaren. In de leeftijdsgroep 0-4 jaar namen de opnamen wegens acute bronchi(oli)tis aanzienlijk toe. Concluderend, de ziekenhuisopnamecijfers voor astma toonden in het algemeen een gunstige ontwikkeling in Nederland over de periode 1980-1999, maar de opnamecijfers

voor de respiratoire aandoeningen bij de zeer jonge kinderen en de toenemende opnamecijfers voor COPD bij oudere vrouwen zijn zorgwekkend.

Hoofdstuk 4 presenteert gegevens betreffende consulten en prescripties voor astma en chronisch obstructieve longziekte (COPD) bij patiënten in de ambulante zorg per leeftijdsgroep (0-4 jaar, 5-11 jaar, 12-19 jaar, 5-39 jaar, 40-64 jaar en ≥65 jaar) en artsencategorie (huisarts, specialist) in Nederland over de periode 1981-1993. We onderscheidden de consulten in eerste consulten en herhalingsconsulten, en de prescripties in (1) pulmonale medicatie: β_2-agonisten, anticholinergica, ketotifen, methylxanthinen, natriumcromoglicaat, inhalatiesteroïden, orale steroïden, (2) antibiotica, en (3) overige geneesmiddelen. We berekenden leeftijdsspecifieke cijfers voor consulten en prescripties per 1000 inwoners. In het algemeen waren de cijfers voor de eerste consulten stabiel en namen de cijfers voor de herhalingsconsulten toe in de leeftijdsgroepen onder 40 jaar. Bij de specialisten namen de eerste consulten echter toe in de leeftijdsgroep 0-4 jaar, en namen alle consulten af in de leeftijdsgroep 40-64 jaar. De prescriptiecijfers voor de pulmonale medicatie stegen, behalve in de leeftijdsgroep 40-64 jaar. De cijfers voor de antibiotica waren stabiel. Het aantal prescripties door de huisarts voor "overige geneesmiddelen" nam af in de leeftijdsgroepen 0-4 jaar en 40-64 jaar. De verhouding van het aantal prescripties voor de anti-inflammatoire geneesmiddelen tot het aantal consulten steeg significant in alle leeftijdsgroepen. Concluderend, de resultaten suggereren een verbeterde zorg voor astma en COPD in Nederland overeenkomstig gepubliceerde richtlijnen, en een toegenomen prevalentie en (of) ernst van obstructieve luchtwegaandoeningen bij kinderen, over de periode 1981-1993.

Hoofdstuk 5 beschouwt prescripties door de huisartsen en specialisten voor astma in Nederland in de jaren 1999, 2000 en 2001. We berekenden verhoudingsgetallen van het aantal prescripties tot het aantal consulten in de leeftijdsgroepen 0-4 jaar, 5-11 jaar, 12-19 jaar, 20-39 jaar, 40-64 jaar en ≥65 jaar. Geneesmiddelen waren gegroepeerd als volgt:

- bronchusverwijders: β_2-agonisten, anticholinergica;
- anti-inflammatoire geneesmiddelen: inhalatiecorticosteroïden, mestcelstabilisatoren, orale en parenterale corticosteroïden;
- gecombineerde β_2-agonisten en corticosteroïden per inhalationem;
- antileukotriënen;
- andere geneesmiddelen.

In het algemeen betrof 90% van de prescripties voor astma pulmonale medicatie, met name β_2-agonisten en inhalatiecorticosteroïden in ongeveer dezelfde frequenties. Anticholinergica werden hoofdzakelijk voorgeschreven in de leeftijdsgroepen 0-4 jaar en $\geq$65 jaar. Het aantal prescripties voor gecombineerde β_2-agonisten en corticosteroïden per inhalationem steeg in de leeftijdsgroepen vanaf 5 jaar tussen 1999 en 2001. De toename reflecteerde voor specialisten globaal een afname in prescripties voor inhalatiecorticosteroïden en voor β_2-agonisten.

Hoofdstuk 6 beschrijft de resultaten van een registratie-onderzoek dat uitgevoerd werd bij kinderen in de leeftijd van 0-4 jaar, die voor het eerst verwezen waren naar de polikliniek van het Juliana Kinderziekenhuis in Den Haag, met symptomen die verdacht zijn voor astma. De leeftijdsgroepen 0-1 jaar en 2-4 jaar, gebaseerd op de leeftijd bij inschrijving, werden afzonderlijk geanalyseerd. Een anamnese werd afgenomen, waarbij gebruik werd gemaakt van een standaardvragenlijst van de afdeling kinderlongziekten, en bloed werd afgenomen voor de bepaling van totaal en specifiek immunoglobuline E (IgE).

Ten eerste analyseerden we voorspellende kenmerken voor het stellen van de diagnose astma bij jonge kinderen in de klinische praktijk. In totaal werden 419 kinderen geregistreerd over een periode van 2 jaar en gedurende 2 jaar gevolgd. De leeftijdsgroep 0-1 jaar bestond uit 231 patiënten, waarvan bij 113 (49%) de diagnose astma werd gesteld. Voorspellende variabelen uit de anamnese waren kortademigheid, eczeem, piepen en invloed van niet-allergische provocerende factoren. De leeftijdsgroep 2-4 jaar bestond uit 188 patiënten, waarvan bij 144 (77%) de diagnose astma werd gesteld.

Voorspellende variabelen waren kortademigheid, invloed van allergische provocerende factoren en de afwezigheid van keel-neus-oor klachten. Uit de laboratoriumgegevens bleek sensibilisatie voor inhalatieallergenen (de aanwezigheid van specifiek IgE) een sterk predisponerende factor.

Ten tweede analyseerden we risicofactoren voor exacerbaties en ziekenhuisopnamen wegens astma bij jonge kinderen. In de leeftijdsgroep 0-1 jaar ondervonden 71 patiënten (63%) exacerbaties, die een verband toonden met vochtige behuizing, verkoudheden en sensibilisatie voor inhalatieallergenen (de aanwezigheid van specifiek IgE), terwijl ziekenhuisopnamen een verband toonden met het aantal exacerbaties. In de leeftijdsgroep 2-4 jaar ondervonden 58 patiënten (40%) exacerbaties, waarvoor de leeftijd bij inschrijving en de waarde van totaal IgE predisponerende risicofactoren waren, terwijl ziekenhuisopnamen een verband toonden met vochtige behuizing.

Ten derde analyseerden we factoren in relatie tot heropnamen wegens astma bij de kinderen die opgenomen werden in het ziekenhuis binnen 1 jaar na de inschrijving (54 patiënten in de leeftijd van 0-1 jaar en 46 patiënten in de leeftijd van 2-4 jaar), zodat zij 1 jaar gevolgd konden worden. In de leeftijdsgroep 0-1 jaar was het aantal heropnamen hoger dan in de leeftijdsgroep 2-4 jaar (33% versus 16%, p-waarde 0,028), zonder dat er een aanwijzing was voor een lagere opnamedrempel. Klinische kenmerken bij de opname verschilden niet tussen de eerste opname en de volgende opname in beide leeftijdsgroepen. In de leeftijdsgroep 0-1 jaar toonde het anamnestisch bestaan van eczeem een negatief verband met heropname. Sensibilisatie voor inhalatieallergenen (de aanwezigheid van specifiek IgE) toonde een positief verband, maar het voorkomen was laag en statistische significantie werd niet bereikt. In de leeftijdsgroep 2-4 jaar hadden de patiënten die gesensibiliseerd waren voor inhalatieallergenen een hogere kans op heropname (relatieve risico 1,54, 95% betrouwbaarheidsinterval 1,22-1,95). In de leeftijdsgroep 0-1 jaar had 60% van de heropnamen plaats binnen twee maanden na de eerste opname, en prescripties voor inhalatiesteroïden bij ontslag zijn mogelijk geïndiceerd om heropnamen te voorkómen.

Population size by gender and age group in the Netherlands, 1980-1999

	Males					Females				
Age group yrs	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	453175	3628376	2269810	670013	7021374	431798	3459322	2278651	958650	7128421
1981	454374	3613155	2320355	677134	7065018	433616	3448218	2322354	978001	7182189
1982	452854	3571030	2385308	682888	7092080	432968	3412433	2379910	995297	7220608
1983	449617	3531788	2444515	687456	7113376	430126	3380304	2432432	1010832	7253694
1984	447162	3499169	2497861	692694	7136886	427864	3353804	2479248	1026408	7287324
1985	446191	3476068	2542093	702731	7167083	427138	3333543	2517143	1046742	7324566
1986	447634	3460637	2580234	715924	7204429	429065	3319318	2549011	1070443	7367837
1987	453590	3444814	2621786	728583	7248773	434700	3303369	2584409	1093421	7415899
1988	462054	3427918	2662846	742276	7295094	442463	3286222	2620037	1116260	7464982
1989	469496	3409743	2703387	754779	7337405	450191	3268706	2655263	1137203	7511363
1990	478502	3398209	2747143	765152	7389006	458757	3254107	2695171	1154483	7562518
1991	487861	3391256	2794566	776156	7449839	466741	3244157	2737923	1170931	7619752
1992	494609	3381485	2844483	787250	7507827	472456	3235150	2783341	1185364	7676311
1993	499601	3368828	2894282	797845	7560556	477326	3224170	2829357	1198939	7729792
1994	504019	3349144	2944615	808903	7606681	481241	3207094	2875931	1211882	7776148
1995	503849	3325586	2993659	821794	7644888	480958	3185888	2921836	1225425	7814107
1996	499948	3303480	3041609	834509	7679546	476890	3167397	2968830	1237846	7850963
1997	497065	3281776	3092204	847389	7718434	473998	3150248	3018568	1249392	7892206
1998	497770	3260926	3147584	860399	7766679	475001	3134165	3071442	1259933	7940541
1999	501574	3238898	3206362	872965	7819799	478260	3117715	3127598	1268726	7992299

Source: Centraal Bureau voor de Statistiek, Voorburg.
Leeftijdsopbouw naar Burgelijke Staat en Geslacht, Gemiddeld 1980-1999.

Table I. Mortality from asthma in the Netherlands, males + females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	4	22	51	125	202	4.5	3.1	11.2	76.8	14.3
1981	2	16	75	159	252	2.3	2.3	16.2	96.1	17.7
1982	0	25	58	160	243	0	3.6	12.2	95.3	17.0
1983	2	24	63	160	249	2.3	3.5	12.9	94.2	17.3
1984	2	14	66	152	234	2.3	2.0	13.3	88.4	16.2
1985	1	18	57	172	248	1.1	2.6	11.3	98.3	17.1
1986	2	12	69	174	257	2.3	1.8	13.5	97.4	17.6
1987	2	14	66	176	258	2.3	2.1	12.7	96.6	17.6
1988	4	17	62	177	260	4.4	2.5	11.7	95.2	17.6
1989	2	7	70	202	281	2.2	1.0	13.1	106.8	18.9
1990	0	7	52	216	275	0	1.1	9.6	112.5	18.4
1991	1	14	56	185	256	1.0	2.1	10.1	95.0	17.0
1992	3	13	41	81	138	3.1	2.0	7.3	41.1	9.1
1993	3	9	37	27	76	3.1	1.4	6.5	13.5	5.0
1994	4	7	28	15	54	4.1	1.1	4.8	7.4	3.5
1995	0	8	18	6	32	0	1.2	3.0	2.9	2.1
1996	0	5	19	15	39	0	0.8	3.2	7.2	2.5
1997	1	9	21	38	69	1.0	1.4	3.4	18.1	4.4
1998	0	11	20	78	109	0	1.7	3.2	36.8	6.9
1999	0	8	26	61	95	0	1.3	4.1	28.5	6.0

International Classification of Diseases: 1980-1995, ICD-9 code 493; 1996-1999, ICD-10 code J45 + J46.

Table II. Mortality from asthma in the Netherlands, males 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	1	14	33	74	122	2.2	3.9	14.5	110.4	17.4
1981	2	13	41	84	140	4.4	3.6	17.7	124.1	19.8
1982	0	16	28	84	128	0	4.5	11.7	123.0	18.0
1983	1	16	33	88	138	2.2	4.5	13.5	128.0	19.4
1984	2	7	34	66	109	4.5	2.0	13.6	95.3	15.3
1985	0	7	19	94	120	0	2.0	7.5	133.8	16.7
1986	2	6	38	84	130	4.5	1.7	14.7	117.3	18.0
1987	2	6	21	88	117	4.4	1.7	8.0	120.8	16.1
1988	4	13	28	90	135	8.7	3.8	10.5	121.2	18.5
1989	2	6	39	113	160	4.3	1.8	14.4	149.7	21.8
1990	0	4	30	132	166	0	1.2	10.9	172.5	22.5
1991	0	6	30	99	135	0	1.8	10.7	127.6	18.1
1992	1	7	16	45	69	2.0	2.1	5.6	57.2	9.2
1993	1	5	21	11	38	2.0	1.5	7.3	13.8	5.0
1994	3	5	14	7	29	6.0	1.5	4.8	8.7	3.8
1995	0	4	5	1	10	0	1.2	1.7	1.2	1.3
1996	0	3	10	8	21	0	0.9	3.3	9.6	2.7
1997	1	3	8	11	23	2.0	0.9	2.6	13.0	3.0
1998	0	5	9	31	45	0	1.5	2.9	36.0	5.8
1999	0	4	10	20	34	0	1.2	3.1	22.9	4.3

International Classification of Diseases: 1980-1995, ICD-9 code 493; 1996-1999, ICD-10 code J45 + J46.

Table III. Mortality from asthma in the Netherlands, females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	3	8	18	51	80	6.9	2.3	7.9	53.2	11.2
1981	0	3	34	75	112	0	0.9	14.6	76.7	15.6
1982	0	9	30	76	115	0	2.6	12.6	76.4	15.9
1983	1	8	30	72	111	2.3	2.4	12.3	71.2	15.3
1984	0	7	32	86	125	0	2.1	12.9	83.8	17.2
1985	1	11	38	78	128	2.3	3.3	15.1	74.5	17.5
1986	0	6	31	90	127	0	1.8	12.2	84.1	17.2
1987	0	8	45	88	141	0	2.4	17.4	80.5	19.0
1988	0	4	34	87	125	0	1.2	13.0	77.9	16.7
1989	0	1	31	89	121	0	0.3	11.7	78.3	16.1
1990	0	3	22	84	109	0	0.9	8.2	72.8	14.4
1991	1	8	26	86	121	2.1	2.5	9.5	73.4	15.9
1992	2	6	25	36	69	4.2	1.9	9.0	30.4	9.0
1993	2	4	16	16	38	4.2	1.2	5.7	13.3	4.9
1994	1	2	14	8	25	2.1	0.6	4.9	6.6	3.2
1995	0	4	13	5	22	0	1.3	4.4	4.1	2.8
1996	0	2	9	7	18	0	0.6	3.0	5.7	2.3
1997	0	6	13	27	46	0	1.9	4.3	21.6	5.8
1998	0	6	11	47	64	0	1.9	3.6	37.3	8.1
1999	0	4	16	41	61	0	1.3	5.1	32.3	7.6

International Classification of Diseases: 1980-1995, ICD-9 code 493; 1996-1999, ICD-10 code J45 + J46.

Table IV. Mortality from chronic obstructive pulmonary disease in the Netherlands, males + females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	2	5	410	2955	3372	2.3	0.7	90.1	1814	238
1981	1	3	393	2987	3384	1.1	0.4	84.6	1805	238
1982	0	14	408	3201	3623	0	2.0	85.6	1907	253
1983	1	8	417	3430	3856	1.1	1.2	85.5	2020	268
1984	1	11	444	3672	4128	1.1	1.6	89.2	2136	286
1985	3	11	477	4041	4532	3.4	1.6	94.3	2310	313
1986	5	7	477	4494	4983	5.7	1.0	93.0	2516	342
1987	3	6	454	4329	4792	3.4	0.9	87.2	2376	327
1988	1	8	450	4676	5135	1.1	1.2	85.2	2516	348
1989	3	4	481	5306	5794	3.3	0.6	89.8	2804	390
1990	0	8	464	5255	5727	0	1.2	85.3	2737	383
1991	4	3	471	5344	5822	4.2	0.5	85.1	2745	386
1992	3	10	415	4949	5377	3.1	1.5	73.7	2509	354
1993	1	7	457	5933	6398	1.0	1.1	79.8	2971	418
1994	1	5	409	5179	5594	1.0	0.8	70.3	2563	364
1995	0	8	407	5823	6238	0	1.2	68.8	2844	404
1996	2	6	436	5950	6394	2.0	0.9	72.5	2871	412
1997	1	4	467	5772	6244	1.0	0.6	76.4	2753	400
1998	0	5	490	6333	6828	0	0.8	78.8	2987	435
1999	0	5	471	6121	6597	0	0.8	74.4	2858	417

International Classification of Diseases: 1980-1995, ICD-9 codes 490, 491, 492, 496; 1996-1999, ICD-10 codes J40-J44.

Table V. Mortality from chronic obstructive pulmonary disease in the Netherlands, males 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	1	4	304	2356	2665	2.2	1.1	134	3516	380
1981	0	1	314	2325	2640	0	0.3	135	3434	374
1982	0	10	314	2498	2822	0	2.8	132	3658	398
1983	1	4	319	2679	3003	2.2	1.1	130	3897	422
1984	1	6	338	2819	3164	2.2	1.7	135	4070	443
1985	3	7	345	3078	3433	6.7	2.0	136	4380	479
1986	3	5	361	3333	3702	6.7	1.4	140	4656	514
1987	2	4	320	3251	3577	4.4	1.2	122	4462	493
1988	0	3	322	3430	3755	0	0.9	121	4621	515
1989	2	2	345	3846	4195	4.3	0.6	128	5096	572
1990	0	6	297	3738	4041	0	1.8	108	4885	547
1991	3	1	300	3796	4100	6.1	0.3	107	4891	550
1992	2	6	268	3447	3723	4.0	1.8	94	4379	496
1993	0	3	287	4055	4345	0	0.9	99	5082	575
1994	0	1	243	3537	3781	0	0.3	83	4373	497
1995	0	7	236	3930	4173	0	2.1	79	4782	546
1996	1	4	261	4008	4274	2.0	1.2	86	4803	557
1997	1	2	276	3774	4053	2.0	0.6	89	4454	525
1998	0	2	281	4131	4414	0	0.6	89	4801	568
1999	0	3	260	3859	4122	0	0.9	81	4421	527

International Classification of Diseases: 1980-1995, ICD-9 codes 490, 491, 492, 496; 1996-1999, ICD-10 codes J40-J44.

Table VI. Mortality from chronic obstructive pulmonary disease in the Netherlands, females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	1	1	106	599	707	2.3	0.3	46.5	625	99
1981	1	2	79	662	744	2.3	0.6	34.0	677	104
1982	0	4	94	703	801	0	1.2	39.5	706	111
1983	0	4	98	751	853	0	1.2	40.3	743	118
1984	0	5	106	853	964	0	1.5	42.8	831	132
1985	0	4	132	963	1099	0	1.2	52.4	920	150
1986	2	2	116	1161	1281	4.7	0.6	45.5	1085	174
1987	1	2	134	1078	1215	2.3	0.6	51.8	986	164
1988	1	5	128	1246	1380	2.3	1.5	48.9	1116	185
1989	1	2	136	1460	1599	2.2	0.6	51.2	1284	213
1990	0	2	167	1517	1686	0	0.6	62.0	1314	223
1991	1	2	171	1548	1722	2.1	0.6	62.5	1322	226
1992	1	4	147	1502	1654	2.1	1.2	52.8	1267	215
1993	1	4	170	1878	2053	2.1	1.2	60.1	1566	266
1994	1	4	166	1642	1813	2.1	1.2	57.7	1355	233
1995	0	1	171	1893	2065	0	0.3	58.5	1545	264
1996	1	2	175	1942	2120	2.1	0.6	58.9	1569	270
1997	0	2	191	1998	2191	0	0.6	63.3	1599	278
1998	0	3	209	2202	2414	0	1.0	68.0	1748	304
1999	0	2	211	2262	2475	0	0.6	67.5	1783	310

International Classification of Diseases: 1980-1995, ICD-9 codes 490, 491, 492, 496; 1996-1999, ICD-10 codes J40-J44.

Table VII. Mortality from asthma, acute bronchi(oli)tis (AB), pneumonia and influenza (P/I), and chronic obstructive pulmonary disease (COPD) in age group 0-4 years (males+females) in the Netherlands, 1980-1999

	Actual number				Rates per million persons			
	Asthma	AB	P/I	COPD	Asthma	AB	P/I	COPD
1980	4	15	23	2	4.5	16.9	26.0	2.3
1981	2	10	32	1	2.3	11.3	36.0	1.1
1982	0	6	28	0	0	6.8	31.6	0
1983	2	2	16	1	2.3	2.3	18.2	1.1
1984	2	8	24	1	2.3	9.1	27.4	1.1
1985	1	7	31	3	1.1	8.0	35.5	3.4
1986	2	4	39	5	2.3	4.6	44.5	5.7
1987	2	5	37	3	2.3	5.6	41.7	3.4
1988	4	7	15	1	4.4	7.7	16.6	1.1
1989	2	7	16	3	2.2	7.6	17.4	3.3
1990	0	4	11	0	0	4.3	11.7	0
1991	1	0	18	4	1.0	0	18.9	4.2
1992	3	0	14	3	3.1	0	14.5	3.1
1993	3	2	8	1	3.1	2.0	8.2	1.0
1994	4	1	13	1	4.1	1.0	13.2	1.0
1995	0	3	12	0	0	3.0	12.2	0
1996	0	1	15	2	0	1.0	15.4	2.0
1997	1	1	12	1	1.0	1.0	12.4	1.0
1998	0	0	15	0	0	0	15.4	0
1999	0	1	8	0	0	1.0	8.2	0

1980-1995: ICD-9 code 493, 466, 480-487, 490-492+496, respectively; 1996-1999: ICD-10 code J45-46, J20-22, J10-18, J40-44, respectively.

Table VIII. Mortality from asthma, acute bronchi(oli)tis (AB), pneumonia and influenza (P/I), and chronic obstructive pulmonary diseases (COPD) in age group 5-14 years (males+females) in the Netherlands, 1980-1999

	Actual number				Rates per million persons			
	Asthma	AB	P/I	COPD	Asthma	AB	P/I	COPD
1980	1	0	4	1	0.4	0	1.8	0.4
1981	3	1	7	0	1.4	0.5	3.2	0
1982	1	0	5	2	0.5	0	2.3	0.9
1983	1	2	9	2	0.5	1.0	4.3	1.0
1984	3	1	4	2	1.5	0.5	2.0	1.0
1985	1	0	4	1	0.5	0	2.1	0.5
1986	0	0	3	1	0	0	1.6	0.5
1987	1	0	2	1	0.5	0	1.1	0.5
1988	2	0	1	1	1.1	0	0.6	0.6
1989	0	0	2	0	0	0	1.1	0
1990	0	0	3	2	0	0	1.7	1.1
1991	1	0	2	2	0.6	0	1.1	1.1
1992	1	0	2	2	0.6	0	1.1	1.1
1993	0	0	9	2	0	0	4.9	1.1
1994	1	0	5	1	0.5	0	2.7	0.5
1995	1	0	5	1	0.5	0	2.7	0.5
1996	0	0	4	3	0	0	2.1	1.6
1997	2	1	10	0	1.1	0.5	5.3	0
1998	0	0	10	1	0	0	5.2	0.5
1999	1	0	7	1	0.5	0	3.6	0.5

1980-1995: ICD-9 code 493, 466, 480-487, 490-492+496, respectively; 1996-1999: ICD-10 code J45-46, J20-22, J10-18, J40-44, respectively.

Table I. Hospital admissions for asthma in the Netherlands, males + females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	900	2544	3007	1324	7775	1017	359	661	813	549
1981	886	2471	2680	1413	7450	998	350	577	854	523
1982	1175	2538	2733	1428	7874	1326	363	574	851	550
1983	1119	2335	2561	1340	7355	1272	338	525	789	512
1984	1327	2350	2346	1294	7317	1517	343	471	753	507
1985	1327	2288	2357	1363	7335	1519	336	466	779	506
1986	1404	2023	2184	1309	6920	1601	298	426	733	475
1987	1444	2291	2022	1218	6975	1626	339	388	668	476
1988	1514	2202	2138	1277	7131	1674	328	405	687	483
1989	1441	1826	1964	1189	6420	1567	273	367	628	432
1990	1752	1698	1711	1073	6234	1869	255	314	559	417
1991	1633	1675	1498	829	5635	1711	252	271	426	374
1992	1720	1563	1452	744	5479	1779	236	258	377	361
1993	2213	1684	1449	734	6080	2265	255	253	368	398
1994	2072	1575	1388	727	5762	2103	240	238	360	375
1995	2111	1618	1444	696	5869	2144	248	244	340	380
1996	2240	1589	1495	637	5961	2293	246	249	307	384
1997	1893	1693	1518	559	5663	1949	263	248	267	363
1998	2256	1875	1582	608	6321	2319	293	254	287	402
1999	1955	1749	1690	583	5977	1995	275	267	272	378

Code 493, International Classification of Diseases (ICD-9).

Table II. Hospital admissions for asthma in the Netherlands, males 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	588	1271	1367	654	3880	1298	350	602	976	553
1981	561	1218	1234	701	3714	1235	337	532	1035	526
1982	757	1223	1179	688	3847	1672	342	494	1007	542
1983	750	1165	1177	661	3753	1668	330	481	962	528
1984	818	1141	1083	611	3653	1829	326	434	882	512
1985	845	1052	992	689	3578	1894	303	390	980	499
1986	849	938	904	624	3315	1897	271	350	872	460
1987	892	1096	821	611	3420	1967	318	313	839	472
1988	941	1003	926	610	3480	2037	293	348	822	477
1989	875	783	811	565	3034	1864	230	300	749	413
1990	1135	728	717	526	3106	2372	214	261	687	420
1991	1102	694	621	395	2812	2259	205	222	509	377
1992	1159	624	547	360	2690	2343	185	192	457	358
1993	1507	681	518	315	3021	3016	202	179	395	400
1994	1417	631	533	315	2896	2811	188	181	389	381
1995	1450	673	559	296	2978	2878	202	187	360	390
1996	1484	709	561	241	2995	2968	215	184	289	390
1997	1282	727	538	171	2718	2579	222	174	202	352
1998	1477	812	540	205	3034	2967	249	172	238	391
1999	1297	786	586	183	2852	2586	243	183	210	365

Code 493, International Classification of Diseases (ICD-9).

Table III. Hospital admissions for asthma in the Netherlands, females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	312	1273	1640	670	3895	723	368	720	699	546
1981	325	1253	1446	712	3736	750	363	623	728	520
1982	418	1315	1554	740	4027	965	385	653	743	558
1983	369	1170	1384	679	3602	858	346	569	672	497
1984	509	1209	1263	683	3664	1190	360	509	665	503
1985	482	1236	1365	674	3757	1128	371	542	644	513
1986	555	1085	1280	685	3605	1294	327	502	640	489
1987	552	1195	1201	607	3555	1270	362	465	555	479
1988	573	1199	1212	667	3651	1295	365	463	598	489
1989	566	1043	1153	624	3386	1257	319	434	549	451
1990	617	970	994	547	3128	1345	298	369	474	414
1991	531	981	877	434	2823	1138	302	320	371	370
1992	561	939	905	384	2789	1187	290	325	324	363
1993	706	1003	931	419	3059	1479	311	329	349	396
1994	655	944	855	412	2866	1361	294	297	340	369
1995	661	945	885	400	2891	1374	297	303	326	370
1996	756	880	934	396	2966	1585	278	315	320	378
1997	611	966	980	388	2945	1289	307	325	311	373
1998	779	1063	1042	403	3287	1640	339	339	320	414
1999	658	963	1104	400	3125	1376	309	353	315	391

Code 493, International Classification of Diseases (ICD-9).

Table IV. Hospital admissions for chronic obstructive pulmonary disease (COPD) in the Netherlands, males + females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	1141	947	4061	6212	12361	1289	134	893	3814	874
1981	1063	905	4000	6506	12474	1197	128	862	3931	876
1982	1108	1019	4546	7342	14015	1251	146	954	4375	979
1983	1049	982	4831	8263	15125	1192	142	991	4865	1053
1984	989	916	5052	9023	15980	1130	134	1015	5249	1108
1985	1073	836	5469	9957	17335	1229	123	1081	5691	1196
1986	1172	816	5282	10420	17690	1337	120	1030	5833	1214
1987	1007	1021	5125	10106	17259	1134	151	984	5547	1177
1988	1356	980	5465	10575	18376	1499	146	1034	5690	1245
1989	1291	876	5532	11687	19386	1404	131	1032	6177	1306
1990	1387	890	5415	12095	19787	1480	134	995	6301	1323
1991	1512	887	5413	11968	19780	1584	134	978	6147	1313
1992	1466	873	5513	12513	20365	1516	132	980	6343	1341
1993	1839	1015	5779	13619	22252	1882	154	1010	6820	1455
1994	1667	892	5596	13525	21680	1692	136	961	6693	1409
1995	1325	824	5663	14464	22276	1345	127	957	7065	1441
1996	1248	591	5701	14651	22191	1278	91	949	7070	1429
1997	943	503	5931	15233	22610	971	78	971	7265	1448
1998	820	472	6163	15669	23124	843	74	991	7390	1472
1999	565	388	5559	14756	21268	577	61	878	6890	1345

Code 490, 491, 492, and 496, International Classification of Diseases (ICD-9).

Table V. Hospital admissions for chronic obstructive pulmonary disease (COPD) in the Netherlands, males 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	725	479	2715	4576	8495	1600	132	1196	6830	1210
1981	688	472	2566	4711	8437	1514	131	1106	6957	1194
1982	694	488	2879	5250	9311	1533	137	1207	7688	1313
1983	662	505	3117	6053	10337	1472	143	1275	8805	1453
1984	644	459	3267	6472	10842	1440	131	1308	9343	1519
1985	709	403	3315	7043	11470	1589	116	1304	10022	1600
1986	749	343	3108	7198	11398	1673	99	1205	10054	1582
1987	657	499	2977	6995	11128	1448	145	1135	9601	1535
1988	887	465	3113	7211	11676	1920	136	1169	9715	1601
1989	844	425	3172	8004	12445	1798	125	1173	10604	1696
1990	914	426	3033	8170	12543	1910	125	1104	10678	1698
1991	983	390	2942	8025	12340	2015	115	1053	10339	1656
1992	983	397	2940	8278	12598	1987	117	1034	10515	1678
1993	1227	482	3074	8905	13688	2456	143	1062	11161	1810
1994	1108	428	2932	8883	13351	2198	128	996	10982	1755
1995	877	393	2874	9586	13730	1741	118	960	11665	1796
1996	846	289	2890	9366	13391	1692	87	950	11223	1744
1997	632	213	2959	9587	13391	1271	65	957	11314	1735
1998	535	191	2889	9777	13392	1075	59	918	11363	1724
1999	348	169	2690	9020	12227	694	52	839	10333	1564

Code 490, 491, 492, and 496, International Classification of Diseases (ICD-9).

Table VI. Hospital admissions for chronic obstructive pulmonary disease (COPD) in the Netherlands, females 1980-1999

	Actual number in the age group (yrs)					Rates per million persons in the age group (yrs)				
	0-4	5-34	35-64	≥65	total	0-4	5-34	35-64	≥65	total
1980	416	468	1346	1636	3866	963	135	591	1707	542
1981	375	433	1434	1795	4037	865	126	617	1835	562
1982	414	531	1667	2092	4704	956	156	700	2102	651
1983	387	477	1714	2210	4788	900	141	705	2186	660
1984	345	457	1785	2551	5138	806	136	720	2485	705
1985	364	433	2154	2914	5865	852	130	856	2784	801
1986	423	473	2174	3222	6292	986	142	853	3010	854
1987	350	522	2148	3111	6131	805	158	831	2845	827
1988	469	515	2352	3364	6700	1060	157	898	3014	898
1989	447	451	2360	3683	6941	993	138	889	3239	924
1990	473	464	2382	3925	7244	1031	143	884	3400	958
1991	529	497	2471	3943	7440	1133	153	903	3367	976
1992	483	476	2573	4235	7767	1022	147	924	3573	1012
1993	612	533	2705	4714	8564	1282	165	956	3932	1108
1994	559	464	2664	4642	8329	1162	145	926	3830	1071
1995	448	431	2789	4878	8546	931	135	955	3981	1094
1996	402	302	2811	5285	8800	843	95	947	4270	1121
1997	311	290	2972	5646	9219	656	92	985	4519	1168
1998	285	281	3274	5892	9732	600	90	1066	4676	1226
1999	217	219	2869	5736	9041	454	70	917	4521	1131

Code 490, 491, 492, and 496, International Classification of Diseases (ICD-9).

Table VII. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 0-4 years, males 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	588	725	271	1568	1298	1600	598	3460
1981	561	688	333	1581	1235	1514	733	3480
1982	757	694	352	1684	1672	1533	777	3719
1983	750	662	381	1707	1668	1472	847	3797
1984	818	644	426	1830	1829	1440	953	4092
1985	845	709	402	1727	1894	1589	901	3871
1986	849	749	501	1807	1897	1673	1119	4037
1987	892	657	357	1406	1967	1448	787	3100
1988	941	887	596	1953	2037	1920	1290	4227
1989	875	844	810	1806	1864	1798	1725	3847
1990	1135	914	565	1522	2372	1910	1181	3181
1991	1102	983	864	1778	2259	2015	1771	3644
1992	1159	983	1099	2002	2343	1987	2222	4048
1993	1507	1227	879	2014	3016	2456	1759	4031
1994	1417	1108	2121	2246	2811	2198	4208	4456
1995	1450	877	892	1662	2878	1741	1770	3299
1996	1484	846	1660	1908	2968	1692	3320	3816
1997	1282	632	1487	1795	2579	1271	2992	3611
1998	1477	535	2645	2350	2967	1075	5314	4721
1999	1297	348	1484	1712	2586	694	2959	3413

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

Table VIII. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 0-4 years, females 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	312	416	216	1101	723	963	500	2550
1981	325	375	215	1107	750	865	496	2553
1982	418	414	226	1194	965	956	522	2758
1983	369	387	220	1126	858	900	511	2618
1984	509	345	230	1357	1190	806	538	3172
1985	482	364	217	1225	1128	852	508	2868
1986	555	423	340	1344	1294	986	792	3132
1987	552	350	254	985	1270	805	584	2266
1988	573	469	404	1435	1295	1060	913	3243
1989	566	447	494	1354	1257	993	1097	3008
1990	617	473	343	1112	1345	1031	748	2424
1991	531	529	572	1181	1138	1133	1226	2530
1992	561	483	750	1505	1187	1022	1587	3185
1993	706	612	610	1421	1479	1282	1278	2977
1994	655	559	1443	1607	1361	1162	2998	3339
1995	661	448	516	1148	1374	931	1073	2387
1996	756	402	1072	1402	1585	843	2248	2940
1997	611	311	1004	1352	1289	656	2118	2852
1998	799	285	1816	1697	1640	600	3823	3573
1999	658	217	989	1193	1376	454	2068	2494

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

Table IX. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 5-9 years, males 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	353	147	15	431	657	274	28	802
1981	357	136	27	360	701	267	53	707
1982	375	148	29	369	772	305	60	760
1983	360	181	51	511	768	386	109	1090
1984	384	152	38	363	837	331	83	791
1985	337	146	26	362	740	321	57	795
1986	346	131	29	282	759	288	64	619
1987	423	198	57	460	929	435	125	1010
1988	352	156	38	299	776	344	84	659
1989	267	156	27	267	590	345	60	590
1990	259	158	39	261	571	349	86	576
1991	256	162	59	375	562	356	130	823
1992	225	155	32	486	487	336	69	1052
1993	277	215	37	432	588	457	79	917
1994	236	169	24	335	493	353	50	699
1995	257	142	30	435	527	291	62	892
1996	287	124	28	396	578	250	56	798
1997	269	73	28	406	536	145	56	809
1998	333	77	22	387	658	152	43	764
1999	327	58	22	304	641	114	43	596

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

Table X. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 5-9 years, females 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	215	108	17	262	418	210	33	510
1981	184	83	20	298	378	170	41	611
1982	190	101	13	288	410	218	28	621
1983	177	95	29	395	396	213	65	884
1984	212	82	23	290	485	187	53	663
1985	204	88	26	253	470	203	60	583
1986	175	88	32	227	402	202	74	522
1987	209	101	31	327	480	232	71	751
1988	188	99	25	239	433	228	58	550
1989	133	87	30	212	307	201	69	490
1990	138	110	19	191	318	253	44	440
1991	167	115	18	286	383	264	41	655
1992	142	99	26	327	321	224	59	739
1993	181	136	30	308	402	302	67	683
1994	139	87	19	231	303	190	41	503
1995	146	93	18	305	313	199	39	653
1996	140	78	17	296	295	164	36	624
1997	174	53	11	320	363	111	23	667
1998	191	58	27	289	395	120	56	597
1999	160	42	18	231	328	86	37	474

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

Table XI. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 10-14 years, males 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	291	83	8	117	465	133	13	187
1981	255	80	11	117	409	128	18	188
1982	278	88	19	130	452	143	31	211
1983	261	90	22	197	436	150	37	329
1984	217	86	4	138	380	150	7	241
1985	200	64	10	93	371	119	19	172
1986	158	67	10	107	309	131	20	210
1987	214	74	9	144	439	152	18	295
1988	180	74	17	76	381	157	36	161
1989	109	47	15	92	235	101	32	198
1990	103	56	13	81	223	121	28	175
1991	125	74	26	101	270	160	56	218
1992	101	67	18	129	218	145	39	278
1993	131	72	4	112	283	156	9	242
1994	101	66	7	75	219	143	15	162
1995	110	65	11	109	238	141	24	236
1996	123	42	13	126	265	91	28	272
1997	129	26	7	132	275	55	15	281
1998	145	19	9	125	303	40	19	261
1999	132	20	9	98	271	41	18	201

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

Table XII. Hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), acute bronchi(oli)tis (AB), and pneumonia and influenza (P/I) in the Netherlands, age group 10-14 years, females 1980-1999

	Actual number				Rates per million persons			
	Asthma	COPD	AB	P/I	Asthma	COPD	AB	P/I
1980	155	51	3	108	259	85	5	181
1981	186	53	10	72	312	89	17	121
1982	167	76	12	102	284	129	20	173
1983	147	59	11	126	257	103	19	220
1984	143	47	8	74	261	86	15	135
1985	156	47	4	83	302	91	8	161
1986	101	45	8	92	207	92	16	188
1987	135	42	9	108	290	90	19	232
1988	121	54	6	79	269	120	13	176
1989	88	33	3	67	199	75	7	152
1990	102	31	7	58	232	70	16	132
1991	89	58	11	79	201	131	25	179
1992	83	40	7	108	187	90	16	244
1993	85	47	10	96	192	106	23	217
1994	91	49	2	76	206	111	5	172
1995	91	37	3	108	206	84	7	244
1996	107	36	7	84	241	81	16	189
1997	110	28	5	76	245	62	11	169
1998	115	24	8	100	251	52	17	218
1999	102	18	3	96	219	39	6	206

ICD-9 codes 493, 490+491+492+496, 466, and 480-487, respectively.

ABBREVIATIONS

AB	Acute bronchi(oli)tis
ATS	American thoracic society
b	Slope
CARA	Chronische aspecifieke respiratoire aandoeningen
CBS	Central bureau of statistics
CI	Confidence interval
CNSLD	Chronic nonspecific lung disease
COPD	Chronic obstructive pulmonary disease
ENT	Ear, nose and throat
Ex	Exacerbation
FEV_1	Forced expiratory volume in one second
GINA	Global initiative for asthma
GP	General practitioner
h	Hours
ICD	International classification of diseases
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IMS	Institute of medical statistics
M	Mother
ns	Not significant
OR	Odds ratio
P	Father
P/I	Pneumonia and influenza
RAST	Radioallergosorbent test
RR	Relative risk
RSV	Respiratory syncytial virus
SD	Standard deviation
SE	Standard error

DANKWOORD

Zonder de hulp van velen was dit proefschrift niet tot stand gekomen. In de loop der jaren zijn er personen geweest die bemiddeld hebben alsmede personen die het daadwerkelijk mogelijk maakten dat ik over de data kon beschikken die ik wilde analyseren. Al worden zij hier anoniem verwerkt, het gaat gepaard met een diep gevoel van erkentelijkheid.

Maar wat zijn data zonder statistische analyse? Dr. J. Hermans, beste Jo, jarenlang heb jij mij bijgestaan met een nuchtere kijk op presentatie van data en met statistische adviezen. Dat de laatste fase plaats vond in Thailand, waar jij en Ank mij zo gastvrij ontvangen hebben, heeft hieraan een gouden glans gegeven. Heel veel dank.

Zonder promotoren geen proefschrift. Prof.dr. J.C. de Jongste, eerste promotor, en prof.dr. E.J. Duiverman, tweede promotor, hartelijk dank dat jullie mij hebben willen begeleiden.
Beste Johan, de communicatie ging voor een groot deel per post. Het vlotte reageren en je aantekeningen op het manuscript heb ik zeer op prijs gesteld, ... lange zinnen, "huisvlijt," orgelpijpen ..., het heeft mij wel eens boven mijn tekst doen grinniken. Je commentaar heeft me altijd aan het denken gezet en verder geholpen. Heel veel dank.
Beste Eric, ook jij bent met je reacties mij tot steun geweest. Ik houd het nu beknopt: heel veel dank voor je kritische opmerkingen.

Vervolgens dank ik de leden van de promotiecommissie, prof.dr. H.A. Büller, prof.dr. A. Hofman en prof.dr. H.C. Hoogsteden, voor hun bereidwilligheid zich in de door mij gepresenteerde epidemiologie van astma te verdiepen en bij te dragen aan de promotie.

Mevrouw den Hartog, lieve Friedel, de manier waarop jij het paranimf-zijn vorm gegeven hebt, heeft mij zeer getroffen. Het laat een scala aan beelden na waar ik met veel plezier en grote dankbaarheid naar "kijk".
Lieve Corrie, jij was er .... De royale schaal die je opdiende met culinaire diversiteiten in de afgelopen periode, vertaalt zich in mijn herinnering als symbool van jouw veel omvattende steun. Bedankt!

Lieve Rombout, Merel en Nander Wever, jullie hebben ieder op eigen wijze mij gesteund en gestimuleerd in mijn wens om een wetenschappelijk bouwsteentje te leveren en mijn proefschrift te voltooien. Heel hartelijk dank. Nander, een extra woord van dank voor jouw niet aflatende interesse en bereidheid om te functioneren als 'computertolk'.

Aan allen die bijgedragen hebben aan het proefschrift zoals het nu ter hand kan worden genomen: DANK!

CURRICULUM VITAE

Johanna Hess werd geboren op 29 juni 1943 te 's-Gravenhage. In 1961 behaalde zij het HBS-B diploma aan het Dalton Lyceum aldaar. Zij ging geneeskunde studeren aan de Medische Faculteit van de Rijksuniversiteit Groningen en behaalde in 1969 haar artsexamen. Daarna volgde zij de Basis Cursus Sociale Geneeskunde aan het toen geheten Nederlands Instituut voor Preventieve Geneeskunde (NIPG) te Leiden. Van maart 1970-april 1973 had zij een aanstelling als arts-assistente in de werkgroep Epidemiologie van CARA van de Gezondheidsorganisatie TNO te 's-Gravenhage. Om haar epidemiologische ervaringen met klinische kennis aan te vullen, werkte zij als geneeskundige op de astma-afdeling van Beatrixoord in Haren (Groningen) van mei 1973-juli 1974. Vervolgens volgde zij als Research Fellow van de British Council de 'Course in Epidemiology and Medical Statistics' aan de 'London School of Hygiene and Tropical Medicine' in Londen van september 1974-maart 1975.

In 1975 werd haar eerste kind geboren en sindsdien werd het moederschap gecombineerd met wetenschappelijk werk. Zij vervulde de volgende functies: gastmedewerker op de afdeling Longziekten van het Academisch Ziekenhuis Leiden in 1977; secretaris-rapporteur van de Werkgroep Epidemiologie van de Commissie Radiotherapie van de Gezondheidsraad te 's-Gravenhage van december 1981-maart 1984; onderzoeker in tijdelijke dienst bij de faculteit der Geneeskunde Leiden van november 1986-maart 1987; gastmedewerker van het Juliana Kinderziekenhuis te 's-Gravenhage ten behoeve van het astma-onderzoek bij 0-4 jarigen van 1991-1994. Daarnaast was zij mede-auteur van een aantal publikaties, met name op het gebied van astma. Het moederschap had zich inmiddels uitgebreid met een tweede kind in 1979 en een derde kind in 1982.

In de loop der jaren verzamelde en analyseerde zij gegevens over de sterfte en ziekenhuisopnamen wegens astma en andere longaandoeningen in Nederland. Deze data lagen aan de basis van het wetenschappelijk werk dat gepresenteerd is in dit proefschrift.

PUBLICATIONS

Van der Lende R, Van der Meulen GG, **Wever-Hess J**. Investigation into observer and seasonal variation of the prevalence of respiratory symptoms at Schiermonnikoog. International Journal of Epidemiology 1972; 1: 47-50.

Van der Lende R, De Kroon JPM, Tammeling GJ, Visser BF, De Vries K, **Wever-Hess J**, Orie NGM. Prevalence of chronic non-specific lung disease in a non-polluted and an air-polluted area of the Netherlands. In: Ecology of chronic nonspecific respiratory diseases. Proceedings international symposium, September 7-8, 1971, Warsaw, Poland, p 27-33. Edited by: Zbigniew Brzezinski MD, Jan Kopczynski MD, Feliks Sawicki MD. Panstwowy Zaklad Wydawnictw Lekarskich, Warszawa, 1972.

Van der Lende R, Van der Meulen GG, Visser BF, **Wever-Hess J**. Onderzoek naar variaties tussen onderzoekers en tussen seizoenen in de prevalentie van respiratoire symptomen bij mannen en vrouwen op Schiermonnikoog. Tijdschrift voor Sociale Geneeskunde 1972; 50: 775-778.

Van der Lende R, Van der Meulen GG, **Wever-Hess J**. Investigation into observer and seasonal variation of the prevalence of respiratory symptoms at Schiermonnikoog. In: Uses of epidemiology in planning health services. Proceedings of the 6th international scientific meeting of the IEA 1973, p 678-682. Editor: A Michael Davies, Savremena Administracya, Belgrade.

Van der Lende R, Visser BF, **Wever-Hess J**, Tammeling GJ, De Vries K, Orie NGM. Epidemiological investigation in the Netherlands into the influence of smoking and atmospheric pollution on respiratory symptoms and lung function disturbances. Pneumonologie 1973; 149: 119-126.

Van der Lende R, Visser BF, **Wever-Hess J**, De Vries K, Orie NGM. Distribution of histamine threshold values in a random population. Revue de l'Institut d'Hygiene des Mines 1973; 28: 186-190.

Wever AMJ, Britton MG, Hughes DTD, Van der Plas KH, **Wever-Hess J**. Clinical evaluation of five spirometers. Eur J Respir Dis 1981; 62: 127-137.

Wever-Hess J, Ribot JG. Deeladvies 1 inzake Epidemiologie (incidentie van kanker). Behorende bij het advies inzake Radiotherapie. Uitgebracht door een Commissie van de Gezondheidsraad. 's-Gravenhage: Gezondheidsraad, 1984.

Wever-Hess J, Ribot JG, Verbeek ALM, Engel GL. Prognose van de kankerincidentie in Nederland. Ned Tijdschr Geneeskd 1986; 130: 961-964.

Wever AMJ, **Wever-Hess J**, Kramps JA, Franken HCM, Dijkman JH, Mulder Dzn JD. Sensibilisatie voor inhalatie-allergenen bij patiënten met pulmonale medicatie in de huisartsenpraktijk. Airways 1988; 7: 118-121.

Wever AMJ, **Wever-Hess J**, Kramps JA, Mulder Dzn JD, Dijkman JH. De "Phadiatop-test", een nieuwe in vitro-test voor inhalatie-allergie. Ned Tijdschr Geneeskd 1989; 133: 70-73.

Wever AMJ, **Wever-Hess J**, Schayck CP van, Weel C van. Evaluation of the Phadiatop test in an epidemiological study. Allergy 1990; 45: 92-97.

Wever AMJ, **Wever-Hess J**, Yntema JL, Hermans J. Sterfte aan astma en chronisch obstructieve longziekte (CARA) in Nederland, 1980-1987. Airways 1990; 9: 64-67.

Jie C, Wever AMJ, Huysmans HA, Franken HCM, **Wever-Hess J**, Hermans J. Time trends and survival in patients presented for surgery with non-small-cell lung cancer 1969-1985. Eur J Cardio-thorac Surg 1990; 4: 653-657.

Wever AMJ, **Wever-Hess J**. Trends in de frequentie van ziekenhuisopname wegens astma en chronisch obstructieve longziekte in Nederland, 1980-1988. Ned Tijdschr Geneeskd 1991; 135: 659-664.

Wever-Hess J, Wever AMJ, Yntema JL. Mortality and morbidity from respiratory diseases in childhoood in the Netherlands, 1980-1987. Eur Respir J 1991; 4: 429-433.

Wever-Hess J, Wever AMJ. Frequentie van ziekenhuisopname wegens respiratoire aandoeningen bij kinderen van 0-14 jaar. Tijdschr Kindergeneeskd 1991; 59: 224-227.

Wever AMJ, **Wever-Hess J**. ß-adrenerge agonisten en sterfte en morbiditeit wegens astma. Ned Tijdschr Geneeskd 1992; 136: 460-465.

Schayck CP van, Wever AMJ, **Wever-Hess J**, Herwaarden CLA van, Weel C van. Screening op inhalatieallergenen: Phadiatop. Tijdschr v Huisartsgeneeskunde 1993; 10: 839-843.

Wever AMJ, **Wever-Hess J**. Testing for inhalant allergy in asthma. Clin Exp Allergy 1993; 23: 976-981.

Wever-Hess J, Kouwenberg JM, Wever AMJ. Trends in consulten en prescripties wegens CARA bij kinderen. Ned Tijdschr Geneeskd 1993; 137: 1246-1251.

Wever AMJ, **Wever-Hess J**, Hensgens HESJ, Hermans J. Serum eosinophil cationic protein (ECP) in chronic asthma. Relationship to spirometry, flow-volume curves, PC_{20}, and exacerbations. Respir Med 1994; 88: 613-621.

Wever AMJ, **Wever-Hess J**, Dahl R. Use of assessment of inflammation in management of drug therapy in asthma. Clin Immunother 1995; 4; 462-470.

Wever AMJ, **Wever-Hess J**, Hermans J. The use of serum eosinophil cationic protein (ECP) in the management of steroid therapy in chronic asthma. Clin Expir Allergy 1997; 27: 519-529.

Wever-Hess J, Wever AMJ. Asthma statistics in the Netherlands 1980-94. Respir Med 1997; 91: 417-422.

Wever AMJ, **Wever-Hess J**, Britton MG. Screening, diagnostic and outcome tools for asthma. Dis Manage Health Outcomes 1998; 3: 229-238.

Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatr 1999; 88: 827-834.

Wever-Hess J, Kouwenberg JM, Duiverman EJ, Hermans J, Wever AMJ. Risk factors for exacerbations and hospital admissions in asthma of early childhood. Pediatr Pulmonol 2000; 29: 250-256.

Wever-Hess J, Hermans J, Kouwenberg JM, Duiverman EJ, Wever AMJ. Hospital admissions and readmissions for asthma in the age group 0-4 years. Pediatr Pulmonol 2001; 31: 30-36.